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# Interaction attention-motricité chez le sujet sain et parkinsonien : mécanismes et modulation

Madli Bayot

► **To cite this version:**

Madli Bayot. Interaction attention-motricité chez le sujet sain et parkinsonien : mécanismes et modulation. Médecine humaine et pathologie. Université de Lille, 2020. Français. NNT : 2020LILUS022 . tel-03668474

**HAL Id: tel-03668474**

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UNIVERSITÉ DE LILLE  
ECOLE DOCTORALE BIOLOGIE-SANTÉ (EDBSL)

## THÈSE D'UNIVERSITÉ

En vue de l'obtention du grade de  
DOCTEUR DE L'UNIVERSITÉ DE LILLE  
*Spécialité Neurosciences*

### « Interaction attention-motricité chez le sujet sain et parkinsonien : mécanismes et modulation »

Présentée et soutenue publiquement le 14 décembre 2020

par Madli BAYOT

#### Jury :

Madame Aurélie BIDEY-CAULET (CR-HDR)	Université de Lyon	Rapporteuse
Monsieur Dominique GUEHL (PU-PH)	Université de Bordeaux	Rapporteur
Madame Kathy DUJARDIN (PU)	Université de Lille	Examinatrice
Monsieur Luc DEFEBVRE (PU-PH)	Université de Lille	Examineur
Monsieur Anaick PERROCHON (MCU-HDR)	Université de Limoges	Examineur
Monsieur Arnaud DELVAL (PU-PH)	Université de Lille	Directeur

Directeur de l'UR : Professeur Régis BORDET



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## RÉSUMÉ (FR)

L'initiation de la marche est un programme moteur qui n'est pas entièrement automatisé et varie selon les capacités attentionnelles. Des troubles moteurs et un déclin cognitif, notamment attentionnel, se développent avec le vieillissement et la maladie de Parkinson, ce qui entraîne un risque de chute.

L'objectif principal a été de mieux caractériser et de moduler l'interaction entre initiation du pas et attention visuo-spatiale au niveau comportemental et cortical.

Nous avons d'abord fait un état des lieux de la littérature sur les paradigmes de double tâche avec initiation de la marche et tâche cognitive. Ceux-ci ont été peu étudiés malgré un potentiel prometteur pour la prédiction du risque de chute.

Pour analyser l'interaction attention-locomotion, nous avons testé un paradigme combinant l'Attention Network Test avec l'initiation du pas chez de jeunes adultes. L'interaction a pu être caractérisée.

Après validation du couplage anormal entre posture initiale et phases de préparation et exécution de la marche chez les patients avec enrayage cinétique, l'interaction attention-initiation du pas y a été étudiée. Un défaut de contrôle exécutif existe, mais sans répercussion spécifique sur l'initiation du pas.

Une analyse de la connectivité fonctionnelle EEG à l'état de repos et lors d'une tâche attentionnelle a permis d'investiguer davantage le déclin cognitif chez les patients avec enrayage cinétique. Une sur-dépendance à l'environnement comme potentiel mécanisme compensateur a été observée.

Enfin, un protocole de recherche qui vise à moduler l'interaction attention-locomotion via la combinaison d'un entraînement cognitif structuré et un traitement au méthylphénidate a été entamé.

### **Mots-clés en français :**

Attention visuo-spatiale ; double tâche ; Attention Network Test ; alerte ; contrôle exécutif ; résolution de conflit ; temps de réaction ; initiation de la marche ; initiation du pas ; control postural ; centre de pression ; analyse 3D du mouvement ; ajustements posturaux anticipés ; temps d'exécution du pas ; vieillissement ; maladie de Parkinson ; enrayage cinétique de la marche ; électroencéphalographie ; potentiels liés à l'événement ; potentiels évoqués ; perturbation spectrale liée à l'événement ; potentiels induits ; puissance spectrale relative ; connectivité fonctionnelle ; état de repos ; cortex moteur ; cortex sensorimoteur ; réseau attentionnel ventral ; chutes.

## **ABSTRACT (EN)**

Gait initiation is a motor program not fully automatized which varies according to attentional capacities. Motor deficits and cognitive decline, including attention, develops with ageing and Parkinson's disease and may lead to risk of falls.

The main objective was to better characterize and modulate the interaction between step initiation and visuospatial attention at behavioral and cortical level.

We first produced a state of the art in the literature on dual tasks' paradigms with gait initiation and a cognitive task. A very limited number of studies on this topic were carried out despite a promising potential for risk of falls' prediction.

To analyze the attention-locomotion interplay, we tested a paradigm combining the Attention Network Test with gait initiation on young subjects. Accordingly, the interaction could be characterized.

After validating abnormal coupling between initial posture, preparation phases and gait execution in patients with freezing of gait, the attention-step initiation interplay was investigated. An impairment in executive control does exist, but without any specific repercussion on step initiation.

A functional connectivity EEG analysis at resting state and during an attentional task allowed to investigate further cognitive decline in patients with freezing of gait. An overdependence on the environment as potential compensatory mechanism was observed.

Eventually, a research protocol that aims to modulate the attention-locomotion interaction via a combination of structured cognitive training and methylphenidate treatment was initiated.

### **Keywords:**

Visuospatial attention ; dual task; Attention Network Test ; alerting ; executive control ; conflict resolution ; reaction time ; gait initiation ; step initiation ; postural control ; centre of pressure ; 3D motion analysis ; anticipatory postural adjustments ; step execution time ; ageing ; Parkinson's disease ; freezing of gait ; electroencephalography ; event-related potential; evoked potential ; event-related spectral perturbation ; relative spectral power ; functional connectivity ; resting-state; motor cortex ; sensorimotor cortex ; ventral attention network; falls.

## REMERCIEMENTS

Je tiens tout d'abord à exprimer mes plus sincères remerciements à mon superviseur, le Pr. Arnaud Delval, pour la confiance accordée au début de cette thèse et les connaissances et conseils qu'il a pu m'apporter tout au long de ce processus.

Mes remerciements à l'égard des membres du jury de thèse, Aurélie Bidet-Caulet, Pr. Dominique Guehl, Pr. Kathy Dujardin, Pr. Luc Defebvre et Anaick Perrochon, pour avoir accepté d'analyser et de discuter mon travail. Une mention particulière pour mes rapporteurs, Aurélie Bidet-Caulet et Pr. Dominique Guehl, qui ont également suivi l'évolution de mon travail au travers des différents comités de suivi individuel au cours desquels j'ai pu recevoir des retours et précieux conseils pour la poursuite de ma thèse.

Lors de ces 3 ans de doctorat, j'ai également eu la chance d'intégrer une équipe de travail au sein du CHU de Lille et particulièrement dans le service de Neurophysiologie Clinique du Pr. Philippe Derambure, qui a su m'accueillir et avec qui j'ai pu échanger au quotidien. Je tiens à cet égard à remercier Jean-Louis, Hervé, Nacim, Aude, Aurore, Laurence, Lucie, Jordan, François, Maxime, Christine et tout le reste de l'équipe, mais également Céline, Etienne, Cedrick, Thibaut et les Professeurs Caroline Moreau, Kathy Dujardin et Luc Defebvre pour les échanges scientifiques et surtout leur chaleureux accueil dans le Nord. Je n'oublierai à cet égard jamais les réunions du CDDB que j'ai eu l'immense honneur de présider ! Mon séjour au sein du service m'a également permis de côtoyer plusieurs étudiants et stagiaires avec qui j'ai pu échanger et avancer sur nos sujets d'étude respectifs. Je tiens donc à remercier, pour leur appui ou leurs échanges : Morgane, Quentin, Jimmy, Charlotte, Alexis, Guillaume, Lucile, Edouard, Léa, Alix et William.

Je tiens également à remercier et saluer tous mes collègues doctorants membres du consortium européen *Keep Control* avec lesquels j'ai pu échanger à de nombreuses reprises, tant à distance que lors de réunions communes. Marta, Andreas, Fabiana, Arash, Leila, Markus, Robbin, Yuhan, Veerle, Rana et Elke, thanks to all of you! Mes remerciements également à toutes les personnes sans qui le programme européen n'aurait pu se mettre en place et grâce à qui *Keep Control* a été piloté d'une main de maître depuis Kiel et Tübingen : Christina Bürger, Linda Pialek, Walter Maeltzer, Birte Zurek et Annemarie Post. En lien avec le réseau européen, je tiens également à adresser mes salutations particulières aux membres des structures auprès desquelles j'ai pu réaliser des séjours de plusieurs semaines (« secondments »), à Kiel, Magdeburg ou Amsterdam. Ces séjours ont permis d'affiner mes

connaissances sur mes perspectives professionnelles et de m'habituer à d'autres environnements de travail. Grâce au séjour à Kiel, j'ai également pu travailler sur un projet additionnel. Je tiens à cet égard à remercier Clint Hansen et surtout Christian Schlenstedt pour les échanges fructueux que nous avons eus.

Pour finir, je tiens à adresser mes plus profonds remerciements à Victor tout particulièrement, ma famille et mes proches pour leurs encouragements ; eux, sans qui cette thèse n'aurait pu aboutir. Merci de croire en moi et de m'encourager au quotidien.



## FINANCEMENT ET CADRE DE THÈSE

### Financement :

Madli Bayot travaille sur le projet « Keep Control » ayant reçu un financement du Programme-Cadre de l'Union européenne pour la Recherche et l'Innovation Horizon 2020 à travers la convention de bourse Marie Skodowska-Curie N° 721577. La rédaction de la présente thèse a été rendue possible grâce à ce soutien.



Pour plus d'informations sur ce projet : <http://www.keep-control.eu/>

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## ABRÉVIATIONS *(anglais en italique)*

AMS / SMA	Aire motrice supplémentaire / <i>Supplementary motor area</i>
ANT	<i>Attention Network Test</i>
APAs	Ajustement posturaux anticipés / <i>Anticipatory postural adjustments</i>
BP (NS')	Bereitschaftspotential (BP tardif)
CdM / CoM	Centre de masse / <i>Center of mass</i>
CdP / CoP	Centre de pression / <i>Center of pressure</i>
CIC	Centre d'Investigation Clinique
COF / FEF	Champ oculomoteur frontal / <i>Frontal eye field</i>
CPP / PPC	Cortex pariétal postérieur
DLE / ERD	Désynchronisation liée à l'événement / <i>Event-related desynchronization</i>
DT	Double tâche / <i>Dual task</i>
EEG / EEG	Electroencéphalographie / <i>Electroencephalography</i>
FdM / FoG	Freezing de la marche ou enrayage cinétique / <i>Freezing of gait</i>
FFT	Transformée de Fourier rapide / <i>Fast Fourier Transform</i>
IRM(f) / (f)MRI	Imagerie par résonance magnétique (fonctionnelle) / <i>(functional) magnetic resonance imaging</i>
JTP / TPJ	Jonction temporo-pariétale / <i>Temporo-parietal junction</i>
LEDD	Dose journalière équivalente de levodopa / <i>Levodopa Equivalent Daily Dose</i>
LPS / SPL	Lobule pariétal supérieur

M1	Cortex moteur primaire / <i>Primary motor cortex</i>
MDS-UPDRS III	<i>Movement Disorder Society - Unified Parkinson's Disease Rating Scale (third part)</i>
MEG	Magnétoencéphalographie
MMSE	<i>Mini Mental State Examination</i>
MMP	<i>Movement-monitoring potential</i>
MoCA	<i>Montreal Cognitive Assessment score</i>
MP / PD	Maladie de Parkinson / <i>Parkinson's disease</i>
MP*	<i>Motor potential</i>
MPH	Méthylphénidate / <i>Methylphenidate</i>
MRCP	Potentiels corticaux liés au mouvement / <i>Movement-related cortical potentials</i>
NGC	Noyaux Gris Centraux
NPP / PPN	Noyau pédonculopontin / <i>Pedunculopontine nucleus</i>
Patients MP / PwPD	Patients atteints de la maladie de Parkinson / <i>Patients with Parkinson's Disease</i>
Patients MP+FdM ou freezers / PD+FoG	Patients atteints de la maladie de Parkinson avec freezing de la marche
Patients MP-FdM ou non freezers / PD-FoG	Patients atteints de la maladie de Parkinson sans freezing de la marche
PE / ERP	Potentiel évoqué lié à l'événement / <i>Event-related potential</i>
PMC	Cortex pré-moteur / <i>Pre-motor cortex</i>

PSLE / ERSP	Perturbation spectrale liée à l'événement / <i>Event-related spectral perturbation</i>
RAP	<i>Re-afferent potential</i>
RLM / MLR	Région locomotrice mésencéphalique / <i>Mesencephalic locomotor region</i>
RLS / SLR	Région locomotrice sous-thalamique / <i>Subthalamic locomotor region</i>
RP	<i>Readiness potential</i>
SAS	Système attentionnel de surveillance / <i>Supervisory attentional system</i>
sIP / IPs	Sillon intrapariétal / <i>Intraparietal sulcus</i>
SLE / ERS	Synchronisation liée à l'événement / <i>Event-related synchronization</i>
STFT	<i>Transformée de Fourier à court terme / short-time Fourier transform</i>
MCI	Troubles cognitifs légers / <i>Mild cognitive impairment</i>
TEP / SET	Temps d'exécution du pas / <i>Step execution time</i>
TR / RT	Temps de Réaction / <i>Reaction time</i>
TTRS	Tâche de temps de réaction simple
TTTC	Tâche de temps de réaction de choix

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**Chapitre 1.**

**INTRODUCTION GÉNÉRALE**

# 1. Chutes liées au vieillissement, à la maladie de Parkinson et au freezing de la marche

Les chutes représentent la seconde cause de morts par blessure accidentelle ou non intentionnelle au niveau mondial et celles-ci sont particulièrement prévalentes chez les personnes âgées. En effet, environ un tiers des sujets de plus de 65 ans fait l'expérience d'une chute chaque année (Campbell et al., 1981; Prudham and Evans, 1981; Blake et al., 1988). Avec l'âge avançant, le nombre de chutes annuelles reportées est encore plus élevé, ce qui entraîne des hospitalisations suite à des blessures plus fréquentes, des risques d'invalidité, une perte d'indépendance et l'augmentation de la mortalité (Spaniolas et al., 2010; Gill et al., 2013). Le risque de chute et sa prévention représentent donc une préoccupation majeure de santé publique. Concernant les causes de ces chutes, le déclin physique mais également cognitif liés au vieillissement cérébral participent tous deux à l'augmentation du risque de chute (Liu et al., 2014):

- d'une manière directe via les moins bonnes performances physiques des personnes âgées : « fragilité » et baisse de performance motrice en double tâche telle que le ralentissement de la vitesse de marche à la cadence habituelle et une variabilité des paramètres de marche globalement plus importante;
- mais également indirectement, via le vieillissement cognitif : fonctions cognitives globalement dégradées, ralentissement de la vitesse de traitement mental, altération de l'attention et des fonctions exécutives telles qu'un contrôle inhibiteur déficient et des coûts de commutation de tâche - *task-switching* en anglais - plus élevés.

Au sein de la population âgée, le développement d'une pathologie neurodégénérative est possible. Citons notamment la maladie de Parkinson (MP), qui est la seconde maladie neurodégénérative la plus courante après la maladie d'Alzheimer et le trouble moteur le plus commun chez les personnes âgées, avec une prévalence d'environ 1% chez les individus de 60 ans et plus habitant les pays industrialisés (de Lau and Breteler, 2006). La MP a été décrite pour la première fois par James Parkinson en 1817 (Parkinson, 2002) et est caractérisée par trois signes moteurs cardinaux principaux : tremblement, bradykinésie (voire akinésie) et rigidité, mais également instabilité posturale (Tysnes and Storstein, 2017). Ces symptômes moteurs sont, entre autres, dus à une perte de neurones dopaminergiques au niveau de la pars compacta de la substance noire (mésencéphale) qui altère le fonctionnement de la voie nigro-striée et mène ainsi à un déficit en dopamine dans le striatum. En conditions physiologiques, les boucles baso-corticales permettent l'ajustement et le contrôle lors de la réalisation d'un

mouvement préalablement acquis. La déplétion dopaminergique au niveau du striatum favorise la voie indirecte, impliquée dans l'inhibition motrice, au détriment de la voie directe, facilitatrice du mouvement. Une augmentation de synchronisation des structures baso-corticales est aussi mise en cause (Brown, 2003). In fine, cette situation résulte en une désadaptation du contrôle moteur chez les patients atteints de la MP (patients MP), avec une facilitation réduite des mouvements volontaires (Tysnes and Storstein, 2017) ainsi qu'un déficit en automaticité dû à l'altération du striatum sensorimoteur (Wu et al., 2015). De plus, le striatum faisant également partie de boucles associative et limbique, les patients MP présentent des symptômes non-moteurs tels que des symptômes neuropsychiatriques (e.g., troubles cognitifs, dépression et anxiété), troubles du sommeil, symptômes autonomes et sensoriels (Chaudhuri et al., 2006). Ce déclin moteur et non-moteur caractéristique de la MP implique que, dans cette population, 30 à 90% des individus chutent au moins une fois par an (Allen et al., 2013).

Un facteur qui amplifie de manière significative le risque de chute dans la MP se manifeste dans le phénomène « d'enrayage cinétique » ou « freezing de la marche » (FdM) (Okuma et al., 2018). Présent chez approximativement 70% des patients MP avec une durée d'évolution de la maladie supérieure à 10 ans (Ge et al., 2020), ce symptôme paroxysmal est souvent défini comme « une absence brève et épisodique ou une réduction marquée de la progression des pieds vers l'avant malgré l'intention de marcher du patient » (Nutt et al., 2011) et est perçu par les patients comme une impression d'avoir « les pieds collés au sol » (Giladi and Nieuwboer, 2008). Le FdM est ainsi associé à une perte d'indépendance et au développement d'une peur de la blessure, qui mènent tous deux à une dégradation de la qualité de vie (Walton et al., 2015). Malgré qu'il ait été démontré que de nombreux troubles de diverses natures tels que des déficits moteurs, cognitifs, limbiques, mais aussi sensori-perceptifs sont associés au FdM (Ehgoetz Martens et al., 2020; Gao et al., 2020), les mécanismes pathophysiologiques à la base de l'apparition des épisodes de freezing restent incertains. Plusieurs modèles ont été proposés (Nieuwboer and Giladi, 2013; Lewis and Shine, 2016; Snijders et al., 2016). Nous pouvons en citer certains :

- (1) Le modèle dit « du seuil » (Plotnik et al., 2012) postule que le cumul de différents déficits moteurs tels que l'augmentation de la fréquence du cycle moteur, une amplitude de pas diminuée et une difficulté accrue de coordination bilatérale et de symétrie peut entraîner in fine une « panne motrice ».
- (2) Le modèle d'interférence (Lewis and Barker, 2009) se base sur la déplétion en neurones dopaminergiques au niveau des noyaux gris centraux (NGC), impliqués dans des circuits

oculomoteur, sensorimoteur, associatif et limbique. Cette diminution de la réserve neuronale centrale commune induirait donc une interférence (ou *cross-talk* en anglais) entre ces différents circuits qui sont à la fois en compétition mais également complémentaires lors de la réalisation de nombreuses tâches de la vie quotidienne. Ainsi, en cas d'augmentation du nombre de tâches concurrentes et du niveau de difficulté de ces tâches, le signal de sortie du globus pallidus interne peut devenir anormal, temporairement inhiber le noyau pédonculo-pontin (NPP ou *PPN* en anglais) et ainsi déclencher le FdM. Les patients MP sont même connus pour adopter une stratégie dite « *posture second* » lors de la réalisation concomitante de plusieurs tâches, ne sacrifiant pas leur performance cognitive pour leur performance posturale et motrice (Bloem et al., 2006).

- (3) Le modèle cognitif (Vandenbossche et al., 2012) met en évidence le déséquilibre entre traitements automatique et contrôlé existant chez les patients MP avec FdM (patients MP+FdM ou *freezers*), notamment lors de situations nécessitant de résoudre un conflit avant d'émettre une réponse.
- (4) Le modèle de découplage (Jacobs et al., 2009b) suggère, finalement, une déconnexion entre les phases de préparation du programme moteur et d'exécution de la réponse motrice chez les *freezers*. La génération automatique d'un mouvement est globalement altérée dans cette population.

Toutefois, ces modèles restent incomplets et ne permettent pas de caractériser entièrement le FdM et le caractère hétérogène de ce phénotype (Ehgoetz Martens et al., 2018b). Une meilleure compréhension des mécanismes sous-jacents est donc nécessaire pour développer de futures thérapies efficaces et personnalisées pouvant allier sur demande à la fois traitements pharmacologiques, chirurgicaux et comportementaux (Gilat et al., 2018b).

Dans les prochaines sections de cette introduction générale, afin d'obtenir une compréhension plus fine de ce risque de chute accru au sein des trois populations précédemment décrites (sujets âgés sains, patients MP et *freezers*), nous passerons en revue les déficits attentionnels existants dans ces groupes ainsi que les troubles moteurs durant l'initiation de la marche. L'interaction entre les capacités attentionnelles, la préparation et l'exécution motrice sera également abordée au travers d'outils permettant, d'une part, une analyse comportementale de cette interaction (les doubles tâches) et, d'autre part, une exploration neurophysiologique (l'électroencéphalographie ou EEG). Les objectifs des différents projets de la présente thèse et les hypothèses sous-jacentes seront finalement exposés.

## 2. Attention

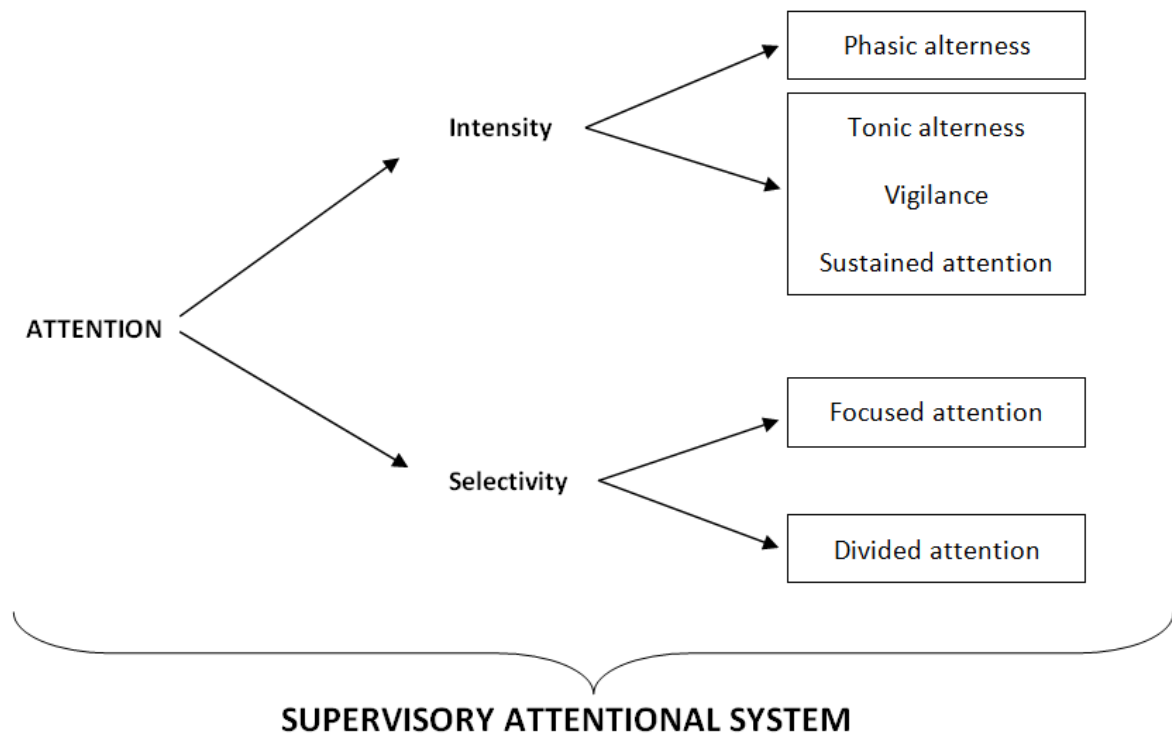
### 2.1. Modèles théoriques et substrats neuronaux

van Zomeren & Brouwer ont témoigné de la difficulté de réduire l'attention à une unique définition (van Zomeren and Brouwer, 1994). Selon Kahneman et Corbetta & Shulman (Kahneman, 1973; Corbetta and Shulman, 2002), l'attention correspond à un processus cognitif qui est entraîné par une interaction dynamique entre des facteurs cognitifs et sensoriels et qui contrôle le niveau de pertinence alloué à un stimulus. Dans ce contexte, les principales fonctions exercées par l'attention sont : la focalisation sur les stimuli disponibles, leur sélection et/ou leur inhibition. L'attention et ses composantes (attention soutenue, sélective, divisée et flexibilité attentionnelle) (McDowd, 2007) peuvent également être conceptualisées comme la capacité d'un individu à traiter de l'information pendant la réalisation d'une tâche (Woollacott and Shumway-Cook, 2002). En particulier, l'attention divisée peut être définie comme la capacité à réaliser plus d'une tâche simultanément (Yogev-Seligmann et al., 2008). L'attention soutient donc les fonctions exécutives de façon significative. Ainsi, van Zomeren & Brouwer (van Zomeren and Brouwer, 1994) ont développé un modèle multi-composantes qui est toujours largement utilisé en psychologie afin d'analyser les différentes sous-composantes de l'attention (Figure 1). Ce modèle se base sur la théorie de la composante de Posner (Posner and Boies, 1971), sur les aspects de sélectivité et d'intensité de l'attention développés par Kahneman (Kahneman, 1973) et sur le concept de système attentionnel de surveillance (SAS) théorisé par Norman & Shallice (Norman and Shallice, 1986). Selon van Zomeren & Brouwer (1994), l'attention peut être divisée en deux dimensions distinctes d'un point de vue neuropsychologique, chacune d'elle étant associée à un réseau neuronal sous-jacent différent :

- l'intensité, qui inclut l'alerte et la vigilance/attention prolongée;
- la sélectivité, qui englobe l'attention focalisée et divisée.

Premièrement, une tâche attentionnelle peut être caractérisée par l'intensité de l'activation mentale qu'elle nécessite. Les composantes attentionnelles qui se différencient au travers de cette dimension d'intensité sont l'alerte tonique (i.e., un niveau d'éveil relativement stable qui varie lentement selon les fluctuations diurnes et physiologiques de l'organisme), l'alerte phasique (i.e., la capacité d'augmenter le niveau d'éveil en réponse à un stimulus de haute priorité), et l'attention soutenue (i.e., la capacité de maintenir son attention sur une longue période de temps durant laquelle, dans un contexte de vigilance, des événements nécessitant une réponse ont lieu de manière occasionnelle).

Deuxièmement, la sélectivité permet à un individu d’orienter son attention et d’ignorer des stimuli non pertinents à deux niveaux : l’attention focalisée prend en compte seulement un stimulus ou une dimension d’un stimulus (sa couleur, sa taille, sa forme, etc), alors que l’attention divisée considère au moins deux stimuli ou deux dimensions pertinentes d’un stimulus. Finalement, le modèle attentionnel de van Zomeren et Brouwer (sur base de la théorie développée par Norman & Shallice en 1986) inclut une composante exécutive (le SAS) qui gère les ressources attentionnelles dans des situations complexes, nouvelles, non automatisées ou de conflit (Norman and Shallice, 1986). Le SAS peut à la fois moduler les dimensions d’intensité et de sélectivité (Figure 1).



**Figure 1** Modèle attentionnel de van Zomeren & Brouwer (van Zomeren and Brouwer, 1994). Image issue de (Bayot et al., 2018)

Toujours dans le contexte de théorisation de l’attention, Norman & Shallice (1986) ont mis en lumière l’existence de deux niveaux d’attention (Norman and Shallice, 1986). Le bas niveau (appelé *contention scheduling*, en anglais) est utilisé pour appréhender les situations familières et automatiques (i.e., les routines), alors que le niveau haut de l’attention (le SAS) est nécessaire pour régler des situations plus difficiles à résoudre et nécessitant plus de ressources. Il est intéressant de noter le parallèle entre ce dernier modèle neuropsychologique et les deux réseaux cérébraux distincts liés à l’attention (Corbetta

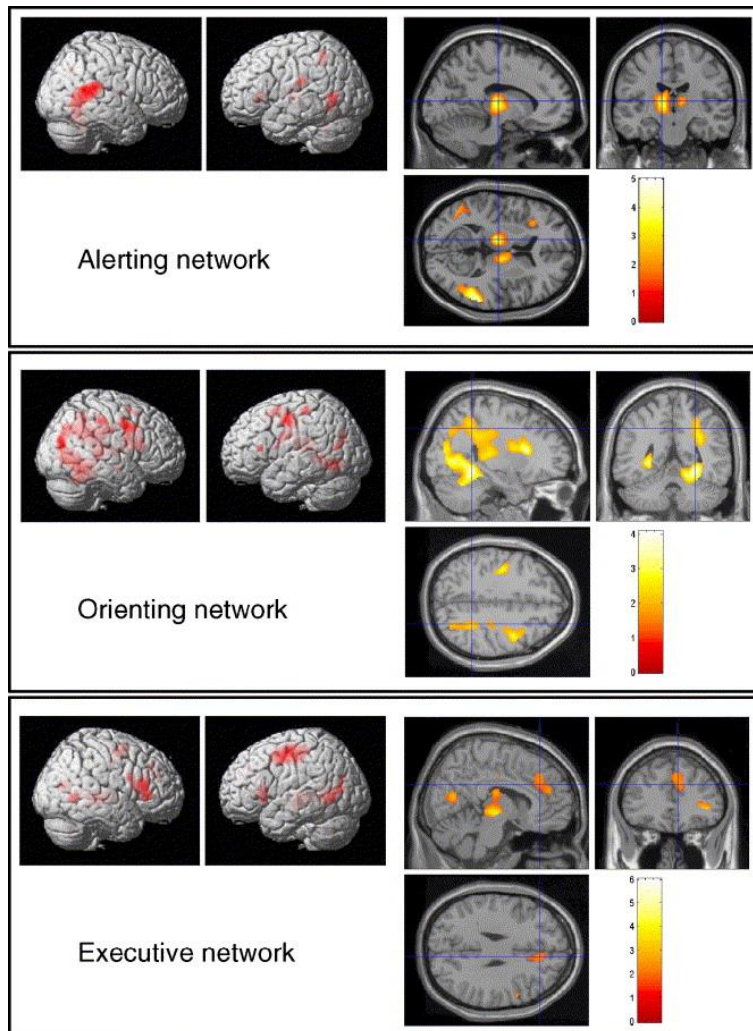
and Shulman, 2002; Fox et al., 2006). D'un côté, le « réseau bilatéral de l'attention dorsale » (comprenant le cortex pariétal postérieur / CPP dorsal le long du sillon intrapariétal / sIP et incluant le lobule pariétal supérieur / LPS, d'une part, et le cortex frontal dorsal au niveau du champ oculomoteur frontal / COF ou *frontal eye field* en anglais, d'autre part) pourrait être impliqué dans l'attention endogène (axée sur l'objectif), avec des processus « descendants » (ou *top-down*, en anglais) pour la détection et la sélection de stimuli et l'émission de réponses. D'un autre côté, l'attention exogène (dirigée vers le stimulus) avec une détection et un traitement « ascendant » (ou *bottom-up*, en anglais) de stimuli saillants ou inattendus serait basée sur le « réseau attentionnel ventral », plutôt latéralisé à droite et qui comprend la jonction temporo-pariétale (JTP) et le cortex ventro-frontal. On considère que les régions préfrontales du cortex (i.e., les gyri frontaux moyen et inférieur) arbitrent l'interaction fonctionnelle entre ces réseaux de par leur corrélation démontrée avec les deux systèmes (Fox et al., 2006).

Dans le cadre de la présente thèse, le modèle attentionnel choisi est celui développé en 1990 et mis à jour en 2012 par Posner et Petersen (Posner and Petersen, 1990; Petersen and Posner, 2012). Selon ce modèle, l'attention visuo-spatiale comprend trois composantes qui sont sous-tendues par trois réseaux neuronaux relativement distincts spatialement, sont différenciellement innervés par des systèmes neuromodulateurs variés, (Fan et al., 2005, 2007; Raz and Buhle, 2006) et interagissent les uns avec les autres (Fan et al., 2009) :

- L'**alerte**, capacité d'atteindre et de maintenir un état d'alerte, englobe l'alerte phasique, tonique ainsi que l'attention soutenue et est gérée par des régions neuronales du système noradrénergique telles que le thalamus et les cortex frontal et pariétal (avec une activation frontale et pariétale gauche en cas d'indigage ainsi qu'une forte activation de l'hémisphère droit dans les régions frontale et pariétale liée à l'attention soutenue impliquée dans les essais avec ou sans indigage en Imagerie par résonance magnétique fonctionnelle, IRMf) (Fan et al., 2005).
- L'**orientation** correspond à la sélection d'informations pertinentes parmi de multiples entrées sensorielles sur base d'une modalité ou d'une localisation choisie. Le réseau de l'orientation comprend des régions du système cholinergique: préfrontales (COF) et pariétales (LPS et JTP) (Fan et al., 2005), mais aussi le pulvinar, le colliculus supérieur et le lobe temporal supérieur (Raz and Buhle, 2006). Une activation particulière de la JTP et du lobe supérieur temporal ainsi qu'une latéralisation à droite ont été observées en cas de désengagement de l'attention suite à un indice invalide. Le LPS participe à la réorientation volontaire de l'attention sans

mouvements oculaires, tandis que le COF et le colliculus supérieur semblent plutôt impliqués dans la réorientation attentionnelle avec mouvements des yeux apparents.

- Le **contrôle exécutif** (encore appelé résolution de conflits) permet la gestion volontaire et la résolution de conflits, la détection d'erreurs, mais aussi l'évaluation de situations nouvelles ou inhabituelles. Ce réseau attentionnel comprend les régions corticales cingulaire antérieure et frontale (i.e., cortex préfrontal dorsolatéral), régions cibles des neurones dopaminergiques de l'aire tegmentale ventrale davantage actives en cas de cible entourée de distracteurs non congruents. De nombreuses autres régions s'activent lors d'une telle tâche de résolution de conflits, suggérant la présence d'une multitude d'opérations n'étant pas nécessairement en lien avec la résolution de conflits (Fan et al., 2005).



*Figure 2* Activation cérébrale liée aux trois réseaux attentionnels. Résultats d'IRMf provenant de (Fan et al., 2005)©



L'« Attention Network Test » (ANT) a été conçu par l'équipe de Jin Fan afin de pouvoir évaluer chacune de ces trois composantes attentionnelles – indépendamment les unes des autres ainsi que les interactions existantes - en utilisant un unique paradigme de temps de réaction (TR) (Fan et al., 2002). Des scores calculés sur base des TR associés à différentes conditions d'indices et de cibles permettent de quantifier les effets (a) de l'alerte, (b) de l'orientation et (c) de la résolution de conflits : différence des TR (a) entre situations sans indiçage et avec indice central ; (b) entre cas de figure avec indice central et avec indice spatial (périphérique) ; (c) entre des situations avec stimulus visuel entouré de distracteurs non congruents, d'une part, et congruents, d'autre part. Pour les effets d'alerte et d'orientation, des scores TR élevés indiquent une plus grande efficacité de ces réseaux, tandis que le réseau exécutif est d'autant plus efficace que le score TR associé est bas. L'ANT (et surtout la version utilisée par notre équipe) est décrit en détail plus loin dans cette thèse (cf. Chapitre 2 - *Matériel et méthodes*). Citons que d'autres paradigmes peuvent évaluer ces composantes attentionnelles une à une, comme c'est par exemple le cas de la « Stroop task » (Stroop, 1935), « flanker task » (Eriksen and Eriksen, 1974) ou « Simon task » (Simon and Small Jr., 1969) pour l'évaluation de la capacité à résoudre des conflits.

## **2.2. Impact du vieillissement, de la maladie de Parkinson et du freezing de la marche**

### *Attention et vieillissement*

La dégradation du traitement sensoriel ascendant (attention exogène ou *bottom-up*) chez les personnes âgées est avérée, tandis que l'impact de l'âge sur le contrôle attentionnel descendant (attention endogène, dirigée vers un but ou *top-down*) reste actuellement sujet à débat, si l'on se réfère aux différents résultats à l'ANT dans cette population (Festa-Martino et al., 2004; Fernandez-Duque and Black, 2006; Jennings et al., 2007; Gamboz et al., 2010; Ishigami and Klein, 2011; Zhou et al., 2011; Deiber et al., 2013; Knight and Mather, 2013; Gamble et al., 2014; Young-Bernier et al., 2015; Kaufman et al., 2016). En effet, malgré qu'il ait été observé que les temps de réaction augmentent globalement avec l'âge et que l'âge ne semble pas influencer de manière significative sur l'effet d'orientation, son impact sur les effets d'alerte et de résolution de conflits ainsi que sur les taux de précision lors de la réalisation de l'ANT varie d'une étude à l'autre. Ceci est probablement dû à des différences au niveau du panel de participants (certains dans un stade préclinique de la maladie d'Alzheimer), du protocole d'expérimentation (version de la tâche et moment de réalisation dans la journée) et du traitement des données. En effet, les scores TR peuvent être corrigés pour tenir compte

du ralentissement général causé par le vieillissement (en utilisant des z-scores, par exemple) (Jennings et al., 2007). Finalement, une revue de la littérature (McDonough et al., 2019) suggère que l'alerte peut être altérée assez tôt avec le vieillissement normal (de 60 à 70 ans), tandis qu'une défaillance au niveau de l'attention exécutive pourrait apparaître seulement vers 80 ans et plus.

### *Attention et maladie de Parkinson*

Concernant les patients MP, comme évoqué ci-avant, ils peuvent présenter des troubles cognitifs, troubles dont l'incidence est croissante avec la durée d'évolution de la maladie et peut concerner plus de 4 patients sur 5 à 20 ans d'évolution (Hely et al., 2008). Un déficit cognitif peut même être présent chez les patients nouvellement diagnostiqués, avec plus de probabilité pour les individus qui développent la MP sur le tard. Cela commence le plus souvent par une atteinte des fonctions exécutives et attentionnelles, mais peut aussi toucher d'autres domaines cognitifs tels que les fonctions visuo-spatiales, le langage, la mémoire et la vitesse de traitement (Muslimovic et al., 2005). Plus particulièrement, toutes les études ayant réalisé la passation de l'ANT chez les patients MP n'ont majoritairement pas montré de différence en termes de précision par rapport aux contrôles âgés sains (Vandenbossche et al., 2011; Zhou et al., 2012; Cristinzio et al., 2013), sauf en cas de fatigue des patients (Pauletti et al., 2017) et pour une étude isolée (Boord et al., 2017). Les patients MP, comparés aux sujets âgés sains, étaient globalement plus lents pour réagir à l'apparition d'une cible (Cristinzio et al., 2013; Boord et al., 2017; Pauletti et al., 2017), même si certaines études n'ont pas décelé de différence significative (Vandenbossche et al., 2011; Zhou et al., 2012). Boord et collaborateurs ont même démontré que la réponse plus lente des patients MP n'était pas uniquement due à leur affaiblissement moteur, car celle-ci n'était pas spécifiquement plus lente lorsqu'elle était générée avec le membre du côté initialement atteint (Boord et al., 2017). En ce qui concerne l'efficacité des différents réseaux attentionnels dans la MP en comparaison avec une population âgée saine, les résultats de la littérature diffèrent quelque peu entre eux : l'effet d'alerte semble plus élevé (Zhou et al., 2012), notamment pour l'alerte phasique manipulée par des sons (Cristinzio et al., 2013) et dans les phases plus sévères de la maladie (Pauletti et al., 2017), mais pas lorsque les patients rapportent une certaine fatigue (Pauletti et al., 2017). Zhou et al. ont été les seuls à montrer une amélioration de l'effet d'orientation chez les patients MP comparés aux contrôles (Zhou et al., 2012). Autrement dit, ils bénéficieraient davantage des indices délivrant une information spatiale que les sujets contrôles, ce qui peut refléter des processus d'inhibition défaillants (i.e., inhibition du retour réduite) ou une orientation hyper-réflexive dans cette population. Finalement, les patients MP peuvent également présenter plus de difficultés dans la résolution des conflits (Boord et al., 2017; Pauletti et al., 2017),

spécifiquement dans les phases avancées de la MP (Zhou et al., 2012) et chez les patients présentant de la fatigue (Pauletti et al., 2017). Toutes les études de l'impact de la MP sur les trois composantes de l'attention visuo-spatiale via l'utilisation de l'ANT évaluaient des patients sous médication. Il a été montré que le traitement antiparkinsonien (lévodopa et agonistes dopaminergiques) n'affecte pas les effets de l'alerte et du contrôle exécutif, mais participerait à l'amélioration de l'effet d'orientation chez les patients MP (Vandenbossche et al., 2011). Ces résultats ne concernent toutefois qu'une étude.

### *Attention et freezing de la marche*

Les patients présentant du FdM ont montré quant à eux une capacité de résolution de conflits encore plus altérée que celle des patients MP sans freezing et des individus âgés sains, aussi bien en condition de médication (i.e., en « ON ») que sans prise de leur traitement (i.e., en « OFF ») (Vandenbossche et al., 2011, 2012). Par ailleurs, l'efficacité des réseaux de l'alerte et de l'orientation semblaient similaires pour les deux groupes de patients MP et les sujets âgés contrôles (Vandenbossche et al., 2011). A l'inverse, Cohen et son équipe (Cohen et al., 2014) n'ont pas observé de performances significativement différentes à une tâche de *flankers* (avec distracteurs, équivalente à l'ANT pour l'évaluation du contrôle exécutif uniquement) entre des populations de freezers, non freezers et contrôles âgés. Ils ont plutôt démontré, à partir de la tâche du Go-noGo, une incapacité à engager et à relâcher l'inhibition de manière appropriée chez les freezers, et cela d'autant plus que la sévérité du freezing est importante, sans autres atteintes exécutives au niveau de la mémoire de travail ou de la flexibilité attentionnelle (Cohen et al., 2014). De manière générale, il y a une divergence dans les résultats de la littérature concernant l'atteinte cognitive chez les patients MP avec FdM, et plus particulièrement pour la résolution de conflits, l'inhibition, la mémoire de travail, mais aussi la flexibilité attentionnelle (Ehgoetz Martens et al., 2020). Cela peut être, en partie, attribué à l'hétérogénéité du phénotype du freezing (Ehgoetz Martens et al., 2018b), mais également à l'hétérogénéité des populations de freezers étudiées et parfois au manque de rigueur dans l'appariement des populations de patients MP en termes de durée d'évolution de la maladie, de sévérité des symptômes moteurs et d'âge (Ehgoetz Martens et al., 2020).

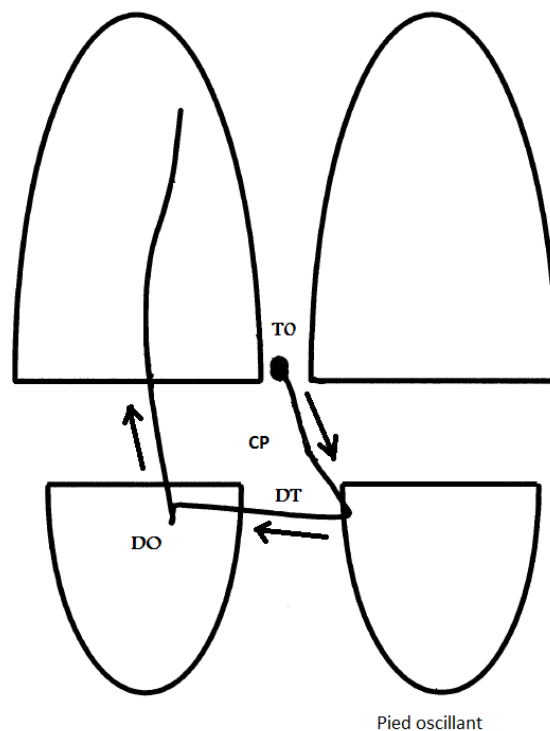
## 3. Initiation de la marche

### 3.1. Caractérisation cinétique et cinématique

L'initiation de la marche est exécutée en deux phases : une phase de préparation posturale, suivie d'une phase d'exécution motrice. En effet, comme c'est le cas pour d'autres mouvements volontaires, l'initiation de la marche est précédée d'ajustements posturaux anticipés (APAs). Il est admis que les APAs ont deux rôles principaux : la correction d'une perturbation causée par le mouvement qui va suivre (ce n'est pas le cas pour l'initiation de la marche) ou l'accélération du mouvement via l'augmentation du déséquilibre (Zattara and Bouisset, 1986; Bouisset and Zattara, 1987; Brenière et al., 1987). Effectivement, la nature du rôle fonctionnel des APAs varie selon que le mouvement volontaire modifie la base de support ou non. Lorsque la base de support est déplacée comme lors de l'initiation du pas, les APAs génèrent les forces propulsives initiales nécessaires pour la progression en avant du corps et jouent un rôle dans le transfert du poids du corps lors de la transition phase d'appui vers phase oscillante (Brenière et al., 1987).

D'une part, les APAs peuvent être analysés en observant la trajectoire stéréotypée du centre de pression (CdP), point d'application de la résultante des forces de réaction au sol : un déplacement du CdP vers l'arrière et vers le membre oscillant est suivi d'un mouvement du CdP vers la jambe d'appui (Brenière et al., 1981; Jian et al., 1993). Le début de la seconde phase de déplacement du CdP (latéralement vers le pied de support) est caractérisé par l'amorce du décollement du sol du talon du pied oscillant, tandis que le décollement des orteils a lieu à la fin de ce mouvement médio-latéral (ML) du CdP, juste avant la phase dite « oscillante ». Cette dernière phase suit les APAs et est caractérisée par le déplacement du CdP vers l'avant jusqu'au moment du contact du pied oscillant avec le sol (Figure 3). En déplaçant le CdP vers l'arrière et latéralement vers le membre oscillant durant l'APA, les composantes de la résultante des forces de réaction au sol vers l'avant et vers le membre d'appui augmentent au cours du temps, générant un moment de force dans ces directions et donc un mouvement du centre de masse (CdM) vers le pied de support et vers l'avant. Il est donc possible d'observer, durant un APA, une accélération du centre de gravité concomitante au déplacement du CdP, mais dans la direction opposée (Jian et al., 1993). Il a notamment été montré que la vitesse du premier pas est corrélée à la durée de l'APA et à l'amplitude de déplacement du CdP vers l'arrière au cours de l'APA (Brenière et al., 1987). Par ailleurs, le contexte d'initiation d'un pas (i.e., pas auto-généré, indicé ou compensateur à la suite d'une perturbation) a un impact significatif sur la

préparation et l'exécution du processus d'initiation de la marche, et particulièrement sur l'amplitude des APAs (Schlenstedt et al., 2017).



*Figure 3* Trajectoire stéréotypée du CdP lors d'un APA. TO = début de l'APA ; DT = décollement du talon du pied oscillant ; DO = décollement des orteils du pied oscillant ; CP = centre de pression

D'autre part, les APAs peuvent également être étudiés par analyse de l'activité électromyographique (Brenière et al., 1981; Lepers and Brenière, 1995). En effet, les APAs sont précédés d'une désactivation des muscles soléaires (extenseurs de la cheville) suivie d'une activation des muscles tibiaux antérieurs (fléchisseurs de la cheville) permettant le mouvement du CdP vers l'arrière, tandis que l'activation des muscles abducteurs des hanches permet le déplacement latéral du CdP vers la jambe oscillante.

### 3.1. Substrats neuronaux

Les substrats neuronaux responsables de la génération des APAs et de la phase d'exécution du pas ne sont pas entièrement connus. En effet, plusieurs études, chez l'animal, ont permis de montrer que la locomotion pouvait être initiée via une activation électrique ou chimique de l'aire motrice supplémentaire (AMS), au niveau cortical, et des régions locomotrices sous-thalamique (RLS ; dans l'aire hypothalamique latérale), mésencéphalique (RLM ; noyau cunéiforme et NPP) et cérébelleuse médiale, au niveau sous-cortical (Mori et al., 1989, 1999; Takakusaki et al., 2004). Cependant, chez

l'homme, le rôle de ces régions cérébrales dans le processus d'initiation de la marche a été peu étudié. Sur base des données existantes dans la littérature, plusieurs structures cérébrales incluant le tronc cérébral, le cervelet et le réseau cortico-basal (en particulier, le cortex frontal avec les aires primaires et prémotrices) participeraient à l'organisation fonctionnelle de l'initiation de la marche et du contrôle postural (Takakusaki, 2017). Il a été suggéré qu'un circuit cortico (AMS)-ponto-cerebello-thalamo-cortical serait à la base de la génération des APAs et de l'exécution du premier pas (Richard et al., 2017).

Premièrement, une stimulation magnétique transcrânienne répétée au niveau de l'AMS a permis de mettre en évidence sa potentielle contribution à la génération et au timing des APAs : la durée des APAs était raccourcie, tandis que leur amplitude n'en était pas affectée (Jacobs et al., 2009a). Cette observation a été confirmée, par la suite, via une stimulation transcrânienne par courant continu (Richard et al., 2017). L'implication de l'AMS dans les phases d'initiation de la marche est confirmée par l'observation de difficultés pour générer des APAs et initier le pas chez des personnes présentant des lésions focales de l'AMS (Viallet et al., 1992; Nadeau, 2007). Son activation est également observée en EEG (Yazawa et al., 1997) et en IRMf lors d'une tâche imaginaire de marche (Wang et al., 2016) et une tâche de lever de jambe dans un protocole d'IRMf lié à l'événement (de Lima-Pardini et al., 2017). Ceci concernerait toutefois plus spécifiquement l'initiation de la marche auto-commandée.

Deuxièmement, l'élicitation précoce des APAs suite à l'apparition d'un stimulus acoustique de sursaut, uniquement dans le cas où il est prévu que le sujet initie un pas, a démontré le rôle de la formation réticulée ponto-mésencéphalique dans la libération des APAs, séquence motrice préalablement planifiée et stockée en sous-cortical (Valls-Solé et al., 1995, 1999; Carlsen et al., 2004; MacKinnon et al., 2007; Delval et al., 2012). Quand le stimulus acoustique de sursaut est délivré au moment du stimulus visuel impératif, la durée des APAs est même raccourcie, sans changements dans les paramètres d'exécution du pas (Queralt et al., 2010). Par ailleurs, les patients avec lésions de la RLM présentent des difficultés pour générer des pas (Masdeu et al., 1994). L'altération des APAs chez les patients MP semblerait liée à une connectivité fonctionnelle réduite entre AMS et RLM (Gallea et al., 2017).

De plus, il a été mis en évidence que la stimulation transcrânienne à courant direct du cervelet affecte les caractéristiques spatiales de la marche durant l'adaptation motrice (Jayaram et al., 2012), tandis qu'une stimulation transcrânienne en courant continu a démontré l'implication probable du cervelet postérieur dans le couplage entre les phases de préparation et d'exécution du pas ainsi qu'au niveau

du pattern d'activité musculaire des jambes (Richard et al., 2017). D'ailleurs, les patients avec une lésion ou un dysfonctionnement cérébelleux ont montré une distorsion de leurs APAs, des pas plus courts et irréguliers (Morton and Bastian, 2007; Fernandez et al., 2013), une augmentation de la largeur et de la durée de l'enjambée ainsi qu'une diminution de sa longueur, une activité musculaire et une co-activation du bas de la jambe intensifiées et une organisation temporelle anormale du pattern musculaire (Timmann et al., 2000; Morton and Bastian, 2007; Fernandez et al., 2013; Martino et al., 2014; Bruttini et al., 2015).

En outre, chez les patients MP, la durée des APAs est plus longue, l'activité musculaire durant l'initiation du pas plus faible, et la longueur du premier pas plus courte (Gantchev et al., 1996), l'initiation de la marche chez les individus présentant des lésions bipallidales ne différant pas de celle des patients MP (Krystkowiak et al., 2006). Les Noyaux Gris Centraux semblent donc également impliqués dans le processus de l'initiation du pas, d'autant plus au regard de ses connexions avec le NPP (Pahapill and Lozano, 2000).

Finalement, en observant l'élicitation d'APAs sans exécution d'un pas (appelés « pré-APAs ») et une amorce plus précoce de la préparation de la marche effective suite à la présentation d'un stimulus acoustique (moins intense que ceux pour le sursaut) qui précède un stimulus visuel impératif « go », Delval et collègues ont suggéré que des mécanismes autres que l'activation des neurones au sein de la substance réticulée pourraient être impliqués dans la génération des APAs (Delval et al., 2012). Les structures mésencéphaliques pourraient être contrôlées par des structures corticales telles que le cortex frontal, lorsque l'on considère le contrôle inhibiteur requis pour stopper les pré-APAs.

Si l'on fait le parallèle avec la tâche de marche plus amplement étudiée, en conditions standardisées (i.e., quand une personne ne doit pas tenir compte de stimuli tels que des obstacles), la marche est principalement sous le contrôle des régions locomotrices sous-corticales et donc fortement automatique et rythmique (Nutt et al., 1993). Cependant, plusieurs études de neuroimagerie ont démontré l'implication d'un nombre important de régions du cerveau dans les performances de la marche (pour une revue complète, voir (Hamacher et al., 2015)). Ces régions ont été classifiées comme faisant partie du « circuit locomoteur direct » (i.e., le cortex moteur primaire, le cervelet et la moelle épinière) ou du « circuit locomoteur indirect » (i.e., le cortex préfrontal, les aires prémotrices, et les NGC) (la Fougère et al., 2010).

En particulier, des études ont démontré que, lors d'une marche complexe ou en situation de double tâche, la marche est associée à des changements d'activation du circuit locomoteur indirect et du réseau fronto-pariétal (i.e., le cortex cingulaire, les aires pariétales et l'insula) (Hamacher et al., 2015). Ces dernières régions du cerveau font partie des régions corticales fronto-pariétales associées à l'attention, à la mémoire de travail et aux fonctions exécutives. Ajoutée à ces résultats de neuroimagerie, l'observation d'interférences cognitivo-motrices pendant une double tâche (Al-Yahya et al., 2011) reflète bien le fait que la marche requière un contrôle cognitif en général et, plus particulièrement, attentionnel. Cette dernière décennie, un nombre important d'études ont investigué l'interaction entre la cognition et la marche dans les paradigmes de double tâche. Nous supposons que des processus attentionnels participeraient également à la préparation posturale et à l'exécution motrice liées à l'initiation de la marche.

### **3.3. Impact du vieillissement, de la maladie de Parkinson et du freezing de la marche**

#### *Initiation de la marche et vieillissement*

Globalement, un ralentissement dû à l'âge explique les altérations des APAs et des paramètres d'exécution du pas (Halliday et al., 1998). Particulièrement, un ralentissement au niveau de chacune des phases de l'initiation du pas a été observé chez les sujets âgés sains en comparaison avec de jeunes adultes, indépendamment de la direction du pas ou de la condition de la tâche (condition de simple ou double tâche) (Melzer and Oddsson, 2004). Melzer et al. (Melzer and Oddsson, 2004) ont suggéré différentes causes de ralentissement, possiblement associées aux différentes phases de préparation et d'exécution du pas. Premièrement, la phase de réaction peut être retardée chez les sujets âgés à cause du ralentissement de la vitesse de conduction nerveuse, l'augmentation des seuils de détection sensorielle et une capacité de traitement central décroissante. Deuxièmement, une plus longue durée des APAs observée chez les sujets âgés sains pourrait provenir d'une rigidité passive des tissus renforcée, un temps plus long pour relâcher la co-activation des muscles antagonistes et un traitement cognitif central plus lent. Finalement, les personnes âgées présentent une durée de la phase oscillante plus grande, probablement parce que certaines d'entre elles peuvent présenter une sarcopénie (i.e., une dégénérescence du muscle liée à l'âge et associée à une réduction de sa section transversale et de sa capacité à générer de la force ainsi qu'à des protéines contractiles défaillantes).



### *Initiation de la marche et maladie de Parkinson*

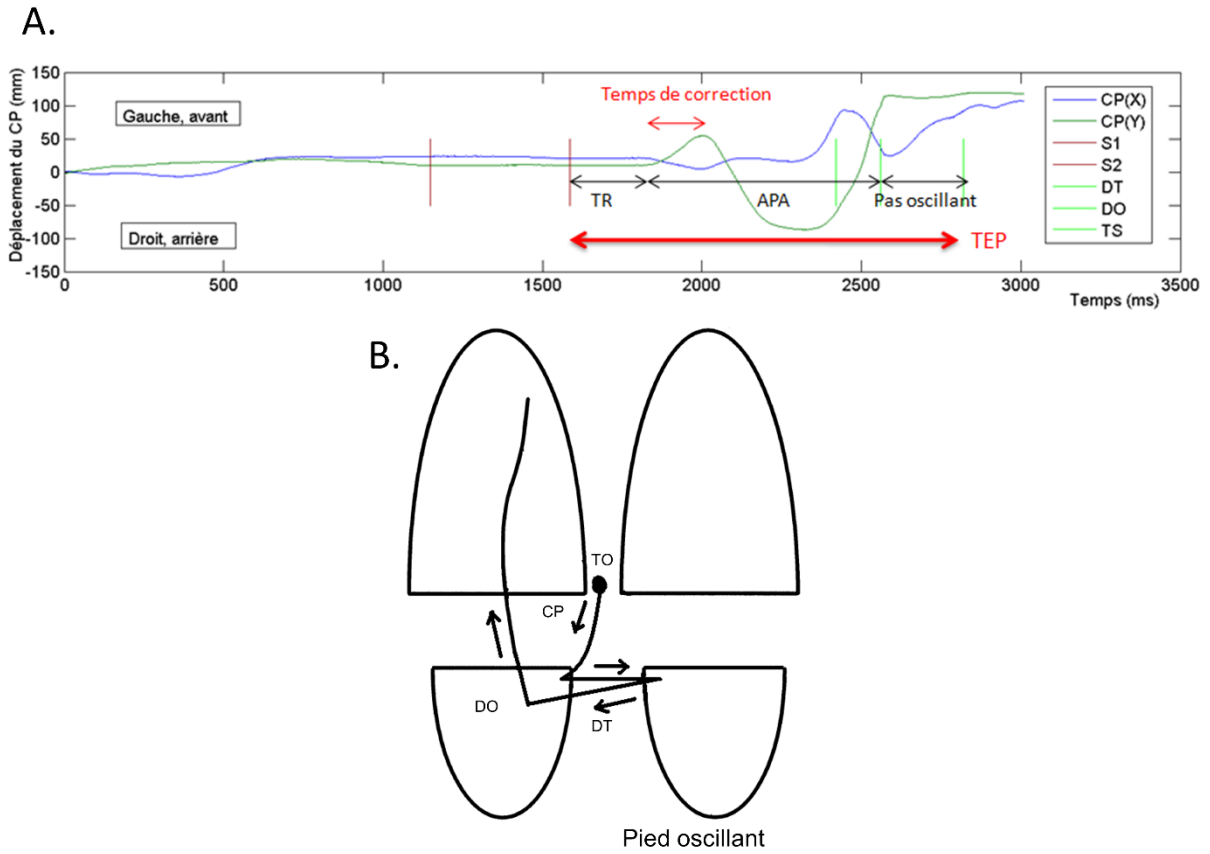
De leur côté, les patients atteints de la MP présentent une phase de préparation motrice plus lente que les individus âgés sains, sans montrer de différence en termes de durée pour la phase d'exécution de l'initiation de la marche (Rosin et al., 1997). Ces difficultés pour initier la marche chez les patients MP peuvent provenir de la défaillance d'indigage interne au niveau de leurs NGC, ce qui expliquerait la préservation des schémas de séquences motrices avec leurs sous-mouvements, mais avec un démarrage retardé et un ralentissement de l'exécution de ces sous-mouvements. En effet, une autre étude menée par Palmisano et collègues (Palmisano et al., 2020) a mis en évidence une réduction de l'amplitude et de la vitesse de déplacement du CdP dans la première phase de l'APA (déplacement en arrière et vers le membre oscillant), mais également une longueur et une vitesse du premier pas réduites, ainsi qu'une diminution de la vitesse et de l'accélération du CdM au moment du décollement du pied d'appui du sol chez les patients MP comparés aux contrôles. Toutes ces mesures sont corrélées avec l'innervation dopaminergique du putamen, mettant à nouveau en évidence que la circuiterie défaillante des NGC pourrait empêcher une configuration optimale de la référence corporelle nécessaire à l'initiation de la marche ainsi qu'une adaptation correcte de la marche à l'environnement (Palmisano et al., 2020). Par ailleurs, les patients MP montrent des déficits posturaux durant l'initiation de la marche (Martin et al., 2002), d'autant plus lorsqu'ils atteignent les phases sévères de la maladie : la distance maximale entre le CdP et CdM durant la phase de support simple est réduite, ce qui traduit un contrôle dynamique de l'équilibre altéré chez ces patients (Hass et al., 2005). Dans une revue de la littérature, Delval et collaborateurs résumant donc les difficultés d'initiation de la marche dans la MP comme suit : démarrage retardé des APAs, hypokinésie (réduction de l'amplitude) et bradykinésie (ralentissement anormal) des APAs (Delval et al., 2014b). La restauration partielle des APAs est possible grâce au traitement par lévodopa (Burleigh-Jacobs et al., 1997), et ce traitement permet également l'amélioration de la plupart des paramètres de la phase d'exécution du pas (Palmisano et al., 2020).

### *Initiation de la marche et freezing de la marche*

Concernant le phénomène de FdM, il est associé à des difficultés posturales lors du contrôle dynamique de l'équilibre ou au cours des APAs précédant la marche (pour des revues, voir (Bekkers et al., 2017, 2018)). Ces troubles du contrôle postural sont encore plus marqués quand un ajustement face à un contexte changeant est nécessaire, lorsque la planification motrice doit être rapide ou dans les cas où le schéma moteur est exigeant, comme pour la tâche *sit-to-walk* (Mezzarobba et al., 2018). Ces défaillances au niveau du « timing » moteur (ou coordination rythmique) ainsi qu'une flexibilité réduite pour basculer entre différentes stratégies motrices chez les MP+FdM pourraient amener à ou

être les conséquences d'un découplage dysfonctionnel du CdP et du CdM pendant la préparation d'une progression en avant. Cette altération du découplage du CdP et CdM peut aussi être vue comme une stratégie protectrice pour atténuer la demande posturale du mouvement préparatoire.

Par ailleurs, il a été suggéré que le FdM serait lié à un couplage altéré entre préparation et exécution de l'initiation de la marche, après l'observation d'APAs multiples et inappropriés précédant le pas chez les MP+FdM comparés aux contrôles sains (Jacobs et al., 2009b). Ces APAs multiples n'étaient pas retardés et étaient de même amplitude par rapport aux APAs des sujets contrôles, ce qui a fait songer à un phénomène d'enrayement cinétique avec difficulté pour basculer dans la phase d'exécution du pas. Un taux plus important d'APAs multiples et l'absence d'APAs ont aussi été observés chez les MP+FdM en condition de médication « ON » comparés aux MP-FdM et aux contrôles sains lors de l'initiation de la marche auto-générée (Delval et al., 2014a). Cependant, dans cette dernière étude, les freezers présentaient une durée d'APA plus longue, un déplacement du CdP en arrière moins ample, ainsi qu'une plus faible vitesse du premier pas et une longueur de pas plus courte. Delval et collègues ont également suggéré l'existence d'un lien perturbé entre la préparation et l'exécution de la marche, suite à l'observation d'une amélioration des paramètres d'APA avec indiçage auditif, mais pas de la performance du premier pas en lui-même. Une autre équipe (Alibiglou et al., 2016) a trouvé un déplacement du CdP en arrière significativement réduit chez les MP+FdM en condition de médication « OFF » par rapport aux MP-FdM et aux contrôles sains. Toujours dans le contexte des pas auto-initiés, une étude a remarqué que les freezers avaient une amplitude des APAs dans la direction ML plus petite en condition de médication « OFF » et en condition de double tâche comparés aux MP-FdM et aux contrôles sains (Schlenstedt et al., 2018). Dans ce cadre, l'amplitude ML des APAs était liée à la sévérité du FdM : les patients avec des APAs plus petits expérimentaient moins de FdM dans leur quotidien, suggérant que de plus grands APAs pourraient être un mécanisme compensateur lors des épisodes de freezing (Schlenstedt et al., 2018). Dans la même étude, la quantité et la durée des APAs ne différaient pas entre les MP+FdM, MP-FdM et les contrôles sains. Pris ensemble, ces quelques résultats et le manque de consensus qui s'en dégage montrent bien l'hétérogénéité du phénomène du FdM et donc, la complexité de son étude.



**Figure 4** Paramètres caractéristiques des phases de préparation et d'exécution du pas : exemple de l'APA erroné. Le TEP représente la somme du TR, durée de l'APA (incluant un temps de correction en cas d'APA erroné ou d'APAs multiples) et phase oscillante. S1 = indice ; S2 = cible ; TO = début de l'APA ; DT = décollement du talon du pied oscillant ; DO = décollement des orteils du pied oscillant ; TS = talon au sol ; CP = centre de pression

## 4. Double tâche

### 4.1. Définition et cadre théorique

Les situations de double tâche (DT), et spécifiquement les DT cognitivo-motrices, sont courantes dans la vie quotidienne : téléphoner en marchant, écouter et interagir lors d'une réunion de travail tout en prenant des notes, rentrer du travail à vélo tout en essayant de se rappeler sa liste de courses pour le dîner du soir... La DT peut effectivement être définie comme « la performance simultanée de deux tâches qui peuvent être réalisées indépendamment l'une de l'autre, mesurées séparément et qui ont des objectifs distincts » (Mclsaac et al., 2015). Les situations de DT peuvent amener à un changement de la performance liée à la tâche primaire relativement à la performance en simple tâche. Ce changement correspond au coût de réalisation de la seconde tâche en concurrence et est appelé « coût de double tâche » ou, plus généralement, « effet de double tâche ». En effet, la réalisation d'une DT n'entraîne pas systématiquement la détérioration de la performance d'une ou des deux tâches comparativement à la performance en simple tâche. A ce titre, dans certains cas, un contexte de DT peut aussi amener à une amélioration de la performance ou ne pas modifier la performance dans les deux tâches (voir Figure 5).

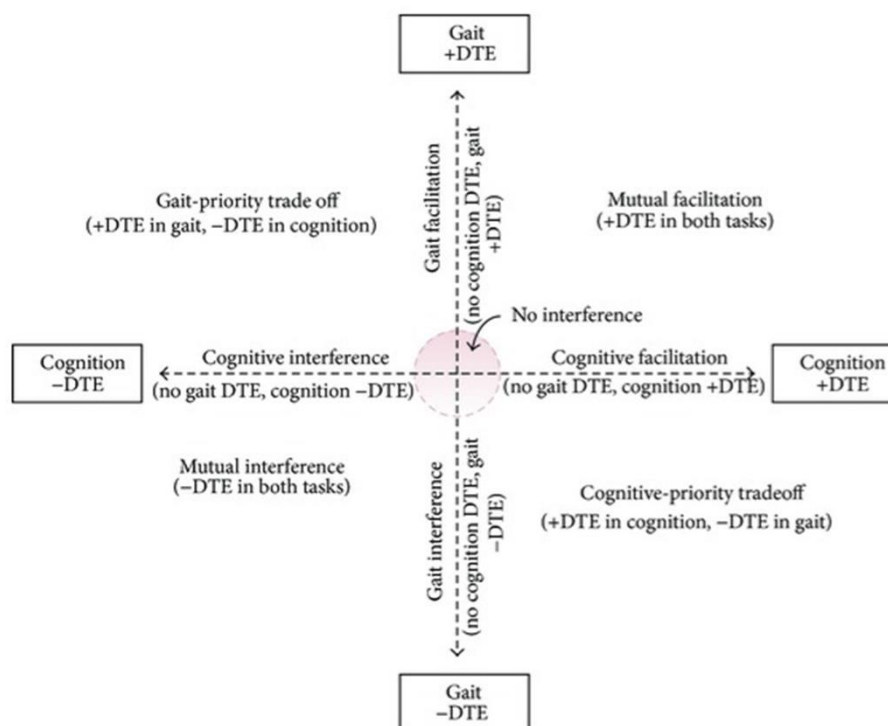


Figure 5 Possibles effets de double tâche cognitivo-motrice par Plummer et al. (Plummer et al., 2014)©

Dans le cas particulier d'une DT cognitivo-motrice incluant la marche comme tâche motrice, à moins que la tâche concurrente ne présente qu'une faible demande cognitive, les deux tâches réalisées simultanément sont décrites comme « interférant » entre elles et mènent ainsi à des coûts de DT, même chez les individus jeunes et sains (Yogev-Seligmann et al., 2008). Ces coûts de DT dépendent, entre autres, de l'âge des sujets, leur état clinique, le type et la complexité de la tâche motrice et de la tâche cognitive concurrente, et l'instruction de priorisation des tâches (Bock, 2008; Al-Yahya et al., 2011; Beurskens and Bock, 2013). Sur base de ces observations, Yogev-Seligmann et al. en ont conclu que la marche requière de l'attention (et plus spécifiquement la capacité à diviser l'attention) ainsi que l'intégrité des fonctions exécutives, même chez les adultes sains avec des fonctions locomotrices et cognitives intactes (Yogev-Seligmann et al., 2008). Autrement, l'exécution simultanée d'une tâche attentionnelle additionnelle n'affecterait pas la performance à la marche et/ou à la tâche cognitive. En fait, les coûts de DT augmentent habituellement lorsque la marche devient moins automatique, comme c'est le cas pour les personnes âgées ou les patients MP.

Ces résultats comportementaux en DT mettent en évidence, comme dit plus haut en abordant les substrats neuronaux de la marche complexe ou en DT, le fait que la marche n'est pas un processus complètement automatique, mais comporte également une composante cognitive en plus d'une composante motrice. L'interaction entre l'attention et le contrôle moteur peut donc être étudiée grâce à des simulations de situations de DT. De plus, le recours à la DT cognitivo-motrice permet d'exacerber les déficits moteurs mais également cognitifs et, à ce titre, elle a été fréquemment étudiée ces dernières décennies en tant que prédicteur du risque de chute (Woollacott and Shumway-Cook, 2002; Wollesen et al., 2019) ou de la démence (Montero-Odasso et al., 2017).

Il est important de noter que, malgré la définition opérationnelle de la DT donnée par Mclsaac et al., l'utilisation de cette terminologie reste sujette à débat. La différence entre une DT et une simple tâche complexe avec deux types de stimuli n'est pas toujours évidente. Par exemple, Mclsaac et collègues considèrent, à l'inverse de nombreux chercheurs, que porter un verre d'eau tout en marchant représente une simple tâche complexe (avec un seul objectif : transporter de l'eau ; et une unique mesure de performance : la stabilité posturale) plutôt qu'une DT (Mclsaac et al., 2015). La présence d'obstacles, une base de support dynamique, un parcours étroit, une manipulation visuelle de l'environnement et même une vitesse rapide sont communément admis dans la littérature comme des facteurs qui perturbent la marche et ne font donc qu'accroître la complexité de la tâche motrice sans résulter en une DT. Par contre, allouer ou non la nature de DT à des situations impliquant une tâche motrice et une charge cognitive représente davantage un sujet de débat. Ces tâches impliquent une

pression temporelle ou des contraintes émotionnelles voire cognitives ; par exemple, marcher au rythme d'un métronome, en écoutant un enregistrement sonore émotionnellement chargé ou en répondant à des indices externes visuels, auditifs ou somatosensoriels. Au vu de ces désaccords sur la terminologie de la DT, la présente thèse a adopté la définition de Mclsaac et al. de la DT (hormis pour la marche en transportant un vers d'eau, incluse dans la catégorie des DT). En effet, ce paradigme est largement répandu et fréquemment étudié dans la littérature autour des DT.

Les théories neuropsychologiques tentant d'expliquer et de modéliser les effets de DT sont variées, comme illustré dans la revue de la littérature élaborée dans le cadre de la thèse et qui constitue l'*Etude 1.1* (cf. Chapitre 3). Les facteurs influençant les résultats de DT chez les jeunes sujets sains sont également passés en revue afin de comprendre la disparité des données de la littérature et donc la multiplicité des modèles de DT proposés. L'attention est portée sur les DT cognitivo-motrices incluant, comme tâche motrice, une tâche posturale, l'initiation de la marche, la marche ou la réalisation de tours. Dans un second temps, l'*Etude 1.2* questionne l'aptitude des DT cognitivo-motrices à prédire le risque de chute chez les individus âgés non-déments et les compare à la puissance prédictive de la simple tâche.

## **4.2. Contrôle cognitif de l'initiation de la marche : incidences comportementales d'une charge attentionnelle**

Peu d'études se sont intéressées aux performances à l'initiation de la marche en DT, au sens de la définition de Mclsaac et al. (Mclsaac et al., 2015) proposée ci-avant. La majorité des études existantes ont plutôt investigué l'impact d'une charge attentionnelle sur l'initiation de la marche afin d'explorer l'interaction entre attention et initiation de la marche. Les conséquences comportementales de l'interaction entre attention et initiation du pas sont ici énumérées pour une population de jeunes adultes.

Tout d'abord, comme précédemment mentionné, plusieurs études (Delval et al., 2012; Tard et al., 2013, 2016b) ont montré, au cours d'une tâche attentionnelle composée d'un stimulus acoustique qui n'était pas un stimulus de sursaut et qui était suivi par un stimulus visuel impératif ordonnant l'initiation de la marche, une possible libération anormale du programme moteur chargé préalablement: les pré-APAs. Durant les études, ces pré-APAs présentaient les mêmes caractéristiques morphologiques que les APAs précédant l'initiation du pas mais n'étaient pas suivis, eux, d'un décollement du pied et, globalement, de l'exécution du premier pas. Ils étaient également plus courts et de moins grande amplitude. Dans un premier temps, la présence de ces pré-APAs pourrait refléter

des difficultés à inhiber un programme moteur indésiré. Dans un second temps, leur durée réduite et le fait que ces pré-APAs n'étaient, la plupart du temps, pas suivis par un mouvement pourraient impliquer des processus d'excitation et d'inhibition motrice et donc, potentiellement le contrôle des structures mésencéphaliques par les structures corticales (au moins en partie par le cortex frontal en charge de l'inhibition). Au niveau cortical, la libération de ces pré-APAs pourrait impliquer différents mécanismes détaillés dans la littérature (Tard et al., 2013) : effet d'alerte, effet d'orientation et effet d'anticipation dirigée vers l'objectif et liée à l'effet d'alerte.

Dans la continuité de l'investigation de l'interaction entre initiation de la marche et cognition via la méthodologie de la DT, plusieurs auteurs ont étudié l'impact des processus attentionnels visuo-spatiaux sur les paramètres d'initiation du pas à travers l'utilisation d'une adaptation du paradigme de l'ANT (Uemura et al., 2013a; Tard et al., 2016b).

Concernant l'influence de l'alerte sur l'initiation du pas, Tard et al. ont trouvé un temps d'exécution du pas (TEP) et un TR avant début de l'APA plus courts dans la condition d'alerte comparée à la condition de contrôle (Tard et al., 2016b). Néanmoins, il n'y avait pas de différence significative au niveau de la durée de l'APA. Dès lors, les chercheurs ont investigué l'hypothèse de « dual-process » (Slijper et al., 2002), selon laquelle les composantes posturale et focale de l'APA proviennent de deux processus de contrôle relativement indépendants recrutant différents programmes moteurs. En effet, ils ont montré que le TR avant début de l'APA reflétait la préparation posturale et était associé à un effet d'alerte, alors que la durée de l'APA reflétait des ajustements posturaux et était liée à un effet d'orientation.

En ce qui concerne l'effet de l'orientation sur l'initiation de la marche, les TR avant début de l'APA étaient plus longs en condition d'indice invalide que valide (Tard et al., 2016b). Ces résultats reflètent les désengagement, déplacement et réengagement attentionnels nécessaires en cas d'indices invalides. De fait, durant l'étude de Tard et al., le défaut de désengagement menait à un nombre plus élevé « d'APAs erronés » (i.e., APAs pour lesquels le CdP se déplace initialement vers le membre de support, et corrige ensuite sa course) pour les indices invalides et donc à une durée d'APA et à un temps d'exécution du pas plus longs qu'avec des indices d'alerte neutres. Cependant, les APAs erronés liés à une condition d'orientation valide étaient aussi observés et peuvent être interprétés comme un comportement d'exploration systématique. Tard et collègues ont trouvé moins d'APAs erronés dans la condition d'orientation avec indices valides qu'en condition d'alerte. Donc, un indice spatial valide semble faciliter la libération d'un programme moteur approprié, tel que mis en avant dans le contexte d'un stimulus auditif (Tard et al., 2013).

Les différences entre les processus d'orientation exogènes et endogènes ont également été investigués à travers l'utilisation d'indices d'orientation périphériques et centraux. En comparaison à la condition avec indices périphériques, la durée de l'APA plus courte (sans différence significative pour le TEP) et la fréquence plus faible d'APAs précoces en condition d'indice central pouvaient refléter l'efficacité des déplacements attentionnels volontaires pour minimiser l'influence de stimuli externes. D'un autre côté, les indices périphériques étaient liés à des déplacements attentionnels automatiques.

Finalement, il a été démontré que le contrôle exécutif modifie la préparation et l'exécution du pas chez les jeunes adultes sains (Uemura et al., 2013a). Un taux plus important d'APAs erronés ainsi qu'un TEP, un TR et une durée de l'APA plus longs étaient associés à la condition de distracteurs non congruents, en comparaison à une condition sans distracteurs et à la condition de cible avec distracteurs congruents. De plus, dans toutes les conditions, les essais avec APAs erronés étaient liés à un TEP et une durée de l'APA plus longs. La prolongation de l'exécution du pas causée par une interférence visuelle est donc principalement due à des erreurs motrices initiales et leur correction. Pour finir, les essais avec des APAs normaux ont montré un TR retardé en condition de cible non congruente, probablement dû au fait que l'inhibition du traitement et de la réponse associés aux cibles avec distracteurs non congruents requièrent un plus grand contrôle attentionnel. Cependant, cette stratégie de prudence résultait tout de même en un TEP plus court comparé aux essais avec APAs erronés.

Il convient de noter que les effets d'interférence de la DT sur l'initiation de la marche dépendent en partie de la stratégie utilisée pour le choix de l'exécution du pas, c'est-à-dire la priorisation de la vitesse, de la précision ou le compromis vitesse-précision (Uemura et al., 2013b). Une stratégie de ce type peut être imposée par des instructions spécifiques données aux participants. En cas d'instruction de priorisation de la vitesse sur la précision, Uemura et collaborateurs ont trouvé un effet du contrôle exécutif moins important au niveau du TR, mais plus marqué pour la durée de l'APA et le taux d'APAs erronés, en comparaison à la stratégie de précision (Uemura et al., 2013b). Cependant, toujours durant l'étude, le nombre de faux pas restait inchangé pour tout type d'instruction ou de condition. En parallèle, la priorisation des tâches dépend également de l'individu, de facteurs environnementaux, de la complexité de la tâche d'initiation du pas avec tâche cognitive concurrente et du taux d'APAs erronés (Sun and Shea, 2016). D'ailleurs, les sujets âgés sains auraient tendance à prioriser la tâche d'initiation du pas quand les deux tâches concurrentes requièrent des ressources importantes, alors que les jeunes individus focaliseraient davantage leur attention sur la tâche cognitive (Melzer et al., 2009).



### **4.3. Interaction attention/initiation de la marche du point de vue comportemental : impact du vieillissement, de la maladie de Parkinson et du freezing de la marche**

#### *Interaction attention/initiation de la marche et vieillissement*

L'évaluation de l'initiation de la marche en situation de DT a permis d'obtenir une meilleure compréhension des mécanismes sous-tendant les déficits de l'initiation du pas chez les adultes âgés sains. Par exemple, Melzer & Oddson ont étudié l'initiation du pas induit par un stimulus cutané lors de la réalisation simultanée d'une tâche de Stroop (Melzer and Oddsson, 2004). Un plus grand effet de DT sur la phase de réaction chez les adultes âgés sains comparés aux jeunes individus a potentiellement mis en évidence un manque de ressources de traitement neuronal pour les situations multitâches chez les personnes âgées. Cela engendrerait une augmentation du temps de traitement neuronal central et donc un ralentissement de la phase de réaction (Melzer and Oddsson, 2004). Par ailleurs, la DT a permis de souligner un effet d'interférence plus élevé sur la latence du pic de force pendant la phase d'APA et la phase oscillante chez les personnes âgées comparées aux sujets jeunes, alors que les pics de puissance et de force n'étaient pas affectés par la condition de DT (Melzer et al., 2009). Cela suggère que le pas volontaire plus lent observé chez les sujets âgés en situation de DT viendrait d'une mauvaise synchronisation et coordination dans la génération de force et non pas d'une réduction de la capacité musculaire. A son tour, ce retard dans la génération de force pourrait être le résultat de ressources de traitement neuronal central limitées, des substrats cérébraux partagés entre le pas et la tâche cognitive et des déficits dans le basculement entre deux tâches.

En outre, à l'aide d'une tâche de temps de réaction simple ou de choix (TTRS ou TTRC) impliquant d'initier le pas pour répondre, les équipes de Cohen et de Sparto ont mis en évidence les déficits du contrôle exécutif liés à l'âge et leur répercussion sur l'initiation du pas (Cohen et al., 2011; Sparto et al., 2013). En effet, durant la TTRS ou la TTRC, les adultes âgés sains présentaient trois fois plus d'essais avec des APAs erronés que les jeunes adultes sains et ces APAs erronés étaient neuf fois plus fréquents pour la TTRC que la TTRS. En conséquence, les adultes âgés montraient une latence de pas retardée lorsqu'ils performaient la TTRC (Cohen et al., 2011). Cette difficulté des personnes âgées à inhiber des réponses non désirées est confortée par l'observation d'une corrélation significative entre le taux d'APAs erronés et la performance à la tâche Stroop. Ultérieurement, Sparto et al. ont confirmé ces déficits de la fonction inhibitrice associés à l'âge, dans le contexte de l'initiation latérale du pas lors d'une TTRS, TTRC, de deux tâches d'inhibition perceptive ou d'une tâche d'inhibition motrice (Sparto

et al., 2013). A nouveau, ce manque d'inhibition affectait le processus de décision du pas principalement en condition de stimulus non congruent et menait à un nombre plus important d'APAs erronés et à une latence de pas retardée. Cependant, contrairement à Cohen et collaborateurs, un démarrage précoce de l'APA survenait également en condition de stimulus non congruent, reflétant l'incapacité des personnes âgées à inhiber un APA initial inapproprié. De façon intéressante, Sparto et al. ont remarqué que l'attention visuelle serait plus attirée par la localisation spatiale de la cible (flèche) comparée à sa direction (Sparto et al., 2013).

Finalement, une TTRC avec l'initiation du pas comme réponse peut être utilisée afin d'explorer les causes de chute pendant l'initiation de la marche chez les personnes âgées. Lors de cette tâche d'initiation avec charge attentionnelle, indépendamment de la direction de la cible, les personnes âgées qui chutent prennent plus de temps pour initier un pas en comparaison avec les sujets qui ne chutent pas à cause d'une durée de l'APA plus longue (Tisserand et al., 2016). En effet, pendant la phase d'APA, les chuteurs semblent utiliser deux stratégies d'équilibre, respectivement dans les directions antéropostérieure (AP) et ML. Ces stratégies amènent à une marge de stabilité plus grande au moment du décollement du pied. Dès lors, Tisserand et al. ont conclu qu'une priorisation de la stabilité posturale par rapport à la tâche cognitive a lieu chez les personnes âgées qui chutent, cette priorisation étant plus prononcée que chez les non chuteurs (Tisserand et al., 2016). Cette stratégie pourrait être justifiée par une capacité musculaire limitée, un choix volontaire pour la stabilité posturale ou une plus grande peur de chuter. En effet, les adultes âgés avec une peur de la chute montrent aussi une plus grande durée d'APA en condition de DT en comparaison aux personnes âgées ne présentant pas de peur de la chute, mais avec des fonctions physiques comparables (Uemura et al., 2012). En plus de la réduction des capacités cognitives liée au vieillissement normal, la peur pourrait réduire la disponibilité des ressources attentionnelles et, dès lors, induire une interférence entre les tâches motrice et cognitive en condition de DT ou de tâche motrice complexe avec charge attentionnelle (Tisserand et al., 2016). A cause de cette interférence, des déficits spécifiques du contrôle de l'équilibre apparaissent : les personnes âgées avec peur de la chute présentent un temps de transfert du poids vers la jambe d'appui plus long (Uemura et al., 2012).

### *Interaction attention/initiation de la marche et maladie de Parkinson*

Peu d'études ont investigué les paradigmes de DT incluant l'initiation de la marche comme tâche motrice dans la MP. En condition de simple ou double tâche (avec tests *0-back* et *2-back* de mémoire de travail), Nocera et al. (Nocera et al., 2013) ont observé des APAs avec une amplitude et une vitesse

de déplacement du CdP davantage réduites chez les patients MP que chez les adultes âgés et sujets jeunes sains. Par ailleurs, ces chercheurs n'ont pas remarqué le moindre effet de DT sur les paramètres cinétiques et cinématiques dans aucun des groupes. Toutefois, lors de l'étude, les patients MP présentaient une baisse significative de leur performance à la tâche cognitive concurrente la plus demandeuse de ressources cognitives, entre la simple tâche et la condition de DT. Ce dernier résultat pourrait suggérer une priorisation de l'initiation de la marche par rapport à la tâche cognitive chez les patients MP (Nocera et al., 2013). En termes d'activité EMG liée à l'initiation de la marche lors de la réalisation concomitante d'un test Stroop (Fernandes et al., 2017), les sujets MP présentaient une latence d'activation des tibialis antérieurs significativement plus tardive en condition de simple tâche comme en DT comparés aux sujets contrôles. Cela pourrait expliquer la durée de déplacement ML du CdP plus longue dans la population MP en situation de DT en comparaison aux contrôles. Pour finir, les patients MP et les contrôles ne montraient pas tous le pattern normal d'inhibition du soleus suivi de l'activation du tibialis antérieur, probablement à cause de la nature intentionnelle et pas entièrement automatique de l'initiation de la marche.

#### *Interaction attention/initiation de la marche et freezing de la marche*

Les paradigmes de DT avec initiation de la marche ou les tâches durant lesquelles une charge attentionnelle est appliquée sur l'initiation du pas ont également permis de mieux comprendre les mécanismes du FdM chez les patients MP.

D'un côté, Tard et collègues (Tard et al., 2014) ont étudié l'impact d'une tâche de discrimination auditive de type « oddball » (juste avant la présentation d'un stimulus visuel impératif « go ») sur les paramètres comportementaux de l'initiation du pas chez les personnes âgées, mais aussi chez les patients MP+FdM et MP-FdM. Comme déjà observé chez les jeunes, la tâche attentionnelle provoque l'apparition de pré-APAs pendant la phase de préparation motrice. Plus particulièrement, ces pré-APAs duraient plus longtemps, étaient plus amples et plus fréquents chez les freezers que chez les non freezers et contrôles. Ceci reflète bien un manque prononcé d'inhibition motrice durant la phase de préparation chez les MP+FdM.

D'un autre côté, le même paradigme a été utilisé dans le cadre d'une étude ultérieure du groupe (Tard et al., 2016a) afin d'observer la modification des oscillations corticales (mesurées via enregistrements EEG) par l'attention durant l'initiation du pas chez les MP+FdM, MP-FdM et personnes âgées contrôles. Le détail des résultats n'est pas rapporté ici, car l'acquisition de données EEG et les différentes analyses

associées seront abordées dans la section suivante. Néanmoins, comme conclusion générale de cette étude de neuroimagerie, il a été suggéré que les MP+FdM, malgré une bonne capacité à discriminer les stimuli, présentent un couplage défectueux entre l'attention et la préparation motrice, ce qui se traduit par des oscillations anormales dans la bande bêta.

Finalement, dans le cadre d'une étude de DT incluant la instrumentée du test version « Stand and Walk » et une tâche de soustractions en série, de Souza Fortaleza et collègues (de Souza Fortaleza et al., 2017) ont observé une différence entre MP+FdM et MP-FdM en termes de coûts de DT: les freezers montraient une durée d'exécution du pas plus longue que les non freezers durant l'initiation de la marche en situation de DT comparée à la condition de simple tâche. Cette dernière observation peut refléter un besoin d'attention plus important chez les MP+FdM pour générer un premier pas.

## 5. Electroencéphalographie

Depuis le premier examen EEG réalisé par Hans Berger en 1929 (Berger, 1929), l'électroencéphalographie est utilisée comme technique d'imagerie permettant l'enregistrement de l'activité électrique du cerveau recueillie au niveau du cuir chevelu. Plus particulièrement, la mesure de sortie d'une acquisition EEG est la répartition dans l'espace et le temps des potentiels électriques produits à la surface du scalp par le passage de courants volumiques dans la boîte crânienne. Ces courants sont, en fait, les courants secondaires post-synaptiques générés principalement par les neurones pyramidaux du cortex, perpendiculaires à la surface corticale. A cause de la dégradation du signal EEG causée par son passage au travers des différentes enveloppes protectrices du cerveau, pour qu'une activité corticale soit visible au niveau du scalp, une décharge simultanée et synchrone d'une population d'un million de neurones orientés dans le même sens est nécessaire, ce qui correspond à une superficie estimée de minimum 6 cm<sup>2</sup> à la surface du cortex (Cooper et al., 1965; Nunez and Srinivasan, 2006). De ce fait, la résolution spatiale de l'EEG est relativement faible (de quelques mm à 1 cm), surtout comparée à celle de la PET (*Positron Emission Tomography*) et de l'IRMf (quelques mm), et empreinte d'incertitude. Cependant, l'EEG présente une résolution temporelle de l'ordre de la milliseconde, intéressante pour l'étude dynamique des substrats corticaux sous-tendant une tâche motrice ou cognitive. L'examen EEG reste également une technique non-invasive et bon marché.

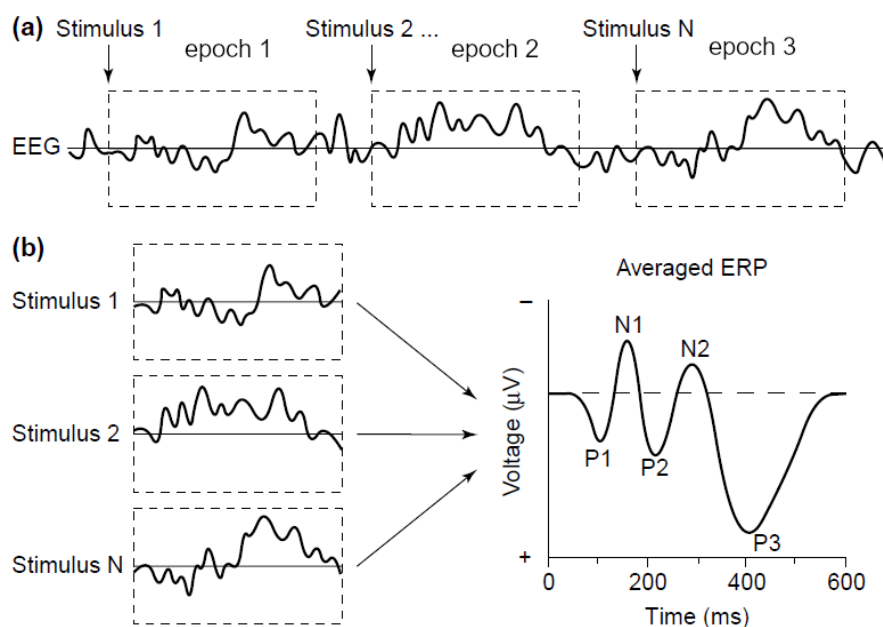
Différentes analyses du signal EEG sont possibles. Nous allons, dans le cadre de la présente thèse, aborder l'évaluation des potentiels évoqués, l'analyse temps-fréquence du signal (ou potentiels induits), ainsi que l'analyse de la connectivité fonctionnelle. Ces méthodes de traitement du signal EEG permettent, toutes trois et de manière complémentaire, une meilleure compréhension des mécanismes neurophysiologiques cachés derrière une observation comportementale, telle que l'impact d'une charge attentionnelle sur l'initiation de la marche.

### 5.1. Potentiels évoqués liés à un événement

#### 5.1.1. *Cadre théorique de l'outil*

L'analyse des potentiels évoqués (PE, ou « potentiels liés à un événement ») compte parmi les méthodes les plus classiques pour l'analyse des données EEG. Un PE peut être défini comme un signal neuronal qui indique l'activité électrique coordonnée d'un ensemble de neurones suite à la présentation d'un stimulus ou suite à tout autre type d'événement (comme une initiation motrice).

Autrement dit, le système nerveux produit une variation transitoire du potentiel électrique au sein d'un certain réseau de neurones, en signe de réponse à un événement. Cependant, une activité aléatoire par rapport à l'événement existe conjointement à cette activité spécifique. Celle-ci peut renfermer un ensemble de phénomènes variables d'un essai à l'autre, mais également des artefacts. De ce fait, le moyennage de plusieurs enregistrements d'un même type d'événements alignés temporellement (i.e., centrés sur l'événement) permet d'atténuer l'activité aléatoire et de mettre en évidence l'activité spécifique. Le signal moyen lié à l'événement est ainsi obtenu, ne prenant donc en compte que l'activité spécifique en phase et répétée à chaque fois au même moment au cours des différents essais. Cependant, en réalité, il arrive couramment que cette activité spécifique apparaisse avec une latence légèrement variable selon l'essai. Ce décalage temporel variable des PE peut donc résulter en une atténuation et une déformation du PE moyen.



**Figure 6** Principe des potentiels liés à l'événement ou potentiels évoqués. Image adaptée de (Luck et al., 2000)®

Classiquement, la fluctuation au cours du temps du potentiel électrique lié à l'événement est décrite par ses différents pics et leur polarité (signe de leur amplitude), amplitude et latence (par rapport à l'événement) respectives.

Les supports fonctionnels cérébraux de l'ANT standard ont notamment été investigués via des PE récoltés par enregistrement EEG (Fan et al., 2007; Neuhaus et al., 2007, 2010; Deiber et al., 2013; Galvao-Carmona et al., 2014; Williams et al., 2016).

Chez les jeunes adultes, Williams et al. ont trouvé une onde **N200** fronto-centrale **liée à la cible** de plus grande amplitude pour les cibles avec distracteurs non congruents en comparaison aux cibles avec distracteurs congruents (Williams et al., 2016), alors que Neuhaus et al. (Neuhaus et al., 2007) n'ont de leur côté mis en évidence aucune relation entre l'amplitude de la N200 et l'aspect congruent ou non des distracteurs. Pour rappel, il a été proposé que la composante N200 liée à la cible - un PE négatif apparaissant environ 200 ms après la cible - reflète soit le recrutement de ressources descendantes (*top-down*) pour améliorer l'évaluation du stimulus quand un conflit est détecté, soit une évaluation des différents résultats possibles plutôt que la détection d'un conflit (Williams et al., 2016).

Des modulations de la composante **P300** fronto-pariétale **liée à la cible** avec l'effet du contrôle exécutif ont également été rapportées (excepté pour (Fan et al., 2007; Williams et al., 2016)) : une augmentation de la P300 frontale peut refléter la rétention de la réponse, l'inhibition de la réponse prépotente, et l'exécution de la réponse correcte associée aux cibles avec distracteurs non congruents (via la « nogo P300 » frontale) (Neuhaus et al., 2010), tandis qu'une diminution de la P300 pariétale peut indiquer une difficulté accrue pour la détection ainsi que l'inhibition d'une cible visuelle dans la condition de cible avec distracteurs non congruents (via la « P300b » pariétale) (Neuhaus et al., 2007, 2010; Deiber et al., 2013; Galvao-Carmona et al., 2014). De surcroît, la latence du pic de la P300 liée à la cible était plus longue pour les cibles avec distracteurs non congruents que pour celles avec distracteurs congruents au niveau des régions centro-pariétale et fronto-centrale, reflétant de ce fait le recours à davantage de temps pour évaluer la cible entourée de distracteurs non congruents (Neuhaus et al., 2007; Williams et al., 2016).

Les ondes **P100** et **N100 liées à la cible** sont également modulées par la présence ou non d'un indice précédant la cible (Neuhaus et al., 2010; Williams et al., 2016). Ce type d'altérations des composantes précoces de PE liés à la cible serait dû à des processus attentionnels descendants (ou endogènes) qui représentent la quantité d'information utilisée pour diriger l'attention visuelle. L'amplitude de la composante **P100 liée à la cible** était significativement plus élevée au niveau des sites pariétaux dans la condition sans indice comparée à la condition avec indice ainsi qu'à la suite d'un indice central comparé à un indice spatial selon certains auteurs (Williams et al., 2016). D'autres chercheurs ont observé un effet d'orientation inverse au niveau de l'amplitude de la P100 liée à la cible dans les régions pariéto-occipitales du scalp (Galvao-Carmona et al., 2014). Comme signe de discrimination perceptive amplifiée, l'alerte induisait une augmentation de l'amplitude de la composante **N100 liée à la cible** au niveau des électrodes pariétales (Neuhaus et al., 2010; Williams et al., 2016), alors que la N100 liée à la cible qui suivait l'orientation était intensifiée au niveau des électrodes pariéto-occipitales

(Neuhaus et al., 2010; Williams et al., 2016), bien que Galvao-Carmona et al. n'aient pas trouvé le moindre effet d'orientation pour la N100 liée à la cible (Galvao-Carmona et al., 2014).

### **5.1.2. Potentiels évoqués lors d'une tâche attentionnelle : impact du vieillissement, de la maladie de Parkinson et du freezing de la marche**

#### *Potentiels évoqués lors d'une tâche attentionnelle et vieillissement*

Quelques études se sont intéressées à l'impact de l'âge sur les PE cognitifs associés au paradigme de l'ANT (Deiber et al., 2013; Kaufman et al., 2016; Williams et al., 2016) et leurs résultats respectifs ne sont pas forcément en parfaite concordance, reflétant ainsi le manque de consensus déjà abordé en ce qui concerne les effets comportementaux d'une charge attentionnelle. Du point de vue des résultats de TR, les équipes de Williams et Kaufman ont constaté un effet de l'alerte réduit chez les adultes âgés, tandis que Deiber et collègues ont observé une amélioration de l'effet de l'orientation dans ce groupe par rapport aux jeunes.

Lors de la réalisation de l'ANT par des participants jeunes mais également âgés, Williams et al. ont montré que les caractéristiques des ondes N100 et P100 liées à la cible ne différaient pas entre groupes (Williams et al., 2016). Cela pourrait signifier que personnes jeunes et âgées montrent tous une attention renforcée envers la cible lorsqu'ils ont reçu des informations via un indice précédant la cible (Williams et al., 2016). Toutefois, Kaufman et collègues n'ont pas trouvé d'effet de l'alerte sur l'amplitude de la N100 liée à la cible chez les sujets âgés, alors que, chez les jeunes, l'amplitude de la N100 suivant un indice central était significativement plus élevée que dans le cas sans indice (Kaufman et al., 2016). Cette équipe a également observé une amplitude de la composante N100 significativement plus élevée chez les jeunes adultes en comparaison aux sujets plus âgés.

Concernant la composante N200 fronto-centrale liée à la cible, son amplitude n'était pas affectée par la congruence de la cible (i.e., le contrôle exécutif) chez les sujets âgés comparés aux jeunes. Ces derniers présentaient une onde N200 plus ample en condition de cible avec distracteurs non congruents comparée à la condition congruente (Williams et al., 2016). Les jeunes adultes sembleraient donc essayer de résoudre le conflit aussi vite que possible, en différenciant déjà les stimuli congruents et non congruents au moment de l'apparition de l'onde N200. A l'inverse, les adultes plus âgés recruteraient la même quantité de ressources pour analyser les stimuli cibles et leur



congruence, comme illustré par l'amplitude invariable de leur composante N200 (Williams et al., 2016).

Enfin, dans les études de William et al. et Deiber et al., l'apparition de l'onde P300 liée à la cible était plus tardive chez les sujets âgés que jeunes, cela étant probablement indicatif du ralentissement généralisé lié au vieillissement (Deiber et al., 2013; Williams et al., 2016). Kaufman et collègues, comme Deiber et al., ont constaté une diminution de l'amplitude de l'onde P300 chez les personnes âgées par rapport aux jeunes (Deiber et al., 2013; Kaufman et al., 2016). Contrairement aux résultats de Kaufman et al. et Deiber et al. ne présentant aucun effet d'interaction significatif entre groupe et cible, Williams et collaborateurs ont rapporté qu'alors que les deux groupes ont montré que le pic de la P300 fronto-centrale était significativement plus tardif dans la condition de cible avec distracteurs non congruents par rapport à la condition congruente, seuls les participants jeunes présentaient le même effet du contrôle exécutif sur le pic de la composante P300 centro-pariétale (Williams et al., 2016). De plus, l'amplitude de la P300 (fronto-centrale mais également centro-pariétale) était réduite dans la condition de cible non congruente par rapport à la condition congruente dans la population âgée, sans observation d'un effet du contrôle exécutif sur l'amplitude de la P300 chez les jeunes (Williams et al., 2016). Au moment du pic de la P300, les jeunes participants sembleraient avoir déjà déterminé une réponse adéquate et ne feraient donc pas preuve d'efforts additionnels pour ajuster cette réponse, présentant une P300 avec une amplitude inchangée entre les deux conditions de cible. Les sujets âgés, quant à eux, déploieraient plus d'effort pour inhiber les distracteurs non congruents et sélectionner la réponse correcte et favoriseraient la précision par rapport à la rapidité, d'où une amplitude de la P300 plus faible en condition de cible non congruente (Williams et al., 2016).

### *Potentiels évoqués lors d'une tâche attentionnelle et maladie de Parkinson*

Jusqu'à présent, aucune étude ne s'est encore intéressée à l'analyse des PE cognitifs lors de la réalisation de l'ANT par des patients atteints de la MP présentant ou non du FdM.

De manière générale, une revue de la littérature (Seer et al., 2016) a rassemblé les premières preuves d'une atténuation de l'amplitude des ondes N200 et nogo P300 chez les patients MP sous médication, ainsi qu'une atténuation plus fréquente du potentiel négatif lié à l'erreur. Ces résultats mettent en évidence une altération du contrôle exécutif dans la MP. La latence de l'onde P300b est prolongée, mais ceci uniquement chez les patients MP déments. Dans ce sens, dans le contexte d'une tâche de type *oddball* auditif, Maidan et collègues ont seulement trouvé des différences significatives en termes

de latence et d'amplitude de la P300 entre des sujets jeunes sains et des patients MP, et non entre participants âgés sains et patients (Maidan et al., 2019a). Cependant, ils ont aussi démontré qu'une latence de la P300 prolongée était corrélée avec des fonctions cognitives et motrices réduites. Ces résultats sont corroborés par Bocquillon et al. (Bocquillon et al., 2012), qui ont observé une P300 liée à la cible plus tardive chez les patients MP de novo par rapport à une population contrôle appariée en âge, lors d'une tâche de type *oddball* visuel avec 3 stimuli (stimuli standard, cibles et distracteurs). De plus, concernant l'amplitude de la P300, cette équipe a également mis en évidence un gradient fronto-pariétal ainsi qu'un gradient ML (i.e., amplitude de la P300 plus importante au niveau des régions antérieures et médianes) chez les personnes âgées saines ; ce qui n'était pas le cas pour les patients. Finalement, Bocquillon et collègues n'ont pas trouvé de différences significatives en termes d'amplitude et de latence de la N200 évoquée par les patients durant cette tâche, comparés au groupe contrôle (Bocquillon et al., 2015).

#### *Potentiels évoqués lors d'une tâche attentionnelle et freezing de la marche*

Concernant l'évaluation des PE cognitifs chez les freezers, Butler et al. n'ont pas observé de différence significative entre MP+FdM et MP-FdM en ce qui concerne la composante P300b, lors de la réalisation d'une tâche de type *oddball* avec stimuli visuels et réponse par pression manuelle sur un bouton (Butler et al., 2017). Cela suggérerait que ces deux groupes de patients MP présentent un traitement cognitif équivalent en ce qui concerne la prise de décision. Ces résultats avaient déjà été obtenus auparavant dans le contexte d'un paradigme *oddball* auditif (Tard et al., 2016a).

#### **5.1.3. Potentiels évoqués lors d'une tâche motrice : impact du vieillissement, de la maladie de Parkinson et du freezing de la marche**

Il est également intéressant d'aligner les époques d'enregistrement EEG sur le démarrage de la réponse motrice afin d'étudier l'activité des régions motrices avant et après le début de l'action. Les PE obtenus sont appelés « potentiels corticaux liés à l'événement » (*MRCPs* en anglais), sont aussi présents dans les mouvements volontaires imaginés et comprennent 4 composantes : le potentiel *Bereitschaft* (*Bereitschaftspotential* / BP) précoce ou potentiel de préparation (*readiness potential* / RP), le BP tardif (ou NS'), le potentiel moteur négatif (*motor potential* / MP\*), et le potentiel positif post-mouvement dit potentiel « ré-afférent » (*re-afferent potential* / RAP) ou potentiel de supervision du mouvement (*movement-monitoring potential* / MMP) (Shibasaki, 2012; Berchicci et al., 2016). Ils sont respectivement en charge de la planification/préparation motrice (pour les deux parties du BP),

de l'exécution et du contrôle de la performance. Le BP précoce est un potentiel négatif bilatéral lent qui apparaît approximativement 2 s avant le début du mouvement au moment de l'intention ou de l'anticipation d'un mouvement à venir (Barrett et al., 1986; Shibasaki and Hallett, 2006). Il démarre bilatéralement au niveau de la pré-AMS et de l'AMS selon son organisation somatotopique, et juste après dans le cortex pré-moteur (PMC) suivant la somatotopie (Shibasaki and Hallett, 2006). Le BP tardif, quant à lui, est un PE avec une pente négative plus prononcée, visible environ 400 ms avant le début du mouvement, de manière controlatérale, au niveau du cortex moteur primaire (M1) et du PMC latéral suivant l'organisation somatotopique (Shibasaki and Hallett, 2006). Le BP et ses composantes précoce et tardive sont générés au niveau de l'AMS, de M1 et du cortex somatosensoriel primaire (Ikeda et al., 1992; Toma et al., 2002). Tous deux sont différenciellement influencés par différents facteurs, tels que la complexité du mouvement qui résulte en une augmentation de l'amplitude du BP tardif (Shibasaki and Hallett, 2006). Le MP\* est un PE négatif présent juste avant le démarrage de l'exécution du mouvement, et qui se situe du côté controlatéral au mouvement (Deecke et al., 1969).

#### *Potentiels évoqués moteurs et vieillissement*

Au vu du peu d'études qui ont traité de l'effet de l'âge sur les MRCPs, il ne semble pas y avoir de consensus sur le sujet. Par exemple, lors d'une tâche de pression manuelle sur un bouton, les jeunes adultes et personnes âgées ne semblaient pas différer les uns des autres au niveau de la programmation motrice (préparation et exécution), c'est-à-dire en ce qui concerne la distribution topographique, la latence et l'amplitude moyenne du RP (BP précoce), BP tardif et MP\* (Singh et al., 1990). Par contre, plus tard, Yordanova et al. ont observé des PE moteurs controlatéraux et sous-tendant la génération de la réponse plus lents chez les personnes âgées, durant une TTRC manuelle (Yordanova et al., 2004). Ils concluent donc que le vieillissement s'accompagne d'une dysrégulation de l'excitabilité du cortex moteur durant le traitement sensorimoteur et ce, d'autant plus que la complexité de la tâche est grande.

#### *Potentiels évoqués moteurs et maladie de Parkinson*

Une revue de la littérature à propos des MRCPs dans la maladie de Parkinson a montré que la plupart des études s'accordaient à observer une atténuation du BP précoce chez les patients parkinsoniens comparés à des contrôles sains (Georgiev et al., 2016). De plus, la médication dopaminergique permet une augmentation de ce BP précoce. Par ailleurs, Shoushatarian et collègues, qui ont étudié les MRCPs durant la performance de 3 pas, n'ont pas trouvé de différence significative concernant le MRCP

précoce chez les patients parkinsoniens par rapport aux sujets âgés sains (Shoushtarian et al., 2011). Les patients montraient seulement une atténuation significative du MRCP précoce en comparaison avec celui des jeunes participants. Cette différence par rapport à la revue de Georgiev et al. (Georgiev et al., 2016) vient sans doute du fait que les études incluses dans cette revue ont traité la plupart du temps de mouvements avec les membres supérieurs, au contraire de l'étude de Shoushtarian et collègues (Shoushtarian et al., 2011) et de leur investigation de la marche. Defebvre et al. soulignent toutefois l'intérêt limité des MRCPs par rapport aux analyses temps-fréquence dans la MP (Defebvre et al., 1994).

### *Potentiels évoqués moteurs et freezing de la marche*

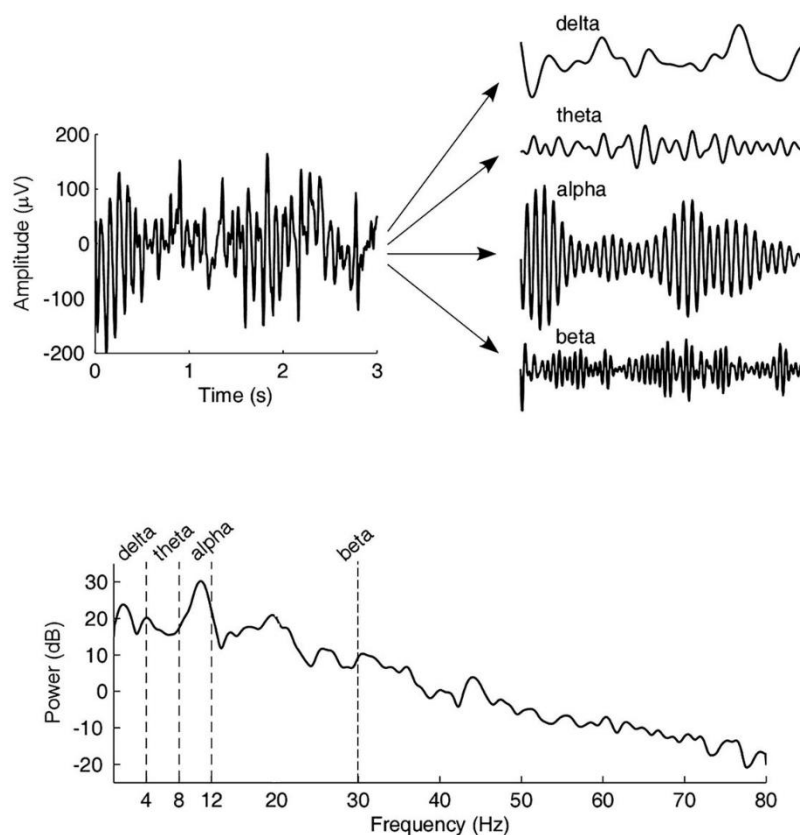
Malgré que l'ensemble des patients MP montrent une atténuation significative de l'amplitude du MRCP précoce en comparaison avec les jeunes adultes, seuls les patients sans difficultés d'initiation de la marche présentent une corrélation significative entre cette amplitude de MRCP précoce et la longueur du cycle de marche : plus le MRCP précoce est faible, plus la longueur de foulée est courte (Shoushtarian et al., 2011). Les patients MP avec difficultés à l'initiation de la marche montreraient donc une altération de ce codage de la longueur d'enjambée. Brugger et collègues ont, par ailleurs, trouvé une amplitude de BP plus faible au niveau de l'AMS chez les MP+FdM comparés aux MP-FdM, juste avant l'initiation d'un mouvement volontaire (Brugger et al., 2020). De surcroît, dans le cadre de l'étude d'une tâche de type *oddball* avec stimuli visuels et réponse par pression manuelle sur un bouton, les MP+FdM présentaient un début plus précoce et une amplitude plus large du RP latéral comparés aux MP-FdM (Butler et al., 2017). Additionnellement, l'amplitude du RP latéral était fortement et significativement corrélée avec le score à la « *Frontal Assessment Battery* ». Mises ensemble, ces observations pourraient ainsi refléter un recrutement excessif des aires prémotrices par les MP+FdM dans le but de compenser pour le dysfonctionnement de l'AMS et, par conséquent, pour le manque de contrôle moteur automatique.

## **5.2. Analyse fréquentielle**

### **5.2.1. Cadre théorique de l'outil**

Le signal EEG est composé par une combinaison d'oscillations périodiques (ou « rythmes ») plus ou moins transitoires. Ainsi, une analyse des données EEG en termes de rythmes est également fréquemment réalisée.

Dans un premier temps, ces oscillations peuvent être étudiées lors d'un enregistrement EEG dit « de repos » au cours duquel aucune tâche n'est réalisée par le participant. Dans ce cas, une transformée de Fourier rapide (FFT) permet la décomposition spectrale du signal EEG. Les puissances spectrales sont ensuite moyennées au cours du temps et pour chaque bande de fréquences d'intérêt : delta (1-4 Hz), thêta (4-8 Hz), alpha (8-12 Hz) et bêta (12-30Hz). Les bornes de chaque fréquence ne font pas consensus, du fait de la variabilité inter-individuelle (Klimesch, 1999, 2012, Anon, 1999). L'analyse de la bande gamma qui comprend toutes les fréquences supérieures à 30 Hz est davantage contestée, car ce rythme est bien souvent généré par de petits volumes et son enregistrement au niveau du scalp n'est donc pas évident (Oostendorp et al., 2000). De plus, la bande gamma est contaminée par l'activité musculaire. Tout comme la bande gamma, l'enregistrement du rythme delta en EEG de scalp est sensible aux artefacts, comme ceux de mouvement ou de transpiration. Ces puissances spectrales moyennes absolues par bande de fréquence permettent de tracer le périodogramme de Welch. D'autres paramètres d'intérêt de l'analyse fréquentielle de repos sont la déviation standard de la puissance spectrale par bande de fréquence, ainsi que la puissance spectrale moyenne relative (i.e., puissance spectrale moyenne absolue dans la bande d'intérêt divisée par la somme des puissances spectrales moyennes absolues calculées dans les autres bandes).



*Figure 7 Principe de l'analyse spectrale du signal EEG : décomposition fréquentielle selon différentes bandes de fréquence afin de tracer le périodogramme, autrement une estimation moyennée de la densité spectrale de puissance en fonction de la fréquence d'intérêt. Image issue de (Zhang, 2019)®*

Lorsque l'on traite d'événements sensoriels, moteurs ou cognitifs, il est possible d'étudier ce que l'on appelle les « perturbations spectrales liées à l'événement » (PSLE ou *ERSP* en anglais) (Makeig, 1993; Makeig et al., 2004). Les paramètres d'intérêt sont alors les augmentations ou diminutions transitoires de l'amplitude spectrale des oscillations pour une fréquence ou bande de fréquences donnée suite à un événement : synchronisations liées à l'événement (SLE ou *ERS* en anglais) ou désynchronisations liées à l'événement (DLE ou *ERD* en anglais) (Pfurtscheller and Aranibar, 1977). Autrement dit, la puissance spectrale associée à un certain rythme EEG (i.e., pour une fréquence ou bande de fréquences donnée) est calculée au cours du temps via une FFT à fenêtre glissante sur chaque essai (ou *short-time Fourier transform* / STFT). Notons que la décomposition spectrale peut également être obtenue via l'utilisation d'une transformée en ondelettes (*Wavelet transform*), la méthode *multi-taper*, ou avec une transformée de Hilbert. En moyennant les puissances spectrales obtenues pour chaque essai, nous déduisons le spectre moyen lié à l'événement. Celui-ci est ensuite normalisé par la puissance spectrale moyenne associée au rythme étudié et calculée le long de la ligne de base (i.e., intervalle de temps dit de « repos » ou d'inaction par rapport à l'événement étudié). Cette normalisation peut se réaliser soit via une division par cette puissance moyenne de référence (« modèle de gain »), soit via une soustraction de la moyenne suivie d'une division par la déviation standard (« modèle additif »). Finalement, la puissance spectrale moyenne de référence associée à la ligne de base peut être calculée sur toutes les époques confondues ou localement au niveau de chaque époque, impliquant dans ce cas que l'étape de moyennage ait lieu après celle de normalisation. La seconde option a démontré une plus faible sensibilité à la variation du bruit entre les différents essais (Grandchamp and Delorme, 2011). Pour résumer, alors que les potentiels évoqués proviennent de variations transitoires du potentiel électrique autour de l'événement qui sont alignées en temps et en phase, nous avons ici à faire à des potentiels dit « induits », résultats des oscillations uniquement synchronisées en temps et non en phase par rapport à l'événement.

D'un point de vue de l'interprétation fonctionnelle, l'étude des différentes bandes de fréquences du signal EEG en condition de repos et de tâche cognitive ou motrice a permis d'émettre des hypothèses sur le rôle de chaque bande.

La **bande alpha** est plus active au repos, bien que lors de la réalisation d'une tâche, sa puissance diminue significativement et devient parfois invisible à l'œil nu (Anon, 1999). L'observation d'une désynchronisation des différents rythmes alpha physiologiques de repos, lors de tâches spécifiques, a

permis d'émettre l'hypothèse d'un rôle inhibiteur de la synchronisation alpha au repos, avec une levée d'inhibition lors du fonctionnement des différentes régions impliquées dans la tâche spécifique. L'exemple le plus illustratif est la disparition du rythme alpha postérieur lors de l'ouverture des yeux, correspondant à une DLE du rythme alpha au niveau des régions visuelles lors de l'apparition d'un stimulus visuel (Scheeringa et al., 2012). Dans les régions centrales, le **rythme mu**, est un rythme physiologique compris dans la bande alpha au repos et sujet à une DLE lors de la préparation et de l'exécution du mouvement (Derambure et al., 1993; Babiloni et al., 1999; Brinkman et al., 2014). Par ailleurs, des études se sont intéressées au rôle de la bande alpha dans l'attention suite à l'observation d'une DLE alpha lors d'une tâche cognitive. De fait, la bande alpha aurait donc aussi un rôle inhibiteur dans les processus attentionnels : plus la tâche requière de l'attention, plus la DLE est prononcée (Dujardin et al., 1995; Klimesch, 2012).

A l'inverse, la **bande thêta** est peu active au repos. La puissance de cette bande augmente en condition de tâche cognitive et, en particulier, lors d'une tâche de mémorisation. Une SLE thêta est présente dans la région temporale lors de l'encodage de nouvelles informations, ce qui signifierait qu'elle joue un rôle dans la mémoire épisodique (Klimesch et al., 1996, 1997). Plus la tâche est difficile, plus la SLE en thêta dans la région préfrontale médiale est importante (Gevins et al., 1997). Cette dernière observation pourrait refléter la demande attentionnelle et suggérer un rôle joué par la synchronisation en thêta dans l'attention.

Finalement, la **bande bêta** est moins fréquemment étudiée dans le domaine cognitif. Ces oscillations semblent plutôt jouer un rôle dans la motricité et la préparation du mouvement. Lors d'un mouvement volontaire, une DLE dans la bande bêta apparaît durant l'étape de préparation motrice, devient maximale lors de l'exécution du mouvement, et enfin une SLE est observée à la fin du mouvement (Salmelin et al., 1995). Cette séquence suggère un rôle de la bande bêta dans la préparation du mouvement, bien que sa fonction précise ne fasse pas l'objet d'un consensus dans la littérature (Müller et al., 2003; Zaepffel et al., 2013).

D'autres bandes ne seront pas étudiées en détail dans la présente thèse. Ainsi, la **bande delta** est associée au sommeil profond mais apparaît également pendant la veille (Sachdev et al., 2015). Une SLE delta a été mise en évidence lors de tâches cognitives internes (Harmony et al., 1996). A son niveau, le **rythme gamma** semble contribuer à l'activation de fonctions cérébrales via une SLE, aussi bien pour les processus cognitifs que sensorimoteurs (Jia and Kohn, 2011).

## **5.2.2. Oscillations de repos : impact du vieillissement, de la maladie de Parkinson et du freezing de la marche**

### *Oscillations de repos et vieillissement*

Avec l'âge, il est courant d'observer une diminution marquée et linéaire de l'activité de repos dans les bandes de fréquences basses : diminution de l'amplitude absolue des bandes delta et thêta (Hartikainen et al., 1992; Barry and De Blasio, 2017), de la puissance absolue delta (Hartikainen et al., 1992) et de la puissance relative delta et thêta (Vlahou et al., 2014). De plus, l'activité dans les bandes de fréquence plus hautes (i.e., alpha et bêta) présente aussi une tendance à diminuer avec l'âge (Hartikainen et al., 1992), même si il y a un moins grand consensus sur ce point. Par exemple, Barry & De Blasio ont observé une augmentation de l'amplitude absolue de la bande bêta (Barry and De Blasio, 2017). Par contre, les résultats divergent dans la littérature quant au lien entre l'activité des bandes de fréquence basses et la performance cognitive chez les sujets âgés (Hartikainen et al., 1992; Vlahou et al., 2014). En effet, avec l'âge avançant, le pic individuel de fréquence alpha ou « fréquence du rythme de fond » typiquement diminue, avec une redistribution vers les régions antérieures (Duffy et al., 1984). Cela induirait donc un biais en ce qui concerne les différences de puissance et connectivité alpha entre jeunes et personnes âgées (Scally et al., 2018). Sur base de ces observations, Finnigan et al. ont proposé deux formes d'oscillations thêta : (i) celles qui, avec l'augmentation de leur puissance spectrale, sont indicatives de la bonne santé des fonctions neurocognitives (Babiloni et al., 2006) ; et (ii) quand l'augmentation d'activité thêta est « biaisée » par l'activité parallèle alpha ralentie, alors son augmentation peut être liée à un (futur) déclin cognitif substantiel et peut être associée à des troubles neurologiques liés à l'âge (Finnigan and Robertson, 2011).

### *Oscillations de repos et maladie de Parkinson*

Des variations dans différentes bandes de fréquence de l'activité oscillatoire dans les circuits cortico-basaux sont assez spécifiques de la MP. Il est toutefois difficile d'assurer de manière définitive que ces oscillations sont réellement pathogènes, ou représentent un symptôme pathologique elles-mêmes ou sont simplement un épiphénomène (Singh, 2018). En effet, sur base de différentes observations, un modèle oscillatoire de la MP a été proposé (Schnitzler and Gross, 2005): l'akinésie (initiation perturbée de tâches motrices volontaires) est induite par une augmentation des oscillations basse fréquence (< 10 Hz) et une diminution des oscillations haute fréquence (> 60 Hz) qui émergent dans les NGC et se propagent dans les régions corticales motrices. Par ailleurs, les effets akinétiques sont aussi dus à des oscillations bêta amplifiées qui proviennent des régions corticales motrices et se répandent au niveau



des NGC. Finalement, des oscillations gamma provenant de NGC (via stimulation cérébrale profonde à haute fréquence et lévodopa) entraînent des effets pro-kinétiques.

La MP est caractérisée par un ralentissement de l'activité cérébrale à l'état de repos (voir (Boon et al., 2019) et (Geraedts et al., 2018) pour une revue de magnétoencéphalographie MEG et EEG, respectivement) : la puissance spectrale relative dans la bande thêta augmente de façon diffuse, la puissance relative bêta diminue de façon concomitante au niveau des électrodes postérieures, et la puissance relative gamma s'atténue au niveau des électrodes centrales et pariétales chez les patients MP non déments comparés aux contrôles sains, dans la condition avec yeux fermés (Bosboom et al., 2006). Pendant l'étude de Bosboom et al., en condition "yeux ouverts", ces patterns différentiels du changement de l'activité cérébrale oscillatoire étaient globalement similaires, bien que moins intenses et moins diffus (Bosboom et al., 2006). Ces résultats ont, par la suite, été confirmés (Yi et al., 2017) et même à des stades cliniques précoces de la maladie, pour des patients MP de novo (Stoffers et al., 2007). De plus, avec une autre approche pour analyser le contenu spectral du signal EEG chez les patients MP, Yi et al ont observé une réduction globale de la complexité de l'activité cérébrale oscillatoire à l'état de repos chez les patients MP comparés aux sujets sains (Yi et al., 2017), avec une plus petite entropie de permutation (la mesure de l'imprévisibilité de séries temporelles) et un index d'ordre plus important (mesure de la prévisibilité de séries temporelles) dans les bandes alpha, bêta et gamma.

Des conclusions divergentes quant à l'association entre puissance spectrale du signal EEG de repos, d'un côté, et durée de la maladie, sévérité des symptômes moteurs ou traitement, d'un autre côté, sont retrouvées dans la littérature (Stoffers et al., 2007; Olde Dubbelink et al., 2013a) et ont été mises en évidence dans des revues systématiques MEG et EEG (Geraedts et al., 2018; Boon et al., 2019).

Par ailleurs, les patients MP déments ont montré un ralentissement encore plus prononcé des oscillations à l'état de repos (impliquant en plus les bandes delta et gamma) et une réactivité nettement réduite à l'ouverture des yeux (Bosboom et al., 2006; Olde Dubbelink et al., 2013a; Geraedts et al., 2018; Boon et al., 2019). En effet, certains déficits cognitifs précoces étaient associés à une faible puissance relative alpha (Stoffers et al., 2007), alors que l'augmentation de la puissance médiane relative de la bande thêta semble être un prédicteur du déclin cognitif sévère des patients MP, comme démontré dans une étude prospective avec une période de suivi de 3 ans (Cozac et al., 2016). De fait, l'analyse spectrale des signaux EEG à l'état de repos semble être une méthode de screening prometteuse puisque peu onéreuse, non invasive et facile à utiliser pour identifier la sévérité des

déficits cognitifs des patients MP (Betrouni et al., 2019). Néanmoins, à notre connaissance, la puissance spectrale de bande associée à l'enregistrement EEG ou MEG n'a ni été analysée chez les patients MP+FdM ni comparée aux patients MP-FdM ou à des sujets sains à ce jour.

### **5.2.3. PSLE lors d'une tâche attentionnelle : impact du vieillissement, de la maladie de Parkinson et du freezing de la marche**

Concernant les PSLE associées à l'ANT standard, selon Fan et al. (Fan et al., 2007), chaque réseau attentionnel peut avoir une collection distincte d'oscillations liées à son activité.

Dans le contexte des réseaux de l'alerte et de l'orientation, il a été montré que l'activité des bandes thêta, alpha et bêta diminue à 200-450 ms après la présentation de l'indice neutre et correspond à l'habituelle désynchronisation de l'activité électrique à la suite d'un signal d'alerte. Contrairement à Fan et al. (Fan et al., 2007), Deiber et ses collègues ont observé une augmentation transitoire de la puissance thêta après présentation d'un indice (Deiber et al., 2013). Ces oscillations connues pour être significativement en phase après la visualisation d'un stimulus contribueraient à la génération de la composante liée à l'événement P100 (Makeig et al., 2002; Klimesch et al., 2011).

En ce qui concerne l'analyse liée à la cible (*target-locked*, en anglais), le réseau du contrôle exécutif (les conditions de cible avec distracteurs congruents versus non congruents) présentait un pattern complexe de modification temps-fréquence : une augmentation précoce (< 400 ms) d'une activité large bande comprenant la bande bêta, suivie d'une diminution tardive (> 400 ms) d'une activité large bande incluant les bandes thêta, alpha et bêta (Fan et al., 2007). En effet, Deiber et al. (Deiber et al., 2013) ont aussi trouvé, en même temps qu'une SLE transitoire dans la bande thêta, une DLE dans les bandes alpha et bêta après présentation de la cible, qui était plus prononcée en cas de distracteurs non congruents. Après cette DLE alpha/bêta, une SLE alpha/bêta suivait pour correspondre au pattern classique de réactivité des oscillations liées au stimulus. Par ailleurs, des effets de l'alerte et de l'orientation sur les PSLE liées à la cible ont été observés (Fan et al., 2007). Premièrement, en conditions sans indice et avec indice central, une SLE précoce dans certaines fréquences de la bande bêta et plus hautes fréquences apparaissait entre 100 et 300 ms après la présentation de la cible et était liée au processus d'orientation nécessaire lorsque la cible et ses distracteurs apparaissait sur l'écran d'ordinateur. Dans le cas où un indice spatial précédait la cible, une telle SLE n'était donc pas observable. Dans un second temps, une DLE tardive liée à la cible dans les bandes thêta, alpha et bêta était plus prononcée en condition sans indice qu'en conditions avec indice central ou spatial, car cette baisse de puissance était associée à un état d'alerte recruté pour la réponse à la cible (Fan et al., 2007).

### *PSLE lors d'une tâche attentionnelle et vieillissement*

Dans le contexte de l'ANT, Deiber et al. n'ont plus retrouvé, avec le vieillissement, les différences au niveau de la DLE alpha/bêta entre les deux conditions de distracteurs, différences détectées via une analyse temps-fréquence chez les jeunes adultes (Deiber et al., 2013). Cette analyse temps-fréquence a également permis de mettre en évidence le fait que l'engagement de circuits attentionnels postérieurs ne serait pas crucial pour obtenir une résolution de conflits performante chez les sujets âgés. En effet, les sujets âgés ont montré une diminution de la DLE alpha postérieure, parallèlement à une augmentation de la DLE bêta au niveau du cortex central. Cela n'a fait que confirmer « l'hypothèse de dédifférenciation » qui postule que les personnes âgées, par manque d'efficacité du point de vue de l'utilisation des ressources neuronales ou de par la dégradation de la sélectivité des réponses, recrutent des régions cérébrales additionnelles (liées à la motricité), en comparaison avec la population plus jeune. Enfin, la SLE alpha/bêta tardive et spatialement étendue était de plus petite amplitude chez les personnes âgées comparées aux jeunes. Ceci pourrait être expliqué par la récupération moins efficace de l'excitabilité corticale induite à la suite d'un stimulus, caractéristique du vieillissement (Deiber et al., 2013).

### *PSLE lors d'une tâche attentionnelle et maladie de Parkinson*

L'activité corticale, et particulièrement l'analyse des PSLE, liée à la réalisation de l'ANT standard par des patients MP n'a encore jamais été étudiée jusqu'à aujourd'hui. Toutefois, dans le cadre d'une étude MEG lors de la performance d'une tâche de Go-noGo (permettant l'évaluation de l'attention soutenue et du contrôle inhibiteur), Wu et collègues (Wu et al., 2019) ont observé une diminution de la DLE bêta durant la condition noGo et de la SLE bêta durant les conditions Go et noGo chez les patients MP comparés aux contrôles. L'atténuation de la DLE noGo peut refléter des anomalies au niveau de l'inhibition de la réponse. Les patients présentaient également un début des DLE et SLE bêta plus tardif dans la condition Go, en lien avec leur temps de réaction plus long dans cette condition, reflétant donc des anomalies dans le programme moteur. Finalement, la SLE noGo était négativement corrélée avec le score UPDRS des patients, alors que la SLE Go était liée à la performance motrice (temps de réaction dans la condition Go) (Wu et al., 2019).

### *PSLE lors d'une tâche attentionnelle et freezing de la marche*

Dans le domaine de recherche du freezing de la marche, les PSLE n'ont pas été non plus grandement étudiées. A titre d'exemple, dans le contexte d'une étude EEG de marche initiée par un stimulus auditif,

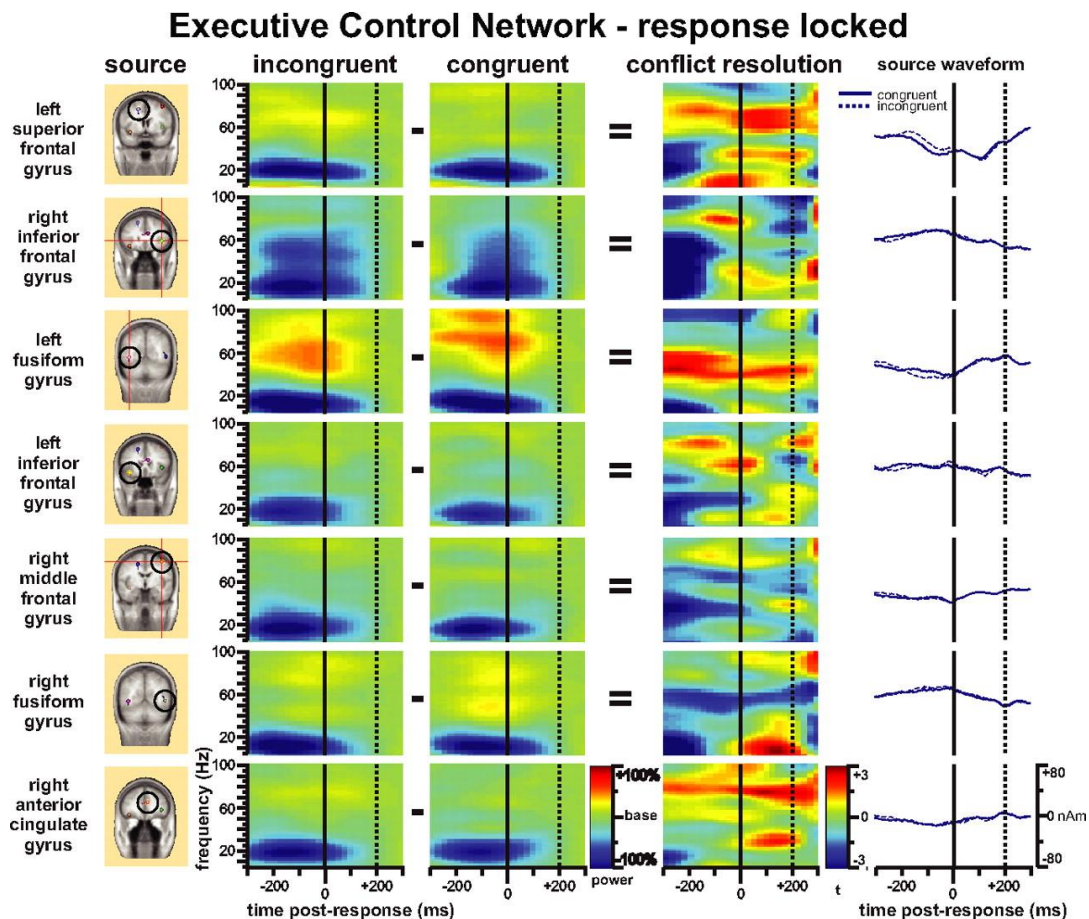
la SLE alpha/thêta aux environs du stimulus et au niveau de l'électrode Fz (supposée AMS) était amplifiée chez les patients MP avec troubles de l'initiation de la marche par rapport aux contrôles (Weersink et al., 2020). Cette SLE peut être mise en parallèle avec la SLE observée au niveau de l'AMS et des régions occipitales durant la transition vers un épisode de freezing. Elle pourrait exprimer une difficulté des patients MP+FdM à gérer des conflits liés à des signaux. Ici, le stimulus auditif manquerait de contextualisation et un conflit entre de potentielles options motrices pourrait avoir lieu. En effet, les patients MP+FdM compteraient trop sur les informations visuelles en compensation d'une perte ou altération du feedback kinesthésique, mais cette plus grande vulnérabilité aux indices externes peut être délétère dans certains cas et induire des réponses « en blocs », par exemple (Weersink et al., 2020). Au contraire, une autre étude EEG menée par Tard et collègues n'a pas mis en évidence de différence inter-groupe (entre MP+FdM, MP-FdM et contrôles) significative en ce qui concerne la SLE thêta-alpha apparaissant à la suite d'un stimulus auditif précédant un stimulus visuel impératif qui signalait l'initiation de la marche (Tard et al., 2016a). Cette observation a donc pu démontrer que la capacité à discriminer correctement un stimulus était maintenue chez les freezers. Dans cette étude, le couplage défectueux entre attention et préparation motrice chez les MP+FdM était plutôt mis en avant.

#### ***5.2.4. PSLE lors d'une tâche motrice : impact du vieillissement, de la maladie de Parkinson et du freezing de la marche***

Les PSLE liées au mouvement sont des DLE/SLE alpha et bêta qui représentent respectivement l'augmentation/la diminution de l'activation des aires corticales impliquées/non impliquées dans la tâche (Pfurtscheller, 1999). Durant la phase de préparation du mouvement et pendant le mouvement en lui-même, des DLE alpha et bêta apparaissent essentiellement au niveau du cortex somatosensoriel et du cortex moteur, respectivement. Cette désynchronisation commence environ 2 s avant le début du mouvement volontaire au niveau de la région rolandique controlatérale et devient bilatéralement symétrique immédiatement avant l'exécution du mouvement. Ensuite, après la fin du mouvement, des SLE sont observables dans la bande bêta (Pfurtscheller, 1999; Shibasaki and Hallett, 2006). Les DLE/SLE, comme les MRCPs, diffèrent selon le type de mouvement (Vidailhet et al., 1993; Pfurtscheller et al., 1997, 1998; Jankelowitz and Colebatch, 2002; Shibasaki and Hallett, 2006)).

Certaines études ont analysé les PSLE durant l'ANT standard assis (Fan et al., 2007; Deiber et al., 2013). En particulier, l'analyse spectrale, liée à la réponse, de l'effet de la résolution de conflit (i.e., le pattern temps-fréquence lié aux cibles avec distracteurs non congruents moins celles avec distracteurs

congruents) montre une DLE dans les bandes thêta et alpha avant le début de la réponse, ainsi que des sursauts thêta et bêta autour ou après la réponse (Fan et al., 2007). En outre, dans un contexte de mobilisation continue des membres inférieurs, l'attention était associée à une plus faible puissance dans les bandes thêta, alpha et bêta au niveau des cortex moteur et somatosensoriel et dans d'autres aires corticales plus largement distribuées, comparée à une condition durant laquelle l'esprit est errant (Melinščak et al., 2014; Melinscak et al., 2016).



*Figure 8 PSLE liées à la réponse manuelle (appui sur une touche d'un clavier d'ordinateur) durant l'ANT standard. La désynchronisation alpha/bêta durant la phase de préparation du mouvement (intervalle de temps pré-réponse) est bien visible et davantage importante en condition de cible avec distracteurs non congruents que congruents. Image issue de (Fan et al., 2007)®*

### *PSLE motrice et vieillissement*

Dans le cadre d'un entraînement comprenant une tâche de *reaching*, il a été montré que, malgré que les personnes âgées étaient plus lentes et moins précises que les jeunes, la différence d'amplitude au niveau du cortex sensorimoteur entre la DLE initiée avant le début du mouvement et la SLE se manifestant après la fin du mouvement n'était pas significativement différente entre les groupes d'âge

(Ricci et al., 2019). La latence de la SLE semblait davantage liée à la performance motrice (Ricci et al., 2019). Par ailleurs, une autre étude examinant les PSLE liées à un mouvement fin de la main a mis en évidence des DLE mu et bêta précédant le mouvement plus rapides chez les sujets jeunes lorsque la main dominante était impliquée dans le mouvement, alors qu'aucune différence de latence de la DLE n'a été observée chez les personnes âgées qui tendaient à devenir ambidextres (Frolov et al., 2020). Les différences liées à l'âge touchent donc encore une fois la latence des DLE liées au mouvement et non leur amplitude. Frolov et collègues ont également observé une augmentation de la SLE thêta au sein de l'aire sensorimotrice. Une troisième étude avec des tâches de tapotement des doigts a seulement mis en évidence une atténuation de l'amplitude de la SLE bêta post-mouvement au niveau du cortex préfrontal médial, pouvant être associée à une désactivation perturbée de cette population de neurones (Liu et al., 2017).

### *PSLE motrice et maladie de Parkinson*

De manière globale (cf. (Shirahige et al., 2020) pour une revue), durant le mouvement, les patients MP présentent un ralentissement généralisé de leur pattern spectral dans les régions du cortex central et frontal et principalement dans le cortex contralatéral au mouvement, comparés aux sujets contrôles sains. Entre autres observations, durant une tâche motrice complexe, les patients MP montrent une activité bêta plus faible que les contrôles, même si cela n'a pas été retrouvé dans toutes les études incluses dans l'article de revue (Shirahige et al., 2020).

### *PSLE motrice et freezing de la marche*

Comme mentionné ci-avant, lors d'une tâche d'initiation de la marche indiquée, les MP+FdM ont montré une SLE bêta, associée à la discrimination du stimulus, prolongée au moment où les MP-FdM et contrôles présentaient une DLE bêta, associée à la préparation motrice (Tard et al., 2016a). Cette situation pourrait illustrer un couplage altéré entre attention et préparation motrice chez les MP+FdM. Que ce soit durant une tâche d'initiation de la marche, d'extension des doigts ou de tapotement du doigt, une DLE alpha/bêta réduite a également été observée durant la préparation et le début du mouvement, mais aussi pendant le mouvement chez les MP+FdM comparés aux MP-FdM et aux contrôles (Brugger et al., 2020; Weersink et al., 2020). Brugger et al. ont visualisé cette différence d'amplitude au niveau de l'AMS (Brugger et al., 2020). Ceci rejoint donc l'observation faite précédemment par Tard et collègues (Tard et al., 2016a): les freezers semblent éprouver des difficultés à supprimer la synchronisation bêta corticale durant la planification du mouvement, ce qui pourrait contribuer à leurs moins bonnes capacités de mouvement. En parallèle à cela, l'activité musculaire des

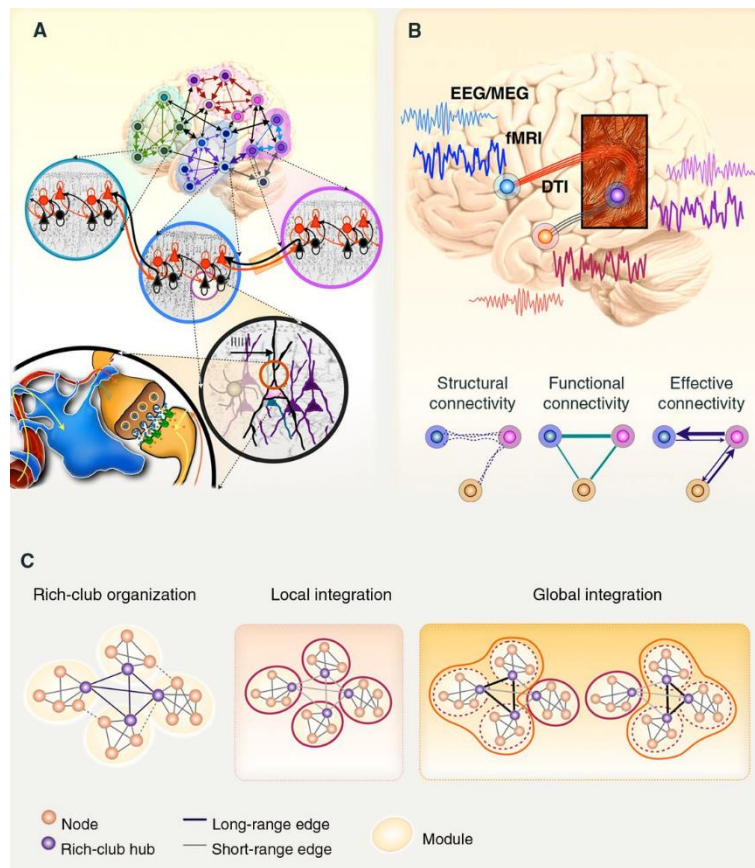
jambes était également atténuée durant la phase de préparation motrice et au moment du démarrage du mouvement, avec une initiation du pas plus tardive chez les MP+FdM par rapport aux contrôles sains (Weersink et al., 2020).

## **5.3. Connectivité fonctionnelle**

### **5.3.1. *Cadre théorique de l'outil***

Les fonctions cérébrales ont longtemps été associées à une organisation par région. Cette théorie localisationniste était appuyée par des modèles lésionnels et a permis une compréhension du mécanisme de nombreuses pathologies neurologiques. Cependant, l'organisation des fonctions cérébrales est en réalité beaucoup plus complexe, et des outils ont dû être développés pour explorer ces fonctions de manière plus fidèle. Il est désormais admis que les fonctions cérébrales reposent sur des réseaux cérébraux et leur interaction.

L'étude de ces réseaux est permise par différentes méthodes. L'analyse de la connectivité fonctionnelle renseigne sur les régions cérébrales liées par leur fonction et qui communiquent entre elles, sans préjuger du sens du lien. Plus précisément, la connectivité fonctionnelle est définie comme la corrélation temporelle entre deux événements neurophysiologiques spatialement distants (Friston, 1994). Différentes modalités d'imagerie sont disponibles pour mesurer cette connectivité fonctionnelle, comme l'IRMf, la MEG et l'EEG.



**Figure 9** (A) L'analyse de l'activité cérébrale peut être réalisée à différentes échelles. (B) Le cerveau est organisé comme un réseau de connexions entre les ensembles de neurones. Les connexions structurales autant que fonctionnelles peuvent être analysées, avec éventuellement une idée de directionnalité de la communication (connectivité effective). (C) La théorie des graphes est utilisée, entre autres, pour la quantification de la topologie de ce réseau. Image issue de (Park and Friston, 2013)<sup>©</sup>

Spécifiquement en EEG, il est possible de travailler à partir du signal enregistré au niveau du scalp ou de projeter ce dernier dans l'espace des sources, au niveau du cortex cérébral, via la résolution du problème inverse. Une étape intermédiaire est la projection du signal des sources sur un atlas du cerveau standardisé afin de réduire le nombre de régions cérébrales à analyser par la suite ou régions d'intérêt (ROIs). Pour une bande fréquence donnée, une matrice de connectivité comportant la mesure de connectivité fonctionnelle pour chaque paire de régions cérébrales d'intérêt peut alors être construite via diverses méthodes. En effet, ces dépendances statistiques entre les signaux de deux sources données peuvent être linéaires ou non-linéaires, estimées dans l'espace temporel ou fréquentiel, ou encore être basées sur la phase ou sur l'amplitude des signaux. Chacune de ces méthodes de mesure de la connectivité fonctionnelle présente des avantages et inconvénients qui ne permettent pas, à ce jour, un consensus unanime sur le choix de l'une par rapport aux autres (van Diessen et al., 2015; Bastos and Schoffelen, 2016; Kida et al., 2016). Il convient d'effectuer ce choix par rapport à la problématique étudiée et de le conforter en comparant les résultats avec ceux obtenus



via d'autres techniques. Par la suite, les matrices de connectivité obtenues peuvent être, d'une part, utilisées de manière brute pour être statistiquement comparées les unes avec les autres. D'autre part, ce genre de matrice peut être considéré comme un graphe pondéré adirectionnel composé de nœuds représentant les régions cérébrales et de liens représentant les valeurs de connectivité fonctionnelle entre chaque paire de nœuds. Après seuillage, cette matrice peut être analysée via la théorie des graphes afin d'obtenir des caractéristiques du réseau cérébral. Pour finir, l'analyse de la connectivité fonctionnelle dynamique des réseaux au cours d'une tâche est également réalisable et représente le principal atout du recours à l'EEG pour l'analyse de la connectivité fonctionnelle par rapport à l'IRMf. A côté de cela, une analyse de la connectivité fonctionnelle de repos est également réalisée, principalement afin de comparer les résultats avec les nombreuses analyses de repos en IRMf.

### **5.3.2 Connectivité fonctionnelle chez les sujets âgés**

De nombreuses études de connectivité en IRMf se sont penchées sur la description des réseaux cérébraux de repos chez le sujet sain (Greicius et al., 2003; Fox et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Mantini et al., 2007). Ces études montrent qu'à l'état de repos, plusieurs réseaux coexistent et s'activent à des temps différents. Le plus présent au repos est le réseau par défaut (ou *Default Mode Network / DMN*, en anglais). Ce réseau est certes dominant au repos, mais subit une désactivation lors d'une tâche cognitive complexe, d'autant plus que la difficulté de la tâche est importante. A l'inverse, un deuxième réseau est présent au repos mais est d'autant plus activé que le sujet réalise une tâche cognitive complexe : le réseau attentionnel dorsal (ou *Dorsal Attention Network / DAN*, en anglais), comprenant les régions du sIP, frontale latérale avec le COF, et la région temporale moyenne. Ces deux réseaux ont un pattern d'activation-désactivation alternant (Fox et al., 2005). La commutation entre le DAN et le DMN est associée au réseau de contrôle fronto-pariétal (*FPN*) (Vincent et al., 2008; Spreng et al., 2010). Comme précédemment notifié (cf. section *Attention* du Chapitre 1), le DAN serait impliqué dans l'attention dirigée vers un but, tandis qu'un autre réseau présent au repos interagirait avec le DAN : le réseau attentionnel ventral (ou *Ventral Attention Network / VAN*, en anglais), comprenant les régions frontale ventrale et la JTP, latéralisé à droite, dirigerait la détection de stimulus inattendu et la sélection d'information pertinente pour déclencher un changement de tâche (Corbetta and Shulman, 2002; Vossel et al., 2014). D'autres réseaux sont décrits au repos, comme le réseau sensorimoteur, le réseau visuel et le réseau auditif.

Plusieurs études sur la connectivité fonctionnelle à l'état de repos ont vu le jour ces dernières années pour étudier l'impact du vieillissement. Ainsi, bien qu'une baisse de la connectivité fonctionnelle au

repos (au niveau des composantes du DMN, mais aussi des réseaux attentionnels et moteurs) soit le pattern le plus commun dans les études en IRMf chez les personnes âgées (Ferreira and Busatto, 2013) et que des preuves croissantes indiquent que l'âge influence l'organisation du cerveau (e.g., vers une organisation de plus en plus aléatoire, un traitement de l'information au sein du réseau moins efficace...) (Ishii et al., 2017), une augmentation de la connectivité a aussi été décrite (Biswal et al., 2010). Une augmentation de connectivité fonctionnelle n'implique donc pas nécessairement une meilleure performance lors d'une tâche, mais peut représenter une réponse compensatrice suite au dysfonctionnement de certains réseaux neuronaux, des changements développementaux liés à l'âge dans l'architecture des réseaux cérébraux, ou cela pourrait encore refléter les effets de la dégénérescence du cerveau ou de changements au niveau d'autres facteurs non neuronaux dus à l'âge (Ferreira and Busatto, 2013).

Dans le cadre de l'analyse de la connectivité fonctionnelle durant une tâche attentionnelle telle que l'ANT standard, une étude EEG a avancé qu'il est possible d'associer un circuit cérébral (dirigé) spécifique à chaque composante de l'attention (Anzolin et al., 2017). Par ailleurs, une étude de la connectivité fonctionnelle IRMf au repos a mis en évidence une corrélation positive significative entre l'efficacité locale de plusieurs régions spécifiques appartenant aux réseaux attentionnels intrinsèques (DAN et VAN) et les performances attentionnelles (évaluées via l'ANT). Dans la même optique, une étude évaluant la connectivité fonctionnelle IRMf au repos après performance de l'ANT auprès de sujets âgés (sains ou avec pathologies) renforce ces observations d'une association possible entre DAN et VAN et capacités d'attention (Zhang et al., 2015). Par exemple, chez les patients atteints de la maladie d'Alzheimer, la connectivité fonctionnelle était détériorée au sein des deux systèmes attentionnels, en lien avec une altération généralisée de l'attention visuospatiale et de ses trois composantes en particulier. Les individus avec troubles cognitifs amnésiques légers, quant à eux, ne présentaient qu'un déficit comportemental au niveau du contrôle exécutif, ce qui était reflété par une baisse de la connectivité fonctionnelle dans le DAN et une préservation ou renforcement dans le VAN (Zhang et al., 2015).

Finalement, le vieillissement impacte également la connectivité fonctionnelle liée à la préparation motrice (Hoffstaedter et al., 2015). Entre autres observations, des différences de connectivité dans la bande thêta durant la phase pré-mouvement de la main entre sujets jeunes et âgés a permis de mettre en évidence différents mécanismes d'interaction corticale qui sous-tendent la planification motrice dans ces deux populations (Frolov et al., 2020). Chez les jeunes, la connectivité fonctionnelle thêta accrue au niveau des électrodes médianes pourrait être interprétée comme une augmentation de la

facilitation perceptivo-motrice et de la mémoire de travail. Avec le déclin avéré de leur mémoire de travail, les sujets âgés ont montré une réponse motrice plus prolongée et associée à une augmentation du couplage entre électrodes centrales, bilatérales temporales et frontales. Cette connectivité fonctionnelle plus importante au sein des régions sensorimotrices durant la phase de préparation motrice indiquerait la prépondérance de mécanismes d'intégration sensorimotrice comme stratégie compensatrice chez les personnes âgées (Frolov et al., 2020).

### **5.3.3. Connectivité fonctionnelle dans la maladie de Parkinson**

Concernant la connectivité fonctionnelle chez les patients MP, les études réalisées sur le sujet sont encore trop peu nombreuses et les résultats de celles-ci encore trop divergents pour tirer des conclusions claires et définitives sur le rôle des analyses de la connectivité fonctionnelle et des réseaux associés dans l'étude de la pathophysiologie de la MP.

A propos de la connectivité fonctionnelle EEG à l'état de repos chez les patients MP (voir (Geraedts et al., 2018) pour une revue EEG), Carmona et ses collègues ont montré une augmentation de la cohérence interhémisphérique frontale dans les bandes delta et thêta comme changement précoce dans les patterns de connectivité des patients MP comparés aux sujets sains (Carmona et al., 2017). Une baisse de la connectivité fonctionnelle à l'état de repos entre les cortex frontal et pariétal gauches dans la bande alpha a également été associée à une dysfonction exécutive chez les patients MP non-déments (Teramoto et al., 2016). De surcroît, les patients MP sans déficit cognitif présentaient une activité bilatérale gamma plus élevée dans les régions cérébrales associées à l'attention dirigée vers le stimulus comparés aux contrôles, ainsi qu'une connectivité alpha2 plus importante entre le CPP gauche et le COF gauche qui sont tous les deux impliqués dans le réseau attentionnel dirigé vers un but (Bin Yoo et al., 2018). Par ailleurs, les réseaux au repos associés aux patients MP cognitivement normaux présentaient une intégration locale plus élevée que chez les contrôles sains dans toutes les bandes de fréquence (Utianski et al., 2016). L'impact du statut cognitif, du fonctionnement moteur et du traitement sur la connectivité fonctionnelle EEG reste à éclaircir puisque, dans le peu d'études qui ont traité ce sujet, le pattern de corrélation dépendait fortement du type de mesure de connectivité (Geraedts et al., 2018).

Plusieurs études MEG ont également investigué les réseaux à l'état de repos en recourant à des méthodologies diverses, ce qui peut expliquer certaines observations contradictoires concernant notamment les effets de la durée de la maladie, des déclin cognitif et moteur, mais aussi les

interventions thérapeutiques sur la connectivité fonctionnelle (voir (Boon et al., 2019) et (Pelzer et al., 2019) pour des revues). En comparaison avec les sujets contrôles sains, les patients de novo non traités présentaient une connectivité fonctionnelle locale et entre les ROIs plus élevée dans la bande alpha1 (Stoffers et al., 2008), une connectivité delta plus basse dans les régions parahippocampale et temporale, et une connectivité temporelle dans la bande alpha1 plus importante (Olde Dubbelink et al., 2013b). Ils montraient également une moins bonne efficacité locale, mais une efficacité globale préservée dans la bande delta, ainsi qu'une décentralisation du réseau (Olde Dubbelink et al., 2014). Dans cette population MP de novo, il a même été montré qu'une augmentation de la connectivité fonctionnelle interhémisphérique dans la bande alpha1 était positivement corrélée à une préservation cognitive (Stoffers et al., 2008). Les patients MP modérément atteints, de leur côté, présentaient une plus grande connectivité fonctionnelle locale dans les bandes thêta, alpha1, alpha2 et bêta (Stoffers et al., 2008; Cao et al., 2019).

Si l'on doit résumer ces résultats sur la connectivité fonctionnelle de repos dans la MP, des modifications de connectivité au sein de réseaux attentionnels, des désorganisations à la fois sur le plan local mais aussi global sont observées. L'impact du déclin moteur et celui du déclin cognitif semblent différents mais vont dans le sens d'une diminution de connectivité entre les différentes régions.

La connectivité fonctionnelle lors d'une tâche attentionnelle a été peu étudiée et encore moins dans la MP. Une étude en IRMf a examiné les réseaux attentionnels activés durant la tâche de l'ANT ainsi que leur relation avec les changements de connectivité fonctionnelle des réseaux au repos chez les patients MP (Boord et al., 2017). Ces derniers ont montré une plus grande activation de quatre régions appartenant au DAN et au FPN durant la tâche de résolution de conflit, comparés aux contrôles. De plus, la connectivité fonctionnelle de repos entre trois de ces régions et le DMN était réduite chez les patients MP, suggérant qu'une interaction altérée entre le DMN et les réseaux associés à la tâche attentionnelle pourrait impacter le contrôle exécutif chez les sujets parkinsoniens.

Concernant le lien entre connectivité fonctionnelle et MP lors de la réalisation d'une tâche motrice, ce sont principalement des études en IRMf qui l'ont investigué (Gao and Wu, 2016). Il a été rapporté que, durant la réalisation d'un mouvement auto-initié de la main, la connectivité fonctionnelle entre le striatum et les aires motrices corticales (i.e., M1, PMC et AMS) était réduite chez les patients MP (Wu et al., 2011). Une altération de la connectivité entre cortex préfrontal, PMC et AMS a également été observée (Rowe et al., 2002, 2010; Wu et al., 2010, 2011).

### **5.3.4. Connectivité fonctionnelle et freezing de la marche**

La connectivité fonctionnelle des réseaux neuronaux chez les patients MP+FdM durant l'état de repos a principalement été étudiée via l'IRMf (voir (Bharti et al., 2019c) pour une revue systématique). Comme principales observations, les MP+FdM présentaient une connectivité fonctionnelle anormale dans les réseaux frontaux et fronto-striataux, régions cérébrales responsables des capacités exécutives et attentionnelles frontales (Tessitore et al., 2012; Zhou et al., 2018; Bharti et al., 2019a; Maidan et al., 2019b), mais aussi au niveau des aires cérébrales postérieures plutôt qu'antérieures, spécialement dans l'hémisphère droit au niveau des réseaux pariéto-occipitaux qui sont des régions responsables des capacités visuo-spatiales (Tessitore et al., 2012; Canu et al., 2015). De plus, des altérations de la connectivité fonctionnelle de ces régions frontales et pariétales mais aussi des régions motrices (principalement l'AMS) avec les structures sous-corticales impliquées dans le réseau locomoteur (i.e., les régions locomotrices cérébelleuse et mésencéphalique, les NGC) ont aussi été observées pour les patients MP présentant du FdM (Fling et al., 2014; Vervoort et al., 2016; Wang et al., 2016; Bharti et al., 2019b; Potvin-Desrochers et al., 2019; Lench et al., 2020). La connectivité fonctionnelle impliquant le circuit limbique semble également pertinente pour étudier la pathophysiologie du FdM et conforter l'association entre l'anxiété et le FdM (Gilat et al., 2018a). Malgré la mesure directe de l'activité neuronale du cerveau et la haute résolution temporelle du signal EEG, moins d'études sur la connectivité fonctionnelle à l'état de repos calculée sur base d'enregistrements EEG chez les patients MP sont disponibles dans la littérature.

Concernant l'analyse de la connectivité fonctionnelle de repos en lien avec les capacités attentionnelles, Maidan et al. ont eu recours à la théorie des graphes pour examiner les différences entre MP+FdM, MP-FdM et contrôles âgés au niveau des réseaux attentionnels ventral et dorsal (Maidan et al., 2019b). Bien qu'aucune différence inter-groupe n'ait été observée pour le VAN, les patients MP+FdM montraient une efficacité globale associée au DAN davantage réduite comparée aux patients MP-FdM et contrôles, parallèlement à une efficacité locale plus importante par rapport aux contrôles. Ainsi, l'organisation altérée du DAN pourrait, en partie, expliquer la plus grande prévalence des épisodes de freezing chez les patients MP+FdM lors de situations de marche complexes, tandis que leur VAN inchangé pourrait partiellement justifier l'efficacité des indices externes sur la performance de marche des patients MP+FdM.

Finalement, la connectivité fonctionnelle durant une tâche s'apparentant à de la marche a également été étudiée chez les freezers. Une étude en IRMf, avec des pédales de pieds pour imiter la marche ainsi

qu'un paradigme de réalité virtuelle pour éliciter des épisodes de freezing, a permis de mettre en avant des anomalies de connectivité survenant au moment du phénomène de freezing (Ehgoetz Martens et al., 2018a). Durant les épisodes de freezing, la connectivité fonctionnelle était perturbée entre le striatum et le réseau du contrôle exécutif et réseau moteur, comparés au tapotement normal du pied. Toutefois, la connectivité fonctionnelle entre le striatum et le réseau limbique était renforcée. Certaines connexions fonctionnelles de ce réseau « signature » du freezing ont été associées à la sévérité du FdM (couplage entre réseaux cognitif et limbique), à une stratégie compensatrice (anti-couplage entre le putamen et les réseaux cognitif et limbique), ou étaient considérés comme indépendants de la sévérité du freezing (anti-couplage entre les régions cognitives corticales et le noyau caudé). Ces associations ont également été réalisées en considérant individuellement chacune des composantes qui définissent la sévérité du freezing (performances cognitive, motrice et affective), mettant à nouveau en avant l'hétérogénéité dans le phénotype du FdM et dans le réseau « signature » associé. Par ailleurs, il a également été trouvé que, durant une tâche d'extension des doigts (Brugger et al., 2020), la cohérence pré-motrice entre l'AMS et M1 dans la bande bêta était plus prononcée chez les MP+FdM que chez les MP-FdM. L'AMS fait partie d'un réseau qui modère principalement des mouvements auto-commandés, sans indiçage. Ce genre de circuit est typiquement perturbé chez les patients MP, et encore plus chez les MP+FdM.

## 6. Objectifs et hypothèses

L'objectif principal de la présente thèse est de mieux caractériser l'interaction entre initiation du pas et attention visuo-spatiale au niveau comportemental et cortical, en vue de tenter de la moduler à des fins thérapeutiques et ainsi réduire le risque de chute dans les populations concernées. A ce titre, nous formulons l'hypothèse générale qu'une charge attentionnelle appliquée durant l'initiation de la marche peut moduler les performances motrices, en particulier et de manière spécifique chez les patients parkinsoniens avec FdM.

Dans un premier temps, nous souhaitons réaliser un état des lieux des études s'étant intéressées à l'interaction entre attention et initiation de la marche et, plus particulièrement, via l'utilisation de DT. Autrement dit, une revue de la littérature est rédigée à propos des DT cognitivo-motrices incluant l'initiation de la marche, mais également une tâche posturale, la marche ou le tour comme tâche motrice chez les jeunes adultes. Dans ce contexte, nous passons en revue les théories neuropsychologiques proposées pour expliquer les effets (ou coûts) de DT obtenus dans la littérature, ainsi que les facteurs pouvant influencer les effets d'interférence en DT et, dès lors, expliquer le manque de consensus actuel sur les mécanismes de DT (**Etude 1.1**). Par la suite, en complément, nous poursuivons une revue systématique de la littérature afin de valider ou non le pouvoir qu'ont les DT cognitivo-motrices (incluant, entre autres, l'initiation de la marche) pour prévenir des chutes chez les personnes âgées non démentes (**Etude 1.2**). Le pouvoir prédictif de la simple tâche motrice est également comparé à celui de la DT pour démontrer ou non l'utilité du recours aux DT dans un examen clinique de routine.

Dans un second temps, nous mettons en place et testons chez de jeunes adultes un paradigme permettant d'évaluer sur un plan comportemental (via analyse du mouvement) et neurophysiologique (via activité corticale) l'interaction entre attention visuo-spatiale et initiation du pas, i.e. un paradigme combinant l'Attention Network Test et l'initiation du pas comme réponse motrice – « ANT-INIT » (**Etude 2**).

- **Objectif principal de l'étude n°2 :** déterminer si une modification de la charge attentionnelle peut moduler ou non l'activation corticale durant l'initiation de la marche via l'analyse des PE et PSLE liées à la réponse (i.e., début de l'APA).
- **Hypothèses :**

- L'activation des réseaux attentionnels modifierait la préparation corticale du mouvement, pouvant par exemple résulter en un BP de plus faible amplitude et une DLE alpha/bêta plus prononcée et plus longue pour la condition de cible avec conflit à résoudre (distracteurs non congruents) ou un BP et une DLE plus précoces dans la condition avec un indice précédant la cible.
- Une plus grande proportion d'APAs multiples dans la condition de résolution de conflit refléterait le contrôle précoce de la préparation du mouvement, tandis que la présence d'un indice pourrait induire un temps de réaction pour l'initiation du pas plus précoce.
- Objectif secondaire de l'étude n°2 (dans la partie *Supplementary material* de l'article, en annexes) : valider le paradigme étudié (ANT-INIT), qui combine l'ANT et l'initiation du pas, en obtenant des résultats liés à la cible similaires à ceux obtenus pour l'ANT standard assis ; c'est-à-dire, des résultats comportementaux et une activation corticale liés à l'influence de l'indiçage sur les réponses, à la discrimination perceptuelle de la cible, au traitement de l'information, à l'inhibition de la réponse prépotente et à l'exécution de la réponse correcte.

Ensuite, avant d'investiguer l'interaction attention-initiation du pas chez les patients MP+FdM, nous nous intéressons à mieux décrire et comprendre les mécanismes strictement posturaux et de préparation motrice associés au FdM (**Etude 3**).

- Objectif principal de l'étude n°3 : déterminer si une posture initialement altérée impacte les APAs et l'exécution du premier pas durant l'initiation de la marche chez les MP+FdM.
- Hypothèse : La position altérée du CoP des MP+FdM juste avant le début des APAs pourrait contribuer au couplage anormal entre préparation et exécution du premier pas au sein de cette population. Cette situation pourrait donc possiblement causer l'apparition d'une hésitation à l'initiation du pas chez les MP+FdM (ou épisodes de freezing).

Par après, l'interaction entre attention visuo-spatiale et initiation du pas est investiguée chez les MP+FdM en comparaison avec les MP-FdM et des contrôles âgés sains via l'utilisation du paradigme ANT-INIT (**Etude 4**). En effet, nous testons le contrôle exécutif, en particulier, combiné à l'initiation de la marche comme facteurs contextuels du FdM.

- Objectif principal de l'étude n°4 : déterminer, d'un point de vue comportemental et au niveau de l'activité corticale (PSLE liées à la réponse), si une charge attentionnelle (particulièrement,



une tâche demandeuse de contrôle exécutif) peut spécifiquement impacter les phases de préparation et d'exécution de l'initiation de la marche chez les MP+FdM.

- Hypothèse :
  - Le contrôle exécutif défaillant caractérisant les MP+FdM entraînerait une altération spécifique des APAs précédant le premier pas et/ou de l'exécution du pas lui-même. La charge attentionnelle durant l'initiation du pas pourrait ainsi entraîner des épisodes de FdM.
  - Similairement, en ce qui concerne l'activité corticale, nous nous attendons à une DLE bêta plus précoce, plus longue et moins prononcée avant l'exécution du premier pas chez les MP+FdM.

Dans une cinquième partie, nous désirons renforcer notre analyse de l'activité corticale chez les MP+FdM, en faisant fi des théories localisationnistes, en considérant le cerveau et ses fonctions comme des réseaux organisés et en poursuivant donc une analyse de la connectivité fonctionnelle (i) au repos, yeux ouverts (**Etude 5**), (ii) durant la réalisation de l'ANT standard assis (**Etude 6**).

- Objectif principal de l'étude n°5 : trouver un biomarqueur du FdM simple à obtenir pour améliorer sa compréhension, son diagnostic et son traitement, sur base de l'analyse des enregistrements EEG au repos : (1) via une analyse spectrale basique dans l'espace des électrodes, (2) à l'aide d'une analyse plus avancée de la connectivité fonctionnelle dans l'espace source.
- Hypothèse : en se basant sur les résultats de la littérature, nous supposons observer un ralentissement plus prononcé des oscillations au repos chez les MP+FdM comparés au MP-FdM, reflétant ainsi leurs fonctions cognitives plus impactées. De plus, nous nous attendons à retrouver une connectivité fonctionnelle anormale dans les réseaux frontaux, responsables des aptitudes attentionnelles et exécutives frontales, mais aussi plus dans les régions cérébrales postérieures qu'antérieures et, spécifiquement, dans les réseaux pariéto-occipitales de l'hémisphère droit qui sont responsables des compétences visuo-spatiales.
- Objectif principal de l'étude n°6 : déterminer l'existence ou non d'anomalies du point de vue de la connectivité fonctionnelle durant une tâche attentionnelle visuelle (ANT standard) chez les MP+FdM comparés aux MP-FdM et contrôles sains.
- Hypothèse : des anomalies en termes de connectivité fonctionnelle dans les réseaux exécutif et attentionnel des MP+FdM pourraient expliquer leur mauvaise performance comportementale lors de tests attentionnels.

A la fin du Chapitre 3, nous décrivons un protocole de recherche (**Etude 7**) qui a été entamé durant la période de doctorat. L'étude PACTE-I vise à moduler l'interaction attention-locomotion via la combinaison d'un entraînement cognitif structuré et d'un traitement au méthylphénidate chez les personnes âgées saines, afin d'améliorer leurs capacités cognitives globales et indirectement motrices (e.g., l'initiation de la marche).

Finalement, nous déterminons, à travers une discussion générale (Chapitre 4), les principales valeurs-ajoutées des études produites ainsi que les points de convergence et de divergence de leurs résultats avec ceux trouvés dans la littérature scientifique. Dans cette optique, les principales limites des designs des protocoles, des méthodes appliquées et des résultats obtenus sont également discutées. Finalement, des perspectives de recherche futures sont proposées.

# **Chapitre 2.**

## **MATÉRIEL ET MÉTHODES**

# 1. Participants

Chaque étude de recherche menée et les collections de données correspondantes sont conformes aux différents protocoles de recherche et aux considérations éthiques validées par les comités indépendants (CPP Nord-Ouest IV, Lille, France : 2015-A00013-46 et le CPP Ile-de-France X, France : 2016-005131-32). Tous les sujets inclus dans les différentes études menées dans le cadre de cette thèse ont donné leur consentement écrit en amont de chaque évaluation.

Certains critères d'exclusion communs à toutes les études ont été retenus pour les sujets étudiés : absence de troubles cognitifs (score au Montreal Cognitive Assessment/MoCA ou au Mini Mental State Examination/MMSE < 24), d'antécédents médicaux impliquant l'usage de médicaments pouvant interférer avec l'attention (neuroleptiques ou benzodiazépines) ou de déficiences visuelles non corrigées.

Des données démographiques et cliniques ont été récoltées dans le cadre de chaque étude telles que : le genre, l'âge, les antécédents médicaux ou la médication actuelle. Pour les participants MP, la durée d'évolution de la maladie et la dose journalière équivalente de lévodopa (*LEDD*) (Tomlinson et al., 2010) étaient calculées et ceux-ci étaient évalués en état « ON » de médication.

Les participants MP ont été définis selon les critères internationaux de Gibb ou de la UK Brain Bank. Les sujets ont été recrutés au sein du service de Neurologie et Pathologie du Mouvement du CHRU de Lille. La sévérité de leurs symptômes moteurs était évaluée par la troisième partie de l'échelle MDS-UPDRS (Movement Disorder Society Task Force for Rating Scales for Parkinson's Disease, 2003) et l'échelle de Hoehn et Yahr (Goetz et al., 2004). Le questionnaire du freezing de la marche (FOG-Q) (Giladi et al., 2000, 2009), et particulièrement son item 3, a permis de classer les patients MP en freezers et non freezers. En complément, le FdM était confirmé par l'historique médical des patients, mais également par l'observation d'épisodes de freezing pendant une trajectoire de marche conçue pour les déclencher (par exemple, un parcours impliquant une initiation de la marche, des tours rapides à 360° et 540°, des passages étroits ou des situations de double-tâche).

Globalement, divers groupes (sujets sains jeunes, âgés, MP+FdM et MP-FdM) ont été analysés pour chacune des études. La plupart des sujets ont été recrutés durant le doctorat, mais certaines données précédemment récoltées ont également été utilisées (notamment des données collectionnées par

Aurore Braquet pour l'étude n°2, et par Delval et al. (Delval et al., 2014a) pour l'étude n°3). Les détails correspondant à chaque étude sont disponibles dans le Chapitre 3.

## **2. Analyse de l'attention via l'*Attention Network Test***

### **2.1. L'ANT standard**

Dans la continuité des travaux menés par Posner et Petersen sur le modèle tri-dimensionnel descriptif de l'attention visuo-spatiale et mentionnés plus haut (Posner and Petersen, 1990; Petersen and Posner, 2012), l'équipe de Fan et al. a poursuivi des recherches mettant en lumière la possible interaction entre ces trois réseaux séparés anatomiquement (Fan et al., 2002, 2009). En effet, les différentes composantes de l'attention visuo-spatiale peuvent être étudiées à partir de l'*Attention Network Test* (ANT), qui permet une évaluation simultanée mais indépendante de l'alerte, de l'orientation et du contrôle exécutif, tout comme de leurs interactions (Fan et al., 2002). Habituellement, l'ANT dite « ANT standard » est réalisée en position assise à partir de réponses apportées par la pression des touches d'un clavier d'ordinateur. La description des différents intervalles de temps séparant indices et cibles dans notre version du paradigme de l'ANT standard est donnée en Figure 10. Des informations complètes et détaillées quant à la description du paradigme de l'ANT standard en lui-même, ainsi qu'à propos de l'évaluation de la précision et du score TR associé à chacune des composantes attentionnelles, sont consultables dans le manuscrit de l'étude n°2.

### **2.2. L'ANT-INIT**

Dans le cadre des études n°2 et 4 réalisées lors de ce doctorat (cf. Chapitre n°3), ce même paradigme a été couplé à une tâche motrice impliquant l'initiation du pas (l'ANT-INIT). Cette version modifiée de l'ANT combine donc une charge attentionnelle avec l'initiation du pas comme réponse motrice. Dans ce contexte, les participants sont positionnés debout sur une plateforme de force dans une position confortable et stable avec leurs pieds parallèles et écartés de quelques centimètres. Un écran d'ordinateur est placé à un 1 mètre d'eux. En lien avec la version assise de l'ANT (Fan et al., 2002), les sujets ont pour instruction de faire un pas en avant aussi rapidement et précisément que possible à la suite de l'apparition d'une cible visuelle (*target*). Ces instructions sont données afin de ne pas prioriser une amélioration du TR ou du nombre d'APA multiples. Par ailleurs, les sujets ont pour consigne de ne pas initier le pas lors de la présentation de l'indice (*cue*).

Plus précisément (cf. Figure 10), les participants ont pour instruction de fixer une croix située au milieu de l'écran. Un indice apparaît ensuite pendant 100 ms : soit un indice central, soit un indice spatial (une étoile située à droite ou à gauche de la croix de fixation). Dans la condition d'indice spatial valide, l'indice spatial est situé dans la même direction que celle de la cible (une flèche centrale pointant vers la gauche ou la droite et apparaissant à la suite de l'indice) ; alors que dans la condition d'indice spatial invalide, l'indice spatial est positionné dans le sens opposé. Après un temps aléatoire ou semi-aléatoire compris entre 100 et 700 ms, la cible apparaît, entourée de flèches pointant soit dans la même direction que cette flèche centrale (distracteurs congruents), soit dans la direction opposée (distracteurs non congruents). Cette cible est présentée à l'écran pendant 1500 ms et le participant a pour objectif d'appuyer sur une touche du clavier d'un ordinateur située soit sur la droite, soit sur la gauche.

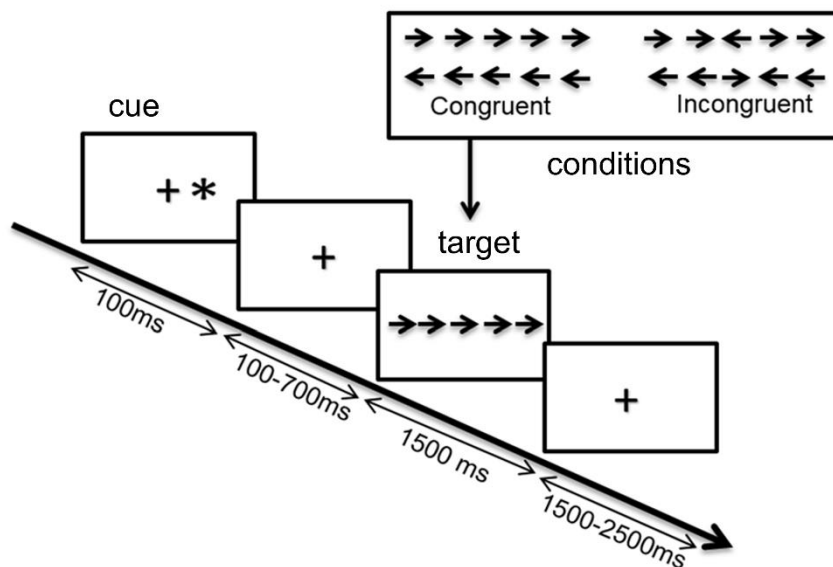


Figure 10 Description des temps de présentation des indices et cibles dans notre version du paradigme de l'ANT standard

### 3. Paramètres biomécaniques posturaux et de locomotion

Deux plateformes de force (modèles OR6 ou ORG-5 développés par AMTI, Waterton, Etats-Unis ; avec fréquence d'échantillonnage de 250 Hz ou 1000 Hz) et un système vidéo d'analyse du mouvement (VICON d'Oxford Metrics Ltd. et VICON 370 d'Oxford Biometrics, Oxford, Royaume-Uni ; avec fréquence d'échantillonnage de 50 Hz ou 100 Hz) équipé de 6 ou 8 caméras infrarouges sont utilisés pour évaluer la cinétique (posture initiale et APAs), mais aussi les mesures cinématiques de la phase d'exécution de l'initiation de la marche. Les deux systèmes sont synchronisés. Six marqueurs

sphériques et rétro-réfléctifs de 2,5 cm de diamètre sont placés bilatéralement sur des repères anatomiques précis et reproductibles sur chaque pied : la malléole latérale, les talons, et le bout du second métatarse.

Afin d'évaluer la préparation et l'exécution de la marche, différents paramètres spatio-temporels du premier pas sont extraits des données en utilisant une routine MATLAB (The MathWorks, Natick, MA, Etats-Unis) développée en interne et basée sur les méthodes présentées dans la littérature pour détecter l'initiation de la marche (Pijnappels et al., 2001; Ghoussayni et al., 2004; Sun et al., 2015; Honeine et al., 2016). Les données de chaque essai sont tracées et les détections automatiques des événements des phases préparatoire et d'exécution du premier pas sont vérifiées visuellement avant validation. Des informations complètes et détaillées quant aux méthodes d'analyse des données comportementales de l'initiation de la marche peuvent être retrouvées, en partie, dans l'étude n°2 (pour la phase de préparation et d'exécution du premier pas dans le cadre de l'ANT-INIT) et dans l'étude n°3 (pour la position moyenne initiale du CoP juste avant le début des APAs et l'analyse de l'initiation de la marche auto-commandée en général).

## 4. Analyse électroencéphalographique

Dans le cadre de 4 études de cette présente thèse ayant présenté des résultats EEG haute résolution (128 voies – études 2, 4, 5 et 6), les méthodes de pré-traitement et d'analyse étaient, autant que possible, communes. En voici les principales caractéristiques :

- La description des **phases d'acquisition et de pré-traitement** peuvent se retrouver dans l'article associé à l'étude n°2.
- L'**analyse des PE liées à la cible** et les analyses statistiques associées sont décrites au sein de l'article associé à l'étude n°2, dans la section *Supplementary material*.
- L'**analyse des PE liées à la réponse** et les analyses statistiques associées sont également détaillées au sein de l'article associé à l'étude n°2.
- Concernant l'**analyse des PSLE liées à la cible**, elle est expliquée dans la section *Supplementary material* de l'étude n°2.
- L'**analyse des PSLE liée à la réponse** diffère, quant à elle, entre l'étude n°2 et l'étude n°4 en raison du début de l'APA qui est plus tardif dans les groupes de patients MP.
- La **décomposition fréquentielle durant l'état de repos** afin d'analyser les puissances spectrales relatives dans chaque bande est détaillée dans le manuscrit de l'étude n°5.

- Une **localisation de sources** est, entre autres, décrite dans l'article associé à l'étude n°5 et recourt à un modèle BEM (*Boundary Element Model*) ainsi qu'à une image IRM standard du cerveau (ICBM152) pour résoudre le problème direct, tandis que le problème inverse est résolu via l'utilisation de la wMNE (*weighted Minimal Norm Estimate*). La description de cette étape d'analyse se retrouve dans l'étude n°5, entre autres.
- Enfin, l'**analyse de la connectivité fonctionnelle** (avec la méthode de *Phase-Locking Value / PLV*) au repos yeux ouverts (étude n°5) ne repose pas sur la même méthodologie que l'**analyse dynamique de la connectivité fonctionnelle** (étude n°6).



# **Chapitre 3.**

# **RÉSULTATS**

# **Etude 1.1 : Double tâche cognitivo-motrice incluant une tâche de marche, de posture, d'initiation de la marche ou des tours : cadre théorique**

“The interaction between cognition and motor control: A theoretical framework for dual-task interference effects on posture, gait initiation, gait and turning”

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Article publié dans *Neurophysiologie Clinique / Clinical Neurophysiology*.

DOI : <https://doi.org/10.1007/s00221-020-05739-5>

## **Apport personnel**

- Co-mise en place du plan de recherche.
- Recherche, sélection des articles et analyse du contenu.
- Rédaction de l'article et intégration des commentaires des co-auteurs et reviewers.

## **Résumé**

Les études sur les doubles tâches (i.e., les situations durant lesquelles un individu réalise deux tâches simultanément) et l'interférence entre tâches qui en résulte ont montré que la locomotion et la posture renferment des composantes motrices et cognitives. Les doubles tâches constituent dès lors une piste prometteuse pour améliorer le diagnostic, la prévention et la gestion des chutes ou des détériorations cognitives dans les populations à risque. Cependant, traiter ces enjeux majeurs de santé publique à l'aide d'interventions utilisant les doubles tâches demande une meilleure compréhension des mécanismes sous-tendant les interférences en double tâche. Dans ce contexte, nous avons passé en revue : (i) les principales théories sur les doubles tâches proposées à ce jour et (ii) les facteurs qui peuvent influencer les effets d'interférence en double tâche chez les sujets jeunes sains et qui pourraient dès lors expliquer le manque de consensus actuel sur les mécanismes de double tâche. Nous avons également considéré les doubles tâches cognitivo-motrices pour lesquelles la tâche motrice est un mouvement transitoire moins fréquemment étudié (comme l'initiation de la marche ou

les tours), plutôt que seulement la marche et les tâches posturales, déjà largement étudiées. En général, la revue s'est concentrée sur les effets comportementaux de la double tâche.

**Mots-clés** : marche, posture, initiation de la marche, tours, double tâche, attention.

## **Articulation avec le projet de thèse**

Malgré une hétérogénéité méthodologique parmi les paradigmes de DT, entraînant une divergence des résultats et ainsi un non-consensus concernant les mécanismes sous-tendant les effets (ou coûts, dans de nombreux cas) de DT, la DT cognitivo-motrice incluant l'initiation de la marche comme tâche motrice a été peu étudiée dans l'ensemble des articles répertoriés dans l'étude. Pourtant, il s'agit d'un mouvement de transfert indispensable pour éviter la chute, associé parfois à des coûts de DT plus importants qu'avec une DT cognitivo-motrice incluant la marche. Enfin, l'initiation de la marche peut être l'un des déclencheurs d'un épisode de freezing chez les MP+FdM.

Ces observations supportent l'idée, dans un premier temps, qu'une meilleure investigation de l'interaction entre attention et initiation de la marche est nécessaire, même chez les sujets jeunes sains, et valident ainsi la pertinence du sujet de thèse étudié au regard de l'actualité et des enjeux futurs de notre société. L'exploration des effets de DT pour mieux comprendre l'interaction attention-initiation de la marche semble donc indiquée.

Dans un second temps, la DT comme outil pour prédire le risque de chute chez les personnes âgées reste une question en suspens. Dans ce sens, il nous a semblé intéressant de réaliser une seconde revue de la littérature, systématique cette fois, pour y répondre. Nous nous sommes intéressés particulièrement au pouvoir prédictif des DT cognitivo-motrices avec initiation de la marche ou du pas et l'avons comparé à celui de la simple tâche d'initiation motrice. A nouveau, des DT cognitivo-motrices comprenant la marche, le contrôle postural et le tour comme tâche motrice ont également été étudiés chez les sujets âgés non déments au sein de cette revue.

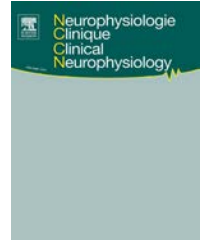


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COMPREHENSIVE REVIEW

# The interaction between cognition and motor control: A theoretical framework for dual-task interference effects on posture, gait initiation, gait and turning



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Received 6 October 2018; accepted 9 October 2018

Available online 26 October 2018

## KEYWORDS

Gait;  
Posture;  
Gait initiation;  
Turns;  
Dual-task;  
Attention

**Summary** Studies of dual-tasks (i.e. situations during which an individual performs two tasks simultaneously) and the subsequent inter-task interference have shown that locomotion and posture involves motor and cognitive components. Dual-tasks therefore constitute a promising avenue for improving the diagnosis, prevention and management of falls or cognitive impairment in populations at risk. However, tackling these major public health concerns with dual-task interventions requires a better understanding of the mechanisms underlying dual-task interference. In this context, we review (i) the main dual-task theories proposed to date and (ii) the factors that can influence dual-task interference effects in healthy young individuals and might therefore explain the current lack of consensus on the mechanisms of dual-tasks. We also consider cognitive-motor dual-tasks in which the motor task is a less frequently studied transition movement (such as gait initiation or turning), rather than only the often-studied gait and posture tasks. In general, the review focuses on the behavioral effects of dual-tasking.

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## Introduction

Gait was long considered to be a fully automatic task. However, it is now clear that cognition and motor control interact extensively. Indeed, in everyday situations with a variable degree of complexity, healthy older adults and patients with neurodegenerative diseases may present gait impairments that may even lead to falls. Healthy younger adults also change the way they walk (with regard to direction or speed, for example) when adaptation is necessary. Importantly, situations in everyday life often involve cognitive-motor dual-tasks, e.g. walking while talking, texting on a cell phone, or thinking about one's shopping list. Consequently, the assessment of cognitive-motor dual-tasks is of great interest for gaining a better understanding of cognition/motor control interplay and for improving the diagnosis, prevention and management of cognitive impairment and falls.

### Definition of a dual-task and its relevance in scientific studies

Dual-tasking (DT) situations (and especially cognitive-motor dual-tasks) are common in everyday life. Mclsaac et al. (2015) defined DT as "the concurrent performance of two tasks that can be performed independently, measured separately and have distinct goals" [53]. Dual-tasking can lead to a change in performance of the primary task (relative to single-task performance); this change corresponds to the cost of carrying out a second task concurrently and is termed "dual-task cost" (DTC) or, more generally, "dual-task effect" (DTE). Indeed, DT does not always result in a cost or a decay in function relative to single-task performance of one or both tasks; it can also lead to a performance benefit in some situations.

It is important to note that despite Mclsaac et al.'s proposed operational definition of DT, the use of this terminology is subject to debate. The difference between a dual-task and a complex single-task with two types of stimuli is not always obvious. For example, Mclsaac and colleagues considered (in contrast to most researchers) that carrying a glass of water while walking is a complex single-task (with a single action goal: transporting the water) rather than a dual-task. Mclsaac et al. also addressed the issue of measuring the performance of each task separately because not spilling the water requires postural control in the same way that gait does. Whereas the presence of obstacles, a dynamic base of support, a narrow pathway, visual manipulation of the environment, and even fast speed are commonly accepted in the literature as factors that impair gait and thus only increase the complexity of the motor task without resulting in a dual-task, the DT nature of situations with a motor task and cognitive overload is a greater matter of debate. These tasks involve time pressure or emotional or cognitive constraints; e.g. walking in time to a metronome beat, while listening to an emotionally charged sound recording or when responding to external visual, auditory or somatosensory cues. In view of these disagreements over DT terminology, the present review will adopt Mclsaac's definition of a dual-task (with the exception of walking while carrying a glass of water, which we include in the dual-task category). Indeed,

this paradigm is widespread and frequently studied in the dual-task literature. It can be perceived as involving two tasks with distinct goals (walking forward without falling, and holding a cup of water without spilling it) and separate assessment measures (i.e. various gait parameters, and the level of water remaining in the glass after a certain time). Depending on the characteristics of the study population, not spilling the water while walking will be associated with differing degrees of difficulty and automaticity (i.e. low or high levels of cognitive demand), and DTEs may or may not be observed. Indeed, carrying a tray with four glasses full of water will be totally automatic when performed by a waiter but will require much attention from older adult subjects with balance disorders or from patients with neurodegenerative disease [87].

In the particular case of a walking-cognitive dual-task, Yogev-Seligmann et al. (2008) reported that walking under DT situations always leads to deterioration in one or both task performances (the extent of which depends on the task and the population's age or disease status) – except when the cognitive demand is very low [110]. Yogev-Seligmann et al. therefore concluded that gait requires attention (the ability to divide attention, specifically) even in healthy adults with intact locomotor and cognitive functions. Otherwise, the simultaneous execution of an additional attentional task would not affect gait or task performance. On the same lines, DTCs usually increase as gait becomes less automatic – such as in older adults and patients with Parkinson's disease [110]. Lastly, an association between gait and executive function (EF) has also been demonstrated, as DT performance requires the integrity of EF [110].

With this in mind, one important reason for investigating DT during gait is the dual-task's important role as a useful clinical marker of both cognitive impairment and the risk of falls, since DT worsens potential cognitive and gait impairments [61]. Firstly, DT enables researchers to discriminate between older adults with mild cognitive impairment (MCI) or Alzheimer's disease (AD) and age-matched normal controls with regard to significantly different time-related gait parameters [62]. Dual-tasking can also distinguish people with MCI from patients with AD [17]. Secondly, Lundin-Olsson et al.'s (1997) seminal DT study found that stopping walking when talking was highly predictive of the risk of falls in frail older adults [50]. Individuals who stopped walking when talking displayed a significantly less safe, slower gait, and had a lower degree of autonomy in activities of daily living. Hence, DT can be viewed as an indirect means of evaluating the automaticity of a primary task by studying the level of performance of a concurrent task [86]. This potential prevention tool is simple and fast to use, does not require any equipment, and thus does not induce any costs. Furthermore, by highlighting the relationship between cognition and motor control and the variation in this interplay with age and disease status, DT can also play a role in rehabilitation [29]. Indeed, DT may help to gain a better understanding of:

- specific associations between gait parameters and executive components, and;
- the related neural correlates, with an ultimate aim of identifying key targets for therapy.

## Objectives of this review

For the reasons mentioned above, the field of DT has attracted growing interest over the last few decades. Hence, results need to be centralized for a better synoptic understanding of these investigations. However, all the reviews of this field are confronted with the same problem: the heterogeneity of the various populations and DT paradigms studied [2,74,84]. As a consequence, a number of questions regarding DT (such as the mechanisms underlying dual-task interference) still need to be answered – often because of a lack of consistency.

The objective of the present review is to first describe the models of dual-task interference developed to date and then to review the factors found to influence DTEs in studies of healthy young adults. In a novel approach, we shall assess the recent literature on cognitive-motor dual-tasks in which the motor task is a less frequently studied transition movement (such as gait initiation or turning) as well as those involving the often-studied gait and posture tasks. In general, the review focuses on the behavioral effects of DT.

A greater awareness of causes of variations in DT results will hopefully encourage researchers to standardize the parameters used in their dual-task studies or at least to report them accurately. These steps would facilitate inter-study comparisons, and thus would probably yield more consistent outcomes and a clearer understanding of the interactions between cognitive functions and motor control.

## The mechanisms underlying dual-tasks

Before describing the various theories used to explain interference in cognitive-motor dual-tasks, we provide an overview of the cognitive processes involved in concurrent tasks and possible patterns of dual-task interference.

### Concurrent cognitive tasks

Above, we described the proven relationship between motor control on the one hand and cognition on the other hand. Nevertheless, DT paradigms comprise various tasks that assess different cognitive functions; these tasks are often inappropriately compared in the literature. To resolve this problem, Al-Yahya et al. (2011) [2] published a classification that discriminates between cognitive tasks on the behavioral and/or cognitive level. Our modified version of this cognitive task classification is shown in Table 1.

On the basis of this classification, one can see that cognitive-motor dual-tasks most frequently studied in the literature involve a cognitive task that requires EF, attention or working memory.

### Executive function, working memory, and attention

Studying attention, EF or working memory in isolation is not easy because all three cognitive processes are closely related.

Executive function encompasses the higher cognitive processes involved in the cognitive control of non-routine, goal-directed behaviors. It comprises action initiation, response inhibition, planning, set-shifting, dealing with several sources of information, and response monitoring [5,48,51]. The domain of EF has also been extended to the behavioral changes observed in frontal lesions [90]. Likewise, recent aspects of control functions (such as social cognition, theory of mind, strategic processes in episodic memory, insight, and metacognition) have sometimes been incorporated into the domain of EF [33]. This cluster of functions integrates representational, somatosensory and motor components that modulate and produce behavior [110]. In order to deal with the wide range of processes involved in EF, Miyake et al. (2000, 2012) developed an empirical model of EF's three main components: shifting from one task/mental set to another, updating and monitoring of working memory representations, and inhibiting prepotent responses [58,59]. The three components were shown to be separable while being moderately correlated – supporting a concept whereby the executive system has both unitary and non-unitary components.

Working memory can be defined as the ability to temporary store and manipulate the information required for completing complex cognitive tasks, such as language comprehension, learning, reasoning, and planning [6]. This limited-capacity brain system has been extensively studied by Baddeley, and his model of working memory is still widely used today [3,4,7–9]. The model comprises four components: a verbal storage system called the phonological loop, a visual storage system called the visuospatial sketchpad, an episodic buffer (which binds information to form integrated episodes), and a central executive (which coordinates these three slave systems and thus controls and regulates cognitive processes).

Attention: van Zomeran and Brouwer (1994) addressed the difficulty of reducing attention to a single definition [113]. According to Kahneman (1973) and Corbetta and Shulman (2002) [22,40], attention corresponds to a cognitive process driven by a dynamic interaction between cognitive and sensory factors and which controls for the level of significance allocated to stimuli. In this context, focusing, selecting and/or inhibiting the available stimuli are the main functions carried out by attention. Attention and its components (sustained, selective, divided, and set-shifting attention) can also be conceptualized as the individual's information processing capacity during the performance of a task [104]. In particular, divided attention can be defined as the ability to perform more than one task at a time [110]. Attention therefore underpins EF in a critical manner. van Zomeran and Brouwer (1994) [113] developed a multicomponent model that is still widely used in psychology to report on the different subcomponents of attention (Fig. 1). The model is based on Posner's component theory (1971) [78], the selectivity and intensity aspects of attention developed by Kahneman (1973) [40], and the concept of the supervisory attentional system (SAS) developed by Norman and Shallice (1986) [68]. According to van Zomeran and Brouwer (1994), attention is divided into two neuropsychologically distinct dimensions, each of which is associated with a different underlying neural network:

**Table 1** A classification of cognitive tasks [2].

Category	Definition	Cognitive processes involved	Examples of cognitive tasks
Reaction time tasks	Tasks assessing the elapsed time between a single sensory stimulus and a behavioral response	Processing speed and vigilance/sustained attention	Push-button simple reaction time
Discrimination and decision-making tasks	Tasks that require selection of a specific stimulus (or feature) and production of a specific response to the stimulus	Selective attention and response inhibition	The Stroop paradigm Visuospatial decision tasks (e.g. the auditory clock task: listening to the time of day and determining whether the clock's hands are on the same side or different sides of the clock face) Color/number classification task: listening to auditory stimuli consisting of colors/numbers and answering "yes" or "no", depending on the stimulus Auditory choice reaction time task: reporting whether the pitch of an auditory tone is high or low
Mental tracking/working memory tasks	Tasks that require information to be kept in mind while possibly manipulating the information in a mental process	Sustained attention, information processing speed and working memory with its four components, according to Baddeley's model [3,7]: the central executive (CE), the phonological loop (PL), the visuospatial sketchpad (VSS) and the episodic buffer (EB)	Serial subtractions; → PL + CE Counting backwards; → PL + CE Backward spelling; → PL + CE Arithmetic tasks; → PL/VSS + CE Reciting the months of the year in reverse order; → PL + CE Repeating a series of digits forwards; → PL Counting how many times predefined words appeared in a text read aloud; → EB + CE Remembering a short item-shopping list; → PL/VSS Listening to a text and answering questions about it; → EB + CE
Verbal fluency tasks	Tasks that require the production of words spontaneously or under pre-specified search conditions	Executive function and semantic memory	Reciting words (e.g. names of animals or professions) with or without specific letters Simple counting Spontaneous speech task

- intensity, with alertness and vigilance/sustained attention as its subcomponents;
- selectivity, which covers focused and divided attention [113].

Firstly, an attentional task can be characterized by the intensity of the mental activation it requires. Intensity components of attention consist of tonic alertness (i.e. a relatively stable level of arousal that varies slowly with the organism's diurnal, physiological fluctuations), phasic alertness (i.e. the ability to increase the arousal level in response to a high-priority stimulus), and sustained attention (the ability to maintain attention over a long period of time during which, in the context of vigilance, infrequent response-demanding events arise). Secondly, selectivity allows an individual to orient his/her attention and to ignore

irrelevant stimuli on two levels; focused attention takes account of only one stimulus or one dimension of a stimulus (color, size, shape, etc.), whereas divided attention considers at least two stimuli or two relevant stimulus dimensions. Lastly, van Zomeren and Brouwer's attentional model (based on the theory developed by Norman and Shallice, 1986) comprises an executive component (the SAS) that manages attentional resources in complex, novel, non-automated or conflicting situations [68]. The SAS can modulate both the intensity and selectivity dimensions (Fig. 1).

On these lines, Norman and Shallice (1986) shed light on the existence of two levels of attention [68]. The lower level (contention scheduling) is used to address familiar and automatic situations (i.e. routines), while the higher attentional level (the SAS) is required to deal with more challenging and resource-demanding situations. It is interesting to note

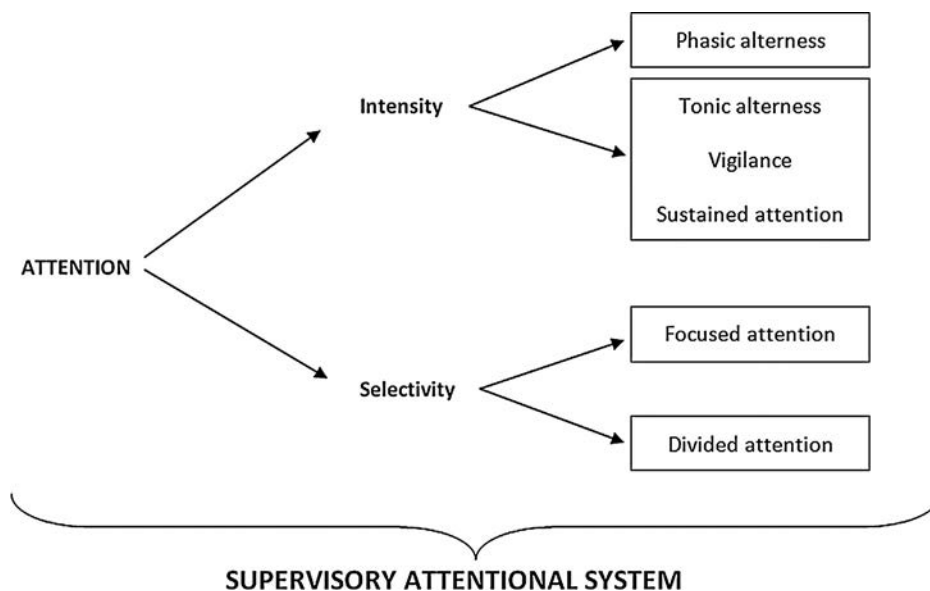


Figure 1 van Zomeren and Brouwer's model of attention [113].

the parallel between the latter neuropsychological model and the two distinct brain networks related to attention [22,28]. On one hand, the bilateral "dorsal attention network" (including the dorsal parietal and frontal cortices) may be involved in endogenous (goal-driven) attention with top-down stimuli detection, selection and responses. On the other hand, exogenous (stimulus-driven) attention with bottom-up detection and processing of salient or unexpected stimuli would be based on the right-lateralized "ventral attentional network" that includes the temporo-parietal junction and the ventral frontal cortex. Prefrontal regions of the cortex (i.e. middle and inferior frontal gyrus) are assumed to mediate the functional interaction between these networks because of their demonstrated correlation with both systems [28].

### Patterns of dual-task interference effects

Plummer et al. (2013) described nine potential patterns of interference (relative to single-task performance) during cognitive-motor DT: no interference, cognitive-related motor interference, motor-related cognitive interference, motor facilitation, cognitive facilitation, cognitive-priority trade-off, motor-priority trade-off, mutual interference, and mutual facilitation (Table 2) [74]. In this classification system, some patterns are more likely than others; overall, variability in patterns of cognitive-motor interference can be explained by the task specificity, individual characteristics, and differences in the measured parameters [74]. For example, Plummer and colleagues' (2013) review of studies in stroke populations found mainly cognitive-related interference and mutual interference patterns but also no interference, motor-related cognitive interference, cognitive-priority trade-off and cognitive facilitation patterns in the context of DT involving gait [74]. With regard to balance activities with an additional cognitive task, stroke patients presented various patterns of DT interference, such as cognitive-related motor interference, mutual

interference, motor facilitation and no interference. In a different disease area, patients with multiple sclerosis exhibited cognitive-related motor interference and mutual interference during dual-task walking, whereas cognitive-related motor interference, mutual interference, and motor facilitation were possible consequences of postural DT [99].

More recently, McIsaac et al. (2015) supplemented this dual-task interference classification by introducing a new dual-task taxonomy [53]. This classification of dual-tasks relies on the characteristics of the tasks and the performer, which lead to the various outcomes described by Plummer and colleagues. In other words, the classification considers each task's level of complexity (i.e. the task's constraints and environmental context) and novelty (i.e. the individual's previous experience with performance of the task). In the future, McIsaac et al.'s taxonomy will probably be expanded to include an index that reflects the similarity of neural structure engagement among tasks; the higher the "similarity index", the greater the putative interference effects.

By improving McIsaac's dual-task taxonomy with the other relevant factors of DT paradigms (reviewed below) and Plummer's classification of DT interference patterns, it should be possible to better understand the specific nature of DT-related interference effects with fewer disparities and uncertainties than at present.

### Dual-task theories

In general, several models have tried to explain dual-tasks and their effects in humans. However, there is no consensus on which theory best predicts the effects of DT [47,110]. The most widely accepted theories are summarized below (Fig. 2).

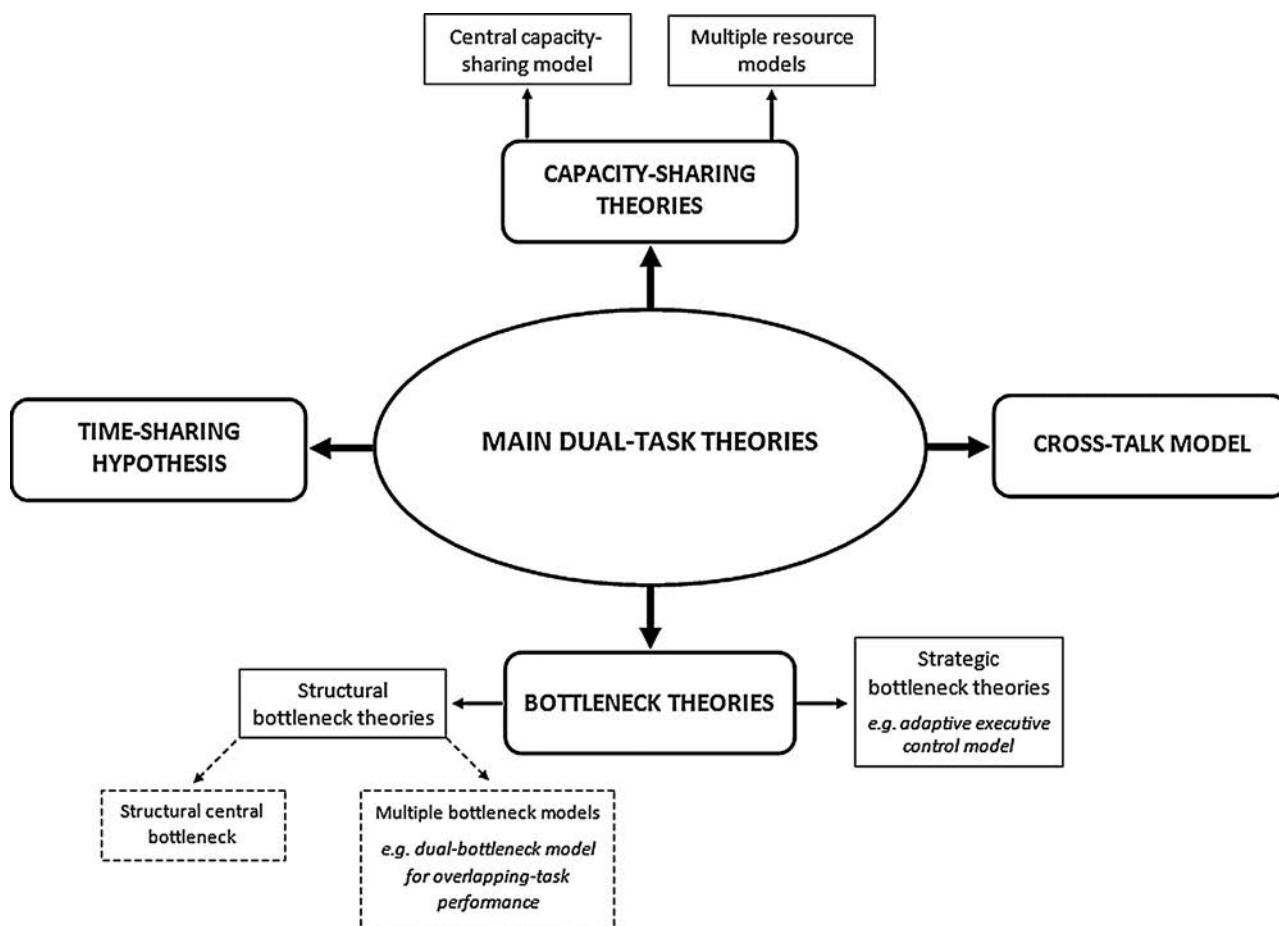
#### Capacity sharing theories

The central capacity sharing model [40,54,95] postulates that cognitive-motor interference is caused by a



**Table 2** The nine potential patterns of cognitive-motor interference proposed by Plummer et al. (2013) [76].

		Cognitive performance		
		No change	Improved	Worsened
Motor performance				
No change	No dual-task interference	Cognitive facilitation	Motor-related cognitive interference	
Improved	Motor facilitation	Mutual facilitation	Motor-priority trade-off	
Worsened	Cognitive-related motor interference	Cognitive-priority trade-off	Mutual interference	



**Figure 2** The main dual-task theories.

limited-capacity parallel processor that divides resources among to-be-performed tasks. This results in lower capacity for each individual-task and so the performance of at least one task will be impaired. When the time delay between presentations of two stimuli is reduced, there is an increase in the processing period during which capacity is shared between tasks; this leads to a rise in the overall time processing of the DT. This theory also predicts that it is also possible to voluntarily allocate capacity to a specific task.

While some capacity theorists claim that a single, central mental resource can account for performance limitations, extensions of the general capacity sharing model (multiple resource models [64,102]) postulate that task processing

may require multiple types of resources. Two tasks will interfere with each other if they require common limited resources. Otherwise, it should be possible to perform them concurrently without interference.

By way of an example, Künstler et al.’s recent results for a continuous motor tapping task and a simultaneous visual information uptake task performed by middle-aged to older adults supported the capacity sharing model [43]. Given that the researchers observed DTCs for visual processing speed and visual short-term memory storage capacity but not for perceptual threshold, they concluded that even the performance of this quite simple motor task required central attentional capacity that was also needed for visual information uptake.

### Bottleneck theories

In the bottleneck model, a deterioration in the performance of one or both tasks results from serial processing when the two tasks need the same neural processor or networks, or when the required networks overlap. In other words, certain processors act only on one input/task at a time. This leads to a bottleneck when processing information related to the two tasks and, ultimately, to a delay in or the impairment of one of both tasks [72,95].

One can further differentiate between structural [72,85,101] and strategic bottleneck theories [55,56].

On one hand, the general (or central) structural bottleneck model holds that so-called “bottleneck processors” are responsible for response selection and decision-making, whereas stimulus identification and response execution can operate in parallel [52,101]. However, as with resource limitations, single or multiple bottlenecks (related to different types of mental operations or different stages of processing) can arise [72]. Indeed, an example of another structural bottleneck model is the dual-bottleneck model for overlapping-task performance [23]. This model postulates the existence of a central bottleneck at the response selection stage and a late bottleneck at the response execution stage.

On the other hand, the adaptive executive control model [55,56] (a strategic bottleneck theory) postulates that under the right set of conditions, two tasks should virtually be able to share time perfectly. However, one or more of these conditions are usually violated, leading to the establishment of either a strategic bottleneck in controlling the response order or a peripheral bottleneck when both tasks require the same input and output processors. In contrast to the bottleneck processors in the general structural bottleneck model, strategic bottleneck processors can be invoked at any point in the information-processing stream.

A dual-task involving a visuomotor compensatory tracking task and a visual detection task in healthy young adults provided evidence of a response processing bottleneck and thus support for a bottleneck theory [30]. Indeed, increased tracking errors and decreased joystick speed were only observed under conditions with target stimuli.

### Cross-talk model

The cross-talk model predicts a sort of facilitation when two tasks are from similar domains and use the same neural populations, since the tasks would not disturb each other [65]. Indeed, use of the same pathway might increase the efficiency of processing by using less attentional resource capacity. This would explain the motor facilitation sometimes observed in patients with Huntington disease, for whom carrying a tray with glasses improves gait speed but counting backwards worsens it [24]. Once again, this motor facilitation was observed in some patients but not others – reflecting heterogeneity in individual processing and concurrent task automatization.

In addition to the three most influential DT theories, an interesting time-sharing hypothesis has also been proposed by Nijboer et al. (2014) [67]. The researchers’ objective was to explain the under-additive, additive and over-additive cortical activations that occur during DT and depend on the nature of the concurrently performed tasks. Firstly,

the time-sharing hypothesis postulates that time has to be shared between the two tasks. Therefore, brain areas that underlie only one task are less activated during a dual-task situation than during a single-task condition because they are less frequently accessed. Secondly, in the case of additive activation, one task does not take away time from the other; the two tasks share time and access to resources perfectly. Nijboer et al. also observed that the greater the resources overlap between two tasks, the greater the degree of interference and the higher the cumulative level of brain activation in overlapping brain regions. Thirdly, the time-sharing hypothesis postulates that over-additive activation is caused by additional processing stages not found in either single-task. In particular, the over-activity observed in visual areas during DT can be explained by the time taken away from a visual task involved in the DT condition, leading to a potentially greater error rate and thus a greater effort required to avoid these errors (Fig. 2).

### Dual-task paradigms

After having highlighted the discordance concerning the mechanisms underlying dual-task interference, we shall review factors that influence DTEs in dual-task paradigms performed by specific populations. Our goal is to better understand the variability in DT patterns and thus in neuropsychological theories. To this end, we shall focus on DT paradigms performed by healthy young adults and involving gait, gait initiation, posture or turns as the motor task; cognitive-motor dual-tasks with various motor tasks and the interplay between attention and motor control have been extensively studied in the literature.

### Motor tasks

#### Gait

Under standardized conditions (i.e. when the person does not have to take account of stimuli such as obstacles), walking is mainly under the control of subcortical locomotor brain regions and is therefore highly automatic and rhythmic [69]. However, several neuroimaging studies (using functional near-infrared spectroscopy, functional magnetic resonance imaging, electroencephalography and positron emission tomography) have evidenced the involvement of a large number of brain regions in walking performance (for a review, see Hamacher et al. (2015) [36]). These regions have been classified into a direct locomotion pathway (i.e. the primary motor cortex, cerebellum, and spinal cord) and an indirect locomotion pathway (i.e. the prefrontal cortex, premotor areas, and basal ganglia) [27].

In particular, it has been found that dual-task walking is associated with changes in the activation of the indirect locomotor pathway and the frontoparietal network (i.e. the cingulate cortex, parietal areas, and the insula) [36]. As mentioned above, these brain regions form part of the frontoparietal cortical regions associated with attention, working memory and EF. Together with the fact that the neural correlates of walking dual-tasks involve high level cognitive areas, the occurrence of cognitive-motor interference during DT reflects that gait requires cognitive control in general and attention in particular. Over the last decade,

a large number of studies have investigated the interplay between cognition and gait in dual-task paradigms [2].

In most dual-task studies, gait speed is the outcome of interest [75]. However, other kinematic variables (e.g. stride length) can be altered in PD [26] and other neurological diseases [29]. Interestingly, the spatiotemporal variability of gait is of relevance for discriminating between patients with MCI and healthy older adults and thus for predicting the fall risk in the older population [60,89].

### Gait initiation

As is the case for other voluntary movements, gait initiation is preceded by anticipatory postural adjustments (APAs). These adjustments are the main variables studied in paradigms involving gait initiation. They are thought to have two main roles: the correction of the a perturbation caused by the subsequent movement (this is not true for gait initiation) or the acceleration of movement by increasing imbalance [18]. Indeed, the nature of an APA's functional role depends on whether the voluntary movement modifies the base of support. When the base of support is displaced as during step initiation, APAs generate the initial propulsive forces required for forward body progression and play a role in the transfer of body weight during the stance-to-swing transition [18,58]. Anticipatory postural adjustments can be assessed by monitoring the stereotypical trajectory of the center of pressure (COP): a backward displacement toward the swing leg is followed by a lateral shift toward the stance leg. The start of the second phase of COP displacement is characterized by heel-off of the swing leg, while toe-off occurs at the end of this mediolateral COP displacement – just before the so-called “swing phase”. The latter follows APAs, and is characterized by a forward COP displacement until foot contact of the swing leg occurs [25].

Under certain conditions (e.g. choice reaction time paradigms [97] involving not only sustained attention but also other attentional components like orientation [94]), APAs may be first executed on the wrong side – i.e. towards the stance leg – and are subsequently corrected at the cost of an increased step latency. This type of APA is referred to as an “APA error” [21].

Furthermore, it has to be noted that APAs also occur during and after the end of a voluntary motion [108]: they are called compensatory postural adjustments and occur at the end of the first step. Their role is to brake the vertical fall of the center of mass. A comprehensive review detailing these aspects can be found in [109].

Even though relatively few research groups are studying gait initiation under DT situations in order to investigate the interaction between cognition and motor control, this is a promising field of research. Indeed, stepping initiation demands more attention than steady-state walking [92]; according to Uemura et al. (2012), dual-task interference may be more apparent during stepping initiation [96]. Accordingly, analyzing the effects of dual-tasks involving auditory [25,93] or visuospatial [94,97] concurrent attentional tasks has demonstrated that attention and its components can modify step preparation and execution. Gait initiation is a key paradigm because we all know how important it is to be able to take a quick step in order to

avoid falling over – regardless of the nature of the fall [13]. In this context, delayed step execution time in a stepping choice reaction time task was viewed as a strong predictor of falls in older adults [49].

### Posture

Posture has been defined as the spatial organization of the body segments [14,103]. In order to maintain an upright stance, the central nervous system (CNS) integrates a variety of sensory cues from visual, somatosensory and vestibular channels [31,63]. Sensory information may concern the body's orientation but may also be related to force vectors that trigger muscle activity [39]. Subsequently, the CNS couples the sensory information to muscle activity. In fact, the CNS must continuously scan the environment and adjust the body's posture as a function of often frequently changing demands.

The main problem with postural studies is that there is no consensus on the parameters that are relevant for the study of postural control. Most of these parameters are not redundant; hence, the minimum set of parameters required for the estimation of overall postural control is still subject to debate. Nevertheless, COP velocity and COP variability (the standard deviation or root-mean-square of the position, etc.) are the most frequently measured parameters in the literature.

If we focus our attention on a specific type of dual-task paradigms involving posture, models of dual-task performance will include the main DT theories described above in addition to other particular models. Again, there is no consensus on a suitable cognitive model that explains postural control in dual-task situations (for a review, see Bonnet and Baudry (2016) [15]). Almost all of the proposed models (other than the synergistic model [16]) suggest that above a certain level of complexity, the two tasks being carried out compete for attentional resources. Accordingly, the capacity sharing model [104] has been developed. Furthermore, the nonlinear interaction model [44] (with a proposed U-shaped relationship between postural control and cognitive demand) tries to explain why body balance improves when performing a relatively easy concurrent cognitive task but diminishes when the concurrent task's cognitive demand increases. The ecological approach is yet another model of postural DT performance [83]; it holds that “postural control is constrained by the perception of the kinematic consequences of control actions”. In other words, postural control may primarily enable and facilitate other activities. For example, marked sway induces saccade variability in a visual concurrent task. Thus, a stable posture would facilitate successful visual task performance [83]. Mitra et al. (2003) have suggested a hybrid DTC model that combines the concepts involved in the capacity sharing model with the ecological approach [57]. The problem with this hybrid model is that it mixes two antagonistic and indeed incompatible explanations of postural control under DT, namely:

- a deterioration in postural control (an increase in postural sway) from the capacity sharing model and;
- an improvement in postural control (a decrease in postural sway) from the ecological approach.

More recently, Bonnet and Baudry (2016) published a higher-order cognitive model of postural control that (unlike all the above-mentioned models) does not seek to quantify sway in one task relative to another [16]. In fact, the model focuses on the presence or absence of synergy between the sensory system and the postural control system. When individuals are performing a dual-task involving exploration of the environment with no specific goal, the synergistic model predicts the absence of a significant relationship between sensory and postural systems: the CNS easily controls the two systems individually. However, when individuals are carrying out a dual-task involving a precise sensory (visual, sound or haptic) interaction with the environment, the CNS controls the sensory and postural systems synergistically. By way of an example, the synergistic model predicts that if a healthy, young individual intends to perform a precise saccade  $10^\circ$  to the left and if his/her body oscillates by  $0.1^\circ$  to the left at the same moment, the saccade required to reach the target without correction should be  $9.9^\circ$  (and not  $10^\circ$ ). This new cognitive model has been tested in healthy young adults [16] and is now being studied in older adults and PD patients.

### Turning

In the field of dual-task gait, many researchers have investigated straight-ahead walking. However, transition movements during walking (such as turning) have not been addressed extensively, despite the frequency of these movements in everyday life. Turning is of special interest because this transient motor activity is closely linked to instability – even under single-task situations. This instability might result from the unique physiological and cognitive requirements of turns (relative to straight-ahead walking [38,70]), such as the cognitive processing of speed [70]. Indeed, it has been hypothesized [20] that turning is not an automatic process but requires cognitive processing (i.e. the integration of information from the visual, vestibular and somatosensory systems) throughout movement, so as to provide feedback and control the body correctly.

### Factors in dual-task paradigms that influence interference effects

The dual-task interference effects reported in the literature are not always consistent because of inter-study differences in the study populations (e.g. demographic aspects, a history of falls, balance-related confidence, level of physical activity, general health, symptoms of depression, health-related quality of life, and motor and cognitive abilities) [35,76], measurement parameters [10] and specific features of the dual-task paradigm. In the following section, we shall review how DTEs in healthy young adults are influenced by:

- the motor task conditions;
- the nature and complexity of the concurrent cognitive task, and;
- the instructions given before and during the task.

### The motor task conditions

The conditions and nature of the motor task are known to influence interference effects in cognitive-motor DT – even in healthy young adults.

Interestingly, Wrightson and Smeeton (2017) suggested the presence of different top-down control strategies as a function of the walking task's modality and thus novelty (e.g. treadmill vs. over-ground walking) in healthy young adults [105]. Despite the absence of differences in perceived task difficulty and cognitive task performance between these dual-task walking paradigms, stride time variability was greater for dual-task over-ground walking (but not for treadmill walking) than in the single-task walking condition.

Furthermore, walking conditions appear to influence the DTCs, since they increase the complexity of the motor task [10,12,19,41]. Beurskens et al. have reported on a main effect of the walking condition (e.g. walking along a wide, narrow or obstructed pathway) on both motor DT cost and overall DT cost (i.e. an average measure of both motor and cognitive DT costs). This effect was consistently observed across dual-task walking conditions that involved different secondary cognitive tasks. Walking along a narrow pathway seemed to have the most negative impact on DT performance in healthy young participants [10].

The walking direction (forward, backward or sideways) also leads to differences in dual-task interference effects [1], with more pronounced motor DTCs for backwards walking than for forward gait and even higher DTCs for sideways walking vs. backwards walking in healthy older adults. The greater DTC for backwards walking vs. forward gait had previously been reported for healthy older adults by Hackney and Earhart [34]. These findings might be due to the novelty and complexity of such motor tasks.

Furthermore, Patel et al. (2014) suggested that walking speed has an impact on cognitive task performance during DT. With high-complexity cognitive tasks (such as the Stroop task), slow walking enables to divert greater attention to the cognitive task; in turn, this produces a lower cognitive cost of dual-task walking and a greater motor cost [73]. In the case of less complex cognitive tasks (such as visuomotor reaction time tasks), healthy young adults prioritized the walking task under a slow speed dual-task condition, in order to maintain the intended, self-selected, slow speed during DT.

Postural dual-tasks and the related DTCs also depend on the postural task's complexity. For instance, changes in the base of support and visual manipulation influence the DTE in healthy young adults – even though these interference effects varied from one study to another because of likely differences in other experimental parameters (such as the cognitive concurrent task or the instructions given) [46,80–82]. Even though changes in the conditions for gait initiation and turning have not yet been thoroughly assessed, a recent study of a complex gait initiation task with walkway obstruction in young individuals [37] reported that the APA phase (but not the reaction time phase or cognitive task performance) slowed as the complexity of the motor task increased.

## The type and complexity of the concurrent cognitive task

### Gait

In the context of walking dual-tasks in healthy young individuals, Beurskens et al. (2012) have demonstrated that gait impairments depend on the type of concomitant task [11]. More particularly, the researchers found that a concurrent motor task (e.g. hand engagement) had a greater negative impact on walking than a complex cognitive secondary task involving EF (e.g. a go/no-go task) did. This finding can be discussed in the light of the above-mentioned multiple resource models or structural bottleneck theories of attention. Indeed, it has been suggested that a walking task and a concurrent motor task share more cognitive resources because they both require motor control. Consequently, the resulting dual-task interference is greater than that related to a cognitive concomitant task, and performance decrements in both motor tasks are more pronounced. However, these results contrast with Walshe et al.'s (2015) report of higher DTCs for a concurrent task involving EF (relative to a non-executive motor task) [100]. It is difficult to draw firm conclusions about the difference in impact between a motor and a cognitive concurrent task because:

- the tasks' level of complexity and novelty influences the DTCs and biases the comparison, and;
- motor tasks always feature a cognitive component to some extent.

In the specific case of a cognitive concurrent task, Patel et al.'s (2014) study in healthy young adults found that the prioritization of cognitive task depends on the type of cognitive task [73]. While simultaneously walking and performing a Stroop task, the young adults prioritized the complex cognitive task over the motor task. However, they prioritized gait when carrying out a dual-task with a visuomotor reaction time task as the concomitant cognitive task. The capacity sharing theory explains these observations by either:

- the supposedly less challenging nature of the visuomotor reaction time task (relative to the walking task) and individual's ability to voluntarily regulate the allocation of attentional capacity, or;
- the use of greater processing resources (i.e. the extensive network of brain areas involved) in the Stroop task than in the other cognitive tasks studied.

Furthermore, Al-Yahya et al.'s (2011) review suggested that a dual-task walking condition in which the cognitive task involves internal interfering factors (e.g. mental tracking tasks) would induce greater gait disturbances than when the cognitive task involves external interfering factors (e.g. a reaction time task) [2]. This would also suggest that higher-order shared networks induce greater interference than lower-order shared networks.

Moreover, Oh and La Pointe (2017) have recently evidenced the impact of cognitive load on gait parameters in a dual-task walking paradigm [71]. Indeed, as the complexity of the concurrent cognitive task rose, young healthy

adults showed a lower Functional Ambulation Profile score, a lower velocity, a shorter stride length, and a greater double-support time. As a lower Functional Ambulation Profile score has been linked a risk of future injurious falls [66], a high cognitive load while walking might be associated with a greater risk of injurious falls.

### Posture

Overall, the outcomes reported in the literature on dual-task postural control differ from one study to another, due to differences in the type of tasks, the sensory modality solicited by the concurrent task, the task's responsiveness, the instructions given, and the nature of the cognitive resources used [79].

With regard the concurrent task's sensory modality, Redfern et al.'s results suggested that postural control would give greater weight to the sensory channel that is significant for both posture and the concurrent task. In other words, a sensory channel required for balance would enhance information processing more than another sensory channel. Since vision is known to be more involved than audition in balance, sensory channels might be shared between the postural task and a concurrent visual task; hence, there would be less interference than with a concurrent auditory task [79]. Therefore, performing a concurrent task that presents sensory conflict with balance could have a negative impact on postural control during a dual-task. This effect might be exacerbated in older adults with reduced sensory abilities, and might lead to poor balance and falls.

Furthermore, Lajoie and colleagues have suggested that the discrete vs. continuous nature of a concurrent cognitive task has an effect on postural control; in young adults, continuous cognitive tasks were associated with more efficient postural control than discrete tasks were [45]. These findings confirm the idea that continuous tasks facilitate automatic postural control by reducing conscious postural control.

Lastly, Boisgontier et al.'s (2013) literature review emphasized the importance of the choice of both the main postural task and the concurrent cognitive task [14]. Indeed, sensitivity to age-related impairments in DT increases with the complexity of the postural task (e.g. an unstable surface, or visual manipulation), and especially with the complexity of the concurrent task [14,79].

### Turning

The nature and complexity of the concurrent task have not yet been thoroughly investigated in the context of dual-tasks involving turning in healthy young adults. However, as has already been seen for gait and posture, dual-task processing appears to depend on the type and complexity of the secondary task. Porciuncila et al. (2016) studied interference effects in dual-task processing during specific phases of a dual-task timed up-and-go test in healthy younger and older adults [77]. The DTCs were calculated from the duration and peak trunk velocity of each phase. The researchers found that the DTCs associated with a manual secondary task were situated between those associated with a cognitive secondary task and a cognitive-manual secondary task; cognitive-manual secondary tasks having showed the highest DT interference.

## The task instructions

### Gait

The instructions given before performing a walking dual-task also influence gait performance, although the influence differs in healthy young adults vs. older adults. Yogeve-Seligmann and colleagues tested the impact of instructions before a DT walking condition in which a verbal fluency task served as the concurrent cognitive task [111]. The researchers asked the participants to prioritize either gait, the cognitive task, or neither. Task prioritization tended to alter gait speed (the outcome) more in healthy young adults than in older adults. Hence, in young adults, the gait speed was significantly higher when gait was prioritized than in the absence of specific prioritization, and tended to diminish when the cognitive task was prioritized. The lesser influence of prioritization instructions on gait speed in older adults might be due to an age-related decline in the ability to flexibly allocate attention to one task or another. Secondly, gait variability was affected only in healthy older adults and, particularly, increased in the same way under all DT conditions compared to the single-task condition. There was therefore no effect of instructions on gait variability. Indeed, older adults seem to have more difficulties for maintaining a “posture first” strategy under DT conditions, whereas gait variability in healthy young people is regulated in a largely nonconscious/automatic way. Lastly, Yogeve-Seligmann et al. (2010) found more changes in gait speed with respect to task prioritization in young women than in young men but were unable to find a clear explanation [111]. Kelly et al. (2010) observed similar DT performance in healthy older adults in response to instructions [42].

### Gait initiation

It is noteworthy that the effects of dual-task interference on gait initiation depend (at least in part) on the strategy used. For example, in the particular case of a choice step execution task (i.e. a dual-task involving gait initiation and a flanker interference task), the participants can choose to prioritize speed (motor task prioritization) or accuracy (cognitive task prioritization) or to aim at a speed-accuracy trade-off [98]. Such a strategy can be imposed by giving specific instructions to the participants. In Uemura et al.'s (2013) study of the instructed prioritization of speed over accuracy in healthy young adults, the researchers observed a shorter RT, swing phase and total step execution time but a greater APA error rate under conflict resolution conditions, compared with the accuracy strategy [98]. However, the step error rate did not differ significantly as a function of the instructions.

Later, Sun and Shea (2016) demonstrated that as well as depending on instructions and environmental factors, task prioritization is also related to the complexity of the step initiation task and concurrent cognitive task, and the APA error rate [91].

### Posture

With regard to the effects of instructed prioritization of one task over another, Yu and Huang (2017) have recently reported that (in contrast to a posture-focused strategy) a supraposture-focused strategy (i.e. a focus on the

concurrent task) was associated with better postural and concomitant task performances in both healthy young adults and older adults performing a posture-motor dual-task [112]. The prioritization of the concurrent task could thus be used as a tool for fall prevention in DT situations. Yu and Huang's results [112] are consistent with the constrained-action hypothesis proposed by Wulf and Prinz (2001) [106]. It should be noted that a similar effect was not observed when the participant focused on a cognitive suprapostural task [112].

### Turning

Concerning dual-tasks involving turns, Smith et al. (2017) [88] observed a significantly more consistent walking turn performance (90° ipsilateral walking turns at a controlled speed of 1.5 m/s) under a dual-task condition involving divided attention (a verbal two-back working memory task) in young healthy individuals instructed to prioritize the cognitive task over the walking turn. In particular, step length variability decreased significantly with divided attention. These results were consistent with Wulf's (2013) [107] statement that motor performance and learning are enhanced when attention is redirected from an internal focus (i.e. a focus on body movements) to an external focus (i.e. a focus on the movement effect) – perhaps because of greater automaticity of the walking turn performance under this condition. With regard to prioritizing the cognitive task, Smith et al. (2017) also found no change in two-back task accuracy but did observe significantly lower intersegmental coordination variability due to divided attention [88]. Although an optimal level of stride-to-stride coordination variability is necessary to ensure an adaptable use of degrees of freedom and therefore correct turning during gait, the lower variability in intersegmental coordination appears to be still enough to consistently improve walking turn performance under DT conditions. Smith et al. observed a less pronounced effect of divided attention on joint excursion.

## Conclusion

Experiments in dual-task situations have shown that not only attention but also other cognitive processes have important roles in posture and locomotion in healthy older adults and especially in patients with neurological disorders. Dual-task paradigms also allow one to measure disability and to monitor disease progression and the effectiveness of interventions. Ultimately, behavioral data and neural correlates related to DT might prompt the identification of key targets for diagnosis and therapy.

Nevertheless, a number of shortcomings persist in the literature with regard to movements of the lower limbs performed under dual-task conditions. Consequently, these shortcomings prevent us from drawing firm conclusions about the specific associations between EF and gait.

Firstly, too many studies still omit to report important details of the DT procedure – details that might enable a clearer analysis of the study outcomes. For example, several studies have not reported dual-task costs of the concurrent task. Nevertheless, cognitive DTCs are essential for understanding the prioritization strategy chosen by the participants and for discriminating between

populations. Moreover, all the variables likely to influence dual-task effects and reported here should always be reported, in order to achieve replicable results.

Along with missing data, there is also a lack of standardization among dual-task paradigms. Inter-study differences variously concern the walking modality (treadmill vs. over-ground), walking conditions (wide, narrow, or obstructed pathway), walking direction and speed, task prioritization instructions, the nature and level of difficulty of the concurrent task, and consistency of the attentional load during DT performance (e.g. discrete vs. continuous cognitive tasks). However, we are now aware of the influence of all these variables on DTEs. Furthermore, this influence depends on the nature of the motor task. The choice of different measurement parameters can also emphasize various DTCs. As we gain more knowledge about gait during DT, researchers should start to normalize their methodology and thus be better able to compare their findings correctly.

Other limitations on inter-study comparisons include variability in the characteristics of individuals – even for those who supposedly belong to the same group. Indeed, too few studies have considered the contribution of individual characteristics – such as physical and cognitive impairments, age, concomitant medications, latent variables (e.g. fatigue, emotional state, motivation, pain or anxiety), and the perceived complexity of both walking and concurrent cognitive tasks – to DTEs during gait. By way of an example, trained athletes are subject to lower DTCs than healthy but sedentary adults [32].

Moreover, many studies performed in the laboratory lack ecological validity. In this respect, the use of mobile brain-body imaging (involving a mobile EEG system and inertial measurement units) appears to be very promising. Pressure-measuring insoles are also likely to have a promising future in home-based measurement.

Lastly, little research has focused on DTs involving gait initiation or turning as the main motor task. However, these motor tasks appear to be able to detect DT interference with high sensitivity. Therefore, future work should seek to better understand step initiation and turning DTEs, and to standardize dual-task methodologies. This standardization might then allow researchers to confirm literature data on a larger scale and thus to identify diagnostic and therapeutic targets with more confidence. For example, an agreement on a standardized DT paradigm for detecting older adults at risk of falls would help to solve this major public health issue. At present, a few therapeutic approaches seek to affect gait indirectly via cognition. Cognitive training and cognitive enhancers (e.g. methylphenidate, cholinesterase inhibitors, and memantine) are encouraging avenues of investigation but have yet to be assessed in large clinical trials in this field.

## Funding

Madli Bayot received a grant from the EU. The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 721577.

## Disclosure of interest

The authors declare that they have no competing interest.

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## **Etude 1.2 : Les paradigmes de double tâche peuvent-ils mieux prédire les chutes chez les personnes âgées saines que la simple tâche ? – Revue systématique des doubles tâches cognitivo-motrices incluant une tâche de marche, de posture, d’initiation de la marche ou des tours**

“Can dual-task paradigms predict falls better than single task? – A systematic literature review”

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Article publié dans *Neurophysiologie Clinique / Clinical Neurophysiology*.

DOI : 10.1016/j.neucli.2020.10.008

### **Apport personnel**

- Co-mise en place de la méthodologie de recherche.
- Recherche, sélection des articles et analyse du contenu.
- Rédaction de l’article et intégration des commentaires des co-auteurs et reviewers.

### **Résumé**

Environ un tiers des adultes âgés de 65 ans ou plus chutent chaque année à travers le monde et ce chiffre augmente encore davantage à mesure que l’âge avance. De ce fait, les chutes liées à l’âge et les conséquences en termes d’invalidité ou de mortalité représentent un enjeu important de santé public. Dans ce contexte, l’identification des risques de chute chez les adultes âgés sains est une composante majeure de la prévention des futures chutes. Puisque les résultats de double tâche reposent sur l’interaction entre la cognition et le contrôle moteur, des études ont démontré le rôle des performances (ou coûts) en situation de double tâche incluant une tâche de marche dans la prédiction des chutes.

Néanmoins, sur base de précédentes revues de la littérature sur le sujet, les pouvoirs (1) discriminatif et (2) prédictif des doubles tâches impliquant la marche et une tâche concurrente sont toujours

sources de débat, tout comme (3) leur supériorité sur les simples tâches en termes de prédiction du risque de chute. Par ailleurs, une attention moindre a été portée sur les doubles tâches impliquant un contrôle postural ou des transferts (tels que l'initiation du pas et les tours) comme tâche motrice.

Dans cet article, nous avons systématiquement passé en revue la littérature récente des 7 dernières années afin de répondre aux trois questions mentionnées plus haut concernant les doubles tâches réalisées en laboratoire (impliquant la posture, l'initiation de la marche, la marche et les tours) en tant que tests facilement applicables pour identifier les adultes âgés sains qui chutent. Comme résultats, malgré une grande hétérogénéité entre les études incluses, nous avons mis en évidence, entre autres, la valeur ajoutée prometteuse des doubles tâches impliquant des tours et autres transferts (tels que le test Timed Up and Go) pour la prédiction des chutes et donc, la nécessité d'investigations plus poussées à cet égard.

**Mots-clés :** marche, posture, initiation de la marche, tours, double tâche, chutes, vieillissement.

## **Articulation avec le projet de thèse**

Dans le contexte de la prédiction des chutes chez les personnes âgées non démentes, l'initiation de la marche ou du pas est finalement très peu étudiée en DT, mais plutôt soit au sein d'une tâche complexe, soit au sein d'un paradigme avec deux tâches successives, une charge attentionnelle appliquée sur l'initiation de la marche dans les deux cas. Toutefois, les DT semblent prometteuses pour la prédiction des risques de chute chez les sujets âgés et nécessiteraient d'être davantage investiguées afin de permettre de réaliser une méta-analyse par la suite et de faire ainsi évoluer le domaine de la prévention des chutes via le développement de tests cliniques simples et efficaces.

Forts de ces deux revues de la littérature, l'impératif d'une exploration « complète » de l'interaction entre attention visuo-spatiale et initiation du pas (et ses phases de préparation et d'exécution) du point de vue des conséquences comportementales et des mécanismes neurophysiologiques sous-tendant l'interaction s'est renforcé. Le test d'un paradigme adéquat pour l'étude de l'impact d'une charge attentionnelle sur l'initiation motrice est donc le sujet de la prochaine étude. Ce test est réalisé pour une première fois sur des jeunes individus sains.



# Can Dual-Task Paradigms Predict Falls Better than Single Task? – A Systematic Literature Review

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## **Abstract**

With about one third of adults aged 65 years and older being reported worldwide to fall each year, and an even higher prevalence with advancing age, aged-related falls and the associated disabilities and mortality are a major public health concern. In this context, identification of fall risk in healthy older adults is a key component of fall prevention. Since dual-task outcomes rely on the interaction between cognition and motor control, some studies have demonstrated the role of dual-task walking performance or costs in predicting future fallers. However, based on previous reviews on the topic, (1) discriminative and (2) predictive powers of dual tasks involving gait and a concurrent task are still a matter of debate, as is (3) their superiority over single tasks in terms of fall-risk prediction. Moreover, less attention has been paid to dual tasks involving postural control and transfers (such as gait initiation and turns) as motor tasks. In the present paper, we therefore systematically reviewed recent literature over the last 7 years in order to answer the three above mentioned questions regarding the future of lab-based dual tasks (involving posture, gait initiation, gait and turning) as easily applicable tests for identifying healthy older adult fallers. Despite great heterogeneity among included studies, we emphasized, among other things, the promising added value of dual tasks including turns and other transfers, such as in the Timed Up and Go test, for prediction of falls. Further investigation of these is thus warranted.

**Keywords:** gait, posture, gait initiation (GI), turns, dual task (DT), attention, falls, ageing

**Short running title:** Predictive value of dual task on falls in healthy older adults

## **Introduction**

Falls are the second leading cause of accidental or unintentional injury deaths worldwide, and these fatal falls are mostly prevalent in older adults. Indeed, approximately one third of individuals aged over 65 years are reported to fall each year, and even more with increasing age [14,22,73], leading to frequent injury-related hospitalizations, disability, loss of independence and increased mortality [31,86]. Fall risk and its prevention represent a major public health concern. Age-related cognitive and physical declines tend to increase risk of falling, directly through poorer motor performance and indirectly through cognitive ageing [50].

### ***Cognitive-motor Dual Tasks and Ageing***

In this context, the paradigm of dual tasks (DT) involving gait has increasingly been investigated over the last decade because of its valuable role as a clinical marker of both cognitive impairment and fall risk [66]. Indeed, dual-tasking situations, i.e. “the concurrent performance of two tasks that can be performed independently, measured separately and have distinct goals” [56], are common in daily life, especially those involving the simultaneous performance of a cognitive and a motor task. Except in the case of a low cognitive demand from the concurrent task, DT walking always leads to a dual-task cost (DTC) even in healthy young adults, that is, a decay relative to single-task performance of one or both tasks [105]. Other motor tasks such as postural tasks [17,29,74,75,84], gait initiation (GI) [25,58,59,87] or turning [23,72,88] can be used to evaluate these DTC. The physiological substrates for these motor tasks are the locomotor regions, which are widespread and thus quite commonly implicated in tasks requiring postural and motor control [91]: the temporo-parietal association cortex for production of cognitive information based on integration of signals from sensory cortex, prefrontal cortex for intention and planification, premotor cortex and supplementary motor area for motor programs, motor cortex for motor command, basal ganglia involved in both automatic and voluntary movement control, as well as the cerebellum for time regulation and feedforward control of ongoing movement, and brainstem and spinal cord for postural control and automatic process of gait. The only difference between various motor tasks would concern the degree of activation of these neural substrates, which depends on the complexity of the task (depending itself on the environment, context and individuals' capabilities). In that way, DT outcomes rely on the interplay between attention and motor control. For example, the recently described motoric cognitive risk syndrome is characterized by cognitive complaints and slow gait, and allows identification of non-demented older individuals at high risk for transitioning to dementia [1]. This demonstrates the interplay between various gait parameters and cognitive functions in elderly people and the added value of gait measurements to assess cognitive impairment.



Since the seminal article of Lundin-Olsson et al. (1997) [52] demonstrating that stopping walking when talking was a sign of fall risk in elderly, it has been proposed that an inability to produce an appropriate postural response to a DT may be due to competition for attentional resources between the postural system and the cognitive task, which increases risk of falls in older adults [104]. DT can affect motor performance differently with ageing. According to the systematic review of Al-Yahya et al. [2] and various subsequent studies [13,54,101], higher DTCs while walking have mostly been shown in healthy older adults compared to young subjects: e.g., greater decrease in gait speed, step length, step duration and concurrent task performance, and higher increase in number of steps. However, some authors found no age-related differences in terms of DTCs on gait velocity [41] or higher DT effects on average stride time in healthy young adults compared to older adults [54]. In fact, the association between age and DT interference effects may vary according to the population (frail versus non-frail older adults, age range, etc.), the type and complexity of the motor task and the cognitive concurrent task, and instruction of task prioritization [2,12,15,106]. Regarding task prioritization strategy without any specific given instruction, despite reduced abilities in reallocating cognitive resources during DT walking in healthy older adults compared to healthy young subjects, studies on DT walking initially suggested that both age groups adopt a common strategy: “posture first” [83]. Both young and older healthy adults would give priority to the stability of gait when simultaneously walking and performing a concurrent cognitive task. However, after noticing that even healthy young adults do not always prioritize gait [27,54], Yogev-Seligmann et al. (2012) [106] proposed a model of task prioritization taking into account the motor and cognitive capabilities of individuals such as postural reserve (i.e., subject’s capability to respond most effectively to a postural threat), hazard estimation (i.e., awareness of one toward himself and toward the situation and the environment), expertise (skills regarding the task), mood and personality, and nature and complexity of the secondary task.

### ***Cognitive-motor Dual Tasks and Prediction of Falls***

The role of DT paradigms in fall risk assessment is still unclear and discrepancies in the literature remain. Do DT-related changes or DT performance discriminate fallers from non-fallers? Are DT-related changes or DT performance predictors of falling? Is the DT-related predictive strength superior compared to the single-task (ST)-related one? Indeed, since 2008, seven systematic literature reviews (and four related meta-analyses) [11,24,46,60,68,103,108] have attempted to answer these questions, the last review that did not exclusively focus on walking DT having been written in 2016 [68].

From these reviews (see Table B.1 in the Supplementary Material section), we can conclude that, despite a few exceptions such as in Beauchet et al. (2008a) [9] and in Swanenburg et al. (2010) [90], most studies considered cognitive-motor dual tasks as predictors of falls in older adults. However, reviews that have attempted to determine whether DT performance or DT-related changes (changes

in performance under DT situation compared to ST condition) represent an added value for fall prediction in comparison with the corresponding single tasks either showed a negative result [60,103] or were not able to conclude [46,68,108]. On the one hand, results from reviews that did not find any superior predictive power for DT compared to ST using meta-analysis [60,103] need to be interpreted with caution. Indeed, these meta-analyses included a majority of retrospective designs for the reporting of fall history and used the mean difference as an appropriate statistical measure for discriminative ability. Thus, it is the discriminative power of DT performance (compared to that of ST) that has been assessed, more than its predictive value for fall risk. Interestingly, in Menant and colleagues' meta-analysis [60], the prediction stayed invariant when only prospective falls studies were kept. On the other hand, inconclusive reviews [46,68,108] reported some cases where DT paradigms involving gait and a mental tracking task such as backward counting [10,38,63,97] or a verbal fluency task [97] and measuring walking speed [10,97] or gait variability [38,63] were better able to predict fall risk than single tasks. The same systematic reviews [46,68,108] also presented studies reporting similar predictive power for DT and ST [6,18,28,57,82]. These studies included dual tasks with the Timed Up and Go (TUG) test, walking back and forth, quiet standing and stepping reaction responses in standing as motor tasks, and mental tracking, verbal fluency, and discrimination and decision-making tasks as the concurrent cognitive task. Therefore, in order to obtain an added value of DT performance for fall prediction over ST performance, DT walking would seem to be a better choice than dual tasks involving postural control, gait initiation or turns. Nevertheless, this cannot be firmly stated, considering the small number of consistent studies investigating such kind of primary motor tasks. Further research is needed for validating the latter observation.

Overall, discrepancies in the literature concerning the potential superior association between DT walking and prediction of falls in comparison with ST can be explained by different parameters characterizing studies: heterogeneous populations, various definitions of fall, retrospective and prospective designs, various sample sizes and follow-up periods, lack of standardization of DT methodology, and various outcome measures. Gait speed assessments, for example, showed equivalent ability in discriminating elderly fallers from non-fallers for ST and DT paradigms [60,103]. Moreover, the form of the assessed DT outcome (i.e., absolute values, relative values, thresholds) and the statistical measures for sensitivity-to-change, discrimination or predictive ability vary among articles. Finally, the type of the cognitive tasks used as well as their level of complexity could also influence the resulting predictive values and should be adapted to the studied population. For instance, Chu et al. (2013) found that, contrary to verbal fluency and manual tasks, mental tracking tasks were the only type of concurrent tasks related to a significant predictive strength for falls [24]. On the contrary, Menant et al. [60] could not differentiate ST and DT performances regarding their

predictive power for fall risk, even when comparing specific types of concurrent task, i.e. mental tracking tasks versus verbal fluency tasks. The team of Wollesen (2019) observed, for its part, an insignificant trend for increased DTC in fallers for verbal fluency and motor concurrent tasks [103]. Performance of both motor and cognitive tasks was not always reported, withholding information about strategy of task prioritization that might discriminate fallers from non-fallers in some cases. Besides, as suggested by Zijlstra et al. (2008) [108], the inconclusive results concerning the predictive power of DT for future falls in healthy older adults may be related to the existence of different fall risk factors such as muscle weakness, impaired vision and poor peripheral sensation [51] that may not all be taken into account at once through a unique DT test. Therefore, only a subgroup of fallers that have increased attention demands for motor control would be identified through a DT assessment.

### ***Objectives***

On that basis, the main objective of this review was, through a systematic review of the recent literature, to better define the role of DT in assessing the fall risk in healthy older adults, without cognitive impairment (i.e., mild cognitive impairment, dementia or neurological conditions) and/or known gait disorders. Even if DT walking conditions as well as cognitive-postural DT are mostly studied, other kinds of cognitive-motor dual tasks such as DT involving GI and turning were also explored here in order to determine if one type of DT could be more promising than another in fall risk assessment. Indeed, given that more than half of all falls of community dwellers aged 85 years and older occur at home and most often in the bedroom [65], not only straight forward walking but also standing and transfers can be associated with high fall risk in healthy older adults.

### **Methods**

#### ***Search Strategy***

This systematic review was performed in order to answer the three previously asked questions regarding cognitive-motor dual tasks involving gait, GI, posture and turning as the motor task. The most recent systematic review investigating falls and cognitive-motor DT with gait, GI, postural control but also turning as primary motor task was published in 2016 [68] and looked at articles with dates of publication up to September 2013. For this reason, we chose to systematically add articles that were published between January 2013 and June 2020 while studying the questions stated above.

In this context, we used PubMed, Cochrane CENTRAL, Scopus, Web of Science and Google Scholar as electronic databases. We did not have access to EMBASE but the use of Cochrane CENTRAL and Scopus that partly include records from EMBASE was an appropriate alternative. The search strategy was based on the PICO (Population Intervention Comparison Outcome) framework in order to formulate a well-structured question related to the problematic of interest [61]; i.e., Population: healthy older

adults, Intervention: cognitive-motor DT, Comparison: single tasks, Outcome: fall-risk prediction. In this line, the search terms were adapted to the assessed motor task and the chosen database. These keywords are summarized in the Table A.1 in the Supplementary Material section.

### ***Inclusion and Exclusion Criteria***

Inclusion criteria for the selection of an article were related to different domains: (1) the objective: relative to the potential predictive power of DT regarding fall risk or to their ability to discriminate between fallers and non-fallers, with or without a comparison with the predictive strength of ST; (2) the studied population: relatively healthy older adults (60 years-old and older or with a mean age of at least 65) without cognitive or gait impairment caused, for example, by neurodegenerative diseases and therefore, without any use of an assistive device for walking (e.g., cane or walker); (3) the assessment tool: detailed DT combining gait, GI, posture or turning with a concurrent cognitive task (a secondary motor task being also accepted) and performed in a lab environment; (4) the study design: prospective and retrospective recording of falls; and (5) the language: paper written in English. Concerning exclusion criteria for selection, articles that aimed to assess the ability of DT to prevent falls as well as interventional studies were rejected. Furthermore, review papers or studies with a secondary analysis of previously reported results or being already part of systematic reviews published prior to 2013 were not included in the systematic literature review.

### ***Quality Assessment***

The risk of bias was assessed for each selected article by the Quality in Prognostic factor Studies (QUIPS) [36,37]. This tool is based on six risk of bias domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding (adjustment for other prognostic factors), and statistical analysis and reporting. From two to four domains with moderate bias or from one to two domains with high bias, we considered the quality of the study to be moderate. A high-quality study was associated with less bias, whereas more bias led to classify the paper as an article of poor quality. Two reviewers (MB and LD) independently performed this quality assessment, with any potential discrepancy resolved thanks to a third independent reviewer (AD).

### ***Data Extraction***

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; [64]) guidelines were followed in order to clearly report the results of our systematic review. Among others, the PRISMA flow diagram was used (see Figure 1) in order to illustrate the process of manuscripts selection. After having performed searches within the selected databases by using the search strategy previously described, duplicates were removed. Subsequently, two independent reviewers (MB and LD) screened articles via their title and abstract and selected them based on the inclusion and exclusion criteria.

Afterwards, other papers were excluded after full-text check if considered to be irrelevant regarding our criteria or with high risk of bias. Again, in case of any disagreement regarding articles selection, a third independent reviewer (AD) was asked to help for solving it. Once all the articles were selected, we extracted a range of information from each paper: authors, year of publication, study design, sample size, sample demographics (gender distribution, mean age, residential setting, cognitive screening, inclusion and exclusion criteria), method of fall ascertainment, fall outcome measure, fall definition, months of follow-up, proportion of fallers, DT test (motor and cognitive tasks descriptions, with details on how the test result variables were used in the analysis; same as for the ST test), instructions of prioritization, statistical results from the study regarding discriminative and/or predictive power of DT (over ST), answers to the three questions asked in this systematic review, risk of bias related to the article (QUIPS score), and limitations of the study. Cognitive tasks involved in DT test were classified according to the system developed in [8] and adapted from [2]. This classification was also used for detailing the previous systematic review on the topic (see Table B.1 in the Supplementary Material section).

## **Results**

Thirty studies were selected according to selection criteria (Figure 1). As expected, a greater number of articles related to walking DT (sixteen studies; see Table 1 or more detailed Table C.1 in the Supplementary Material section) were found in comparison with the other sorts of cognitive-motor DT involving GI (one paper; see Table 2 or more detailed Table D.1 in the Supplementary Material section), postural control (seven papers; see Table 3 or more detailed Table E.1 in the Supplementary Material section) and turns (six papers; see Table 4 or more detailed Table F.1 in the Supplementary Material section).

### ***Dual-task Walking***

In the context of DT involving gait, three selected manuscripts [32,44,45] also referred respectively to outcomes from a previous study from the same research group on the same amount of subjects from the same dataset, but with other research questions and methodologies [33,42,43]. Only the recent studies were thus included, at the expense of the previous ones, but all the results were considered. Among the sixteen selected papers that included cohorts from 27 to 1350 older adults (with a mean age exceeding 65 years and a healthy cognitive status), nine were retrospective, whereas the others had a prospective design. Information regarding fall occurrences was collected thanks to questionnaires, interviews, postal surveys, calendars, phone calls or diaries. Regarding the walking task being part of the DT condition, subjects were mainly asked to walk straight forward on the ground at self-selected comfortable speed, and sometimes on a narrow path [34], avoiding obstacles or reaching

targets [19]. According to our classification of concurrent cognitive tasks ([8], adapted from a previous one proposed by Al-Yahya and colleagues [2]), eleven studies investigated walking DT involving mental tracking/working memory tasks [7,19,21,26,32,34,35,53,62,98], while one [40] and four [30,44,45,69] papers respectively studied a discrimination and decision-making task and verbal fluency tasks as cognitive tasks. One study compared two concurrent tasks: a verbal fluency task and a motor task [30]. Finally, in terms of strategies of task prioritization between both simultaneously performed tasks, instructions were either not given or indicated equal prioritization. Most DT walking studies (eleven out of twelve) agreed on the power of DT walking in discriminating between fallers and non-fallers (i.e., presenting DT-related parameters that significantly differ between both groups), except in a single study from this systematic review [30]. Moreover, the predictive power of DT walking for future falls was also confirmed in most papers included in the present review (eleven out of twelve), with few exceptions such as in Gimmon et al.'s manuscript [34]. However, as in previous reviews, we obtained inconclusive results concerning the superiority or added value of DT over ST tests in terms of fall prediction in healthy older adults. Indeed, based on the ten recent studies that attempted to answer this particular question, only five of them [7,32,35,47,98] showed the superior predictive strength of DT over ST, two articles observed the same predictive value of both ST and DT [19,45], and three studies demonstrated the superiority of ST over DT in terms of fall risk prediction [21,34,44].

### ***Dual Tasks Involving Gait Initiation***

When searching for studies assessing gait initiation (GI) DT, only one prospective study [20] was found to instruct participants to perform a real DT test according to the definition from McIsaac et al. (2015) [56]. Falls were reported via postal surveys, a falls calendar, as well as phone calls. One hundred and twenty-four cognitively healthy participants, with a minimum mean age of 70 years in each group, were assessed. As motor task, subjects were asked to start walking straight forward in response to a buzzer activated at random times, whereas the concurrent cognitive task was a mental tracking/working memory task. Instructions of prioritization were not given or at least, not reported. DT involving GI seem to be useful tools for identifying future fallers. As conclusions, Callisaya et al. [20] showed that their DT paradigm involving GI was a good predictor of future falls, but no improvement of the prediction value compared to the ST alone was observed.

### ***Postural Dual Tasks***

Among the papers that have investigated the predictive power of postural DT for risk of falls, one of them [76] also related the results from a previous study led by the same research group on the same data [77]. The cohort used in Zhou et al. (2017) [107] was based on the population analyzed in Kang et al. (2013) [48], but with additional subjects, for which reason we considered these two articles

separately. Five studies were designed as retrospective studies [55,76,79,96,102], whereas the two others were prospective [48,107], with information about falls provided through interviews, falls calendar or phone calls. The populations involved ranged from 23 to 738 cognitively healthy older adults, aged on average from 69 to 81 years. Regarding the postural task, quiet standing with eyes open was performed in all the selected studies, except for that led by Westlake and colleagues [102], where postural stability had to be maintained under predictable and unpredictable perturbations. Moreover, the postural DT condition was compared with a walking DT condition in the works of Rinaldi et al. [77] and Santos et al. [79]. In terms of concurrent tasks, four studies used a mental tracking/working memory task (backward counting and 1-back verb generation task) [48,55,102,107], but a verbal fluency task [102], a discrimination and decision-making task [96], and a grasping task [76,79] were also carried out. While participants were clearly instructed to prioritize balance over the concurrent task in the context of two studies [48,96], either no instructions of prioritization were given or no instructions were reported in the others. In terms of outcomes, recent literature concerning postural DT seems to confirm the fall-risk discriminative (six studies out of six [55,76,79,96,102,107]) and predictive (two papers out of two [48,107]) power of such tasks in healthy old people (see Table 3). However, their superiority over single tasks is still a matter of debate (demonstrated by one manuscript [107] out of two prospective studies).

### ***Dual Tasks Involving Turns***

Finally, there were 6 papers studying DT that involve turns as the motor task: from 36 to 649 older adults participated and the maximum mean age was 82 years. Four [3,4,71,93] and two [5,67] papers presented results from studies with respectively a retrospective design and a prospective design. Falls were described via self-administrated questionnaires, interviews, phone calls or diaries. All the studies asked to perform a Timed Up and Go test (TUG test, a test that includes walking, turning and transfers) or a walking task with turns [67]. The latter study used different DT paradigms with straight walking with or without obstacles, walking with turns, stair descent or TUG test as primary motor task. The concurrent task was a motor task in three papers [3,67,71], a mental tracking/working memory task in five manuscripts [3,5,67,71,93], and a verbal fluency task in one study [67]. No instruction for prioritizing one task over the other was found in any of the articles. In terms of the questions asked in the context of the present systematic review, five papers out of a total of five respectively agreed on the fall-risk discriminative [3–5,71,93] and predictive [4,5,67,71,93] power of DT involving turns. Besides, among five articles that compared DT and ST in terms of fall prediction, four concluded in favor of the DT condition [4,5,71,93] and the last one was inconclusive [67].

## **Discussion**

### ***Dual-task Walking***

When considering recent literature over the last 7 years, only one study [30] out of twelve did not agree on the power of DT walking in discriminating between fallers and non-fallers. Various explanations can be proposed regarding this controversial result: healthy older adults that only fell once were studied; a relatively easy verbal fluency task (naming animals without repeating names) and motor task (transferring a coin from one pocket to the other) were used as concurrent tasks; and fallers might have prioritized the walking task over the concurrent task, unknown information since the concurrent tasks were not assessed separately.

Moreover, a paper written by Gimmon and colleagues [34] was the sole recent study (out of twelve selected studies) that did not confirm the predictive power of DT walking for future falls in healthy older adults. This latter study investigated a DT involving a narrow path walking test simultaneously performed with three different mental tracking/working memory tasks. While trial velocity during both ST and DT conditions similarly remained significantly slower in fallers compared to non-fallers after adjustment for covariates (with no added value of DT over ST condition in identification of fallers), significant predictive abilities (in terms of area under the curve or AUC) were found for ST trial velocity, but not for DT trial velocity. This might be due to the difficulty of the walking task alone that could already be interpreted as a DT. By consequence, a ceiling effect might have been observed under the DT situation that could be rather considered as a triple task.

However, inconclusive results were obtained concerning the superiority or added value of DT over ST tests for predicting future falls in a population of healthy older adults. All the studies that demonstrated the superior predictive strength of DT over ST presented a prospective design (except the paper from Halliday et al. [35]), allowing to induce causal inferences. They also all investigated DT conditions with a mental tracking/working memory task as a concurrent task. The DT-related gait parameters that seemed to be good predictors of future falls were: poorer performance in the PCA-derived DT pace domain (including velocity and step length) [7], increased variability (coefficient of variation; CoV) [47] for step width, step length [35,47], step time, stance time, stride time, stride velocity and swing time [35,47], and symmetry DTC [32]. Moreover, Verghese et al. (2017) did not observe any change in gait pattern under DT conditions, but higher prefrontal activation levels on fNIRS during DT walking [98]. In a second study [32], Gillain and colleagues used a supervised machine learning algorithm (J48 classifier) in order to build a classification tree for identifying future fallers. The obtained model included: symmetry DTC, stride length in fast walking ST, stiffness, mean MTC (minimum toe clearance) in normal speed walking ST, MTC CoV DTC, MTC variance and mean MTC in



fast walking ST, difference between maximum and mean MTC in DT and gender. Although the sample size was small, with more non-fallers than fallers, and no external validation was performed in another independent sample, this classification tree showed good performance, with an accuracy of 84%, a sensitivity of 80%, a specificity of 87% and an area under the ROC (receiver operating characteristic) curve of 0.84.

On the contrary, articles that either observed the same predictive value of both ST and DT [19,45] or the superiority of ST over DT in terms of fall risk prediction [21,34,44] were all designed as retrospective studies, except for the study of Howcroft and colleagues (2018) [45]. These conclusions have thus to be taken more cautiously in view of possible inaccurate recall of falls and changes to gait patterns between falls and gait assessment either due to fear of falling or in order to increase stability after a fall. Indeed, Howcroft et al. (2018) [45] have demonstrated, on quite similar data collections, that the study design has an impact on gait differences between fallers and non-fallers. The studies that did not observe a significant added value of the use of DT over ST tests for prediction of fall risk involved a mental tracking/working memory task [19,21,34] or a verbal fluency task [44,45] as a concurrent cognitive task. Some gait parameters that were shown to be better predictors of future fallers under the ST condition compared to the DT situation were: slower ST trial velocity versus slower DT trial velocity (assessed via ROC curves and related parameters) [34], and longer time for ascending stairs compared to slower DT walking speed (evaluated by a multivariable logistic regression model) [21]. Furthermore, ST sensor-based gait assessment models (including 30 pressure insole parameters and 29 accelerometers parameters at different body locations) were demonstrated to outperform models based on DT walking (on the basis of supervised machine learning models such as multi-layer perceptron neural network, naïve Bayesian, and support vector machine) [44]. Afterwards, the same research group (Howcroft and colleagues) did not find any difference in terms of predictive strength between normal walking and DT gait, when similarly analyzing prospective data [45]. In this way, through a binary logistic regression analysis and investigation of ROC curves, Caetano et al. did not allocate greater predictive power of fall risk to gait adaptability test (walking with/without obstacles and/or targets) performed under DT condition compared to ST gait adaptability test. This might be due to the fact that the ST test can be understood as a DT situation and thus, ST velocity would already be a sufficient predictor of fall risk.

The above results should be cautiously interpreted because of discrepancies across studies regarding population, study design, DT paradigm, measurements and statistical analyses. In this regard, interesting findings have been reported. Firstly, DT decrements seem to be greater in women than in men, inducing a greater risk of falls in females and explaining therefore their higher fracture risk [47]. Secondly, the use of a cognitive concurrent task seems more appropriate than a manual task for

predicting falls in older adults walking. Indeed, although Freire et al. (2017) [30] did not manage to discriminate fallers from non-fallers under DT situations, they showed a significant larger reduction (DTC) in step length in older adults during the cognitive-motor DT condition in comparison with the motor-motor DT condition, as well as a greater DTC (i.e., DT-related increase) in stride time variability in non-fallers performing the cognitive task instead of the manual task while walking. Muhaidat and colleagues, for their part, found the best predictive values for walking while avoiding a moving obstacle as well as for a triple-task test that consists in straight walking while performing a visuospatial clock task and carrying a cup [67].

### ***Dual Tasks Involving Gait Initiation***

With regard to the unique recent paper on the topic [20], DT involving gait initiation (GI) seem to be useful tools for identifying future fallers. The prospective design of this study added even more reliability to DT-related prediction power. The statistical test for assessing the predictive strength of DT condition was log multinomial regression analysis. Slower first step execution time under both ST and DT conditions, slower swing time during DT and slower time to first lateral movement under ST were significantly associated with higher risk of multiple falls, while parameters of GI were not found to be predictors of single falls. However, Callisaya et al. [20], with their DT comprising GI in response to a buzzer activated at random times and a mental tracking task (3-serial subtraction), did not observe any improvement of the prediction value compared to the ST alone. Indeed, slower time to first lateral movement under ST showed the strongest association with multiple falls. Once again, a potential explanation of such a result could be the fact that the ST condition can already be considered as a DT situation: stepping forward as soon as the buzzer sounds (i.e., reaction time task), while maintaining balance and preparing for sufficient motor performances (as perceived in [92]). Therefore, due to the high level of difficulty of the DT test, two consequent behaviors may potentially be observed: older adults globally exhibited poorer features of the first step (longer step execution time and time to first lateral movement) than under ST, and some non-fallers may therefore be less separable from fallers on the basis of such parameters; or multiple fallers may choose a “posture first” strategy under the DT (i.e., more attention allocated to the GI task compared to the concurrent cognitive task) because of their lack of cognitive resources to manage two tasks at the same time. In this line, performance related to the concurrent cognitive task alone should be assessed in [20] and, more generally, in DT studies. In any case, more investigations need to be carried out in order to clearly and reliably answer to the question of the additional value of GI DT for fall prediction. In fact, too few papers were interested in GI under DT condition for predicting falls and the previously written (discriminative) papers did not show outcomes in accordance with the ones obtained by Callisaya and colleagues. St George et al. (2007) investigated a choice stepping reaction time (CSRT) test coupled with a

visuospatial working memory task and found a significantly greater increase in step response time under DT compared to ST in healthy older adult fallers versus non-fallers, as well as a higher amount of secondary task errors in fallers [89]. Uemura and colleagues (2012) [95], for their part, studied the completion of a DT test composed of a GI task as soon as a LED was switched on, and a backward counting task (i.e., mental tracking task). Despite the suspected cognitive impairment of the population in view of their RDST score, the authors observed a lower backward displacement and velocity of the COP in DT condition in fallers compared to non-fallers, and not under ST conditions.

Other recent papers found during the present systematic search, that assessed challenged step or gait initiation in healthy older adults [80,81,94], were also able to predict future falls. Nevertheless, they were not retained in this systematic review because the tasks used (e.g., “ordered multi-stepping over hoop”(OMO) test, CSRT test, inhibitory CSRT/iCSRT test, and Stroop stepping test/STT) were not clearly considered as DT (according to the definition proposed by [56]), but rather as two successive ST. Indeed, such kind of tasks consisted of a reaction time task, discrimination and decision-making task or mental tracking/working memory task waiting for the initiation of a step as response. Slower OMO performance [94] and increased amount of SST errors [81] were significant predictors of fall risk. Furthermore, iCSRT was demonstrated to better identify future fallers than SST and CSRT test: decreased RT remained significantly associated with falls, independently of balance, attention or processing speed [80]. On the other side, as explained above, these tasks can also be seen as cognitive-motor DT that require to simultaneously maintain stability and perform a cognitive task with a motor response. In any case, these high-load tasks involving GI need to be further investigated, by comparing their prediction power with their DT equivalent and by exploring additional parameters directly related to the motor task such as spatial and temporal features of APAs (as done in [92]).

The interest of studying GI more thoroughly under DT condition (or challenged step initiation) in the future can be supported, for instance, by findings from [95]: neither a ST steady-state walking nor a DT condition involving steady-state walking and a mental tracking task would be a predictor of falls in older adults, whereas a DT comprising GI and the same concomitant task performed on the same population would present an added value for fall-risk prediction over ST. Because tests such as OMO, CSRT, iCSRT tests and STT ask to perform steps in multiple directions, it should also be explored whether the combination between GI and turns is not even better for predicting future fallers.

### ***Postural Dual Tasks***

When the fall-risk discriminative and predictive powers of postural DT were mostly proven (in respectively six studies out of six and two studies out of two, in the present review), the additional value of such tasks compared to single tasks is still uncertain. Here again, the choice of the postural

outcomes to assess seem to be crucial. Indeed, a possible reason why Kang et al. [48] did not manage to show the added value of DT on a reduced but similar data collection compared to the one used in Zhou and colleagues' investigations [107] is probably the different postural parameters measured in both studies. The concurrent cognitive task consisted in a usual backward counting task, with an individual adaptation of the task in case of difficulty, and a negative binomial regression analysis was carried out in these manuscripts. Lower DT postural sway complexity (calculated by using multiscale entropy) was shown to be a better predictor of future fall risk than ST postural sway complexity in [107]. On the contrary, independently of the condition (ST versus DT), greater postural stiffness and damping were significantly associated with lower outdoor fall risks, while greater COM root mean square (RMS) and damping in the AP direction were respectively associated with higher and lower rates of indoor falls [48].

In view of the small number of papers comparing the fall-risk prediction power between postural ST and DT conditions, DT-related features that allowed to discriminate between fallers and non-fallers in retrospective studies may be a useful starting point. For example, in a DT with postural perturbations and a verbal fluency or a mental tracking/working memory task as concomitant task, fallers exhibited a higher amount of grasp errors (i.e., failing to grab a handrail in order to maintain postural stability) under both DT conditions in comparison with older adult non-fallers [102]. Besides, a DT task that combined a quiet stance on a firm surface with a backward counting task [55] allowed discrimination between frequent fallers (with more than two falls) and non-fallers (via the maximum distance between two points of the AP time series and the average COP in the AP and ML directions), and between infrequent and frequent fallers (through the maximum distance between two points of the AP time series). Nevertheless, performing a postural ST with eyes open on a compliant surface and using the parameter derived from the first principal component coming from a PCA on posturographic parameters were the only conditions for discriminate infrequent and frequent fallers from non-fallers, and between both groups of fallers. The first principal component included posturographic parameters concerning the AP variation in COP displacement: average AP distance from the mean COP, AP RMS distance and maximum distance between two points of the AP time series. Moreover, in a study comparing a quiet standing ST and DT with a simultaneous tone-counting task [96], fallers had a significantly greater area of sway, AP and ML standard deviation of COP displacement compared to non-fallers, but without any significant interaction between task condition and group. This might be due to the fact that quiet standing is a relatively easy task. Finally, when analyzing a concurrent motor task that consisted in grasping a dowel with different levels of difficulty while staying stationary or while walking [76,79], a generalized slowing down in movement performance (including upper limbs movements) was observed in fallers [77], as well as a greater decoupling between walking and

prehension [76]. In another study that investigated walking or postural control during a manual task (grasping, transporting and placing a dowel as close as possible to the center of a target) [79], fallers and non-fallers were significantly different only in terms of manual task performance. Regarding the dowel-positioning task, fallers were less accurate particularly during the walking DT combined with an 8-cm target, and slower especially during the postural DT and for a target located at a long distance.

From all these studies of postural DT, interesting methodological observations can be made. Dual task-related discriminant parameters did not differ when using a verbal fluency task or a mental tracking/working memory task as concurrent cognitive task [102]. We have also learnt that a concomitant manual task was useful to discriminate between fallers and non-fallers [76,77,79], through different DT-related changes in manual task according to the primary motor task (gait versus quiet stance in [77] and [79]). A study that was excluded due to the lack of information and criteria regarding global cognitive functions of the studied population [78] compared two postural DT conditions involving respectively a mental tracking/working memory task and a manual task as a concomitant task. As results, using a manual concurrent task with traditional analyses of postural control (larger AP and ML sway range and 95% confidence ellipse area) or using a concomitant cognitive task with non-linear analyses of balance control (larger ML  $\alpha$ -scaling exponent and smaller ML sample entropy) were efficient ways to discriminate fallers from non-fallers. Whereas Maranesi et al. (2016) [55] failed to differentiate infrequent from frequent fallers by means of a postural DT involving a backward counting task, other types of DT should be examined.

### ***Dual Tasks Involving Turns***

Regarding DT involving turns, most of the recent studies found in the context of the present systematic search agreed on the fall-risk discriminative and predictive powers of such task (in five papers out of five for both aspects), as well as on their added value in terms of fall prediction over the associated ST (in four selected articles out of five). Particularly, better predictive properties were allocated to the frequency-based and distance-based features (the fusion of the distance-based features being the best predictors of fall risk) compared to the traditional parameters, and especially for the cognitive DT version of TUG test (combination with a mental tracking/working memory task) in comparison with ST and manual-TUG DT [71]. Moreover, in the context of a DT involving the TUG and a serial-1 subtraction task, both TUG-ST score and DTC value (proportionate difference, with the mean completion time among ST and DT as divisor) were significantly associated with falls history, in particular in a transitional functioning group but not in a well-functioning group [4]. Either the tasks or the measured parameters were thus not sufficient to identify any kind of fallers. Tomas-Carus et al. [93] studied exactly the same type of DT, but focused on fall predictors according to gender. In men, a significant AUC for predicting risk of falls was found for mean TUG-DT time, the sum of the mean TUG-DT time and the mean number

of cognitive stops, the sum of the mean TUG-DT time, the mean number of cognitive stops and the mean amount of cognitive errors, and the DTC value (difference in time spent between TUG-ST and TUG-DT, divided by the average score between both tasks), which was shown to be the best predictor. In women, on the contrary, the best predictor for future falls was the sum of the mean TUG-DT time, the mean number of cognitive stops (i.e., stopping while walking for performing the concurrent cognitive task) and the mean amount of cognitive errors, whereas the sum of the mean TUG-DT time and the mean number of cognitive stops was also able to identify elderly women at high risk of falls. Still regarding the same cognitive-TUG DT, Asai et al. (2020) [5] performed the only conclusive prospective study and demonstrated that DT may provide an additional value in TUG for predicting falls among old-older adults, with a longer TUG-ST time and a lower DTC value that were significantly associated with falls occurrence. However, it was not the case among young-older adults. Finally, a last study from Muhaidat and colleagues [67] presented inconclusive outcomes. In fact, based on univariate binary logistic regression analyses, several variables related to ST and DT conditions were found to be significantly associated with fall risk: time for avoiding a moving obstacle in ST and DT while carrying a cup, time required to perform the walking task in a triple-task test, time for TUG in DT involving a concurrent manual task, and absolute difference for TUG time between ST and DT. Nevertheless, a multivariate analysis with these parameters failed to identify a useful predictive tool.

In the future, it will be necessary to carry out more prospective studies regarding DT with the TUG test and a cognitive task, while specifically analyzing the turning phase of this task. Indeed, the predictive power of a cognitive-motor DT involving gait, turn and transfers has been proven but the DT situations with turning as the only motor task have not yet been investigated. It is also interesting to note that absolute differences of performance between ST and DT TUG seem to be better predictors of falls in older adults than proportionate differences [67]. Next, concerning the nature of the concomitant task, while Ponti et al. [71] emphasized the fall prediction power of a concurrent mental tracking/working memory task over a manual task, Ansai et al. (2016) did not show differences in discriminative power of both TUG tests with a cognitive or a motor concurrent task in terms of fall status [3]. Unselected studies due to a poorly described population have provided supplementary information [85,100]. In line with [3], Smith and colleagues [85] observed a more disturbed overall performance in older adults during TUG-DT with a mental tracking/memory working task compare to a manual task, but no significant interaction between group and task condition was found. Finally, a verbal fluency task combined with a TUG test did not allow fall prediction, when using standard completion time as tested independent variable [100].

### ***Limitations***

This systematic review presented some limitations that may have impacted on our conclusions. Firstly, the studied population was restricted to healthy older adults (without cognitive or motor impairments), limiting therefore the generalization of our results. However, two reasons justified the choice of studying this particular group. On the one hand, studying the strength of dual tasks in predicting falls in a limited population makes sense when we assume that particular group characteristics (e.g., neurodegenerative diseases) may influence DT testing parameters in a unique manner compared to other groups. On the other hand, while older individuals living with assistance, in institutions or suffering from diseases such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease (PD) or stroke are already considered at high risk of falling, the ability to discriminate fallers from non-fallers in a population of healthy community-dwelling older adults is of high interest. Secondly, another limitation of the present review was the selection of studies assessing DT only in a lab environment. Indeed, these conditions do not reflect the reality, but one of our objectives was to inform health workers about the most promising kind of DT for assessing fall risk in health structures. Nevertheless, indoor, ecologically valid approaches still need to be investigated.

### **Conclusion**

Recent literature confirms the discriminative and predictive values of a cognitive-motor DT for fall risk in healthy older adults but does not allow definitive conclusions to be drawn regarding the potential added value of DT over ST. Indeed, the global motor capacity of the subject also seem highly predictive of falls and has even been proposed as a marker of cognitive decline in older adults [99]. Overall, cognitive-motor DT involving GI or postural control for the motor task have not been enough tested for their fall prediction power in the literature. On the contrary, cognitive-walking DT tests are widespread, but a lot of different DT paradigms were investigated, leading therefore to only half of the studies that proved the superiority of DT over ST in terms of prediction of future falls. Dual tasks with turns (mostly involving walking and transfers with a turn through the TUG test) represent quite useful tools thanks to consistent results about their additional value over ST for the identification of future healthy older adult fallers.

Future prospective studies (with a homogenous definition of falls and a substantial follow-up period) should assess DT and corresponding ST in sufficiently large and heterogeneous elderly populations, while investigating different motor tasks (i.e., gait, step initiation, standing and turning, with various stages of complexity) and cognitive tasks (i.e., one task of each category [8], with different levels of difficulty). Preference should be given to mental tracking/working memory tasks (e.g., backward counting) because of their easy implementation and their proven superiority compared to other

concurrent cognitive and motor tasks involved in any kind of cognitive-motor DT in previous reviews and recent literature. Dual-task paradigms, tools of assessment, further calculations of parameters of interest and statistical tests have to be clearly and fully reported for further potential replications. Including confounders such as gender, age, cognitive abilities, physical performance, mobility assessments and concern about falling within regression models or models of classification is necessary. The performance of both the cognitive and motor tasks under DT and ST conditions must be reported in order to understand which strategies of prioritization have been used by the participants. It is also important not to instruct any task prioritization to subjects (and not to forget to mention these given instructions) and to randomize the order between ST and DT among participants. A special concern should also be given to the identification of infrequent fallers, and not only frequent fallers.

Because fall risk is dependent on different factors in addition to deficits in physical and cognitive functions [16], the most relevant cognitive-motor DT for fall prediction in healthy older adults that will have been found by following the above listed recommendations will then have to be compared with other fall-risk assessment tools and probably integrated within a multimodal clinical assessment.

Continuing investigations of cognitive-motor DT for fall-risk prediction is encouraging by the fact that daily-living walking bouts have been recently shown to be more similar to in-lab DT walking in comparison with ST gait [39]. Along with the usual behavioral assessments of motor and cognitive tasks under ST and DT conditions, measuring neural activity during DT [98], during a computerized cognitive task [35] or through transcranial magnetic stimulation [69] can provide additional information concerning a risk of falls. When light will be shed on this concern of falls prediction in healthy older adults, it will be interesting to extend the research through other specific populations such as older adults with cognitive impairment or neurological diseases. For example, Plotnik and colleagues (2011) have demonstrated the superior fall-risk predictive power of DT walking over ST in adults with PD [70].



### **Funding**

Madli Bayot works on a project that has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 721577.

### **Disclosure of interest**

The authors declare that they have no competing interest.

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## **Figure legends**

**Figure 1** PRISMA flow diagram that summarizes the process of manuscript selection.

## Tables

**Table 1 Articles regarding walking dual tasks that were included in the systematic literature review.** Abbreviations: y. = years; F = females; M = males; # = number; GDS = Geriatric Depression Scale; MMSE = Minimal Mental State Examination; AP = anteroposterior; ML = mediolateral; CoV = coefficient of variation; PFC = prefrontal cortex; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; EF = executive function; REOH = ratio of even to odd harmonics; MLE = maximum Lyapunov exponent.

Authors	Population	Falls	Dual-task paradigm	(1) Do DT-related changes or DT performance discriminate fallers from non-fallers? (2) Are DT-related changes or DT performance predictors of falling? (3) Is the DT-related predictive strength superior compared to the ST-related one? (Yes/No/Inconclusive/Not addressed)	Risk of bias via QUIPS tool
Ayers et al., 2014 [7]	646 community-dwelling older adults: 337 fallers (80.5 ± 5.4 y.; 219 F; Blessed score: 1.7 ± 1.5) and 309 non-fallers (79.2 ± 5.5 y.; 176 F; Blessed Score: 1.7 ± 1.6)	<b>Prospective</b> study; Mean follow-up of 2.6 years; → Fallers = (# of falls ≥ 1) during the follow-up period	<u>Motor task:</u> walking 4.6 m at normal pace <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> reciting alternate letters of the alphabet	<b>(1) Not addressed, (2) Yes &amp; (3) Yes:</b> Shorter step length in DT condition predicted falls. <b>Poorer performance in the DT “pace” domain (including DT velocity and step length)</b> remained a significant predictor of falls. → <b>Incremental validity of DT over ST walking assessment in the prediction of falls.</b>	Low risk of bias
Hirashima et al., 2015 [40]	92 volunteers from a community senior club: 16 fallers (78.1 ± 5.6 y.; 13 F; MMSE: 28.1 ± 1.6) and 76 non-fallers (74.9 ± 5.3 y.; 65 F; MMSE: 28.1 ± 1.7)	<b>Prospective</b> cohort study; Over a follow-up period of 12 months; → Fallers = (injured because of falls or # of falls ≥ 2)	<u>Motor task:</u> walking 60 m (10 m walkway with 3 returns) at usual speed <u>Concurrent cognitive task:</u> <b>discrimination and decision-making task:</b> not stepping on the unequal lines	<b>(1) Yes, (2) Yes &amp; (3) Not addressed:</b> Fallers and non-fallers significantly <b>differed in terms of the presence of missteps at 40 m and 60 m.</b> Subjects who had made <b>missteps during the DT test with an extended walking distance of ≥ 40 m</b> were significantly more likely to be fallers.	Low risk of bias
MacAulay et al., 2015 [53]	416 relatively healthy and cognitively intact older adults, 67.5% female: 81 fallers (69.6 ± 6.81 y.; initial MMSE: 29.47 ± 0.87) and 312 non-fallers (70.13 ± 6.62 y.; initial MMSE: 29.25 ± 1.02)	Longitudinal ( <b>prospective</b> ) study; Structured clinical interview after 1 year in order to obtain participant’s fall history for the past year; → Fallers = (# of falls ≥ 1)	<u>Motor task:</u> straight walking at normal everyday walking speed <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> spelling a word of 5 letters in length backwards aloud	<b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b> At baseline as well as at follow-up, fallers exhibited <b>shorter stride length</b> than non-fallers within both walking task conditions ( <b>ST and DT</b> ). There was <b>no significant interaction between group and task conditions on gait stride length.</b> Shorter strides during DT at follow-up were predicted by worse executive attention/processing speed performance 1 year before.	Low risk of bias
Gimmon et al., 2016 [34]	160 older adults: 61 fallers (79.4 ± 5.7 y.; 49 F; MMSE: 28.19 ± 1.53) and 99 non-	Participants were asked to <b>retrospectively</b> recall fall	<u>Motor task:</u>	<b>(1) Yes, (2) No &amp; (3) No:</b> <b>Trial velocity during ST</b> remained significantly <b>slower</b> in fallers compared to non-fallers.	Low risk of bias

	fallers (81.5 ± 5 y.; 69 F; MMSE: 27.9 ± 1.65)	events during the past year; → Fallers = (# of falls ≥ 1)	narrow path <b>walking</b> test = walking at a comfortable pace within a 6 m long narrow path <u>Concurrent cognitive tasks:</u> <b>3 mental tracking/working memory tasks:</b> reciting the days of the week backwards, reciting the months of the year backwards, serial-5 subtraction loudly from 100 to 50	There was no significant interaction between group and task. → <b>No added value of DT condition over ST condition in identification of fallers.</b> <b>Significant predictive abilities of ST trial velocity and not for DT trial velocity.</b>	
Howcroft et al., 2016 [43,44]	100 community-dwelling older adults: 24 fallers (76.3 ± 7 y.; 11 F) and 76 non-fallers (75.5 ± 6.6; 45 F)	<b>Retrospective</b> study; Classification based on 6-month retrospective fall occurrences; → Fallers = (# of falls ≥ 1)	<u>Motor task:</u> <b>walking</b> 7.62 m <u>Concurrent cognitive task:</u> <b>verbal fluency task:</b> saying words starting with A, F or S	<u>(1) Yes, (2) Yes &amp; (3) No:</u> Fallers showed significantly <b>greater head posterior standard deviation decreased posterior pelvis AP REOH during ST, and greater posterior pelvis vertical MLE during DT gait.</b> In the context of models of wearable-sensor based fall-risk classification in older adults, <b>ST sensor-based gait assessment models outperformed models based on DT walking</b> or clinical assessment data.	Moderate risk of bias
Johansson et al., 2016 [47]	1390 fairly healthy community-dwelling older adults aged 70 years (684 F; MMSE: F → 28.5 ± 1.6 vs. M → 28.3 ± 1.7): over 1350 → 148 fallers (88 F)	<b>Prospective</b> study; Self-reported fall data by telephone 6 and 12 months after examination; → Fallers = (# of falls ≥ 1)	<u>Motor task:</u> <b>walking</b> 8.6 m at preferred pace (+ walking at fast speed only under ST condition) <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> counting backward from 100 in increments of 1	<u>(1) Yes, (2) Yes &amp; (3) Yes:</u> Significantly <b>greater step width, step length, step time and stance time variability</b> in fallers <b>during the fast-speed trial.</b> Nevertheless, <b>during DT</b> , fallers exhibited significantly <b>increased variability for step width, step length, stride length, step time, stance time, stride time, stride velocity and swing time</b> in comparison with non-fallers. Moreover, <b>step width variance from the DT trial</b> represented an <b>independent predictor</b> of incident falls, <b>as well as other gait parameters under DT.</b>	Low risk of bias
Pelosin et al., 2016 [69]	31 older adults: 17 fallers (73.4 ± 4.2 y., 10 F, MoCA score: 26.4 ± 1.6) and 14 age-matched non-fallers (72.1 ± 4.9 y., 5 F, MoCA: 28.3 ± 2)	Cross-sectional ( <b>retrospective</b> ) study; Self-reported falls over the previous 6 months; → Fallers = (# of falls ≥ 2)	<u>Motor task:</u> <b>walking</b> in a corridor at a comfortable speed for 1 min <u>Concurrent cognitive task:</u> <b>verbal fluency task:</b> talking	<u>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</u> <b>Gait speed</b> was significantly <b>lower</b> in fallers than in non-fallers <b>during ST and DT.</b> Unlike non-fallers, fallers significantly <b>reduced their gait speed under DT gait with respect to normal gait.</b>	Moderate risk of bias
Freire Júnior et al., 2017 [30]	62 community-dwelling older adults: 27 fallers (67.96 ± 5.7 y.; 26 F; MMSE: 25, 95% CI 23.5-26.5) and 35 non-fallers (67.97 ± 4.82 y.; 24 F; MMSE: 26.57, 95% CI 25.63-27.52)	<b>Retrospective</b> study; Questionnaire about the history of falls in the 6 months preceding the assessment day; → Fallers = (# of falls = 1)	<u>Motor task:</u> <b>walking</b> 8 m at self-selected speed <u>Concurrent tasks:</u> - <b>verbal fluency task:</b> naming animals without repeating names - <b>motor task:</b> transferring a coin from one pocket to the other	<u>(1) No, (2) Not addressed &amp; (3) Not addressed:</u> There was <b>neither a significant main effect of the faller status nor significant interaction effects between group and walking condition.</b>	Moderate risk of bias
Vergheze et al., 2017	166 high-functioning older adults (74.5 ± 6.07 y.; 85 F; RBANS: 91.56 ± 12): 71 fallers	<b>Prospective</b> cohort study;	<u>Motor task:</u>	<u>(1) Not addressed, (2) Yes &amp; (3) Yes:</u> <b>Higher PFC activation levels on fNIRS during DT predicted falls.</b>	Moderate risk of bias

[98]	(34 with # of falls > 1) and 85 non-fallers	50-month follow-up period (mean follow-up: 33.9 ± 11.9 months)	<b>walking</b> at normal pace on an electronic walkway (for 3 continuous loops consisting of 6 straight segments and 5 turns) <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> recitation of alternate letters of the alphabet (under ST: for 30 seconds while standing)	However, <b>PFC activation during both motor and cognitive ST</b> , as well as <b>gait velocity and letter rate during DT</b> were not significantly associated with risk of falls.	
Caetano et al., 2018 [19]	50 healthy community-dwelling older adults: high-risk of falling group (n=22; 77 ± 8 y.; 16 F) and low-risk of falling group (n=28; 72 ± 4 y.; 18 F)	<b>Retrospective study;</b> Classification based on falls experienced in the past 12 months and on the PPA score; → High fall-risk group = (history of multiple falls and/or PPA score ≥ 1.5)	<u>Motor task:</u> gait adaptability test (GAT) → <b>walking</b> over a 6-m path at self-selected speed under 4 conditions: while avoiding an obstacle, stepping onto close or far targets, or walking without any stimulus on the pathway <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-3 subtraction from a two-digit number	<b>(1) Yes, (2) Yes &amp; (3) No:</b> <b>At least one stepping error in the single GAT and reduced GAT velocity in both ST and DT conditions</b> were found to <b>discriminate</b> low- from high-risk of falling groups and to be <b>independent predictors of high risk of falling</b> . The <b>association between ST GAT errors and fall risk</b> was <b>mediated by impaired EF</b> , while the <b>association between GAT velocity and fall risk in ST and DT situations</b> was <b>mediated by high concern about falling, weak quadriceps strength and impaired EF</b> . However, <b>GAT under DT condition did not provide greater predictive power of fall risk over ST GAT</b> .	Moderate risk of bias
Callisaya et al., 2018 [21]	424 older adults (77.8 ± 6.4 y.; 234 F; RBANS: 93.5 ± 12.6)	<b>Retrospective study;</b> Participants were asked if they had fallen in the past year; → Fallers = (# of falls ≥ 1)	<u>Motor task:</u> <b>walking</b> on a computerized mat (457.2 cm long) at normal walking speed <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> recitation of alternate letters of the alphabet starting with the letter 'A'	<b>(1) Not addressed, (2) Yes &amp; (3) No:</b> <b>In separate regression models</b> , falls in previous year were significantly associated with <b>slower DT walking speed, ascending and descending stairs</b> . However, in the <b>final model, only time for ascending stairs</b> remained significant.	Moderate risk of bias
Commandeur et al., 2018 [26]	42 community-dwelling older adults: 27 fallers (75.9 ± 3.3 y.; 19 F; MMSE: 28.5 ± 1.6) and 15 non-fallers (75.8 ± 3.4 y.; 6 F; MMSE: 28.5 ± 1.1)	<b>Retrospective study;</b> Self-reported falls over the previous 12 months; → Fallers = (# of falls ≥ 1)	<u>Motor task:</u> <b>walking</b> there and back (10 ST and 10 DT walking passes) at a self-selected preferred speed along a 6.4 m instrumented walkway <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-7 subtraction aloud from a randomly generated three-digit number	<b>(1) Not addressed, (2) Yes &amp; (3) Not addressed:</b> <b>Larger stride length difference and stride time difference significantly and uniquely contributed to the increase of fall risk</b> . These DTC gait measures <b>outperformed traditional clinical tests of strength, mobility and balance, and physiological assessments</b> .	Low risk of bias
Halliday et al., 2018 [35]	27 older adults: 12 fallers (76.25 ± 3.19 y.; 8 F) and 15 non-fallers (75.93 ± 3.41 y.; 7 F)	<b>Retrospective study;</b> Follow-up period: the two-years leading up to the first study visit; → Fallers = (# of falls ≥ 1)	<u>Motor task:</u> <b>walking</b> at self-selected, normal walking speed along a 6.4 m instrumented walkway → 10 passes * total recorded walking distance of about 6.1 m	<b>(1) Yes, (2) Yes &amp; (3) Yes:</b> <b>Mean step length, step length CoV and swing time CoV</b> were significantly larger in fallers compared to non-fallers <b>in DT</b> , and not in ST. <b>Step length variability in DT</b> showed a <b>significant effect within the logistic regression model</b> .	Moderate risk of bias

			<u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-7 subtraction from a given three-digit starting number		
Howcroft et al., 2018 [42,45]	75 community-dwelling older adults: 28 fallers (75 ± 8.2 y.; 14 F) and 47 non-fallers (75.3 ± 5.5 y.; 30 F)	<b>Prospective</b> study (and comparison with retrospective studies from the same group [43,44]); → Fallers = (# of falls ≥ 1 during the 6-month follow-up period)	<u>Motor task:</u> <b>walking</b> 7.62 m <u>Concurrent cognitive task:</u> <b>verbal fluency task:</b> saying words starting with A, F or S	<u>(1) Yes, (2) Yes &amp; (3) No:</u> For DT gait, fallers had significantly <b>lower stance AP COP path CoV and AP FFT first quartile for the head accelerometer</b> compared to non-fallers, whereas, <b>during ST</b> , fallers showed significantly <b>lower ML FFT first quartile for the left shank accelerometer</b> as well as <b>lower superior maximum acceleration for the right shank accelerometer</b> . Although the <b>best overall models were based on DT walking</b> , the <b>comparison between ST- and DT-gait-based models did not reveal a clearly superior gait assessment for fall-risk prediction</b> (similar accuracies for the top ST- and DT-gait-based models).	Moderate risk of bias
Minet et al., 2018 [62]	322 older women: 117 fallers from the falls clinic, 99 fallers (79 [76-85] y.; MMSE: 27 [25-29]) and 106 non-fallers (80 [75-86] y.; MMSE: 28 [26-29]) from the community	Observational case-control ( <b>retrospective</b> ) study; Self-reported questionnaire to assess falls history over 1 year; → Once only faller and recurrent fallers (> 1 fall)	<u>Motor task:</u> 4-meter <b>walking</b> test at preferred walking speed <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-3 subtractions	<u>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</u> <b>Under both ST and DT, gait speed</b> was significantly <b>slower</b> in fallers compared to non-fallers from the community. However, gait speed was <b>not significantly different between community-dwelling once only fallers and recurrent fallers</b> .	Moderate risk of bias
Gillain et al., 2019b [32,33]	96 community-dwelling older adults: 35 fallers (69 [67-76] y.; 17 F; MoCA: 27 [26-29]) and 61 non-fallers (70 [67-74] y.; 31 F; MoCA: 28 [26-29])	Longitudinal ( <b>prospective</b> ), observational study; 2-year follow-up; → Fallers = (# of falls ≥ 1)	<u>Motor task:</u> <b>walking</b> at self-selected comfortable speed (+ walking at self-selected fast speed) <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-7 subtraction from 100	<u>(1) Yes, (2) Yes &amp; (3) Inconclusive:</u> Fallers had <b>lower gait speed during fast walking ST, shorter stride length during normal speed and fast walking ST and higher symmetry DTC</b> . Among the discriminative variables, <b>symmetry DTC was the only one significantly related to the risk of falls</b> . The <b>model</b> obtained in [32] <b>included symmetry DTC, stride length in fast walking ST, stiffness, mean MTC in normal speed walking ST, MTC CoV DTC, MTC variance and mean MTC in fast walking ST, delta1 MTC in DT and gender</b> .	Low risk of bias

**Table 2 Articles about dual tasks involving gait initiation that were included in the systematic literature review.** Abbreviations: y. = years; F = females; M = males; # = number; MMSE = Minimal Mental State Examination; RDST = Rapid Dementia Screening Test; EF = executive function; RT = reaction time.

Authors	Population	Falls	Dual-task paradigm	<p>(1) Do DT-related changes or DT performance discriminate fallers from non-fallers?</p> <p>(2) Are DT-related changes or DT performance predictors of falling?</p> <p>(3) Is the DT-related predictive strength superior compared to the ST-related one?</p> <p>(Yes/No/Inconclusive/Not addressed)</p>	Risk of bias via QUIPS tool
Callisaya et al., 2016 [20]	124 older adults: 27 single fallers (71.3 ± 5.3 y.; 13 F), 20 multiple fallers (73.5 ± 9 y.; 11 F) and 77 non-fallers (70.2 ± 6.6 y.; 29 F)	<p><b>Prospective study;</b> Falls questionnaire sent every 2 months for 12 months + falls calendar + phone call; → Fallers = (# of falls ≥ 1) (single fallers or multiple fallers);</p>	<p><u>Motor task:</u> <b>starting walking</b> in response to a buzzer activated at random times</p> <p><u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> 3-serial subtraction</p>	<p><u>(1) Not addressed, (2) Yes &amp; (3) No:</u> <b>Slower overall GI time under ST and DT, swing time under DT and slower time to first lateral movement under ST increased the risk of multiple falls.</b> However, <b>GI under DT did not increase the discrimination of multiple fallers over ST condition:</b> slower time to first lateral movement under ST showed the strongest association with multiple falls.</p>	Moderate risk of bias

**Table 3 Articles about dual tasks involving postural control that were included in the systematic literature review.** Abbreviations: y. = years; F = females; M = males; # = number; MMSE = Minimal Mental State Examination; AP = anteroposterior; ML = mediolateral; PCA = Principal Component Analysis; RMS = root mean square; RT = reaction time; COM = center of mass; RANGE = maximum distance between 2 points of the COP time series; MVELO = average velocity of the COP; MDIST = mean distance, average distance from the mean COP; RDIST = RMS distance.

Authors	Population	Falls	Dual-task paradigm	<p>(1) Do DT-related changes or DT performance discriminate fallers from non-fallers?</p> <p>(2) Are DT-related changes or DT performance predictors of falling?</p> <p>(3) Is the DT-related predictive strength superior compared to the ST-related one?</p> <p>(Yes/No/Inconclusive/Not addressed)</p>	Risk of bias via QUIPS tool
Kang et al., 2013 [48]	717 relatively healthy community-dwelling older adults (77.9 ± 5.3 y.; 458 F; MMSE: 27.1 ± 2.6): 131 outdoor fallers, 137 indoor fallers, 129 fallers with both outdoor and indoor falls and 320 non-fallers	<p><b>Prospective</b> study;</p> <p>Falls monitored over 6-36 months;</p> <p>→ Fallers = (# of falls ≥ 1)</p>	<p><u>Motor task:</u></p> <p><b>quiet standing</b> barefoot with eyes open for 30 s</p> <p><u>Concurrent cognitive task:</u></p> <p><b>mental tracking/working memory task:</b> serial-3 subtraction from 500 (individual adaptation of the task in case of difficulty)</p>	<p><u>(1) Not addressed, (2) Yes &amp; (3) No:</u></p> <p><b>Only AP COM RMS was significantly smaller in non-fallers</b> compared to fallers. <b>Greater postural stiffness and damping were associated with lower outdoor fall risks.</b> Furthermore, <b>greater COM RMS was associated with higher indoor falls</b>, whereas <b>greater damping in the AP direction was related to lower rates of indoor falls.</b> Except for the last predictor, the associations of postural measures with indoor and outdoor fall rates were invariant by direction (AP vs. ML) and by condition (ST vs. DT).</p> <p>→ <b>Measuring postural control under DT did not improve fall prediction.</b></p>	Moderate risk of bias
Maranesi et al., 2015 [55]	130 older adults: 45 infrequent fallers (79 ± 6 y.; 26 F; MMSE: 25 ± 3), 18 frequent fallers (81 ± 6 y.; 16 F; MMSE: 25 ± 3) and 67 non-fallers (79 ± 5 y.; 38 F; MMSE: 26 ± 3)	<p><b>Retrospective</b> study;</p> <p>Last year fall history;</p> <p>→ Infrequent fallers = 1 or 2 falls, frequent fallers ≥ 2 falls</p>	<p><u>Motor task:</u></p> <p><b>quiet standing</b> with eyes open and closed on both a firm and a compliant surface during 30 s</p> <p><u>Concurrent cognitive task:</u></p> <p><b>mental tracking/working memory task:</b> serial-7 subtraction (performed while standing with eyes open on a firm surface)</p>	<p><u>(1) Yes but..., (2) Not addressed &amp; (3) Not addressed:</u></p> <p><b>Postural DT on a firm surface</b> and related posturographic parameters (<b>RANGE-AP, MVELO-AP and MVELO-ML</b>) were significantly <b>different between non-fallers and frequent fallers</b>, while <b>RANGE-AP</b> was also found to be significantly <b>different between infrequent and frequent fallers.</b></p> <p><b>However, performing postural ST with eyes open on a compliant surface and using PCA-derived parameters allowed to discriminate between non-fallers and (infrequent and frequent) fallers and between infrequent fallers and frequent fallers.</b> Indeed, the parameter derived from the first principal component (PC1) was significantly different between all pairs of groups. For this task, PC1 involved posturographic parameters concerning the AP variation in COP displacement: MDIST-AP, RDIST-AP, RANGE-AP.</p>	Moderate risk of bias
Westlake et al., 2016 [102]	23 older adults: 12 fallers (70 ± 5 y.; MMSE = 29) and 11 non-fallers (69 ± 4 y.; MMSE = 30)	<p><b>Retrospective</b> study;</p> <p>Falls history over the last year;</p> <p>→ Fallers = (# of falls ≥ 1)</p>	<p><u>Motor task:</u></p> <p>maintaining <b>postural stability</b> under 2 different perturbation conditions (“quickly grab one handrail and do not take a step”): predictable and unpredictable</p> <p><u>Concurrent cognitive tasks:</u></p>	<p><u>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</u></p> <p>The only significant difference between older adult fallers and non-fallers concerned <b>grasp errors under both DT conditions</b>, with a <b>higher amount of errors</b> in fallers compared to non-fallers.</p>	Moderate risk of bias



			<p>- <b>verbal fluency task:</b> associated verb generation as quickly as possible after having heard a noun</p> <p>- <b>mental tracking/working memory task:</b> 1-back verb generation task</p>		
Rinaldi et al., 2017 [76,77]	30 older adults: 15 fallers (70.1 ± 5.1 y.; 15 F; MMSE: 27 ± 3.2) and 15 non-fallers (71.8 ± 5.8 y., 15 F; MMSE: 28 ± 1.3)	<p><b>Retrospective study;</b> 12-month follow-up period prior to data collection; → Fallers = (# of falls ≥ 1)</p>	<p><u>Motor task:</u> <b>walking</b> at self-selected speed (also perform as ST) (or <b>postural control:</b> performing the concurrent task while staying stationary → in [77])</p> <p><u>Concurrent task:</u> <b>motor task:</b> to reach and grasp a dowel with the right hand and without contacting the obstacles and knocking down the support, under different difficulty levels: stable (SB) and unstable (UB) bases without obstacles, stable base with obstacles at short (SSD) and long (SLD) distances, and unstable base with obstacles at short (USD) and long (ULD) distances</p>	<p><b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b></p> <p>In a previous study from the group using the same dataset but other sort of analyses [77], <b>step width and step duration</b> were <b>greater</b> in fallers than in non-fallers. Furthermore, <b>step velocity</b> was <b>lower</b> in fallers in <b>step at dowel contact</b>. Moreover, fallers exhibited a <b>greater reduction in AP COM velocity and a significantly earlier minimum AP COM velocity before dowel contact</b> than non-fallers. Finally, fallers showed <b>greater AP and ML margins of dynamic stability, a greater movement time and temporal difference between right heel contact and reaching onset, and lower peak wrist velocity, time-to-peak grip aperture only during walking DT, peak grip aperture velocity during postural DT and time-to-peak grip aperture velocity.</b> → <b>Generalized slowing down in movement performance in fallers.</b></p> <p>Here (in [76]), <b>mean walking speed during both ST and DT</b> was significantly <b>lower</b> in fallers compared to non-fallers. Fallers presented a <b>higher frequency of grasping the dowel in double support</b>, whereas <b>non-fallers</b> showed a <b>greater frequency of dowel grasping using a contralateral single support.</b> → <b>Greater decoupling between walking and prehension in fallers.</b></p>	Low risk of bias
Zhou et al., 2017 [107]	738 older adults: 460 fallers (78.1 ± 5.5 y.; 292 F) and 278 non-fallers (77.9 ± 5.3 y.; 178 F)	<p><b>Prospective study;</b> Over a follow-up period of 48 months; → Fallers = (# of falls ≥ 1)</p>	<p><u>Motor task:</u> <b>quiet standing</b> barefoot with eyes open for 30 s</p> <p><u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-3 subtraction from 500 (individual adaptation of the task in case of difficulty)</p>	<p><b>(1) Yes, (2) Yes &amp; (3) Yes:</b></p> <p>Fallers exhibited <b>lower AP postural sway complexity</b> (measured by multiscale entropy) <b>under both ST and DT</b> in comparison with non-fallers.</p> <p><b>AP complexity of postural sway during ST and DT was independently negatively associated with the incidence of future falls.</b></p> <p><b>During ST</b>, older adults in the <b>quintile 1</b> had a significantly <b>higher falls rate than those in quintiles 4 and 5</b>, whereas, <b>during DT</b>, those in <b>quintiles 1,2 and 3 of complexity presented higher fall rates than those in quintiles 4 and 5.</b></p> <p><b>In the DT condition</b>, older adults in the <b>lower quintiles of complexity (quintiles 1, 2 and 3) experienced significantly more falls during the follow-up compared to those in the highest quintile of complexity (quintile 5).</b></p> <p><b>DT postural sway complexity</b>, with its particular sensitivity, was a <b>better predictor of future falls risk than ST postural sway complexity.</b></p>	Moderate risk of bias
Santos et al., 2018 [79]	30 older women: 15 fallers (79 ± 6 y.; 26 F; MMSE: 25 ± 3) and 15 non-fallers (81 ± 6 y.; 16 F; MMSE: 25 ± 3)	<p><b>Retrospective study;</b> 6-month follow-up period; → Fallers = (# of falls ≥ 1).</p>	<p><u>Motor task:</u> <b>walking</b> (also perform as ST) or <b>postural control</b> (performing the concurrent task while staying stationary)</p> <p><u>Concurrent task:</u></p>	<p><b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b></p> <p><b>During ST walking</b>, <b>step length</b> was significantly <b>smaller</b> in fallers compared to non-fallers.</p> <p>Fallers were <b>less accurate</b> (significantly <b>larger AP constant error</b>, particularly for <b>the walking DT combine with the 8-cm target</b>) and <b>slower</b> (<b>during the postural</b></p>	Moderate risk of bias

			<p><b>manual task:</b> grasping, transporting and placing the dowel as close as possible to the center of the target, with 4 different levels of difficulty according to target distance (short versus long distance) and target size (target of either 8 or 12 cm)</p>	<p><b>DT and for the long distance</b> in comparison with the walking DT and short distance, respectively) <b>in the dowel-positioning task</b> than were non-fallers.</p>	
<p>Uiga et al., 2018 [96]</p>	<p>78 older adults: 34 fallers (69 ± 3.52 y.; 29 F; MMSE: 29.03 ± 0.98) and 36 non-fallers (68.89 ± 3.7 y.; 28 F; MMSE: 29.23 ± 1.11)</p>	<p><b>Retrospective study;</b> Falls history over the last 2 years; → Fallers = (# of falls ≥ 1)</p>	<p><u>Motor task:</u> 1-minute <b>quiet standing</b></p> <p><u>Concurrent cognitive task:</u> <b>discrimination and decision-making task:</b> tone-counting task → monitoring and subsequently reporting the number of high-pitched tones presented via computer speakers</p>	<p><b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b> Regarding traditional COP sway variables, there was a significant effect of group on balance performance, with <b>greater area of sway, SD-ML and SD-AP</b> in fallers compared to non-fallers. However, <b>no significant interaction between task condition and group</b> was observed. Concerning complexity-based COP sway variables, there was no significant group effect and no interaction between group and task condition. Moreover, no significant difference between older adult fallers and non-fallers was found for mean tone-counting accuracy.</p>	<p>Low risk of bias</p>

**Table 4 Articles about dual tasks involving turns that were included in the systematic literature review.** Abbreviations: y. = years; F = females; M = males; # = number; OR = odds ratio; MMSE = Minimal Mental State Examination; RDST = Rapid Dementia Screening Test; AUC = Area Under the Curve; PSE = Power Spectral Entropy; PSP = Power Spectrum Peak; PSPF = Power Spectrum Peak Frequency; WPSP = Weighted Power Spectrum Peak.

Authors	Population	Falls	Dual-task paradigm	<p>(1) Do DT-related changes or DT performance discriminate fallers from non-fallers?</p> <p>(2) Are DT-related changes or DT performance predictors of falling?</p> <p>(3) Is the DT-related predictive strength superior compared to the ST-related one?</p> <p>(Yes/No/Inconclusive/Not addressed)</p>	Risk of bias via QUIPS tool
Muhaidat et al., 2014 [67]	62 independently ambulant community-dwelling older adults: 13 fallers (82 ± 12 y.; 9 F; MMSE: 29 ± 3) and 49 non-fallers (75 ± 11.5 y.; 32 F; MMSE: 29 ± 2)	<p><b>Prospective</b> study;</p> <p>6-month follow-up validation cohort study;</p> <p>→ Fallers = (# of falls ≥ 1);</p> <p>+ falls in the previous year</p>	<p>8 dual-task tests and 1 triple-task test, with <b>straight walking with or without obstacles, walking with turns and stair descent</b> as motor tasks and <b>motor, verbal fluency, mental tracking/working memory, and discrimination and decision-making tasks</b> as concurrent tasks:</p> <ul style="list-style-type: none"> <li>- straight walking and visuospatial clock task;</li> <li>- walking with turns and naming animals;</li> <li>- walking with turns and counting backwards in 3s;</li> <li>- avoiding stationary obstacles and naming animals;</li> <li>- avoiding a moving obstacle and carrying a cup;</li> <li>- timed Up &amp; Go (TUG) and carrying a cup;</li> <li>- stair descent and naming animals;</li> <li>- walking while talking complex;</li> <li>- straight walking, visuospatial clock task, and carrying a cup</li> </ul>	<p><b>(1) Not addressed, (2) Yes &amp; (3) Inconclusive:</b></p> <p>This multivariate analysis <b>failed to identify a useful predictive tool</b>, but gave an indication regarding <b>the most useful variables in predicting falls in a multivariate analysis</b>; that is, <b>time for avoiding a moving obstacle in ST and DT while carrying a cup, time required to perform the walking task in the triple-task test, time for TUG in DT, and absolute difference for TUG time between ST and DT.</b></p> <p><b>For these 5 variables</b>, the ORs obtained with binary logistic regression were all <b>statistically significant.</b></p> <p>Moreover, in terms of the form of DT outcomes, <b>absolute difference could be a better predictor of falls than the proportionate difference.</b></p>	Moderate risk of bias
Ansai et al., 2016 [3]	67 community-dwelling older adults: 24 fallers (80-85 y.; 18 F; MMSE = 24) and 43 non-fallers (80-83 y.; 27 F; MMSE = 27)	<p>Cross-sectional (<b>retrospective</b>) study;</p> <p>Self-report of falls over the past 3 months;</p> <p>→ Fallers = (# of falls ≥ 1)</p>	<p><u>Motor task:</u></p> <p><b>TUG test (walking, turning and transfers)</b></p> <p><u>Concurrent tasks:</u></p> <ul style="list-style-type: none"> <li>- <b>mental tracking task/working memory task:</b> repeating days of the week in reverse order;</li> <li>- <b>motor task:</b> grasping a drinking filled with water</li> </ul>	<p><b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b></p> <p>Most balance and DT variables were significantly correlated.</p> <p>Fallers <b>took significantly more time and steps during both TUG tests with cognitive or motor concurrent task.</b></p> <p>→ <b>DT-TUG outperformed balance tests regarding prediction of falls.</b></p>	Low risk of bias

Ponti et al., 2017 [71]	36 community-dwelling healthy older adults: 18 fallers (75.25 ± 8.2 y.; 15 F; MMSE: 23.75 ± 3.93) and 18 non-fallers (70.94 ± 6.69 y.; 10 F; MMSE: 26.46 ± 4.35)	<b>Retrospective</b> study; Participants questioned about their history of falls over the past year	<u>Motor task:</u> <b>TUG</b> test <u>Concurrent tasks:</u> - <b>motor task:</b> carrying a cup filled with water (TUG-M) - <b>mental tracking/working memory task:</b> continuous simple subtraction questions (TUG-C)	<u>(1) Yes, (2) Yes &amp; (3) Yes:</u> Regarding frequency domain features, only <b>lower PSE, WPS2 and WPS3 related to TUG-C</b> as well as <b>lower features fusion, lower PSE and PSP differences between the whole signal and the TUG-C, lower PSPF difference between TUG and TUG-M, and lower WPSP difference between TUG-M and TUG-C</b> as well as <b>lower distances fusion</b> were significantly able to identify fallers from non-fallers. Regarding ROC analysis, <b>the extracted frequency and distance-based features had higher values of AUC, f1-Scores, sensitivity and specificity compared to the traditional parameters</b> (e.g., completion times) related to TUG tests. However, <b>the best results were allocated to the fusion of distance-based features.</b> → The use of both distance-based features and fusion might improve the results.	Low risk of bias
Asai et al., 2018 [4,5]	537 community-dwelling older adults: 103 fallers (77.5 ± 6 y.; 68 F; RDST: 9.5 ± 3.1) and 434 non-fallers (76.5 ± 6.4 y.; 278 F; RDST: 9.6 ± 2.8)	<b>Retrospective</b> study; Self-administered questionnaire; Definition of a fall: [49].	<u>Motor task:</u> <b>TUG</b> test (walking at a comfortable and safe pace) <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-1 subtraction aloud from 100	<u>(1) Yes, (2) Yes &amp; (3) Yes – additional value:</u> Fallers took significantly <b>longer to complete ST-TUG</b> and presented a <b>lower DTC value</b> in comparison with non-fallers. <b>ST-TUG score and DTC value were significantly associated with fall history.</b> Compared to the other 3 fall risk groups (based on cut-off values), a <b>higher proportion of older adults from the fall risk group characterized by a slower ST-TUG score and a lower DTC value reported a history of falls.</b> <b>Both above mentioned predictors were similarly significantly associated with falls history in the transitional functioning group</b> (ST-TUG time = 7-16 s), but <b>not in the well-functioning group</b> (ST-TUG score < 7 s).	Low risk of bias
Toma-Carus et al., 2019 [93]	367 community-dwelling older adults: 96 fallers (78 F/18 M; 71.5 ± 9/73.5 ± 8 y.; Clock Drawing Test score: 19 ± 2/20 ± 1) and 271 non-fallers (179 F/92 M; 70 ± 7/73 ± 8 y.; Clock Drawing Test score: 19 ± 2/19 ± 1)	Cross-sectional ( <b>retrospective</b> ) study; Fall history over the last year; → Fallers = (# of falls ≥ 1)	<u>Motor task:</u> <b>TUG</b> test <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-1 subtraction from 100	<u>(1) Yes, (2) Yes &amp; (3) Yes:</u> Among men, mean <b>TUG-DT time spent, mean cognitive stops, mean motor stops, DTC, [TUG-DT time + cognitive stops] and [TUG-DT time + cognitive stops + cognitive errors]</b> were significantly <b>higher</b> in fallers compared to non-fallers. Regarding women, only significantly <b>greater [TUG-DT time + cognitive stops + cognitive errors] and mean motor stops</b> were characteristic of fallers. In men, a significant <b>AUC for predicting risk of falls</b> was found for <b>mean TUG-DT time spent, [TUG-DT time + cognitive stops], [TUG-DT time + cognitive stops + cognitive errors] and DTC</b> , whereas it was only for <b>[TUG-DT time + cognitive stops] and [TUG-DT time + cognitive stops + cognitive errors]</b> in women. The <b>best predictor</b> (in terms of AUC) was <b>DTC in men and [TUG-DT time + cognitive stops + cognitive errors] in women.</b>	Low risk of bias
Asai et al., 2020 [5]	649 community-dwelling older adults: 331 young-older adults (60–74 y.), with 78 fallers (72.1 ± 2.9 y.; 53 F; RDST: 10.6 ± 2.5) and 253 non-fallers (71.7 ± 2.8 y.; 164 F; RDST: 11 ± 1.7), and 318 old-older adults (≥ 75 y.),	Longitudinal observation study ( <b>prospective</b> study); 1-year follow-up	<u>Motor task:</u> <b>TUG</b> test (walking at a comfortable and safe pace) <u>Concurrent cognitive task:</u>	<u>(1) Yes, (2) Yes &amp; (3) Yes – additional value:</u> <b>In young-older adults</b> , fallers took <b>longer to perform ST-TUG</b> in comparison with non-fallers. <b>Old-older adult fallers</b> showed <b>lower DTC</b> than non-fallers. Regarding <b>predictive power for risk of falls, in old older adults, a longer ST-TUG time and lower DTC value</b> were significantly associated with falls occurrence.	Moderate risk of bias

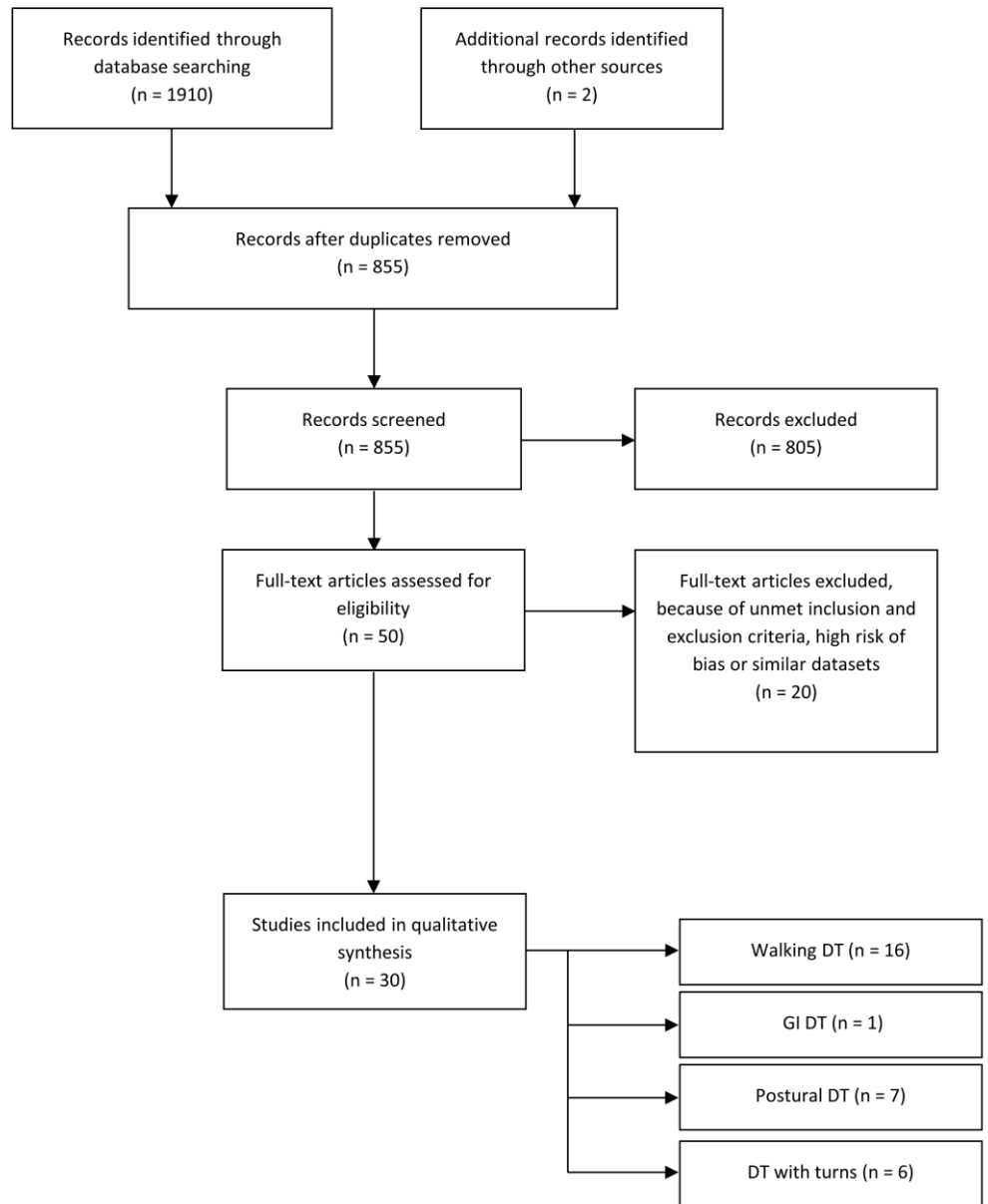
	<p>with 97 fallers (80.4 ± 3.6 y.; 69 F; RDST: 9.3 ± 2.9) and 221 non-fallers (80.8 ± 3.9 y.; 139 F; RDST: 9.1 ± 2.9)</p>		<p><b>mental tracking/working memory task:</b> serial-1 subtraction aloud from 100</p>	<p>→ DT may provide an additional value in TUG for predicting falls among older adults.</p>	
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**Identification**

**Screening**

**Eligibility**

**Included**



## **Etude 2 : Impact des capacités attentionnelles sur l'initiation du pas chez des sujets sains – Etude comportementale et électroencéphalographique (potentiels évoqués et analyse fréquentielle)**

“A new paradigm to study the influence of attentional load on cortical activity for motor preparation of step initiation”

Aurore Braquet, **Madli Bayot\***, Céline Tard, Luc Defebvre, Philippe Derambure, Kathy Dujardin, Arnaud Delval.

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Article publié dans *Experimental Brain Research*.

DOI : <https://doi.org/10.1007/s00221-020-05739-5>

### **Apport personnel**

- Développement des méthodes d'analyse des données et traitement.
- Réalisation des tests statistiques.
- Rédaction et correction du manuscrit suite aux retours des co-auteurs et reviewers.

### **Résumé**

Le programme moteur pour l'initiation de la marche peut varier en fonction des ressources attentionnelles.

L'objectif de cette étude était de déterminer si l'alerte, l'orientation et le contrôle exécutif peuvent moduler l'activation corticale durant l'initiation du pas.

L'« Attention Network Test » (ANT) a été utilisé afin de contrôler l'influence des différentes composantes attentionnelles sur les caractéristiques cinétiques de l'initiation du pas et sur l'activité corticale associée. Trente adultes sains ont réalisé l'ANT combiné à l'initiation du pas en tant que réponse motrice. Le temps d'exécution du pas (TEP) et les ajustements posturaux anticipés (APAs) ont

été enregistrés. Les potentiels corticaux liés au mouvement (ou MRCPs) et les perturbations spectrales (PSLE) liées à l'émission de la réponse motrice ont été analysés en fonction la présence ou non d'un indice ou d'un conflit à résoudre au niveau de la cible.

Le temps de réaction avant début des APAs et donc également le TEP ont été significativement plus courts en cas d'indiçage, alors que la durée des APAs et le TEP étaient plus longs lors de la résolution de conflit. De plus, l'alerte était liée à un taux plus élevé de réponses anticipées et les situations de conflit n'étaient pas associées à un plus grand nombre d'APAs multiples. La charge attentionnelle n'a pas affecté les MRCPs mais bien les PSLE : les essais avec indiçage montraient des désynchronisations alpha et bêta postérieures précédant le début des APAs. Par ailleurs, nous avons trouvé des désynchronisations plus précoces, prononcées et longues dans les bandes alpha et bêta au niveau du cortex sensorimoteur pour les essais avec distracteurs non congruents. Nos résultats ont montré que l'attention a un impact sur l'initiation du pas.

Un profil spécifique des PSLE liées à la réponse motrice semble donc refléter les effets comportementaux de la charge attentionnelle sur l'initiation du pas. Ce nouveau paradigme combinant l'ANT et l'initiation du pas est, dès lors, prometteur pour investiguer l'interaction entre attention et initiation de la marche des populations pathologiques.

**Mots-clés :** Attention Network Test, initiation du pas, électroencéphalographie, ajustements posturaux anticipés.

## **Articulation avec le projet de thèse**

Le paradigme ANT-INIT a été validé (cf. *Supplementary material* dans la section Annexe 2 du Chapitre 6), car (i) les effets des différents réseaux attentionnels sur le TEP, TR comportemental, sont similaires à ceux obtenus classiquement sur le TR avec l'ANT standard ; (ii) les PE et PSLE liés à la cible et associés à ces réseaux attentionnels ressemblent aux résultats des précédentes investigations EEG relatives à l'ANT standard assis. Autrement dit, l'activité corticale en lien avec les traitements attentionnels est cohérente avec ce qui a été constaté pour le paradigme de quantification de l'attention qu'est l'ANT standard.

L'interaction attention-motricité étant maintenant décrite au sein d'une population jeune, nous pouvons désormais nous intéresser aux populations présentant des troubles cognitifs, et en particulier attentionnels, qui pourraient impacter et/ou expliquer leurs troubles moteurs : les patients MP avec



FdM. Le paradigme de l'ANT-INIT pouvant mettre en évidence avec précision l'impact d'une déficience attentionnelle sur les paramètres spatio-temporaux des phases de préparation et d'exécution du premier pas, la majeure partie des résultats de l'influence cognitive est donnée pour la préparation motrice. Le paradigme se limite, en effet, à l'analyse de l'exécution du premier pas uniquement. Il était donc nécessaire d'étudier les liens existants entre contrôle postural initial, APAs et performances d'exécution de la marche chez les patients MP avec FdM. En effet, ces 3 aspects de l'initiation motrice ont été étudiés séparément, deux à deux, mais jamais tous ensemble dans une population MP+FdM.





# A new paradigm to study the influence of attentional load on cortical activity for motor preparation of step initiation

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Received: 22 May 2019 / Accepted: 23 January 2020  
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## Abstract

Motor programme for gait initiation can vary as a function of attentional resources. The objective of the present study was to determine whether alertness, orientation and executive control can modulate cortical activation during step initiation. The attention network test (ANT) was used to control the influence of different attentional components on kinetic characteristics of step initiation and the associated cortical activity. Thirty healthy adults performed ANT combined with step initiation. The step execution time (SET) and anticipatory postural adjustments (APAs) were recorded. Movement-related cortical potentials (MRCPs) and event-related spectral perturbations (ERSPs) after response emission were analysed according to the presence or absence of cueing or conflict resolution. Step reaction time and thus SET were significantly shorter with cueing, whereas APA duration and SET were longer during conflict resolution. Moreover, alertness was related to a higher rate of anticipated responses, and conflicting situations were associated with a greater amount of multiple APAs. Attentional load did not affect MRCPs but ERSPs: trials with a cue showed earlier posterior alpha and beta desynchronisations before APA onset. Furthermore, we found earlier, more pronounced and longer alpha- and beta-band desynchronisations over the sensorimotor cortex for trials with incongruent flankers. Our results showed that attention has an impact on step initiation. A specific pattern of response-locked ERSPs seems to mirror behavioural effects of attentional load on step initiation. This new paradigm combining ANT and step initiation is, therefore, promising to investigate the interaction between attention and gait initiation in pathological populations.

**Keywords** Attention network test · Step initiation · Electroencephalography · Anticipatory postural adjustments

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Communicated by Francesco Lacquaniti.

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Aurore Braquet, Madli Bayot are first co-authors.

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**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s00221-020-05739-5>) contains supplementary material, which is available to authorized users.

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## Introduction

Gait initiation is a motor programme whose characteristics can vary as a function of the attentional resources (Uemura et al. 2013a; Tard et al. 2013, 2016). They are known to modulate anticipatory postural adjustments (APAs) before movement execution (Lajoie et al. 1996; Delval et al. 2012; de Souza Fortaleza et al. 2017). Indeed, gait initiation requires more attentional resources than gait (Suzuki et al. 2004, 2008) and may cause more dual-task interference with an attentional task than steady-state walking does (Uemura et al. 2012). For instance, errors in motor programming have been exhibited in tasks requiring executive control (Uemura et al. 2013a; Delval et al. 2018), and particularly in elderly subjects (Cohen et al. 2011; Sparto et al. 2014). Gait initiation is executed in two phases: the preparation phase (corresponding to APAs) and then the execution phase (corresponding to the time interval between “toe-off” and “heel

strike” for the swing leg). During APAs, the centre of pressure (CoP) is displaced according to a stereotypical pattern: first backwards and towards the swing leg, and then towards the stance leg (Brenière and Do 1991; Jian et al. 1993).

APAs can be modulated by attentional alerting (Tard et al. 2013) and orienting (Tard et al. 2016) processes. Indeed, when a cue preceded the gait initiation signal, we observed that early APAs occurred more frequently (Tard et al. 2013). Moreover, indicating the direction of the subsequent target which will state the required foot to initiate gait had a beneficial effect on step execution time (that includes earlier APAs as well as the subsequent step) (Tard et al. 2016). Cohen et al. (2011) and Uemura et al. (2013a) have also shown that when subjects are in a conflict situation, APAs can be first executed on the wrong side and then lengthen the step latency. This constitutes “APA errors”. Attention can modulate these APA errors for orientation mechanisms (Tard et al. 2016). Healthy subjects can also exhibit steps with several APAs before being able to perform the step execution phase. This kind of abnormal APAs together with APA errors will be named “multiple APAs” in the present paper [as in Cohen et al. (2017)].

Posner and Petersen (1990), Petersen and Posner (2012) proposed a three-network model of visuospatial attention: alerting, orientation and executive control. These three networks, although anatomically separated and with uncorrelated efficiencies (Fan et al. 2002), may interact amongst themselves (Fan et al. 2009). Achieving and maintaining an alert state is the usual definition of *alertness*, *orientation* consists in the selection of relevant information from sensory inputs, whereas *executive control* is involved in monitoring and solving potential conflicts between contradictory responses. The latter network can be evaluated by a flanker task for example (Cohen et al. 2011). All different aspects of visuospatial attention can be investigated by the now widely used attention network test (ANT), which allows independent assessment of alertness, orientation and executive control, as well as their interaction (Fan et al. 2002). Usually, ANT is administered with a response by manual pressing on a computer keyboard.

Since Posner and Petersen model’s description, several studies have evaluated the cortical and behavioural characteristics of each attentional network (Fan et al. 2002; Gamboz et al. 2010): in these behavioural studies, reaction time (RT) was shorter when a neutral cue was presented before the target compared to the situation without cueing (“alerting effect”). It was also shorter in presence of a spatial cue than in presence of a neutral cue (“orienting effect”). Likewise, RT was longer with incongruent than with congruent flankers (“conflict/executive control effect”). Few studies have evaluated the influence of attentional capacities on step initiation (Cohen et al. 2011; Uemura et al. 2013a, b; Tard et al. 2013, 2016). The step initiation task is of particular

interest, because it is known to reflect early mechanisms of motor preparation that are not shown by analysing simple reaction times (Tard et al. 2016). The choice of investigating gait initiation can also be easily understood when we know the ability to take a quick step represents an important motor skill that can prevent a fall from occurring, regardless of the nature of the fall, in older adults as well as in patients with Parkinson’s disease and freezing of gait (Lord and Fitzpatrick 2001; van den Bogert et al. 2002).

The cerebral functional substrates of standard ANT have been namely explored with event-related potentials (ERPs) based on electroencephalographic (EEG) recordings (Fan et al. 2007; Neuhaus et al. 2007, 2010; Deiber et al. 2013; Galvao-Carmona et al. 2014; Williams et al. 2016). In young adults, Williams et al. found a larger fronto-central target N200 for incongruent targets compared to congruent targets (Williams et al. 2016), whereas Neuhaus et al. (2007) did not emphasise any relationship between the amplitude of N200 and target congruency. As a reminder, N200 component was proposed either to mirror the recruitment of top-down resources to improve stimulus evaluation when conflict is detected or to reflect an evaluation of the possible outcomes rather than conflict detection (Williams et al. 2016). Fronto-parietal P300 modulations during executive control have also been reported [except in Fan et al. (2007), Williams et al. (2016)], with frontal P300 increment and parietal P300 decrement that may mirror on the one hand, response withholding, prepotent response inhibition and correct response execution related to incongruent flankers (via frontal “nogo P300”) (Neuhaus et al. 2010) and, on the other hand, increased difficulty of visual target detection as well as inhibition in the condition with an incongruent target (via parietal “P300b”) (Neuhaus et al. 2007, 2010; Deiber et al. 2013; Galvao-Carmona et al. 2014). Additionally, peak latency of target P300 was longer for incongruent targets than for congruent ones at centro-parietal and fronto-central sites, reflecting the use of more time to evaluate the incongruent target (Neuhaus et al. 2007; Williams et al. 2016). Some studies have also measured the event-related spectral perturbations (ERSPs) during standard seated ANT (Fan et al. 2007; Deiber et al. 2013): in particular, the response-locked spectral analysis of conflict effect (i.e. the time–frequency pattern related to incongruent minus congruent target conditions) involved event-related desynchronisation (ERD) in theta and alpha bands before response onset and theta and beta bursts near or after response (Fan et al. 2007). Similarly, in the context of continuous mobilisation of the lower limbs, attention was related to lower power in theta, alpha and beta bands over the motor and somatosensory cortex and other more widely distributed cortical areas compared to mind wandering (Melinščak et al. 2014; Melinscak et al. 2016).

So far, no study has assessed ERPs or ERSs associated with an attentional paradigm like the ANT in a

step-initiation task. Characteristics of cortical activation in a conflict or non-conflict situation task with or without cueing during step initiation remain to be better characterised. Additional knowledge at the cortical level regarding the interaction between attention and step initiation would, therefore, allow for a better pathophysiological understanding of public health issues associated with an impaired initiation of gait (e.g. falls and Parkinson's disease with freezing of gait). The new paradigm used in the current study combines ANT and step initiation and, consequently, only differs from the standard ANT by the motor task. That is the reason why, next to the stimulus-locked ERP and ERSP analyses that allow to track the sensory and cognitive stages of information in time, it is mainly interesting to lock EEG epochs to the motor response to study the activity of motor-related regions in the stages preceding and following action. Such ERPs are called movement-related cortical potentials or MRCPs and are comprised of four components: early Bereitschaftspotential/readiness potential (BP), late BP, negative motor potential (MP) and re-afferent potential/positive post-movement potential (RAP) (Shibasaki 2012; Berchicci et al. 2016). Motor-related ERSPs are alpha and beta ERD/S that represent, respectively, increased/decreased activation of cortical areas involved/not involved in the task (Pfurtscheller 1999). In the preparation phase toward the movement and during the movement itself, alpha and beta ERDs occur predominantly over the somatosensory cortex and the motor cortex, respectively. Then, after the termination of movement, ERSPs are observable in the beta band (Pfurtscheller 1999; Shibasaki and Hallett 2006). The relevance of analysing response-locked EEG correlates with our paradigm relies on the fact that ERD/S and MRCP differ according to the type of movement (Vidailhet et al. 1993; Pfurtscheller et al. 1997, 1998; Jankelowitz and Colebatch 2002; Shibasaki and Hallett 2006). The ones related to the ANT carried out while standing will, therefore, specifically characterise step initiation in comparison with the standard ANT and its finger pushing on a computer keyboard.

The primary objective of the present study was to establish whether or not attentional load modification [using the ANT (Fan et al. 2002)] can modulate cortical activation during gait initiation through the analysis of response-locked ERPs and ERSPs. The study's secondary objective was to validate the current paradigm combining ANT and step initiation by obtaining outputs similar to those of the standard button-pushing-based ANT, i.e. behavioural results and cortical activation related to the influence of cueing on responses, target perceptual discrimination, information processing, inhibition of a prepotent response and execution of the correct response. This secondary aim is addressed in Online Resource 1.

Our hypotheses regarding ERPs and ERSPs were that activation of attentional networks [mainly fronto-parietal

areas for the conflict resolution network, frontal and parietal regions, particularly of the left hemisphere, for the alerting network, and parietal sites and frontal eye fields for the orienting network (Fan et al. 2005; Raz and Buhle 2006; Cohen and Ridderinkhof 2013)] would modify cortical preparation of movement. Indeed, a conflict situation could affect either the Bereitschaftspotential or alpha/beta ERD, with a smaller BP and a more pronounced and longer ERD for the condition with incongruent flankers. We expected differences in ERSPs in these EEG bands that are either sensitive to motor preparation (Pfurtscheller 1999) or attentional tasks (Fan et al. 2007). Similarly, cueing before target presentation could lead to a decreased latency of BP as well as an earlier ERD. As an additional assumption, in the ANT's conflict resolution condition, we would observe a higher proportion of multiple APAs—reflecting the early control of movement preparation, whereas the presence of a cue would induce an earlier step reaction time.

## Material and methods

### Participants

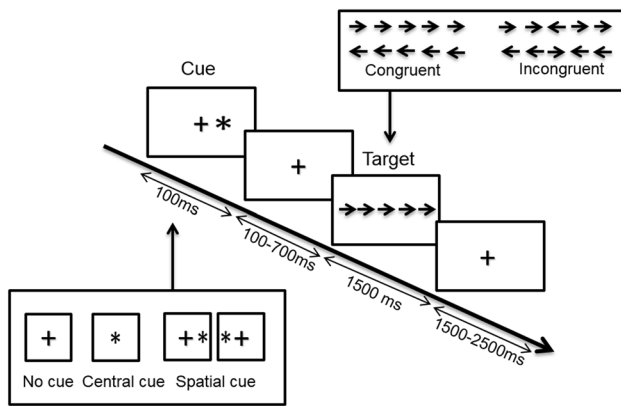
Thirty healthy adult volunteers [16 females, 14 males; 29 right-handed; mean (standard deviation) age: 39.4 (14.2)] participated in the study after providing their informed written consent. According to self-report data, none of the participants had a history of medication use or disease that could interfere with gait. The study was approved by the local independent ethics committee (CPP Nord-Ouest, Lille, France; reference: 2015-A00013-46).

### Experimental setting

#### The attentional task

The attentional task (Fig. 1) was an adaptation of the ANT (Fan et al. 2002). In our modified version combining an attentional load with the initiation of a step, the participant was instructed to stand centrally on a force platform, in a comfortable and stable posture, with his/her feet parallel and apart from few centimetres. A computer display screen was placed 1 m in front of the subject. By analogy with the seated ANT paradigm, the participant was instructed to initiate a forward step as fast and as accurately as possible after presentation of a visual target not to prioritise an improvement of either reaction time or proportion of multiple APAs (Uemura et al. 2013b). Besides, he/she was told not to initiate gait during the presentation of a cue.

More particularly, the participant was instructed to stare at a cross located at the centre of the screen. A cue could then appear for 100 ms: either a central cue (central star),



**Fig. 1** Experimental set-up of the modified version of the ANT that is used in the current study

or a spatial cue (a star located at the right or left of the fixation cross). In the “valid cue” condition, the spatial cue was located where the target (a central arrow pointing to the right or left side) was going to point to, whereas in the “invalid cue” condition, the spatial cue was positioned on the opposite side. In more detail, the spatial cue was presented in the form of an asterisk positioned 7 cm to the right or left of the central fixation cross (corresponding to a visual angle of between  $12^\circ$  and  $15^\circ$  of eccentricity for central vision). The lack of a cue constituted the “no cue” condition. After a variable duration (from 100 to 700 ms), the target appeared for 1500 ms. The latter was presented centrally, at the level of the fixation cross, and was surrounded by flankers, either congruent or incongruent (Fig. 1). If the target appeared to point to the left, the participant had to initiate a step with his/her left foot; conversely, if the target was directed to the right, the participant had to start walking with his/her right foot. Subsequently, the fixation cross reappeared for a random period ranging between 1500 and 2500 ms after the target presentation.

The participant was instructed to step. Indeed, the assessment of step initiation and not gait initiation represents a limit of the current study. However, participants often performed a second step and, in any case, APAs during step initiation are similar to the ones carried out during gait initiation, except for the COP backward shift which is more ample during gait initiation. Finally, a good reason to having chosen to study step initiation instead of gait initiation is the nature of the ANT as a paradigm with time pressure. The combination of ANT with step initiation, therefore, allows to keep this time pressure that is essential for the comparison with the standard ANT.

Overall, four blocks of 75 trials each—separated by short breaks—were performed. Through those experimental blocks, each cue and target condition was presented in a pseudo-randomised order: 156 congruent trials, 144

incongruent trials, and 49, 61, 142 and 48 trials corresponding respectively to no cue condition, central cue condition, and both valid and invalid spatial cue conditions.

While previous studies using standard seated ANT assessed the reaction time for key press, the behavioural reaction time in the context of our paradigm combining ANT and step initiation is the step execution time [SET, i.e. the time interval between target presentation and heel contact of the swing foot (Uemura et al. 2013a)]. The median SET was, therefore, calculated for each cue and target condition for each subject. Trials without any step, with an incorrect response (i.e. step initiation with the wrong foot) or an anticipated response (i.e. with a reaction time or the time interval between the appearance of the target and APA onset,  $RT < 100$  ms) were excluded from the analyses. It is noteworthy that, after exclusion of trials without any step, with an incorrect response or with an anticipated response, subjects presented trials that were distributed as follows [median (first quartile–third quartile)]: 113 (104.25–126.25) congruent trials, 108.5 (89–116.5) incongruent trials, and 40 (32.25–42), 42 (36.25–47), 106 (93.5–114.75), 35 (31–38.75) corresponding to no cue condition, central cue condition, and both valid and invalid spatial cue conditions. Subsequently, the different attentional networks defined by Posner and Petersen were evaluated in this way:

Alerting effect = SET without cue – SET with central cue;

Orienting effect = SET with central cue – SET with valid spatial cue;

Executive control effect = SET with congruent flankers  
– SET with incongruent flankers;

Validity effect = SET with invalid spatial cue  
– SET with valid spatial cue.

It has to be noted that both incorrect and anticipated steps were quantified for each cue and target condition and each subject.

### Motion analysis

Data were collected with a three-dimensional motion analysis system (VICON 370<sup>®</sup>, Oxford Biometrics, Oxford, UK), using eight infrared cameras sampled at 100 Hz. Centre of pressure was measured with two force platforms (the ORG-5 model from AMTI<sup>®</sup>, Watertown, MA, USA) sampled at 1000 Hz. Reflective markers were placed on precise, reproducible anatomical landmarks on each foot: the toe (the head of the second metatarsal), the lateral malleolus and the heel. Data were then computed by the same operator using an in-house MATLAB<sup>®</sup> script (The MathWorks, Natick, MA,

USA). The SET and its components were assessed by controlling, from the appearance of the target to heel contact, the vertical forces exerted on the force platform as well as kinematic features obtained with the 3D motion analysis system (Fig. 2). The SET includes:

- the reaction time RT, i.e. the time interval between the appearance of target S2 and APA onset  $T_0$ ;
- the anticipatory postural adjustments APAs. The APA duration was assessed by subtracting  $T_0$  from the toe-off time. The direction of the APA was considered to be normal if the CoP moved backwards and laterally towards the swing foot. Multiple APAs were defined as either an incorrect CoP displacement or unstoppable CoP displacement leading to several APAs. In case of multiple APAs, the correction time was described as the time interval between  $T_0$  and the lateral corrector shift, corresponding to the beginning of the effective APA;
- the swing phase started at the end of the APA and finished with heel strike.

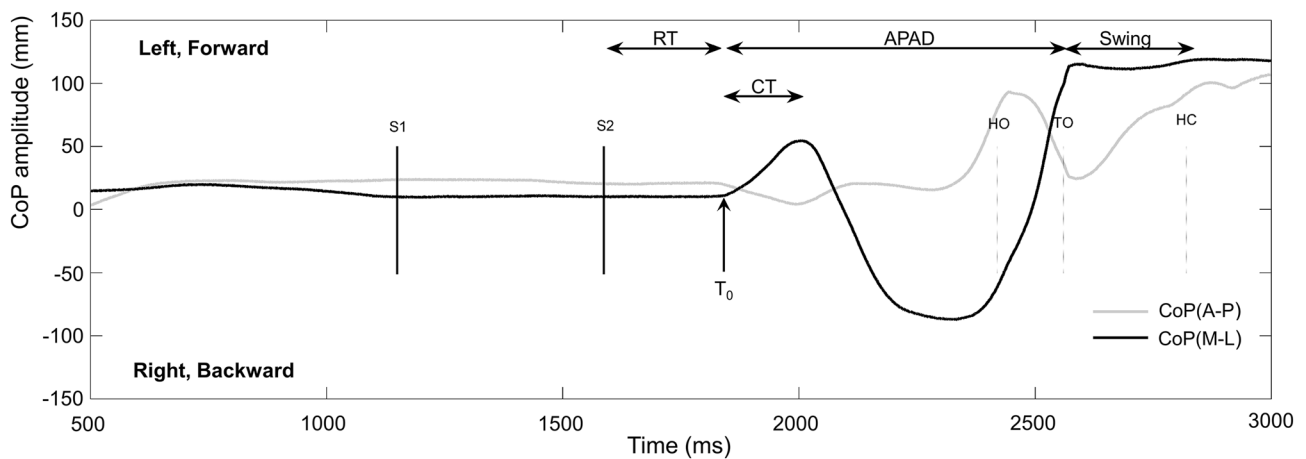
Hence, SET was quantified by subtracting S2 from the time of heel strike.

From a methodological point of view, as mentioned above, a MATLAB® script detected events related to the first step and then the evaluator had either to visually confirm the proposed detections or to choose visually more suitable times of events. Heel-off was detected as the instant when the heel velocity in the sagittal plane exceeded the value at baseline (from the start of the trial

until S2) by 100 mm/s (Ghoussayni et al. 2004; Lambrecht et al. 2017). This algorithm method has been shown to be both reliable in comparison to the visual inspection and accurate. Another proposed detection of heel-off was based on the time when the vertical position of the heel marker of the swing leg was beyond the value at baseline (from the start of the trial until S2) plus 1 mm (Honeine et al. 2016). Furthermore, toe-off was defined as the time of a local maximum in the vertical velocity component of the heel marker, whereas heel strike was associated with the time of a local minimum in the vertical velocity component of the toe marker (Pijnappels et al. 2001). Finally,  $T_0$  was defined as the time when mediolateral CoP exceeded  $\text{mean}(\text{baseline}) + 1 \times \text{standard deviation}(\text{baseline})$  just before exceeding  $\text{mean}(\text{baseline}) + 3 \times \text{standard deviation}(\text{baseline})$  (Sun et al. 2015; Sun and Shea 2016). The baseline used was the time interval from the start of the trial to the appearance of the cue to avoid postural sway related to the occurrence of visual stimuli as much as possible.

### Electroencephalographic acquisition

The electroencephalogram was recorded with an Ag/AgCl 128-scalp-electrode cap (Waveguard®, ANT Neuro) positioned according to the 10/05 international system (Oostenveld and Praamstra 2001). Data were acquired with ASA™ software (ANT Neuro), using a sampling frequency of 512 Hz and impedances below 20 kΩ during the experiment. The data were pre-processed with EEGLAB, a MATLAB® toolbox (Delorme and Makeig 2004). Firstly, EEG data



**Fig. 2** Step initiation with the right foot, with APA error. Depiction of the step execution time (SET) and its three components: reaction time RT (time interval between the appearance of the target S2 and APA onset  $T_0$ ), duration of anticipatory postural adjustments APAD (time interval between  $T_0$  and toe-off), and swing phase *Swing* (from the end of APA to heel strike). The direction of the APA was considered to be normal if the CoP moved backwards and laterally towards the swing foot. An APA error was described as an incorrect CoP displacement.

The correction time CT was defined as the time interval between  $T_0$  and the lateral corrector shift, corresponding to the beginning of the effective APA. In the figure, the correct APA is preceded by an APA error. CoP (A-P) and CoP (M-L) represent CoP displacements along the anteroposterior axis and mediolateral axis, respectively. Vertical lines on the horizontal (time) axis indicate (from left to right) S1 (the cue), S2 (the target), heel-off (HO), toe-off (TO), and heel contact (HC)

were downsampled at 256 Hz. Then, a low-pass filter was applied to remove the first harmonic of the line noise at 100 Hz, as well as a high-pass filter with a cut-off frequency of 0.5 Hz and a 50-Hz Notch filter for removing baseline drift caused, for example, by sweating and line noise. After filtering, only a time interval from 1500 ms before the first trial to 1000 ms following the last trial was kept as EEG signal of interest. Next, flat electrodes were automatically removed based on a maximum tolerated flatline duration of 5 s (using an EEGLAB plugin called *clean\_rawdata()*). The artefact-affected electrodes were, for their part, semi-automatically detected: first, still using *clean\_rawdata()*, a channel was considered abnormal when it was correlated at less than a minimum correlation value to a reconstruction of itself based on other channels in a given time window; second, a final manual rejection of bad electrodes was performed using the EEGLAB plugin *trimOutlier()*, with lower-and upper-accepted standard deviation for EEG signal of each channel. Thereafter, a spherical interpolation was performed for identified artefact-affected electrodes, with a maximum interpolation rate of 10% ( $n = 13$ ) for the whole set of 128 scalp electrodes. The next pre-processing step aimed at removing transient, non-biological, large-amplitude noise/artifacts (e.g. abrupt impedance changes due to headset motions) using a non-stationary method based on sliding window PCA and implemented in the EEGLAB plugin *clean\_rawdata()*: the artifact subspace reconstruction (ASR) method (Mullen et al. 2015; Chang et al. 2018). The ASR parameter (i.e. the standard deviation cut-off for removal of bursts) was fixed at 20 [as recommended by Chang et al. (2018)]. Average reference was then chosen as re-referencing method. Subsequently, EEG signal during breaks between blocks was removed before using a stationary method for decomposing constant fixed-source noise/artefacts/signals of stationary data: the independent component analysis (ICA), and the Infomax algorithm in particular (Delorme et al. 2012). The artefact-affected components that must be removed were automatically selected among the first half of the components, thanks to a highly trained IC classifier: *ICLabel* (Pion-Tonachini et al. 2019). Afterwards, a manual confirmation of the components representing non-neural sources was required and the maximum number of removed IC was fixed at 20. We finally segmented the EEG data into 2500-ms epochs that were time locked with respect to target onset (1500 ms before and 1000 ms afterwards; see Online Resource 1 for methodology and results of the target-locked analysis of EEG data) or into 2150-ms epochs that were response locked (i.e. epochs from 1500 ms before APA onset until 650 ms after). A final visual inspection was needed to manually remove epochs containing remaining muscle artefacts or others.

After the manual rejection of epochs of EEG data with artefacts, participants showed trials that were distributed

as follows [median (first quartile–third quartile)]: 89 (74.25–100) congruent trials, 88.5 (75–98.25) incongruent trials, and 32 (29–35.75), 32 (26–38), 83.5 (72.75–92), 30 (26.25–32.75) trials corresponding, respectively, to no cue condition, central cue condition, and both valid and invalid spatial cue conditions.

### ERP data analysis

Response-locked ERPs (see Online Resource 1 for methodology and results of the target-locked analysis of EEG data) were analysed with the EEGLAB toolbox (Delorme and Makeig 2004), with a baseline interval from 1500 to 1300 ms before APA onset. The time window analysis was from -800 ms before S2 to 650 ms after. In the context of comparison of target conditions as well as cue conditions, we first analysed ERP scalp distribution maps between -400 and 400 ms. Next, based on the observation of topographic maps of ERPs and according to the well-known topography of such ERP components (Shibasaki and Hallett 2006; Berchicci et al. 2012), BP and P300 waves' characteristics were assessed and collected by grand averaging over the relevant midline electrodes: FCz, Cz, CPz and Pz for BP, and Pz for P300. Indeed, we studied movements triggered by external stimuli and, for this reason, late BP and MP components of MRCP were covered by stimulus-evoked activity: P300 was observed instead of late BP and MP, and late P300 seemed to coincide with RAP (Berchicci et al. 2016). BP and P300 peak latencies and amplitudes of all the subjects were compared as a function of the attentional condition. The amplitude of potentials was measured as the difference between the maximum peak of the ERP waveform and the mean baseline voltage. Latency was defined as the interval between APA onset and the point of peak amplitude in the time window of the potential. Time window of BP ranged from -400 to 0 ms before response onset, whereas time window associated with P300 was between 0 and 400 ms after APA onset. The grand-averaged ERPs were low-pass filtered at 40 Hz for displaying purpose only.

To have a more accurate idea of generators of MRCP, we finally performed source localisation (see Online Resource 1 for methodology and detailed results).

### ERSP data analysis

ERSP data were also analysed using the EEGLAB toolbox (Delorme and Makeig 2004) with a baseline interval between 1500 and 1100 ms before APA onset (see Online Resource 1 for methodology and results of the target-locked analysis of EEG data). To characterise event-related EEG oscillations such as ERD and ERS in theta (4–7 Hz), alpha (8–12 Hz) and beta (13–30 Hz) bands, we applied a time–frequency analysis using a continuous Morlet wavelet



transform, with 1.5 cycles at the lowest frequency and 7.875 at highest (factor: 0.3), and analysed ERSP scalp distribution maps between – 200 ms before APA onset and 400 ms after.

## Statistical analyses

To evaluate alerting, orienting and conflict resolution effects on behavioural data, a Student's *t* test was applied on medians of first step characteristics (SET, RT, APA, swing phase and speed, as well as rates of multiple APAs, incorrect steps and anticipated responses) calculated for each participant in conditions with no cue versus a central cue, with a central cue versus a spatial cue, and with a congruent versus an incongruent target, respectively. When data were not normally distributed, Wilcoxon's signed rank test was carried out. Analyses were performed with SPSS 16.0 software, with the exception of ERP and ERSP analyses (performed with EEGLAB toolbox). Permutation tests for multiple comparisons were performed on overall ERP and ERSP data with FDR correction. Afterwards, conflict resolution, alerting and orienting effects on specific ERP waveforms' features (i.e. peak amplitude and latency) at particular scalp sites were assessed using the same statistical tests as for behavioural data, with SPSS 16.0 software. The threshold for statistical significance was set to  $p=0.05$ .

## Results

### Behavioural data

**SET** Alerting effect was observed on SET (mean  $\pm$  standard deviation of  $969 \pm 94$  and  $935 \pm 99$  ms in the no cue and central cue conditions, respectively;  $p < 0.001$ ) and RT ( $237 \pm 29$  and  $217 \pm 31$  ms, respectively;  $p < 0.001$ ), but duration of APA ( $492 \pm 58$  and  $487 \pm 62$  ms, respectively), swing phase ( $220 \pm 60$  and  $218 \pm 57$  ms, respectively) and speed of first step ( $934 \pm 128$  and  $935 \pm 133$  mm/s, respectively) did not significantly differ between cue conditions ( $p = 0.312$  for APA duration,  $p = 0.163$  for swing phase and  $p = 0.904$  for first step velocity). Besides, orienting effect was not shown on any of the behavioural features of step initiation, as it was the case for validity effect. Furthermore, the SET was significantly longer in trials with incongruent flankers than in trials with congruent flankers ( $979 \pm 91$  and  $928 \pm 101$  ms, respectively;  $p < 0.001$ ), as was the APA duration ( $520 \pm 64$  and  $470 \pm 58$  ms, respectively;  $p < 0.001$ ). There was no effect of executive control for the reaction time ( $222 \pm 29$  and  $224 \pm 29$  ms in the incongruent and congruent conditions, respectively;  $p = 0.269$ ), the duration of the swing phase ( $219 \pm 56$  and  $219 \pm 56$  ms, respectively;

$p = 0.696$ ), or the speed of the first step ( $936 \pm 129$  and  $933 \pm 128$  mm/s, respectively;  $p = 0.352$ ).

**Multiple APAs** The rate of multiple APAs was significantly higher in trials with incongruent flankers than in trials with congruent flankers (average rates of 39 and 18%, respectively;  $p < 0.001$ ). Likewise, the duration of multiple APAs was significantly longer in trials with incongruent flankers than in trials with congruent flankers (mean  $\pm$  standard deviation of  $633 \pm 66$  and  $610 \pm 75$  ms, respectively;  $p = 0.007$ ), as was, therefore, the SET ( $1056 \pm 99$  and  $1017 \pm 95$  ms, respectively;  $p < 0.001$ ). Furthermore, this increased SET in the target condition with incongruent flankers may also be explained by a higher RT in this condition (average medians of  $199 \pm 23$  and  $185 \pm 24$  ms, respectively;  $p < 0.001$ ). Thanks to a Pearson's partial correlation test, a significant positive association between SET and APA duration in the incongruent condition of target was found, even when controlling for RT ( $r = 0.787$ ;  $p < 0.001$ ). However, RT was not significantly correlated to SET after correcting for APA duration ( $r = 0.372$ ;  $p = 0.172$ ). Finally, there were no alerting, orienting or validity effect on the percentage of multiple APAs in each participant.

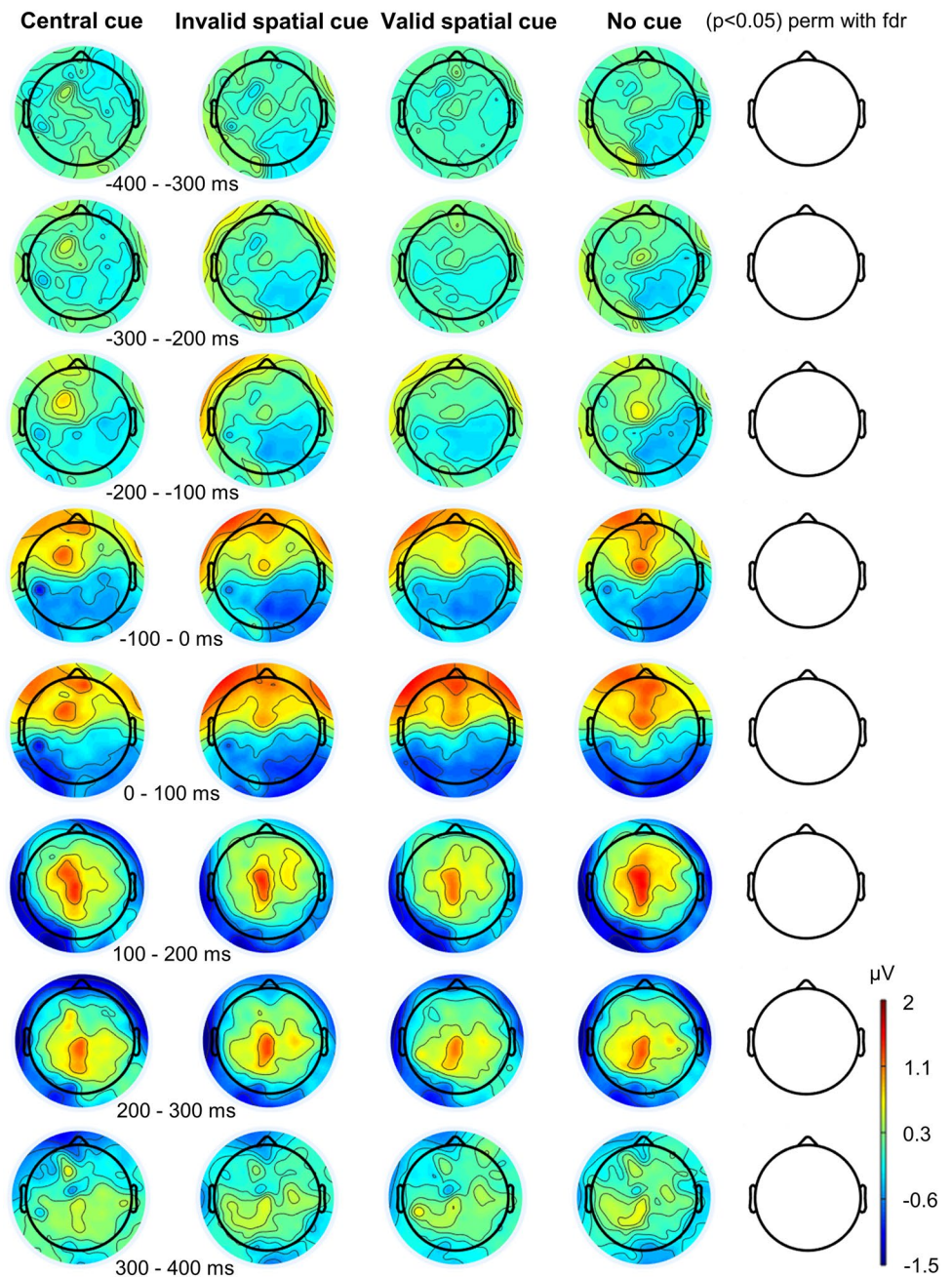
**Rate of incorrect responses** There was no significant difference in incorrect starts between the flanker conditions (0.8% with congruent flankers, and 0.6% with incongruent flankers;  $p = 0.305$ ), but also no alerting, orienting or validity effect ( $p = 0.275$ ,  $p = 0.547$  and  $p = 0.313$ , respectively).

**Rate of anticipated responses** Again, no significant difference was found in the rate of anticipated steps when comparing congruent and incongruent conditions (16 and 18%, respectively;  $p = 0.2$ ). Orienting and validity effects were also absent ( $p = 0.973$  and  $p = 0.463$ , respectively). Nevertheless, anticipated steps occurred more frequently in trials with a central cue compared to trials without cue (average rates of 18 and 11%, respectively;  $p < 0.001$ ).

### Response-locked ERPs

Neither orientation nor alertness affected response-locked ERPs as seen in Fig. 3. The comparison of topographic maps of response-locked ERPs between both target conditions (Fig. 4) only showed a posterior positive wave included in a time interval ranging from 100 to 400 ms after APA onset [corresponding to the target-locked P300 (Berchicci et al. 2016)] that was of significantly higher amplitude for the target condition with congruent flankers and lasted longer in the case of incongruent flankers. After analysis of ERPs at Pz, we confirmed that there were no differences in terms of amplitude and latency of BP between the two target conditions. Moreover, the peak latency of the P300 wave was not significantly different between both conditions of target, but a significantly higher peak amplitude of P300 was found

**Fig. 3** Influence of cue modality on MRCP. ERP scalp distribution maps between 400 ms before APA onset and 400 ms after, for trials with a central cue (first column), an invalid spatial cue (second column), a valid spatial cue (third column) and without cue (fourth column) in the step initiation ANT. Column to the right of ERP scalp distribution maps: significant differences in a permutation test with FDR correction (threshold at  $p < 0.05$ ) are marked as red dots



at Pz for congruent targets (respectively  $2.59 \pm 2.28 \mu\text{V}$  vs.  $2.31 \pm 2.02 \mu\text{V}$  at Pz;  $p = 0.048$ ).

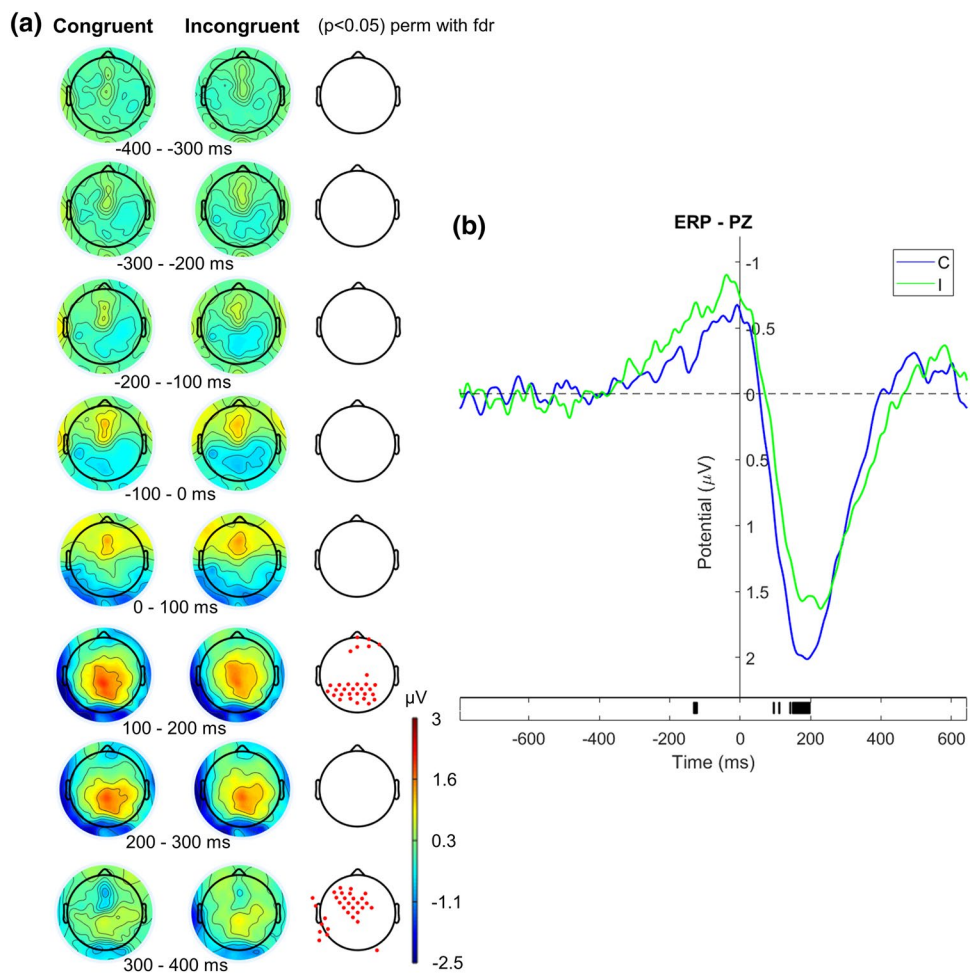
It was surprising to have observed a maximal BP at parietal leads while this motor potential is supposed to be symmetrically distributed and maximal at the midline centro-parietal area (Shibasaki and Hallett 2006). Thanks to MRCP source localisation (see Online Resource 1 for further details), we confirmed the location of BP over the

sensorimotor cortex, with the supplementary motor area as the main potential generator.

### Response-locked ERSPs

Concerning the impact of cueing on response-locked ERSPs (Fig. 5), an alerting effect on posterior alpha and mainly beta ERDs was only seen in a 200-ms time interval before APA

**Fig. 4** Influence of target modality on MRCP. **a** ERP scalp distribution maps between 400 ms before APA onset and 400 ms after, for trials with congruent flankers (first column) or incongruent flankers (second column) in the step initiation ANT. Column to the right of ERP scalp distribution maps: significant differences in a permutation test with FDR correction (threshold at  $p < 0.05$ ) are marked as red dots. **b** ERPs at Pz. A negative wave (i.e. the Bereitschaftspotential BP) was observable from around 400 ms before response onset, followed by a positive wave (corresponding to P300). At the bottom, time intervals highlighted in black represent those for which the  $p$  value related to permutation statistics with FDR correction is significant (i.e.  $< 0.05$ ). *C* trials with congruent flankers, *I* trials with incongruent flankers



onset: trials without a cue were not related to any posterior desynchronisation during this period unlike trials with a neutral or a spatial cue. Based on topographic representations of response-locked EEG spectral activity (Fig. 6a), with a focus on spectral activity at CPz (Fig. 6b), we found an earlier, of higher amplitude and longer duration beta-band ERD over the sensorimotor cortex for trials with incongruent flankers in comparison with congruent trials. Desynchronisation was also greater and lasted longer in alpha band in incongruent conditions, whereas earlier synchronisation occurred in trials with congruent flankers.

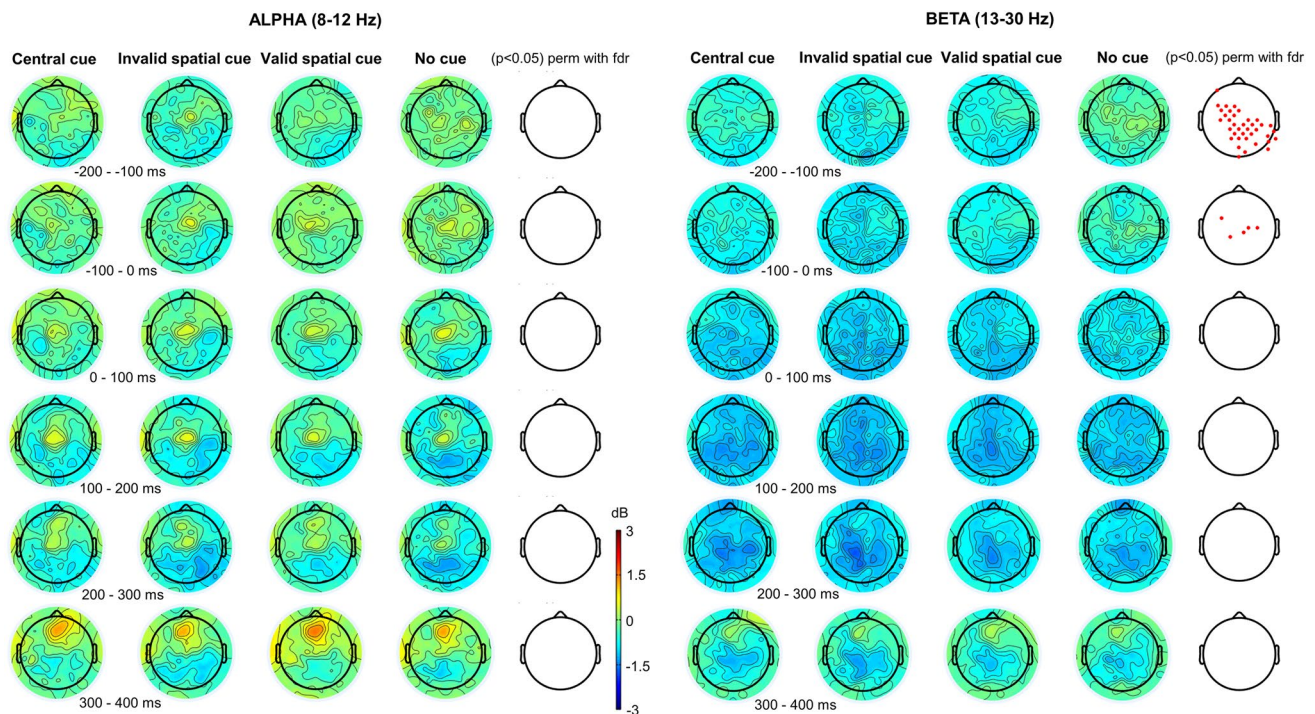
### Discussion

The results of the present study demonstrate that attention can modulate cortical activation during gait initiation in healthy adults. This study is the first to have evaluated the cortical characteristics of attentional modulation (through ANT) during step initiation. Here, we observed that an attentional load does not modify MRCPs, but that ERD in alpha and beta bands were modified either by a variation of cue

modality (alertness) or target modality (executive control). These cortical oscillations have direct consequences on movement preparation with an effect either on reaction time or on duration of the preparation phase. The absence of an orienting effect in the overall study results will be discussed in the section related to the behavioural results.

### Effects on cortical activity

*Response-locked ERPs* After having mapped ERPs between 400 ms before APA onset and 400 ms after, we observed a centro-parietal negative ERP starting approximately 500 ms before APA onset and corresponding to the BP. However, neither BP amplitude nor BP latency were significantly different between cue and target conditions. Those results are confirmed by a study of Di Russo and colleagues (Di Russo et al. 2017): they found similar waveforms and topographies for BP associated with “go” and “nogo” conditions of a go/nogo paradigm, independently of the presence or not of a warning cue and of a variable or constant inter-stimulus interval. Rather, a reduced BP was observed in the post-error trials (Perri et al. 2016). Another response-locked



**Fig. 5** Influence of cue modality on alpha- and beta-band ERD. Response-locked topographic distributions of time–frequency energy [left: in alpha band (8–12 Hz); right: in beta band (13–30 Hz)], corresponding to the four cue conditions (central cue, invalid spatial cue, valid spatial cue and no cue) in the step initiation ANT. Time

interval: between – 200 ms before APA onset and 400 ms after. ERD is shown in blue and ERS is shown in red. Column to the right of spectral distributions in each frequency band: significant differences in a permutation test with FDR correction (threshold at  $p < 0.05$ ) are marked as red dots

ERP showed in our study was a centro-parietal positivity occurring between 100 and 400 ms after APA onset: the response-locked equivalent of target-locked P300 (Berchicci et al. 2016). Response-locked P300 did not significantly differ by its latency between both target conditions (contrary to target-locked P300). It only presented a lower amplitude for trials with incongruent flankers. The greater executive control effect on peak amplitude for response compared to target-locked P300 can be explained by the fact that this ERP component seems to be more related to the response than to the stimulus (Berchicci et al. 2016). Indeed, a late component such as P300 reflects a function that bridges perception with response processing and, as found by Berchicci and colleagues, P300 presents a larger amplitude in response- than in stimulus-locked averaging. Finally, the reason why the exogenous components (e.g. P100 and N100) were not visible in the response-locked ERP waveform is because such components are enhanced by stimulus locking (Berchicci et al. 2016). One of the limits of the present study remains the restricted number of trials for some cue conditions related to a few participants, which may weaken the reliability of the results. However, for each subject, the evoked potentials of interest have been clearly observed.

*Response-locked ERSPs* Alpha/beta ERD is thought to reflect the activation of regions engaged in visuospatial

attention or motor execution (Pfurtscheller, 1999). The alerting effect on the amplitude of alpha and beta ERD in a 200-ms time interval before APA onset is rather related to the phase of sensory processing than associated with step preparation. Moreover, the earlier, of higher amplitude and longer duration alpha- and beta-band ERD observed over the sensorimotor cortex for trials with incongruent flankers instead of congruent ones was in line with the higher task complexity (i.e. higher rate of multiple APAs) and the longer APA duration related to trials with incongruent flankers. ERSPs with target locking were also able to reflect the executive control effect. As reported in studies investigating the standard seated ANT and carried out by Deiber et al. (2013) and Fan et al. (2007), target-locked alpha-band ERD was more pronounced as well as of longer duration in trials with incongruent flankers than in trials with congruent flankers—reflecting the greater attentional load. Concerning target-locked beta-band oscillations, our results showed that central ERD was more pronounced and lasted longer for incongruent trials than congruent trials in the step initiation ANT (as also reported by Deiber et al. (2013)). This mirrors the specific participation of areas involved in motor preparation and execution.

## Behavioural effects

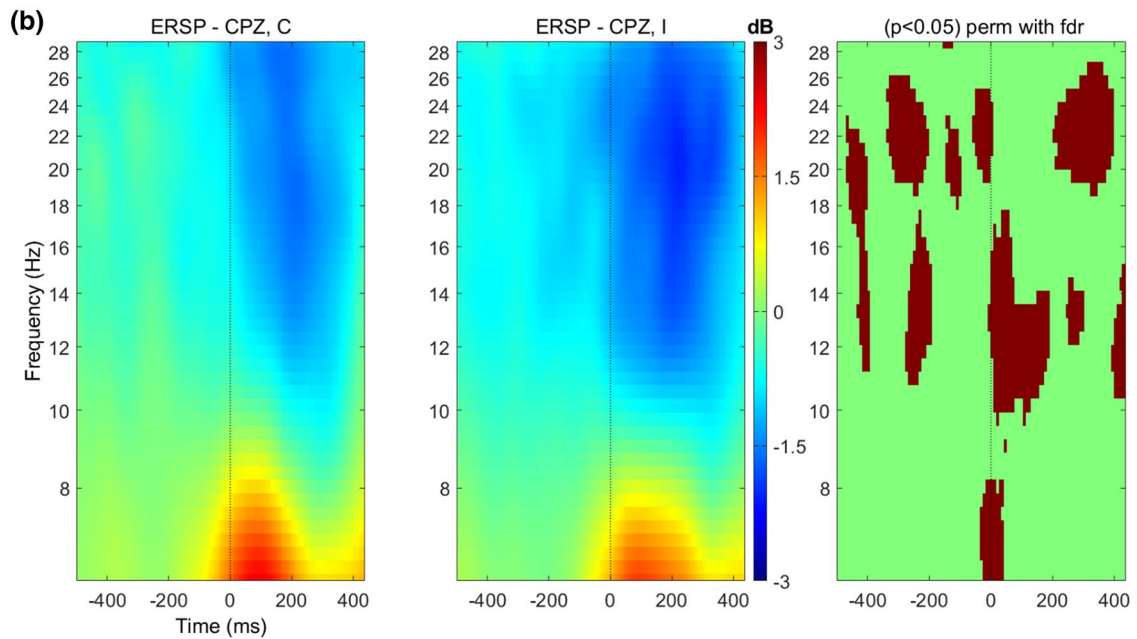
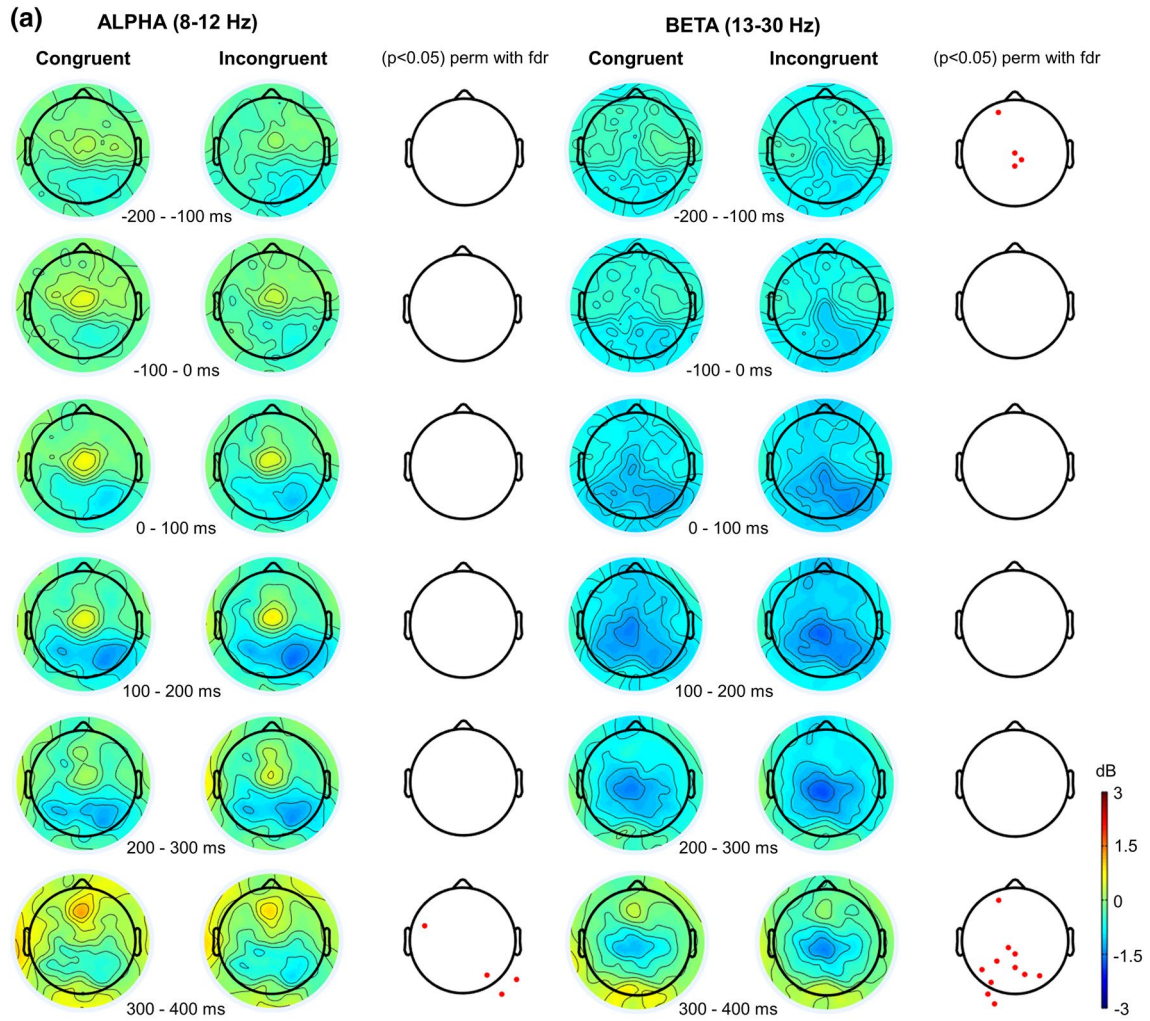
In terms of behavioural characteristics of first step, alertness had an effect on RT, with shorter RT in the presence of a cue just before target appearance in comparison with trials without any cue. This result was associated with a greater rate of anticipated steps in trials with a central cue. It finally led to an alerting effect on SET, with a longer SET related to trials without any cue compared to trials with a central cue. SET representing the behavioural reaction time, this observation of an alerting effect on SET confirms a result found previously in studies using the standard seated ANT, that is a significant effect of alertness on RT (Fan et al. 2002, 2005; 2007,2009; Neuhaus et al. 2010; Deiber et al. 2013; Galvao-Carmona et al. 2014; Williams et al. 2016). Still in line with results from the literature related to the standard ANT, an executive control effect was found on SET, with longer SET in target condition with incongruent flankers compared to congruent trials. This longer SET in conflicting situations can be explained by an increased duration of APA. Nevertheless, unlike our expectations and the orienting effect on RT found in the standard ANT (Fan et al. 2002, 2005; 2007,2009; Neuhaus et al. 2010; Gamboz et al. 2010; Deiber et al. 2013; Galvao-Carmona et al. 2014; Williams et al. 2016), no orienting effect was exhibited on any of the behavioural features of first step. Besides, a previous study of our group that studied only alerting and orienting effects during step initiation (Tard et al. 2016) has shown significant alerting and orienting effects on RT and SET. One possible reason for the absence of a significant effect of orientation in our present results may be the differences in task design between our version of the ANT and the original version (Fan et al. 2002). With our centrally located spatial cue that gives information concerning the direction of the subsequent target, we assessed rather top-down orienting attention, whereas Fan et al. (2002) and most of the researchers in the field used a spatial cue that was located where the target was subsequently placed on the screen (on the top or bottom), without any indication regarding target direction. The classical ANT thus evaluates bottom-up orienting attention and it may explain why our outcomes differed.

During the step initiation task, we did not record any differences in the rate of incorrect steps as a function of the type of flanker or cue. In contrast, multiple APAs were more frequent and lasted longer in incongruent trials than in congruent trials leading to a longer SET. Presence of multiple APAs reflects the cost of processing conflicting items of information: the CoP shifts contralaterally towards the flankers before being corrected and shifting towards the target, or the stereotyped CoP displacement is repeated in loop before step execution. It is noteworthy that multiple APAs were also observed in the presence of congruent flankers, as already reported by Uemura et al. (2013b). Here, these

multiple APAs are probably rather caused by haste than associated with conflict resolution because, in trials with multiple APAs, RT was significantly shorter in congruent trials in comparison with incongruent ones. Furthermore, subjects seem to recover from multiple APAs with more difficulty when a conflict has to be solved. Overall, RT was diminished in trials with multiples APAs compared to trials with usual APAs (mean  $\pm$  standard deviation of  $192 \pm 22$  and  $234 \pm 31$  ms, respectively;  $p < 0.001$ ). Therefore, haste could represent one of the causes of multiple APAs occurrence, in congruent conditions as well as in conflicting situations. Healthy adults might adopt one of two different strategies: (i) waiting for the identification of the target before choosing the correct motor programme immediately, or (ii) initiating the step by chance or when a large number of arrows appear, and then rectifying the motor programme once it is executed. Thus, the motor programme may be initiated before target identification and, therefore, without having been precisely selected. Adjustments of the motor programme are possible during execution, and might involve rapid, direct sensorimotor loops via visual afferences. Hence, healthy subjects are able to adjust the motor programme after initiation, rather than delaying initiation until the correct motor programme has been selected. It is known that younger adults make fewer APA errors than elderly adults in a choice RT task (Cohen et al. 2011). Our results suggest that multiple APAs do not solely occur under pathological conditions (i.e. when step execution errors are compensated for). They may well correspond to a physiological phenomenon used in attentional situations, when the motor programme needs to be adapted to environmental constraints. This proposal is supported by a study from Cohen et al. (2017) who have found the same amount of multiple APAs in patients with Parkinson's disease compared to healthy controls.

## Conclusion

The simultaneous study of cortical activity and motor behaviour during ANT combined with step initiation allows to better and more fully understand the influence of attentional load on step initiation. In young adults, alertness only impacts the reaction time phase: a longer RT is associated with trials without a cue, because a longer time is needed for perceptual discrimination of the subsequent target unlike situations with a cue preceding the target. Indeed, the presence of a cue would stress the sensory perception phase occurring just after target presentation and would lead to an earlier motor preparation. At a cortical level, this alerting effect is reflected into the early target-locked ERP components and ERSPs: a significantly more pronounced target N100 at parietal and occipito-parietal sites and an earlier posterior ERD in alpha band and central posterior ERD in



**Fig. 6** Influence of target modality on alpha- and beta-band ERD. **a** Response-locked topographic distributions of time–frequency energy [left: in alpha band (8–12 Hz); right: in beta band (13–30 Hz)], corresponding to the two flanker conditions (congruent or incongruent) in the step initiation ANT. Time interval: between 200 ms before response onset and 400 ms after. **b** Response-locked ERSs at CPz, with onset of APAs aligned with zero on the time axis. ERD is shown in blue and ERS is shown in red. Column to the right of spectral distributions in each frequency band and to the right of spectral distribution among frequency bands from 4 to 30 Hz at CPz: significant differences in a permutation test with FDR correction (threshold at  $p < 0.05$ ) are marked as red dots. **c** trials with congruent flankers, **d** trials with incongruent flankers

beta band, in the presence of a cue. Cueing can also result in a higher rate of anticipated responses. The executive control effect leads to longer APAs and thus a longer SET, and to a higher rate a multiple APAs. These behavioural results have an equivalence at the cortical level, with a specific pattern of response-locked ERD in alpha and beta bands over the sensorimotor cortex that clearly illustrates the effect of conflict resolution in young adults. After having led studies in larger populations of healthy adults, this new paradigm combining ANT and step initiation could, therefore, be used to explore the interaction between attention and step initiation and the neural substrates underlying this interaction in populations with impaired step initiation, such as elderly fallers or patients with Parkinson's disease and freezing of gait.

## Compliance with ethical standards

**Conflict of interest** Madli Bayot is working on a project that received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 721577.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (the Committee for the Protection of Persons North West IV-CPP 15/09, 2015 A00013 46) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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## **Etude 3 : Impact de la posture initiale sur l'initiation de la marche chez les patients parkinsoniens avec et sans freezing de la marche**

“Initial center of pressure position prior to anticipatory postural adjustments during gait initiation in people with Parkinson’s disease with freezing of gait”

**Madli Bayot**, Arnaud Delval, Caroline Moreau, Luc Defebvre, Clint Hansen, Walter Maetzler, Christian Schlenstedt.

Article publié dans *Parkinsonism & Related Disorders*.

### **Apport personnel**

- Développement des méthodes d’analyse des données (précédemment enregistrées) et traitement.
- Réalisation des tests statistiques.
- Rédaction et correction du manuscrit suite aux retours des co-auteurs et reviewers.

### **Résumé**

#### **Introduction**

Le freezing de la marche (FdM) dans la maladie de Parkinson (MP) est associé à une posture altérée en position debout au repos, ainsi qu’à une préparation et exécution détériorées du processus d’initiation de la marche. Le but de cette étude était d’investiguer si une posture initiale altérée impacte spécifiquement les ajustements posturaux anticipés (APAs) et l’exécution du premier pas durant l’initiation de la marche chez les personnes avec MP et FdM (MP+FdM).

#### **Méthodes**

Vingt-sept MP+FdM, 30 patients avec MP sans FdM et 27 contrôles sains appariés en âge ont initié la marche de manière « auto-déclenchée ». La position initiale moyenne du centre de pression (CdP) avant le début des APAs, les caractéristiques des APAs et les paramètres d’exécution du premier pas ont été investigués.

## Résultats

Contrairement aux contrôles, les patients avec MP montraient un CdP initialement positionné davantage vers la jambe d'appui ( $p = 0,007$ ). De plus, un déplacement du CdP vers l'arrière significativement plus réduit, une plus longue durée de la phase de décharge du pied oscillant, et un premier pas plus lent et de plus petite longueur caractérisaient les MP+FdM comparés aux contrôles. Tandis que l'amplitude et la durée du mouvement du CdP en arrière durant l'APA et du déplacement latéral du CdP durant la phase de décharge du membre oscillant représentaient les prédicteurs principaux de la longueur et de la vitesse du premier pas dans tous les groupes, la position médio-latérale initiale du CdP chez les MP+FdM a également été un prédicteur de la performance du premier pas ( $\beta = -0,191$ ,  $p = 0,001$  pour la vitesse).

## Conclusion

Chez les freezers, plus le CdP était positionné vers le pied d'appui, plus le premier pas était lent et de courte longueur. La position médio-latérale initiale du CdP pourrait représenter une stratégie compensatrice pour pallier l'instabilité posturale existante chez les MP+FdM. Un entraînement spécifique au niveau du contrôle postural juste avant les phases de préparation et d'exécution de la marche pourrait améliorer la mobilité fonctionnelle des freezers.

**Mots-clés :** contrôle postural, ajustements posturaux anticipés (APAs), initiation de la marche, maladie de Parkinson (MP), freezing de la marche (FdM).

## Articulation avec le projet de thèse

Le résultat majeur de cette étude met en évidence le fait que, quel que soit la population étudiée, les APAs et leurs caractéristiques sont prédicteurs de la performance motrice. Chez les patients MP et encore davantage chez les MP+FdM, la posture initiale juste avant le début des APAs est également utilisée pour impacter l'exécution du premier pas. Contrôle postural initial et APAs peuvent, en partie, expliquer les faibles performances motrices des freezers et peut-être donc, en partie également, l'apparition d'épisodes de freezing.

Maintenant que nous avons démontré chez les MP+FdM la pertinence de la tâche motrice utilisée dans le paradigme de l'ANT-INT, l'analyse de l'interaction attention-motricité chez les MP+FdM, MP-FdM et contrôles peut être réalisée.



1 **Initial center of pressure position prior to anticipatory**  
2 **postural adjustments during gait initiation in people with**  
3 **Parkinson's disease with freezing of gait**  
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# Abstract

## Introduction

Freezing of gait (FOG) in Parkinson's disease (PD) is associated with an altered posture during quiet stance as well as an impaired preparation and execution of the gait initiation process. We aimed to investigate whether an altered initial posture impacts anticipatory postural adjustments (APAs) and first-step execution during gait initiation in people with PD with FOG (PD+FOG).

## Methods

Twenty-seven PD+FOG, 30 PD patients without FOG and 27 age-matched healthy controls performed self-generated gait initiation. Initial mean center of pressure (COP) position prior to APA onset, characteristics of APAs and features of first-step execution were investigated.

## Results

Contrarily to controls, PD patients showed a COP that was initially positioned more towards the stance leg ( $p = 0.007$ ). Moreover, significantly smaller backward COP shift, longer duration of swing-foot unloading phase, and lower first-step length and velocity characterized PD+FOG compared to controls. While size and duration of backward COP shift during APA and lateral COP shift during the unloading phase were main predictors of first-step length and velocity in all groups, the medio-lateral shift of the initial COP position in PD+FOG was a main predictor of first-step execution ( $\beta = -0.191$ ,  $p = 0.001$  for velocity).

## Conclusion

In PD+FOG, the more the COP was initially positioned towards the stance foot, the slower and shorter the first step. The initial medio-lateral COP position may be a compensatory strategy to address postural instability of PD+FOG. A specific training regarding postural control prior to gait preparation and execution could improve functional mobility in PD+FOG.

**Keywords:** Postural control; anticipatory postural adjustments (APAs); gait initiation; Parkinson's disease (PD); freezing of gait (FOG)

## Background and aim

Occurring in about 80 % of people with Parkinson's disease (PD) in the later stages of the disease [1], freezing of gait (FOG) is a paroxysmal axial symptom that is usually described as a "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [2]. While the underlying pathophysiological mechanisms are still not fully understood, several hypotheses have been proposed. Among them, abnormal coupling of posture with gait was suggested [3], based for example on the observation of an increased head-pelvis coupling during turning in PD patients with FOG (PD+FOG) [4].

However, the relationship between FOG and postural control seems complex. PD+FOG present worse postural control in comparison with PD patients without FOG (PD-FOG) [5], particularly regarding dynamic postural control and anticipatory postural adjustments (APAs) preceding gait (for a review, see [6]). Motor timing impairments and reduced flexibility to shift between motor strategies in PD+FOG might lead to or be the consequence of a dysfunctional uncoupling of the center of pressure (COP) and the center of mass (COM) during preparation of forward progression [7]. This impaired uncoupling can also be seen as a protective strategy to attenuate the postural demand on preparatory movement. FOG has thus been related to poor spatio-temporal characteristics of APAs [8,9], and even impaired coupling between preparation and execution of gait [10,11].

Postural control during quiet stance was also found to be different in PD+FOG compared to PD-FOG [6,12,13]. In a previous study [14], in contrast to PD-FOG and healthy controls (HC), PD+FOG presented a shift of their mean COP position towards the heels and this COP displacement was positively correlated to FOG severity. It remains unclear whether this altered COP position during quiet stance might contribute to the abnormal coupling between APAs and the step motor program and might thus be a possible cause for the occurrence of start hesitation in PD+FOG.

The present study aims to investigate the impact of the initial posture during stance prior to APA onset on first-step preparation and execution, and on their coupling in PD+FOG.

## Methods

### Participants

People with PD and HC were included in this study. PD was diagnosed according to the UK Brain Bank criteria. The group of PD+FOG was composed of patients with an unambiguous previous history of FOG, reported through the third item of the Freezing of Gait Questionnaire and the observation of overt FOG episodes during a specific gait trajectory that was thought to trigger FOG (i.e., pathway including gait initiation and stopping, rapid 360° and 540° turns, a narrow passage and dual tasking) [15]. Exclusion criteria were cognitive impairment (i.e., Mini Mental State Examination or MMSE score < 24), other causes of gait disorders, major psychiatric disorders or severe co-morbidities. PD patients were tested in the ON-state of medication. The study was approved by the ethical committee and a written informed consent was signed by all the participants prior to their participation. Data came in part from [11].

## **Task**

Participants were standing centrally on a force platform, with their feet parallel and hip-width apart. The investigator then gave a precise instruction: “When you are ready, start to walk as fast as possible and with the starting foot of your choice”, while checking that the subjects did not start immediately after this instruction. After four or five steps, participants were asked to stop by the examiner.

## **Material**

Two force platforms (the OR6 from AMTI, Watertown, USA) and a video motion analysis system (VICON from Oxford Metrics Ltd., Oxford, UK) equipped with 6 infrared cameras were used to assess kinetic, but also kinematic measurements of gait initiation. Both systems were synchronized: the force platforms with a sampling rate of 250 Hz, and the VICON system with a video sampling frequency of 50 Hz. Six spherical, retroreflective markers of 2.5 cm in diameter were placed bilaterally on the lateral malleoli, the heels, and the head of second metatarsals.

## **Kinetic and kinematic data analysis**

In order to assess preparation and execution of gait, different spatio-temporal features of the first step were extracted from the data, by using an in-house MATLAB script (The MathWorks, Natick, MA, USA) based on methodologies found in the literature to detect gait events [16–19]. Data of each trial were plotted and visually checked. Studied parameters were stance width, initial mean AP and ML COP positions (averaged over 1 s prior to APA onset and expressed respectively as percentage of foot length and stance width), APA onset ( $T_o$ ), duration of APA, AP and ML sizes of APA, duration ( $T_u$ ) and lateral COP shift ( $COP_u$ ) during the swing-foot unloading phase, swing phase duration, and length and velocity of first step. Details of calculation of such features are illustrated in Figures 1 and A.1 and detailed in Supplementary material file.

## **Clinical measures**

The MMSE was conducted to evaluate cognition. For patients with PD, disease severity was assessed with the Unified Parkinson’s Disease Rating Scale part III; disease duration was also reported.

## **Statistical analysis**

Demographic and clinical data between PD+FOG, PD-FOG and HC were compared with Kruskal-Wallis test, and between PD+FOG and PD-FOG with Mann-Whitney U test. Dichotomous data were compared using Chi-Square test.

Because each participant performed a different amount of trials, differences between groups in terms of initial mean COP position and characteristics of the first-step preparation (features of APA) and execution (the step itself) were statistically tested using a linear mixed model with group as fixed effect, participant as random effect and stance width as covariate (except for the analysis of the initial mean ML COP position). In order to control for a significantly different clinical variable between PD groups (i.e. disease duration), a second ANCOVA related to the PD patients only was carried out. A Tukey correction for post-hoc tests was used to adjust for multiple comparisons. When

1 the assumptions of normal distribution and homoscedasticity of residuals among groups were  
2 violated, generalized linear mixed models were used.

3 Furthermore, in order to investigate the relationships between the initial mean COP position, gait  
4 preparation and first-step execution in each group, repeated measures correlation coefficients were  
5 assessed and allowed to determine the common within-individual association for paired measures  
6 evaluated in a given population. Based on that, different linear mixed models including uncorrelated  
7 features of quiet stance prior to gait initiation and characteristics of APAs as potential predictors of  
8 first-step length and velocity were the starting point for choosing the best regression model  
9 associated with each group by Akaike's Information Criteria in a backward stepwise algorithm.  
10 Disease duration was also tested as an independent variable in the regression analysis related to  
11 each PD group.  
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15 All statistical analyses were conducted in R [20], and the statistical significance threshold was  $p <$   
16  $0.05$ . More details are reported in Supplementary material file.  
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## 21 **Results**

### 22 **Subjects**

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27 Twenty-seven PD+FOG, 30 PD-FOG and 27 HC were included. The three groups were well balanced  
28 for age, gender, height, cognition and disease severity for PD patients (Table 1). PD+FOG had  
29 significantly longer disease duration than PD-FOG. On average, three (between one and five)  
30 consecutive trials were recorded for each participant, with a period of quiet stance just before APA  
31 onset related to the initiation of the first step.  
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### 36 **People with PD showed altered initial COP position prior to gait initiation in ML** 37 **direction**

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39 A significant group effect was found for the initial mean ML COP position: PD patients had a COP  
40 initially positioned towards the stance leg whereas controls' COP was rather located towards the  
41 swing leg. Besides, when controlling for disease duration, a significantly more posterior initial mean  
42 COP position was found for PD-FOG compared to PD+FOG (Table 1 and Figure 2). This means that PD-  
43 FOG in later stages of the disease would have shown a COP prior to gait initiation positioned  
44 significantly more backwards than PD+FOG. Moreover, initial stance width was significantly larger in  
45 PD+FOG compared to PD-FOG, but this difference was not significant anymore when controlling for  
46 disease duration.  
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50 Regarding first-step preparation and execution, PD+FOG presented a significantly lower backward  
51 COP displacement than HC, and any difference with PD-FOG was not observed anymore after  
52 considering disease duration as covariate. When controlling for stance width, there was no  
53 significant group effect for  $COP_u$ . Furthermore, despite similar duration of APAs across groups,  
54 PD+FOG took longer for unloading the swing foot and moving their COP towards the stance leg than  
55 PD-FOG and HC. Finally, PD+FOG showed significantly smaller first-step length and velocity than HC,  
56 whereas taking into account the difference in disease duration between the two PD groups did not  
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1 reveal any significant differences between them (Table 1 and Figure C.1 in the Supplementary  
2 material section). Swing phase duration did not differ between populations.  
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### 5 **Initial mean COP position prior to gait initiation predicted first-step length and velocity** 6 **in individuals with PD** 7

8 After the exclusion of correlated parameters of quiet stance, gait preparation and execution in all  
9 groups (Table D.1), regression analysis showed that, for all the participants, a fast first step was the  
10 consequence of a large backward COP shift during APA (see Table 2). Moreover, for people with PD, a  
11 fast first step was also explained in part by a great  $COP_U$  or by a large stance width, both being highly  
12 significantly correlated. Particularly for PD+FOG, a COP initially located closer to the swing foot and  
13 positioned more towards posterior was also part of the causes for a fast first step. In PD-FOG, a  
14 shorter  $T_U$  was found to be a significant predictor for a first step of high velocity.  
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17 Concerning first-step length, an initial mean COP position towards posterior and a great  $COP_U$  (stance  
18 width as equivalent in PD-FOG) were main predictors for a large first-step length in people with PD.  
19 In PD+FOG, an initial mean COP position towards the swing foot was also significantly associated with  
20 a first step of long length. Besides, within PD-FOG, a large backward COP shift during APA allowed to  
21 partly explain a long first step, as in the case of first-step velocity. Finally, HC seemed to take time for  
22 completing the unloading phase in order to initiate a first step of long length.  
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## 29 **Discussion** 30

31 To the best of our knowledge this is the first study investigating the impact of the initial COP position  
32 relative to the feet prior to APA onset on the preparation and execution of the gait initiation process  
33 and on their coupling in PD+FOG, even if previously explored in HC [21].  
34

35 Among all groups, a large backward COP displacement during APA allowed to perform a step rapidly,  
36 thanks to a subsequent efficient forward propulsion of the COM (as found in [22]). Within people  
37 with PD, ML COP excursion (the stance width or  $COP_U$ , by extension) was used to control the length  
38 and velocity of first step. Contrary to Brenière and colleagues' findings [22], longer APAs were not  
39 correlated to high velocity of first step because they are often the consequence of multiple APAs  
40 [11]. Such APAs can be deleterious for first-step velocity. In this context,  $T_U$  seems more interesting  
41 to analyze: it helps to control first-step length in HC and velocity of first step in PD-FOG. The  
42 significantly longer  $T_U$  in PD+FOG compared to the other groups might consist in a balance strategy  
43 along the ML axis, reinforcing the strategy of the initial ML COP position towards the stance foot  
44 (detailed below). In fact, similarly to healthy older adult fallers in comparison with non-fallers [23],  
45 for a comparable ML COP excursion during the swing-foot unloading phase, a longer duration of this  
46 phase would imply that the COP stays lateral to the COM for a longer time in PD+FOG. Consequently,  
47 a more efficient torque would propel the COM towards the stance foot, increasing the margin of  
48 stability at foot off and therefore, reducing the ML instability.  
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54 We found an initial mean ML COP position which was significantly positioned towards the stance leg  
55 in people with PD compared to HC. Regression analysis revealed that, in PD+FOG, the more the COP  
56 was shifted towards the stance leg prior to APA onset, the smaller and slower the first step. This may  
57 therefore partly explain why PD+FOG often perform small and slow first steps during the gait  
58 initiation process as often reported [24]. More specifically, the ML displacement of the COP towards  
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1 the swing limb during APAs, by increasing the component of the ground reaction force towards the  
2 stance limb over a period of time, generates a momentum in this direction and consequently, a shift  
3 of the COM towards the stance leg. This ML shift of the COM aims in turn to provide postural stability  
4 during gait execution: it reduces the gap between the COP and COM at the time of toe off and thus  
5 attenuates the induced body disequilibrium and fall towards the swing leg [25]. By initially  
6 positioning the COP (and therefore the COM which is “tracked” by the COP [26], both vertical  
7 projections being aligned during stable quiet stance) more towards the stance leg while showing  
8 similar ML size of APA and therefore the same momentum compared to HC, PD patients displaced  
9 their COM closer to the support leg at the time of foot off. They thus showed a smaller gap between  
10 COP and COM, attenuating the ML fall of the COM towards the swing leg due to gravity during the  
11 execution phase. This specific initial mean COP position in PD patients might reflect postural  
12 instability, since a short COP-COM distance during the locomotor phase of gait initiation would be  
13 related to impaired postural control [27,28]. Indeed, it might mirror a safe strategy regarding balance  
14 in the ML direction, an inability to generate adequate momentum using COP shifts in order to  
15 dynamically control the COM towards the stance leg, or a combination of both. This conservative  
16 initial COP position can in turn lead to poorer performance of first-step execution.  
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21 With respect to the AP direction, a previous study which investigated the COP position relative to the  
22 feet during quiet stance found a shift of the COP towards the heels in PD+FOG compared to PD-FOG  
23 and HC [14]. This may either compromise the ability to create propulsive forces (and therefore impair  
24 the step initiation process) or may be a compensatory mechanism to avoid forward falls. As we  
25 rather found a COP displacement towards anterior in PD+FOG right before APA onset, the results of  
26 the present study give a hint that the altered mean COP position relative to feet during quiet stance  
27 (without any intention to start walking) may play a minor role for the occurrence of start hesitation.  
28 It seems to be more relevant to study postural control just before preparation of gait in this  
29 population.  
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33 Concerning the associations between initial COP position and performance of first step, results were  
34 not always consistent for PD+FOG and PD-FOG, indicating different mechanisms for these two  
35 subgroups. While positioning their COP initially more towards their stance leg compared to HC, PD-  
36 FOG might compensate this conservative strategy in ML direction by positioning their COP  
37 significantly more posteriorly than PD+FOG and reducing their basis of support with a decreased  
38 initial stance width. In this way, they were able to play with their initial AP COP position in order to  
39 generate a more or less large backward excursion of their COP during APAs and thus to compensate  
40 for their smaller amplitudes of APA as PD patients [29,30]. Indeed, it is more difficult to initiate a  
41 backward COP shift from an anterior COP position than from a more posterior location, since an AP  
42 unbalance towards forward before APA onset would not help the subsequent backward COP shift. In  
43 the end, this initial mean AP COP position seemed to have a higher impact on gait initiation than the  
44 conservative initial mean ML COP position and, consequently, AP size of APA was especially a good  
45 predictor of first-step length and velocity in PD-FOG. A shorter  $T_u$  also allowed to counteract the  
46 conservative initial ML COP position, allowing to increase first-step velocity.  
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51 Contrarily, PD+FOG also seemed to prioritize postural stability in ML direction but do not present the  
52 same compensatory strategy in AP direction during gait initiation. Indeed, their initial mean AP and  
53 ML COP positions were significant predictors of first-step length and velocity. A reason why the initial  
54 mean AP COP position is a better predictor of first-step execution than AP size of APA in PD+FOG,  
55 contrarily to PD-FOG, might be due to their more limited backward COP displacement during APAs.  
56 Therefore, the initial AP COP position prior to gait will represent a compensatory strategy for a better  
57 performance of first step. Indeed, for a given AP size of APA, the more posteriorly the COP starts its  
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backward excursion, the smaller the AP margin of stability related to the heels at APA onset is, and thus the larger the initial AP disequilibrium is. This unbalance will help the subsequent backward COP shift for a more efficient forward COM displacement. However, the compensatory strategy of PD-FOG in AP direction seem to be more effective than the one of PD+FOG, since the conservative strategy in ML direction keeps still a significant impact on characteristics of first step.

Limits of the study were the mismatch of PD patients in terms of disease duration, and the short time interval prior to gait initiation not allowing to investigate the COP position during extended quiet stance.

## Conclusion

People with PD showed a shift of the initial COP position prior to APA onset towards the stance foot, whereas HC initially placed their COP towards the swing foot. In PD+FOG, the more the COP was initially positioned towards the stance foot, the slower and shorter the first step. This characteristic initial ML COP position may be a compensatory strategy for addressing postural instability of PD+FOG. Whether PD+FOG may benefit from training altered initial posture prior to the gait initiation process should be investigated in future rehabilitation studies.

1 **Declaration of interest**

2 None.

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8 **Contributors**

9 1) Research project: A. Conception, B. Data collection, C. Data analysis;

10 2) Statistical Analysis: A. Design, B. Execution, C. Review and critique; 3)

11 Manuscript: A. Writing of the first draft, B. Review and critique.

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13 (1B, 2C, 3B); Clint Hansen (2B, 3C); Walter Maetzler (2B, 3C); Christian Schlenstedt (1A, 2A/C, 3B).

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16 **Acknowledgements**

17 This work was supported by the European Union's Horizon 2020 research and innovation programme

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## Legends

**Figure 1.** Determination of the mean AP and ML COP positions over 1 s prior to APA onset, expressed as a percentage of foot length and stance width, respectively. Crosses on the left = markers at left heel, malleolus and toe, and orthogonal projection of the middle point between left heel and toe markers on a parallel line passing by the marker at the left ankle; crosses on the right = markers at right heel, malleolus and toe, and orthogonal projection of the middle point between right heel and toe markers on a parallel line passing by the marker at the right ankle; crosses in the middle = middle points between heels and between toes;  $T_0$  = APA onset; HO = heel off; TO = toe off; mCOP = mean COP position over 1 s prior to APA onset; SWF = swing foot; STF = stance foot

**Table 1.** Differences between groups in terms of demographic and clinical data, initial mean COP position prior to gait initiation, and characteristics of the preparation (APAs) and execution of the first step. For each group, the mean and standard deviation of gait and balance parameters averaged through each subject's trials were reported. MMSE = Mini Mental State Examination; UPDRS III (Med ON) = Unified Parkinson's disease Rating Scale, part III, in the ON-state of medication; FOGQ = Freezing of Gait Questionnaire; NS = non-significant; \* for p-value < 0.05; \*\* for p-value < 0.01; \*\*\* for p-value < 0.001

**Figure 2.** Characteristics of quiet stance and gait preparation that were significantly different between groups: (a) initial mean AP COP position over 1 s prior to APA onset (expressed as a percentage of foot length, starting from the mean distance between both heel markers (0%)); (b) initial mean ML COP position over 1 s prior to APA onset (expressed as a percentage of stance width, starting from the swing leg (0%) towards the stance leg (100%)), dotted line represents the middle distance between stance and swing feet (50%); (c) AP size of APA; (d) unloading phase duration. SW = swing foot; ST = stance foot; # significant group difference between PD patients and controls (PD+FOG and PD-FOG > HC, with p-values < 0.05); \* p-value of post-hoc tests < 0.05; \*\* p-value of post-hoc tests < 0.01; \*\*\* p-value of post-hoc tests < 0.001

**Table 2.** Backward stepwise multiple regressions for prediction of first step length and velocity in each group, with (linear mixed) models selection based on AIC. \* for p-value < 0.05; \*\* for p-value < 0.01; \*\*\* for p-value < 0.001

Table1

Classification	Variable	PD+FOG (n=27) Mean (SD)	PD-FOG (n=30) Mean (SD)	HC (n=27) Mean (SD)	Effect of Group (p-values)	Post-hoc tests	Post-hoc tests when controlling for disease duration
<b>Demographic and clinical data</b>	Age (years)	64 (10.187)	64.633 (9.027)	61.346 (8.681)	0.407	/	/
	Gender (M/F)	15/12	19/11	12/15	0.358	/	
	Height (cm)	164.1 (9.629)	168.965 (9.671)	169.905 (8.16)	0.128	/	
	MMSE	27.692 (1.594)	28 (2.038)	> 27	0.364	/	
	Disease duration (years)	16.185 (6.349)	3.19 (3.511)	/	< 0.001 ***	PD+FOG > PD-FOG	
	UPDRS III (Med ON)	24.222 (11.914)	20.407 (6.71)	/	0.229	/	
	FOGQ	13.815 (4.17)	/	/	/	/	
<b>Prior to APA</b>	AP COP position (% of foot length)	56.875 (7.693)	53.794 (10.936)	56.229 (10.457)	NS (0.306)	/	PD+FOG > PD-FOG (0.003**)
	ML COP position (% of stance width)	54.383 (6.142)	53.328 (9.512)	48.34 (4.208)	0.007**	PD+FOG > HC (0.011*) PD-FOG > HC (0.026*)	NS (0.627)
	Stance width (mm)	278.432 (46.221)	248.716 (41.207)	262.572 (42.164)	0.041*	PD+FOG > PD-FOG (0.031*)	NS (0.29)
<b>During APA</b>	AP size of APA (mm)	27.117 (22.179)	40.95 (23.805)	51.678 (23.325)	< 0.001 ***	PD+FOG < PD-FOG (0.019*) PD+FOG < HC (< 0.001***)	NS (0.565)
	ML size of APA (mm)	23.475 (18.676)	24.013 (16.576)	28.87 (16.538)	NS (0.202)	/	NS (0.536)
	APA duration (s)	0.872 (0.288)	0.8 (0.3)	0.656 (0.253)	NS (0.085)	/	NS (0.707)

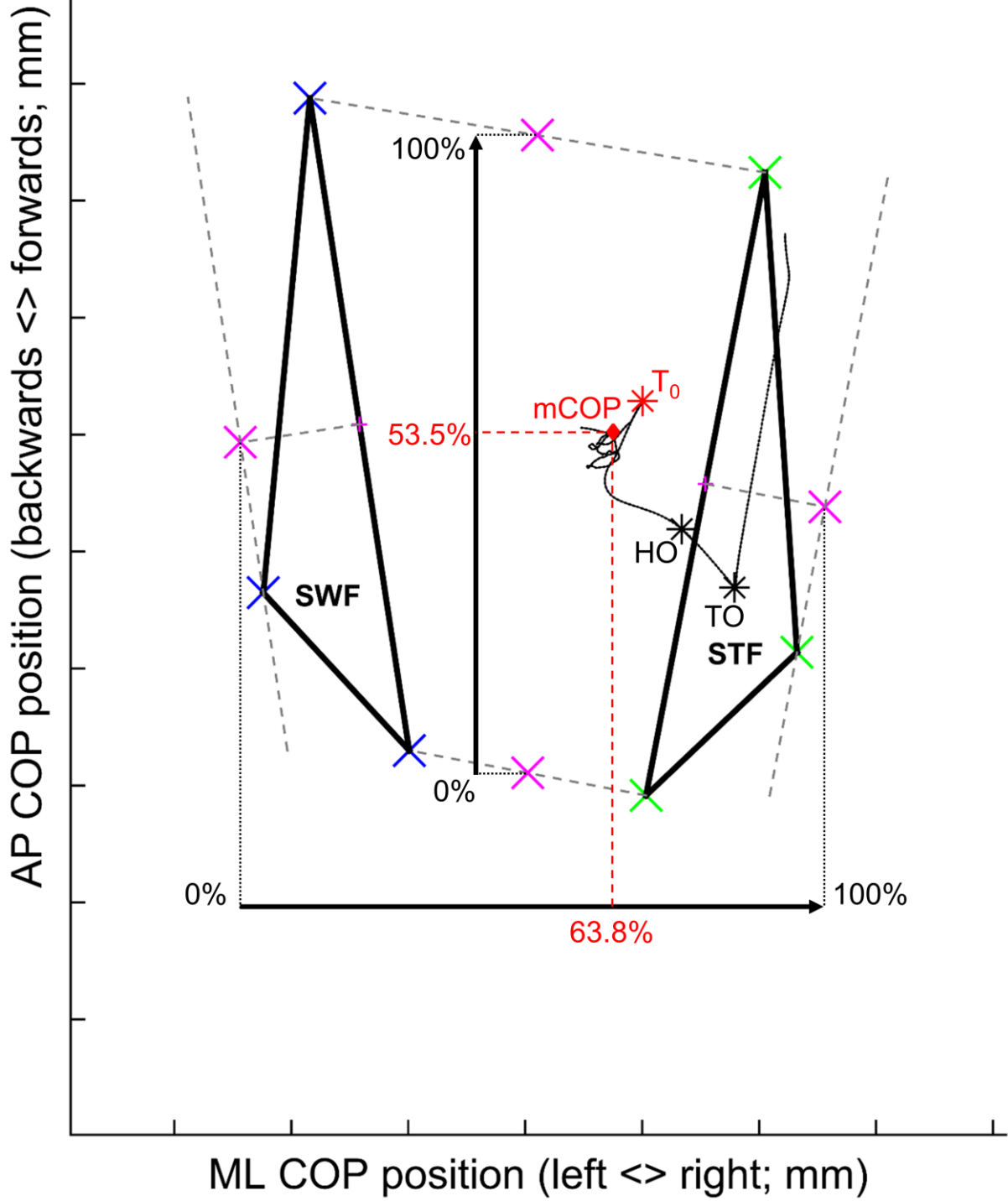


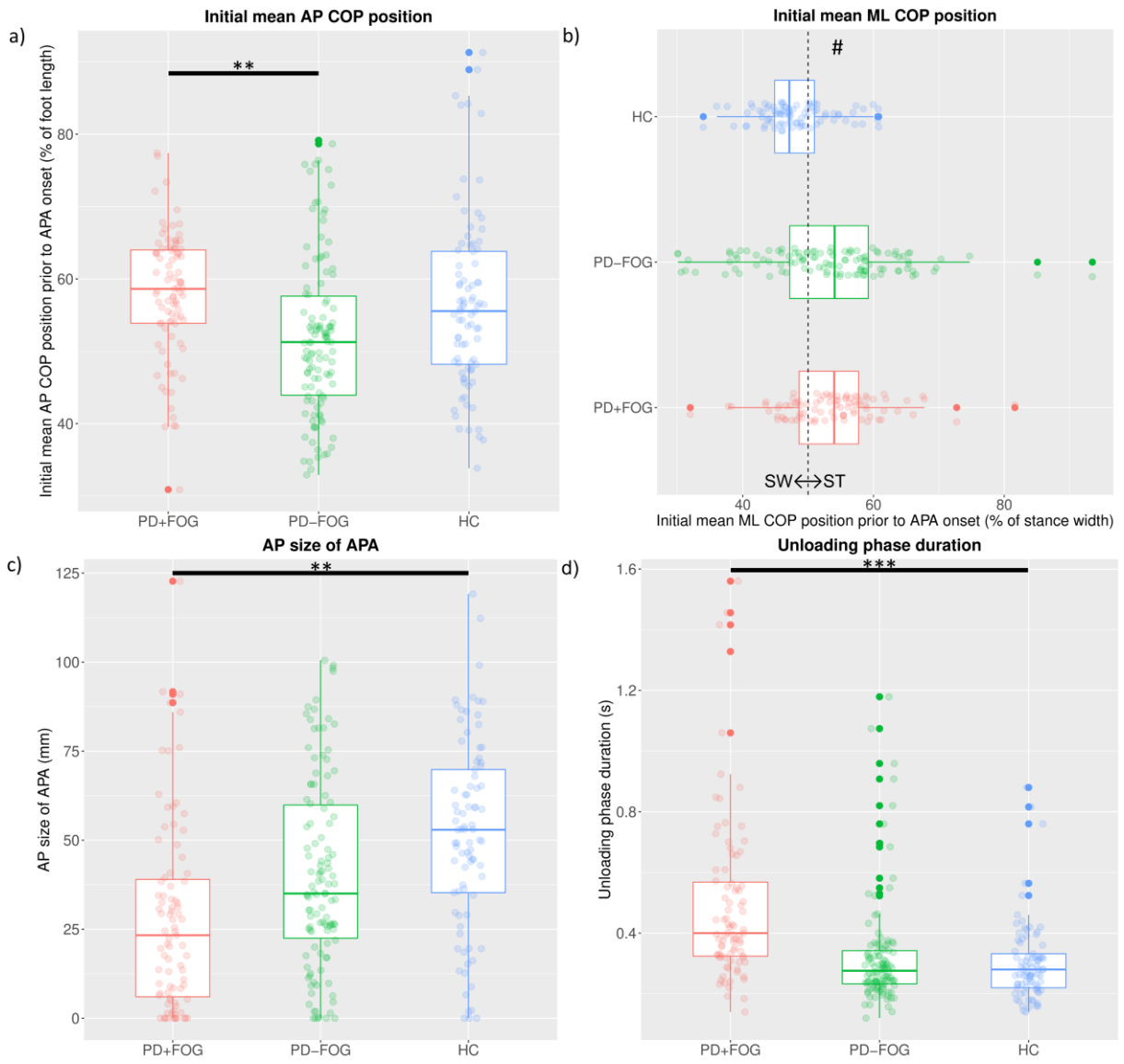
	<b>Lateral COP shift during unloading phase (mm)</b>	109.661 (42.321)	86.828 (32.847)	110.674 (38.173)	NS (0.076)	/	NS (0.373)
	<b>Unloading phase duration (s)</b>	0.485 (0.182)	0.326 (0.115)	0.317 (0.141)	<b>&lt; 0.001***</b>	PD+FOG > PD-FOG ( <b>&lt; 0.001***</b> ) PD+FOG > HC ( <b>&lt; 0.001***</b> )	NS (0.059)
<b><u>First step</u></b>	<b>Swing phase duration (s)</b>	0.548 (0.114)	0.517 (0.08)	0.502 (0.075)	0.19	/	NS (0.894)
	<b>First step length (m)</b>	0.511 (0.17)	0.603 (0.113)	0.643 (0.095)	<b>&lt; 0.001***</b>	PD+FOG < PD-FOG (0.012*) PD+FOG < HC ( <b>&lt; 0.001***</b> )	NS (0.557)
	<b>First step velocity (m/s)</b>	0.979 (0.374)	1.211 (0.335)	1.314 (0.256)	<b>&lt; 0.001 ***</b>	PD+FOG < PD-FOG (0.016*) PD+FOG < HC ( <b>&lt; 0.001***</b> )	NS (0.557)

Table2

Dependent variable	Group	Best model	Standardized regression coefficients	p-values	AIC	BIC	logLik	Conditional R2	Marginal R2
<u>1<sup>ST</sup> STEP LENGTH</u>	PD+FOG	~ AP COP position + ML COP position + stance width	<b>-0.138**</b> <b>-0.129*</b> <b>0.179*</b>	0.005 0.015 0.011	1015.218	1029.944	-501.609	0.926	0.068
	PD-FOG	~ AP COP position + AP size of APA + COP <sub>U</sub> + T <sub>U</sub> + disease duration	<b>-0.21*</b> <b>0.196**</b> <b>0.228**</b> -0.091 -0.211	0.034 0.008 0.003 0.096 0.138	1280.387	1302.135	-632.194	0.768	0.233
	HC	~ APA duration + T <sub>U</sub> + stance width	-0.137 <b>0.181*</b> 0.189	0.09 0.041 0.12	992.862	1007.518	-490.431	0.703	0.099
<u>1<sup>ST</sup> STEP VELOCITY</u>	PD+FOG	~ AP COP position + ML COP position + AP size of APA + stance width	<b>-0.114*</b> <b>-0.191**</b> <b>0.171**</b> <b>0.201**</b>	0.039 0.001 0.007 0.008	1157.477	1174.658	-571.739	0.886	0.161
	PD-FOG	~ AP size of APA + COP <sub>U</sub> + T <sub>U</sub>	<b>0.227***</b> <b>0.236***</b> <b>-0.12*</b>	< 0.001 < 0.001 0.011	1514.989	1531.406	-751.494	0.83	0.21
	HC	~ AP size of APA + COP <sub>U</sub>	<b>0.241*</b> 0.17	0.015 0.135	1172.152	1184.365	-581.076	0.535	0.103

# COP trajectory prior to APA onset





## **Etude 4 : Impact des capacités attentionnelles sur l'initiation du pas chez les patients avec maladie de Parkinson et freezing de la marche – Etude comportementale et électroencéphalographique (analyse fréquentielle)**

“Is Impaired Executive Control Associated with Abnormal Gait Initiation in Parkinsonian Patients with Freezing of Gait?”

**Madli Bayot**, Morgane Gerard, Aurore Braquet, Kathy Dujardin, Céline Tard, Caroline Moreau, Luc Defebvre, Arnaud Delval

Article en préparation pour soumission prochaine.

### **Apport personnel**

- Enregistrement de la plupart des données.
- Développement des méthodes d'analyse des données et traitement.
- Réalisation des tests statistiques.
- Rédaction de la première version du manuscrit.

### **Résumé**

#### **Objectif :**

Le but était d'étudier, à travers l'observation de modulations (1) comportementales et (2) cortico-motrices, l'impact d'une charge attentionnelle (particulièrement, une situation de conflit) sur les phases de préparation et d'exécution du processus d'initiation de la marche chez les patients avec maladie de Parkinson (MP) avec freezing de la marche (MP+FdM).

#### **Méthodes :**

Quinze MP+FdM, 16 MP-FdM et 15 contrôles sains ont réalisé une version adaptée de l'Attention Network Test (ANT), avec initiation du pas comme réponse à la place de l'appui manuel sur les touches d'un clavier dans le cadre de l'ANT standard. Les paramètres cinétiques et cinématiques de l'initiation

du pas ainsi que le signal électroencéphalographique haute résolution ont été enregistrés durant la tâche.

### **Résultats :**

Bien que les MP+FdM présentaient un déficit au niveau du contrôle exécutif et que le temps d'exécution du pas (TEP) était plus long chez les patients MP, l'effet du contrôle exécutif sur le TEP n'était pas significativement différent entre les groupes. Comparés aux patients MP, les contrôles sains ont montré une désynchronisation alpha liée à la réponse plus courte, et une désynchronisation bêta plus précoce, plus intense et plus courte au niveau du cortex sensorimoteur. Globalement, même si les sujets contrôles étaient plus rapides, l'activité alpha et bêta induite associée à l'effet du contrôle exécutif ne différait pas significativement entre les patients MP et les contrôles.

### **Conclusions :**

Les tâches de résolution de conflit mènent à une altération de l'initiation du pas et de l'activité cérébrale sous-jacente qui est comparable entre les groupes. Les liens entre contrôle exécutif, initiation de la marche et FdM semblent être plus complexes qu'attendus.

### **Pertinence :**

Cette étude remet en question l'hypothèse cognitive émise dans le cadre de l'étude pathophysiologique du FdM.

**Mots-clés :** maladie de Parkinson (MP), freezing de la marche (FdM), initiation du pas, Attention Network Test (ANT), électroencéphalographie (EEG).

## **Articulation avec le projet de thèse**

A côté des théories localisationnistes classiques, il est également admis que les régions cérébrales communiquent entre elles et forment ainsi des réseaux fonctionnels. L'analyse de ces réseaux à la place de l'analyse de l'activation de régions cérébrales spécifiques (comme investiguée dans l'étude ci-dessus) pourrait permettre une meilleure compréhension des troubles attentionnels observés chez les MP et particulièrement chez les MP+FdM. Cette analyse de la connectivité fonctionnelle EEG peut être réalisée : (i) soit au repos (**Etude 5**), avec l'analyse de la connectivité fonctionnelle intrinsèque qui

a montré, via analyse de régression, pouvoir expliquer les performances cognitives dans différentes populations et permettre la comparaison avec de nombreuses études en IRMf ; (ii) soit durant la performance de l'ANT standard assis (**Etude 6**).





# Is Impaired Executive Control Associated with Abnormal Gait Initiation in Parkinsonian Patients with Freezing of Gait?

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## Abstract

### Objective:

We aimed to investigate at a behavioral and cortical level whether an attentional load (particularly, a conflicting situation) can specifically impact preparation and execution phases of gait initiation in parkinsonian patients (PwPD) with freezing of gait.

### Methods:

Fifteen freezers, 16 non-freezers and 15 healthy controls performed an adapted version of the Attention Network Test, with step initiation as response instead of the standard keypress. Kinetic and kinematic features of gait initiation as well as high-resolution electroencephalography were recorded during the task.

### Results:

Although freezers presented an impaired executive control and step execution time (SET) was longer in PwPD, the executive control effect on SET was not significantly different between all groups. Compared to PwPD, HC showed a shorter response-locked alpha desynchronization, and an earlier, more intense and shorter beta desynchronization over the sensorimotor cortex. Globally, even if controls were faster, the induced alpha and beta activity associated with the effect of executive control did not significantly differ between PwPD and controls.

### Conclusions:

Tasks of conflict resolution lead to a comparable alteration of step initiation and its underlying brain activity in all groups. Links between executive control, gait initiation and FoG seem more complex than expected.

### Significance:

This study questions the cognitive hypothesis in the pathophysiology of FoG.

**Keywords:** Parkinson's disease (PD), freezing of gait (FoG), step initiation, Attention Network Test (ANT), electroencephalography (EEG)

## 1. Introduction

As the second most common neurodegenerative disorder of aging and the most common movement disorder, Parkinson's disease (PD) is characterized by motor symptoms (typically tremor, bradykinesia, akinesia, rigidity and postural instability), but also by non-motor impairments such as cognitive decline (Chaudhuri et al., 2006). Indeed, a spectrum of severity for cognitive impairment was observed in people with PD (PwPD) (Dujardin et al., 2015). Patients with severe global cognitive deficits can especially present decline in executive functions, but also in working memory and verbal episodic memory (Dujardin et al., 2015). Non-demented PwPD also exhibit attentional deficits and, in particular, an impaired mental flexibility (Dujardin et al., 2013) and a failure of top-down attentional control (i.e., voluntary, internal allocation of attention based on prior knowledge, willful plans and current goals) (Bin Yoo et al., 2018; Cools et al., 2010). Next to that, an automaticity deficit is shown as a result of basal ganglia dysfunction in PwPD (Gilat et al., 2017). Altogether, this would lead to an over-dependence on external cues for guiding PD patients' behavior (i.e., over-use of bottom-up attentional control) (Cools et al., 2010; Cristinzio et al., 2013). As consequences, the impaired attention may, on the one hand, exacerbate the poor dual-tasking performance of PwPD and therefore contributes to falls (Allcock et al., 2009; Lord et al., 2010). On the other hand, even if external cues can compensate for deficits in internal cueing and can thus improve gait and balance performance in PwPD (Ginis et al., 2017; Nieuwboer et al., 2007; Spaulding et al., 2013), excessive dependence on the environment may also facilitate release of motor program and may therefore lead to abnormal gait initiation that can in turn induce freezing of gait (FoG) and falls (Azulay et al., 2006; Tard et al., 2014, 2013).

PD patients with FoG (PD+FoG) are even more cognitively altered than PwPD without FoG (PD-FoG) regarding attention (divided attention and attentional switching), executive function (shifting and inhibition) and visuospatial functions (Peterson et al., 2016). In particular, Vandebossche and colleagues emphasized a deficit in executive control in PD+FoG compared to PD-FoG and healthy controls (HC), that is an impairment in a component of visuospatial attention that allows to resolve conflict among responses (Vandebossche et al., 2011). A disequilibrium between automaticity and controlled processing in PD+FoG, leading to a breakdown in both motor action and cognitive processing, would explain their worse performance in resolving conflicts (Vandebossche et al., 2012). According to a proposed pathophysiological model called the "cognitive model" (Nieuwboer and Giladi, 2013), this failure to process response conflict is assumed to lead to behavioral indecision and thus to the FoG phenomenon: "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (Nutt et al., 2011). FoG is, among others, triggered by the gait initiation process.

We here studied contextual factors of FoG, which represents the type of study that provides the most convincing insights into the underlying mechanisms of FoG (Ehgoetz Martens et al., 2020). Indeed, the primary aim was to investigate at a behavioral and cortical level whether an attentional load (particularly an executive control demanding task) can specifically impact preparation and execution phases of gait initiation in PD+FoG. We hypothesized that the impaired executive control characterizing PD+FoG would induce altered anticipatory postural adjustments (APAs) preceding the first step, such as APAs starting with a displacement of the center of pressure (COP) in the wrong direction ("APA errors"; (Cohen et al., 2011)) or multiple APAs (more than one APA in a row before step execution; (Jacobs et al., 2009)). As suggested by Jacobs and collaborators (Jacobs et al., 2009), these multiple APAs could even reflect an impaired coupling between preparation and execution of

the first step in PD+FoG, explaining their poor performance of the first step and the potential occurrence of FoG episodes. Regarding cortical activity, we similarly expected earlier, longer and less pronounced event-related desynchronization (ERD) in beta band during the preparatory phase of the first step in PD+FoG (Heinrichs-Graham et al., 2014).

## **2. Methods**

### **2.1. Subjects and task**

Thirty-one PwPD (15 PD+FoG and 16 PD-FoG) followed in the movement disorders department of the Lille University Hospital Center and 15 healthy older adult volunteers participated in the study after providing their informed written consent. Patients did not present any cognitive impairment (i.e., Montreal Cognitive Assessment or MoCA score < 24), history of medication use that could interfere with attention (neuroleptics or benzodiazepines) or an uncorrected visual impairment. Moreover, participants had to be able to understand fairly simple instructions, to stand 5 minutes in a row and to walk 10 meters without any help. The study was approved by the local independent ethics committee (CPP Nord-Ouest, Lille, France; reference: 2015-A00013-46).

Demographic and clinical data (gender and age, medical history and current medication) were collected for each subject. Patients were assessed in ON-state of medication during this clinical study and their levodopa equivalent daily dose (LEDD) was calculated (Tomlinson et al., 2010). In addition, motor and neuropsychological functions were evaluated via different tests: the MoCA (Nasreddine et al., 2005) for overall cognition of all participants, the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008), Hoehn and Yahr scale (Goetz et al., 2004) and disease duration for the disease severity in PD patients, and the Freezing of Gait Questionnaire (FOG-Q) (Giladi et al., 2009, 2000) and particularly its third item for the classification of PD patients as PD+FoG or PD-FoG. The freezing phenotype associated with certain PwPD was also validated thanks to their medical history as well as the observation of overt FoG episodes during a specific gait trajectory that was thought to trigger FoG (Snijders et al., 2008).

Subsequently, participants performed an adapted version of the Attention Network Test (ANT) (Fan et al., 2002): first, while sitting with a keypress for answering (i.e., the "standard ANT"; see Figure 1A) and then, while standing with the initiation of a step as a response (i.e., the "ANT-INIT", previously described in (Braquet et al., 2020); see Figure 1B). A detailed description of our version of the well-known paradigm ANT that evaluates simultaneously three components of visuospatial attention (alertness, orientation and executive control), with its time intervals for the presentation of cues and targets, can be found in a previous study of our research group (Braquet et al., 2020). Behavioral results from the standard ANT were used as reference for the assessment of the executive control or conflict resolution. During the ANT-INIT, high-resolution electroencephalography (EEG) was used for recording the cortical activity related to the task, along with a behavioral analysis of the impact of an attentional load on step initiation.

*[Insert Figure 1 here]*

### **2.2. Behavioral data**

Regarding the objectives of the present study, we focused on the executive control and its impact on step initiation.

In order to avoid any learning effect, the 20 first trials of the standard ANT out of the total 300 trials were not taken into account, as well as those with a related reaction time (RT) of less than 100 ms. Participants' response rate and accuracy were calculated: first, when removing trials with an omission error and then, when also excluding trials with a commission error. Median RT in both conditions of target (target surrounded by either congruent flankers or incongruent flankers) were subsequently obtained. The subtraction of the median RT related to the incongruent condition of target from the median RT associated with the congruent condition of target was used to quantify the executive control effect thanks to the standard ANT.

Concerning the behavioral analysis of results from the ANT-INIT, calculation of the studied parameters was detailed in a previous study of our research team (Braquet et al., 2020). We were thus here interested in different features of step initiation: rate of trials with an incorrect step, rate of trials with an anticipated step (with the APA onset starting less than 100 ms after target presentation), and rate of trials with no APA (without any excursion of the COP towards the swing foot). Among the trials left, percentages of normal APAs, APA errors and multiple APAs were evaluated, as well as the related step execution time (SET), RT, APA duration, swing phase, anteroposterior (AP) size of APA (or the backward shift of the COP during APA), mediolateral (ML) COP shift during the swing-foot unloading phase (or the lateral shift towards the stance foot), and length and velocity of the first step. In case of trial with an APA error or with multiple APAs, backward and lateral COP displacements were evaluated for the last effective and correct APA. Correction time (CT) or time interval between APA onset and the last COP shift towards the swing foot just before step execution, in case of APA errors or multiple APAs, was also analyzed. In the context of the ANT-INIT, SET represented the behavioral RT and the executive control effect was thus evaluated by subtracting SET in the non-conflict trials (with incongruent flankers) from SET in the conflict trials (with congruent flankers).

It is noteworthy that, after exclusion of trials without any step, with an incorrect step, an anticipated step or with no APA, subjects presented trials that were distributed as follows (median [first quartile–third quartile]): 113 [97.5–122.75] out of 156 trials with congruent flankers, and 111 [97.5–121] out of 144 trials with incongruent flankers.

### **2.3. Electroencephalographic recordings**

The acquisition and preprocessing of EEG data were similar to what was described for a previous study from our research group (Braquet et al., 2020), until the EEG signal segmentation step. Indeed, epoch length had to be adapted to the mean SET, which was increased in PwPD compared to HC and particularly in PD+FoG. EEG data were segmented here into 4000-ms epochs that were response-locked (i.e., epochs from 2000 ms before APA onset until 2000 ms after). A final visual inspection was carried out to manually remove epochs containing remaining muscle artefacts or others. After this last preprocessing step, PD+FoG, PD-FoG and HC showed trials that were distributed as follows (median [first quartile - third quartile]): 87 [71.5 – 98.5], 88 [76 – 103.5] and 92 [72.5 – 100.5] congruent trials, and 86 [77 – 97.5], 94 [75 - 104] and 89 [82.5 - 101] incongruent trials.

Regarding EEG analysis, we decided not to investigate response-locked event-related potentials (ERP), and motor-related cortical potentials (MRCP) in particular, because no effect of target was previously observed on MRCP in healthy subjects (Braquet et al., 2020). The same observation was made with the present populations (hence not shown here). Instead, a spectral analysis was first performed at the sensor level thanks to EEGLAB (Delorme and Makeig, 2004), a MATLAB toolbox already used for the

signal preprocessing steps. Response-locked EEG oscillations in theta (4-7 Hz), alpha (8-12 Hz) and beta (13-30 Hz) bands were explored via a time-frequency analysis using a continuous Morlet wavelet transform, with 3 cycles at the lowest frequency and 11.25 at the highest (factor: 0.5). Event-related spectral perturbations (ERSP) were calculated by using the gain model and a single-trial normalization (Grandchamp and Delorme, 2011), with a baseline interval between 1500 and 1300 ms before APA onset. ERSP scalp distribution maps allowed the visualization of EEG oscillations from -200 ms before APA onset until 800 ms after (approximate duration of the slowest median APA duration across all subjects).

A further processing step was the spectral analysis of EEG data in the source space via the MATLAB toolbox Brainstorm (Tadel et al., 2011). Firstly, in order to predict the potentials generated by any arbitrary source model, for any possible location, orientation and amplitude parameter values (i.e., forward modelling), the Boundary Element Method (BEM (Gramfort et al., 2010; Kybic et al., 2005), with assumptions of homogeneous and isotropic conductivity within each envelope) was applied on a MRI template anatomy (ICBM152 (Fonov et al., 2009)) of the head, on the basis of sensor locations obtained from the montage template. Secondly, a distributed source imaging method allowed to solve the inverse problem (i.e., finding brain sources which are responsible for the measured scalp potentials): the weighted Minimum Norm Estimate (wMNE) (Baillet et al., 2001). Visualization of EEG oscillations in theta, alpha and beta bands throughout the ANT-INIT was also performed with Brainstorm, after having applied a Morlet wavelet transform. In particular, mean ERSP within each frequency band was plotted on the cortex over time.

#### **2.4. Statistical analyses**

Demographic and clinical data were compared across groups thanks to a Chi-square test for gender, and a one-way ANOVA or a Kruskal-Wallis test for quantitative variables, depending whether the assumptions for general linear models were met or not. For comparing groups of patients, a Student's t test or a Mann-Whitney U test were used. A visual inspection followed by Shapiro-Wilk and Levene tests allowed to verify normal distribution and homoscedasticity of residuals. Characteristics that significantly differed across groups were used as covariates in all the subsequent statistical analyses: gender, but also MDS-UPDRS III that was insignificantly higher in PD+FoG than in PD-FoG (correction by motor severity which is largely recommended at the moment (Ehgoetz Martens et al., 2020; Morris et al., 2020)).

For the group comparison of performance to the standard ANT, percentages of response rate and accuracy were compared by using a generalized linear mixed model and, in particular, a logistic regression with a binomial distribution and logit as a link function. Group and target were the fixed factors (between-subjects and within-subject factors, respectively), while subject and effect of target on subject was used as random factors. Bonferroni correction was associated with post-hoc tests. Moreover, for assessing group difference regarding the executive control effect, a 3x2 repeated measures ANCOVA was conducted, with RT as dependent variable, group and target as between-subjects and within-subject factors, and gender and MDS-UPDRS III score as covariates. Post-hoc Student's t tests were then carried out with a Bonferroni correction for multiple comparisons.

Indeed, the accuracy during the standard seated ANT remained quite high in all participants and therefore induced an amount of correct trials of around 280 trials in each subject. This was not the case when we considered results from the ANT-INIT: participants presented a variable amount of trials

left after removing those with no step, incorrect step, anticipated step and no APA. For this reason, differences between groups, target conditions and types of APA in terms of step initiation parameters were statistically tested by using a (generalized) linear mixed model (GLMM) with group, target condition and APA status (normal APA, APA error or multiple APA) as fixed effects, participant and effect of target and effect of APA type on subject as random effects, and gender as covariate. In PD groups, a second ANCOVA was carried out with MDS-UPDRS III score as additional covariate. A Bonferroni correction for post-hoc tests was used to adjust for multiple comparisons. For comparing rates of the different APA types across groups and target conditions or when the assumptions of normal distribution and homoscedasticity of residuals among groups were violated, generalized linear mixed models were used (Lo and Andrews, 2015). For example, SET, RT, APA duration and CT, as sorts of reaction time, presented a positively skewed distribution and therefore required to be tested via a GLMM with Gamma distribution of the data and an inverse link function (Lo and Andrews, 2015). The size of APA in AP direction included some zero values while exhibiting a positively skewed distribution. The glmmTMB package was thus useful in order to fit a zero-inflated GLMM (Brooks et al., 2017), with a modified Gamma distribution of the data (skipping checks for zero values and fitting therefore hurdle-Gamma models) and a log link function. In general, the use of lme4 package (Bates et al., 2015) was necessary for performing (generalized) linear mixed analyses. Before that, outliers were detected as larger than three times the median absolute deviation and were then removed (Leys et al., 2013). Post-hoc test were performed with the phia package (Rosario-Martinez et al., 2015).

All statistical analyses on demographic, clinical and behavioral data were conducted in R (R Core Team, 2018), with a statistical significance threshold defined as  $p < 0.05$ . Regarding EEG spectral analysis, a permutation-based 3x2 repeated measures ANOVA (group and target as between-subjects and within-subject factors, respectively) was computed on scalp-based ERSP data. EEGLAB toolbox allowed to perform these statistics.

### **3. Results**

#### **3.1. Participants**

All subjects that performed the ANT-INIT were matched for age and MoCA score, but differed in gender (see Table 1). Groups of PwPD were paired for disease duration, severity of motor symptoms and medication. However, it is noteworthy that PD+FoG tended to show a higher MDS-UPDRS III score in the ON-state of medication than PD-FoG. For this reason, gender and MDS-UPDRS III score were used as covariates when performing subsequent statistical analyses.

*[Insert Table 1 here]*

Performance of 2 PD+FoG and 2 PD-FoG on the standard ANT was excluded from the analyses due to rigidity or tremor in the hands during the task. Comparison of demographic and clinical data across these reduced groups were similar to the results for the whole study population and can be found in the Supplementary material file (Table A.1).

#### **3.2. Impact of conflict resolution on step initiation**

##### ***Standard ANT***

Concerning performance on the standard ANT (see Table B.1 in the Supplementary material file and Figure 2), PwPD and HC rarely omitted to answer via a keypress (with a response rate of  $98.242 \pm 2.294$ ,

99.158 ± 1.673 and 99.808 ± 0.236 % of the all trials in PD+FoG, PD-FoG and HC). However, PD+FoG presented a significantly higher rate of omission errors than HC ( $p = 0.006$ ) and these omissions occurred more often in condition of congruent flankers in comparison with incongruent flankers ( $p = 0.016$ ). Furthermore, all participants wrongly answered significantly more frequently to a target surrounded by incongruent flankers versus congruent flankers ( $p < 0.001$ ). Besides, PD+FoG reacted to a visual target significantly slower than HC ( $p = 0.029$ ). A significant executive control effect on RT was observed in all groups ( $p$ -values  $< 0.001$ ): slower RT in incongruent condition of target than in congruent condition of target. In particular (see Figure 2), PD+FoG presented a significantly impaired executive control effect compared to PD-FoG and HC ( $p = 0.048$  and  $0.018$ , respectively). After having corrected by gender and MDS-UPDRS III score, the executive control effect in PD+FoG was not significantly greater (meaning more impaired attention) than in PD-FoG anymore ( $p = 0.134$ ).

*[Insert Figure 2 here]*

### **APA types**

During the ANT-INIT, no freezing episode was observed in any of the PD+FoG. Healthy controls showed a higher rate of anticipated APAs compared to PD+FoG ( $p < 0.001$ ), and they tended to exhibit more anticipated APAs than PD-FoG. In all groups, there were more normal APAs in case of trials in the congruent condition of target, whereas more APA errors and multiple APAs were observed in trials with a target surrounded by incongruent flankers ( $p$ -values  $< 0.001$ ). However, similar percentages of normal APAs, APA errors and multiple APAs were found across the three groups, without any significative interaction between group and target condition (see Table C.1 in the Supplementary material file and Figure 3).

*[Insert Figure 3 here]*

### **SET**

As seen in Table 2 and Figure 4, the step execution time – the behavioral RT in the context of the ANT-INIT – was significantly longer in PD+FoG compared to HC ( $p = 0.006$ ), but the same executive control effect (i.e., a longer SET in the incongruent condition of target in comparison with the condition with congruent flankers) was found in each group ( $p < 0.001$ ). Indeed, there was no significant interaction between group and target condition ( $p = 0.758$ ). SET also depended on the type of APAs, with longer SET in case of APA errors and multiple APAs in comparison with normal APAs ( $p$ -values  $< 0.001$ ). Furthermore, the executive control effect on SET was larger in trials with an APA error than in those with normal APA ( $p = 0.011$ ) or multiple APAs ( $p = 0.007$ ).

*[Insert Table 2 here]*

*[Insert Figure 4 here]*

### **Detailed parameters of preparatory and execution phases of the step initiation process**

The main effect of group on SET may be due to longer RT and swing phase in PwPD compared to HC ( $p < 0.001$  and  $p = 0.0099$ , respectively). Moreover, PD+FoG tended to take more time than HC to perform APAs ( $p = 0.061$ ). Particularly, the correction time in the context of multiple APAs was significantly



longer in PD+FoG than in HC ( $p = 0.022$ ), with only a trend for a longer correction time in PD-FoG compared to HC ( $p = 0.057$ ).

Besides, an executive control effect was observed on RT, correction time in case of APA errors and thus APA duration ( $p < 0.001$ ,  $p = 0.003$  and  $p = 0.012$ , respectively), while an opposite effect was seen on swing phase, with longer swing phase in trials with a target surrounded by congruent versus incongruent flankers ( $p = 0.025$ ). More particularly, RT was significantly shorter during trials with multiple APAs compared to other trials, and during trials with APA errors compared to trials with normal APAs (main effect of APA type:  $p < 0.001$ ). The effect of conflict resolution on RT was significantly more important in trials with APA errors in comparison with other trials ( $p < 0.001$ ), and this interaction between target condition and APA type is even more pronounced in HC than in PwPD ( $p = 0.034$  for PD+FoG and  $p = 0.09$  for PD-FoG). Regarding APA duration, a main effect of APA type was also found ( $p < 0.001$ ): multiple APAs were longer than APA errors and normal APAs, whereas APA errors were significantly longer than normal APAs. Moreover, swing phase was significantly longer in trials with normal APAs than in trials with APA errors ( $p < 0.001$ ). In opposition to PwPD, HC showed longer swing phase in trials with multiple APAs compared to cases with normal APAs and APA errors ( $p < 0.001$ ).

No significant group effect was found regarding the amplitude of COP excursion during APAs. However, backward COP shift was lower in the incongruent condition of target than in the congruent condition ( $p < 0.001$ ), and significantly smaller in trials with multiple APAs compared to others, as well as in case of APA errors compared to normal APAs ( $p < 0.001$ ). The executive control effect on AP size of APAs is even more pronounced during trials with multiple APAs and APA errors in comparison with normal APAs. Concerning the lateral COP shift during the swing-foot unloading phase, it was significantly larger for trials with APA errors than for trials with multiple APAs and normal APAs, but also in case of multiple APAs compared to normal APAs (main effect of APA type:  $p < 0.001$ ). Especially, HC showed a bigger difference between lateral COP excursion in trials with normal APAs versus APA errors and multiple APAs than PD+FoG ( $p = 0.002$  and  $0.028$ , respectively). After correction for gender and MDS-UPDRS III score, PD-FoG also exhibited a greater lateral COP displacement towards the stance foot in case of APA errors relative to trials with normal APAs in comparison with PD+FoG ( $p = 0.01$ ). Compared to trials with normal APAs and APA errors, those with multiple APAs presented a significantly lower lateral COP displacement in the target condition with incongruent flankers than in the congruent condition of target.

Regarding parameters of execution of the first step, step length was not found to significantly differ between groups, whereas PwPD executed a first step at a lower velocity than HC ( $p = 0.047$  and  $0.045$  for PD+FoG and PD-FoG, respectively). No effect of conflict resolution was observed on first step length and velocity. On the one hand, first step velocity was significantly higher in trials with APA errors and multiple APAs compared to those with normal APAs ( $p$ -values  $< 0.001$ ). On the other hand, compared to cases with normal APAs, first step length was longer in trials with multiple APAs ( $p = 0.04$ ). These are particularly HC that carried out longer steps in trials with multiple APAs in comparison with trials with normal APAs and APA errors.

### **3.3. Impact of conflict resolution on cortical activity underpinning motor preparation**

At the time of APA onset, a central event-related synchronization (ERS) could be observed in the theta band (see Figures D.1 and E.1 in the Supplementary material file). This ERS was more pronounced in HC than in PwPD. A significant executive control effect was seen, with a more increased and longer ERS in the target condition with incongruent flankers than in trials with congruent flankers in HC and PD-FoG. The theta ERS was then observed in mesial frontal and temporal cortex (from around 400-600 ms after APA onset), with a larger synchronization in HC compared to PwPD.

In the alpha band, an event-related desynchronization (ERD) was seen in parieto-occipital regions (see Figures 5 and 7). This alpha ERD occurred earlier, was more pronounced and lasted longer in trials with incongruent versus congruent flankers. This executive control effect already started before APA onset for HC. In the time interval 400-600 ms after APA onset, alpha ERD was disappearing in controls, earlier than in the PD groups. In the context of the source localization analysis, alpha ERD in PD+FoG seemed to be located more anteriorly, in centro-parietal regions.

*[Insert Figure 5 here]*

*[Insert Figure 7 here]*

Finally, a response-locked ERD was visible in the beta band and was located in centro-parietal regions at the time of APA onset, before progressing towards the sensorimotor cortex (see Figures 6 and 8). This beta ERD occurred earlier, was more intense and lasted less longer in HC compared to the PD groups. In the incongruent versus congruent condition of target, the ERD started earlier and was more pronounced. Compared to PD-FoG and HC, the effect of conflict resolution on beta ERD occurred later in PD+FoG.

*[Insert Figure 6 here]*

*[Insert Figure 8 here]*

It is noteworthy that no significant interaction between group and target condition was observed in any frequency band.

## 4. Discussion

### 4.1. Executive control deficit in freezers

As previously found in the literature (Vandenbossche et al., 2012, 2011), we emphasized a significant deficit in executive control in PD+FoG compared to PD-FoG and HC, thanks to the ANT. In other words, the difference in RT between a situation with conflicting information and a situation without any conflict was specifically larger in freezers, highlighting their difficulty in monitoring and resolving conflict among responses. It is noteworthy that executive control also involves planning or decision-making, detection of errors, novel or not well-learned responses, situations judged to be dangerous or difficult, regulation of feelings and thoughts, and overcoming of habitual actions (Raz and Buhle, 2006).

However, even if our PD groups only differed in gender and were otherwise matched for age, overall cognition, disease duration, severity of motor symptoms and medication, we decided to perform our statistical analyses a second time, with gender and the MDS-UPDRS III score as covariates. Indeed, as FoG usually occurs later in the disease course, it is recommended to compare PwPD at comparable stage of the disease in order to disentangle the FoG phenotype from the consequences of a longer disease duration (Ehgoetz Martens et al., 2020). In the present study, the group of PD+FoG showed an insignificant higher severity score for motor symptoms than PD-FoG. After correction for gender and the MDS-UPDRS III score, the significant difference in executive control between PD+FoG and PD-FoG was not observed anymore. Similar results were recently found in a bigger cohort involving 81 PD-FoG and 66 PD+FoG that performed a flanker task in OFF-state of medication (Morris et al., 2020). After adjustment for age, gender, years of education and MDS-UPDRS III score, conflict resolution as well as global cognition did not differ anymore between PD+FoG and PD-FoG. In the context of the ANT, Vandenbossche and colleagues only used disease duration as covariate in their study on PD patients in ON-state of medication (Vandenbossche et al., 2012). Considering this covariate did not affect the significant difference in executive control between PD+FoG and PD-FoG.

Therefore, our results to the standard seated ANT suggest that the association between FoG and executive control is not as clear as previously reported. Severity of the motor symptoms seems to partly explain the deficit in conflict resolution in freezers. Indeed, as disease severity increases, cognitive impairment but also incidence of FoG increases. However, whether cognitive decline and FoG evolve in parallel or whether there is an indirect association between cognitive impairment and FoG remains unclear. Moreover, in the second case, whether this disease-related cognitive deterioration participates in reducing the ability to compensate for a loss of automaticity and thus to exacerbate FoG, or whether the cognitive decline beyond a threshold may contribute to the development of FoG is also a current matter of debate. Especially, additional analyses of our data showed that the RT score related to the executive control effect (i.e., subtraction of the median RT in trials with congruent flankers from the median RT associated with trials in the incongruent condition of target) was significantly positively correlated to the MDS-UPRS III score in PD-FoG ( $r_s = 0.645$ ,  $p = 0.013$ ), which was not the case for PD+FoG ( $r_s = 0.14$ ,  $p = 0.648$ ). The study of conflict resolution as a contextual factor of FoG, together with step initiation, thus appears useful for better characterizing the relationship between executive control, FoG but also gait initiation.

## **4.2. Impact of conflict resolution on step initiation in freezers**

Contrarily to our expectations and to the standard ANT that was associated with an impaired conflict resolution effect on RT in PD+FoG, the main result of the ANT-INIT is an executive control effect on the rate of APA errors and multiple APAs and on the SET but without any significant difference regarding this executive control effect across the three groups. Surprisingly, a similar rate of multiple APAs during step initiation under an attentional load between PD+FoG, PD-FoG and HC was found, as already reported in a relatively recent study (Cohen et al., 2017). Moreover, no freezing episodes was observed during this task, not even in the particular condition of target with incongruent flankers. However, as expected, PD+FoG were globally slower than HC (in terms of SET, RT, APA duration, swing phase and first step velocity), PD-FoG presenting intermediate values.

As previously found by our research group in healthy young adults (Braquet et al., 2020), the executive control effect on SET was here accompanied by such an effect on APA duration, but also on RT. A longer SET in incongruent condition of target can be partly explained by a higher rate of APA errors and multiple APAs in this condition of target, along with the fact that SET was longer in trials with those kinds of APAs compared to trials with normal APAs, and that the executive control effect on SET was particularly larger in trials with APA errors.

The effect of conflict resolution on RT was also significantly more important in trials with APA errors in comparison with other trials, thereby contributing to the executive control effect on SET. In fact, in trials with normal or multiple APAs, RT seemed nearly similar across conditions of target, whereas the executive control effect on RT was particularly seen in case of APA errors and in HC. A possible interpretation for this observation is the following: HC, with their higher rate of anticipated APAs and their shorter RT, may perform APA errors under congruent condition of target due mainly to haste (associated with a short RT) rather than because of a difficulty in choosing the correct motor program. Indeed, as we previously suggested (Braquet et al., 2020), these APA errors may correspond to a physiological phenomenon: healthy subjects seem able to adjust the motor program after initiation, rather than delaying initiation until the correct motor program is selected. Therefore, the RT difference between the congruent condition of target and the incongruent one (condition under which a conflict needs to be solved and which can thus be more probably associated with the selection of a wrong motor program) is more pronounced in HC than in the PD groups. In this line, we also found that HC showed a larger difference in lateral COP excursion between trials with normal APAs versus APA errors and multiple APAs than PD+FoG (COP excursion being lower in case of normal APAs), suggesting that controls might strategically start their APAs towards the wrong side (i.e., towards the stance foot) in order to gain in amplitude of the ML COP shift and therefore to generate a more efficient momentum towards the stance leg.

Duration of APAs also contributes to the executive control effect observed on SET, because it was significantly longer in target condition with incongruent versus congruent flankers, in trials with multiple APAs versus normal APAs and APA errors, as well as in trials with APA errors compared to normal APAs. More particularly, in case of APA errors, the correction time was significantly prolonged in trials with a target surrounded by incongruent flankers. Even if there was no significant interaction between group and target condition on APA duration, PwPD tended to present a smaller conflict resolution effect than HC, probably due to their general slowness compared to controls (in turn, mainly due to the greater time needed for correcting multiple APAs in PD+FoG). This slowness limited the APA

duration difference between target conditions. The amplitude of the COP backward shift during APA was also impacted by a conflicting situation, in line with the executive control effect on APA duration.

It appears to be useful to distinguish APA errors from multiple APAs. Indeed, the nature of multiple APAs seems different than the potentially physiological nature of APA errors, since their association with the execution phase of step initiation differed. Firstly, unlike APA errors, during multiple APAs, correction time under congruent condition of target seems to be as long as under incongruent condition of target, even if HC tended to take more time in case of incongruent flankers. Secondly, in opposition to PwPD, HC showed longer swing phase in trials with multiple APAs compared to cases with normal APAs and APA errors, and they carried out longer steps in trials with multiple APAs in comparison with trials with normal APAs and APA errors. It might reflect an impaired coupling between APAs and first step execution, suggested to be one possible mechanism behind the phenomenon of FoG (Jacobs et al., 2009). However, in our case, this observation was met for PwPD, without distinction between PD+FoG and PD-FoG.

### **4.3. Cortical preparation of step initiation reflects behavioral changes**

The results of the present study demonstrate that attention (and particularly, executive control) modulates cortical activation during motor preparation differently in PwPD and in HC. Patterns of response-locked spectral perturbations were globally in accordance with behavioral results.

A central theta ERS was visible from 200 ms before APA onset until 400 ms, and then became mesial frontal and temporal. This early theta ERS is commonly described in attentional processes (Fan et al., 2007; Luu et al., 2004; Song et al., 2014; Tard et al., 2016) such as an alerting effect (Luu et al., 2004) or error detection or conflict monitoring (van Driel et al., 2012; Wang et al., 2005). Theta ERS might also reflect the cognitive load related to a task and the sensorimotor coordination (from the sensory integration to movement adaptation) (Caplan et al., 2003; Makeig et al., 2004). Here, the effect of condition (with a stronger and longer theta response-locked ERS in the target condition with incongruent flankers for HC and PD-FoG) mirrored target discrimination and performance monitoring during APAs, that were even more intense in conflicting situations. The significantly larger amplitude of theta ERS in HC compared to PwPD may mirror a more efficient target discrimination and adjustment of the movement according to the context in this group; adjustment that is even more necessary in the incongruent condition of target. The insignificant target effect on early theta ERS in PD+FoG may mirror their deficit in executive control compared to the other groups, as observed during the standard ANT. However, there was no significant interaction between group and target condition on theta response-locked ERS.

Concerning response-locked ERSPs in alpha band, an ERD appeared a bit before APA onset and during APAs in parieto-occipital regions because these desynchronized oscillations may aid in the integration of sensory cues that are necessary for accurate movements. They can be seen as a proprioceptive checking before and during the movement to ensure the appropriate movement execution (Heinrichs-Graham et al., 2014). Activation in visual areas was increasingly more intense and widespread, reflecting the recruitment of associative visual areas. Characteristics of alpha response-locked ERD were in line with behavioral results. Indeed, as APA duration tended to be shorter in HC than in PD+FoG, with an intermediate APA duration in PD-FoG, alpha ERD ended earlier in the control group. Furthermore, the significant executive control effect on APA duration may correspond to the earlier, more pronounced and more prolonged alpha ERD in trials with a target surrounded by incongruent

flankers. As for behavioral results, the executive control effect on alpha ERD was not significantly different across groups. Interestingly, alpha ERD in PD+FoG seemed to be located more anteriorly, maybe due to their impaired visuospatial function (Nantel et al., 2012), but more investigation is still needed. It is noteworthy that alpha ERD is not only associated with motor preparation and execution, but also with attention (Dujardin et al., 1995; Klimesch, 2012). Alpha desynchronization is, more particularly, related to visual perception and task anticipation (Capotosto et al., 2017). Therefore, it can sometimes be difficult to distinguish between alpha ERD reflecting the activation of regions engaged in visuospatial attention or in motor execution (Pfurtscheller, 1999).

Finally, at the time of APA onset, a beta response-locked ERD was also observed over the sensorimotor cortex. Indeed, the desynchronized oscillations in the beta band have been suggested to participate in movement preparation and cognitive selection of a proper motor response (Heinrichs-Graham et al., 2014). As already noticed for alpha ERD, the group effect on APA duration (i.e., a shorter duration of APA in HC compared to PwPD) can also be found on beta ERD: beta desynchronization occurred earlier, was more intense and lasted less longer in HC compared to the PD groups. In fact, as emphasized several times in previous studies about cortical oscillations related to different motor tasks (Brugger et al., 2020; Heinrichs-Graham et al., 2014; Shirahige et al., 2020; Weersink et al., 2020), beta ERD during motor preparation was globally diminished in PwPD in comparison with HC. Indeed, during movement planning, PwPD may be unable to suppress the pathological beta synchronization throughout the cortical-basal ganglia motor network that characterizes patients. This would lead to a delayed (Tard et al., 2016) and lower premovement beta ERD which is necessary for proper movement, and would therefore contribute to the diminished movement capacities of PwPD. Similarly, the conflict resolution effect was also visible: the beta ERD started earlier and was more pronounced in the incongruent condition of target compared to the congruent condition. Compared to PD-FoG and HC, the effect of conflict resolution on beta ERD occurred later in PD+FoG, but no significant interaction between group and target condition was observed.

#### **4.4. Limitations**

This study presents some limitations. First, given the heterogeneity of the FoG symptom behaviorally and at the level of the underpinning brain activity (Ehgoetz Martens et al., 2020, 2018), a larger cohort should be used, with PD-FoG and PD+FoG exhibiting normal overall cognition, but also mild cognitive impairment and dementia, in order to even better understand the interaction between attention and gait initiation and its influence on FoG. Secondly, in this study, PD patients were assessed in ON-state of medication. However, we know that abnormal beta synchronization in PD is partly normalized by levodopa, and that FoG episodes can occur in OFF-state as well as in ON-state of medication depending on each patient. Additional assessments in OFF-state of medication could thus bring a larger overview of the FoG symptom. Besides, trials could be separated by larger time intervals of rest (i.e., without any cue, target or movement) in order to increase the baseline duration and therefore to improve the accuracy and reliability of ERSPs. Furthermore, the absence of FoG episodes may come to the fact that ANT-INIT is not an ecological task. Finally, because of the small number of wrong steps during the ANT-INIT, it was possible to determine the prioritization strategy of the different groups between speed or accuracy. It would have allowed a better understanding of the difference in nature between APA errors and multiple APAs across groups.

## 5. Conclusions

This study questions the cognitive hypothesis in the pathophysiology of FoG. Indeed, our results from the standard ANT have shown that the association between FoG and executive control is less straightforward than previously suggested, with disease severity as a significant covariate. This means that cognitive deficits and FoG incidence may occur concomitantly as PD progresses. The remaining question is whether cognitive decline and FoG evolve in parallel or whether a deficit in executive control due to disease progression can trigger and eventually exacerbate episodes of FoG. In this context, we did not observe any instance of FoG during the ANT-INIT. Our results from the ANT-INIT concluded in the same executive control effect on SET and on the induced alpha and beta activity over the sensorimotor cortex in PD+FoG, PD-FoG and HC. Only significant group differences were observed, reflecting the overall motor slowness associated with PD. In this line, although similar rates of APA errors and multiple APAs than HC, PD showed more difficulty for recovering from multiples APAs than controls (as previously found in (Cohen et al., 2017)). In summary, the relationship between executive control, gait initiation and FoG seems more complex than expected. Further investigations with a larger cohort that better mirrors the heterogeneity of the FoG symptom (e.g., with various cognitive status) should be performed in order to generalize our observations.

**Declarations of interest:** none.

**Funding:**

No author had conflict of interests related to this study.

M. Bayot received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 721577.

M. Gerard received a grant from Lille University for a research year and no other financial disclosure.

A. Braquet, P. Derambure, K. Dujardin and A. Delval were employed by the French Government (Enseignement supérieur) and had no other financial disclosure.

L. Defebvre was employed by French Government (enseignement supérieur), gave consultancies to "Abbvie" and "Orkyn" and earned honoraria for lectures from "UCB" and "Abbvie".

Under preparation



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## 7. Legends

**Figure 1.** Performed tasks: (A) the standard Attention Network Test (ANT) with a keypress as response to a target surrounded by congruent or incongruent flankers, and (B) the ANT-INIT with step initiation as response

**Table 1.** Demographic and clinical data characterizing participants who performed the ANT-INIT (mean  $\pm$  standard deviation).

**Notes.** MoCA = Montreal Cognitive Assessment; MDS-UPDRS III – Med ON = Movement Disorder Society-sponsored revision of the Unified Parkinson's disease Rating Scale, part III, in the ON-state of medication; H&Y scale – Med ON = Hoehn and Yahr scale, in the ON-state of medication; LEDD = Levodopa Equivalent Daily Dose. \* for p-value < 0.05

**Figure 2.** Executive control effect on RT measured thanks to the standard ANT. Statistical results without correction for gender and MDS-UPDRS III in ON-state of medication. Bars represent means of the median RT of each subject from each group, and error bars are standard errors. C = congruent condition of target; I = incongruent condition of target; \* for p-value < 0.05

**Figure 3.** Executive control effect on step initiation measured thanks to the ANT-INIT: rate of the different APA types; (A) Rate of anticipated APAs (with RT < 100 ms); (B) Rate of normal APAs; (C) Rate of APA errors; (D) Rate of multiple APAs. Statistical results with correction for gender and MDS-UPDRS III in ON-state of medication. Bars represent means of the median RT of each subject from each group, and error bars are standard errors. C = condition of target surrounded by congruent flankers; I = condition of target surrounded by incongruent flankers. \* for p-value < 0.05; \*\* for p-value < 0.01; \*\*\* for p-value < 0.001

**Table 2.** Executive control effect on step initiation measured thanks to the ANT-INIT: spatio-temporal characteristics of APAs and step execution.

**Notes.** EC = executive control; C = condition of target surrounded by congruent flankers; I = condition of target surrounded by incongruent flankers; (a) without covariate taken into account; (b) corrected for gender; (c) corrected for gender and MDS-UPDRS III in ON-state of medication. Only p-values below 0.1 were presented. \* for p-value < 0.05; \*\* for p-value < 0.01; \*\*\* for p-value < 0.001

**Figure 4.** Executive control effect on preparatory and execution phases of the gait initiation process measured thanks to the ANT-INIT: (A) SET across groups and target conditions; (B) RT across APA types and target conditions; (C) APA duration SET across groups and target conditions; (D) Correction time for multiple APAs across groups and target conditions. Statistical results with correction for gender and MDS-UPDRS III in ON-state of medication. Bars represent means of the median RT of each subject from each group, and error bars are standard errors. C = condition of target surrounded by congruent flankers; I = condition of target surrounded by incongruent flankers; nAPA = normal APAs; APAe = APA errors; mAPA = multiple APAs. \* for p-value < 0.05; \*\* for p-value < 0.01; \*\*\* for p-value < 0.001

**Figure 5.** Executive control effect on response-locked ERSPs in alpha band over the scalp and throughout a trial of the ANT-INIT. APA onset occurs at 0 ms. Topographic distribution of EEG power, with warm colors corresponding to ERS, while cold colors correspond to ERD. In the column to the right and in the row below spectral distributions, red dots mark significant differences in a permutation test with target condition (column) and group (row) as respective within-subject and between-subject factors, and a statistical significance threshold at  $p < 0.05$ . The intersection between this column and this row show the potential significant interaction existing between target and group. C = congruent condition of target; I = incongruent condition of target

**Figure 6.** Executive control effect on response-locked ERSPs in beta band over the scalp and throughout a trial of the ANT-INIT. APA onset occurs at 0 ms. Topographic distribution of EEG power, with warm colors corresponding to ERS, while cold colors correspond to ERD. In the column to the right and in the row below spectral distributions, red dots mark significant differences in a permutation test with target condition (column) and group (row) as respective within-subject and between-subject factors, and a statistical significance threshold at  $p < 0.05$ . The intersection between this column and this row show the potential significant interaction existing between target and group. C = congruent condition of target; I = incongruent condition of target

**Figure 7.** Source localization of response-locked ERSPs in alpha band throughout a trial of the ANT-INIT. APA onset occurs at 0 ms. Warm colors correspond to ERS, while cold colors correspond to ERD. On the right, only the sources that have a value superior to 50% of the colorbar maximum are here displayed. C = congruent condition of target; I = incongruent condition of target; Post = posterior; Ant = anterior; L = left; R = right

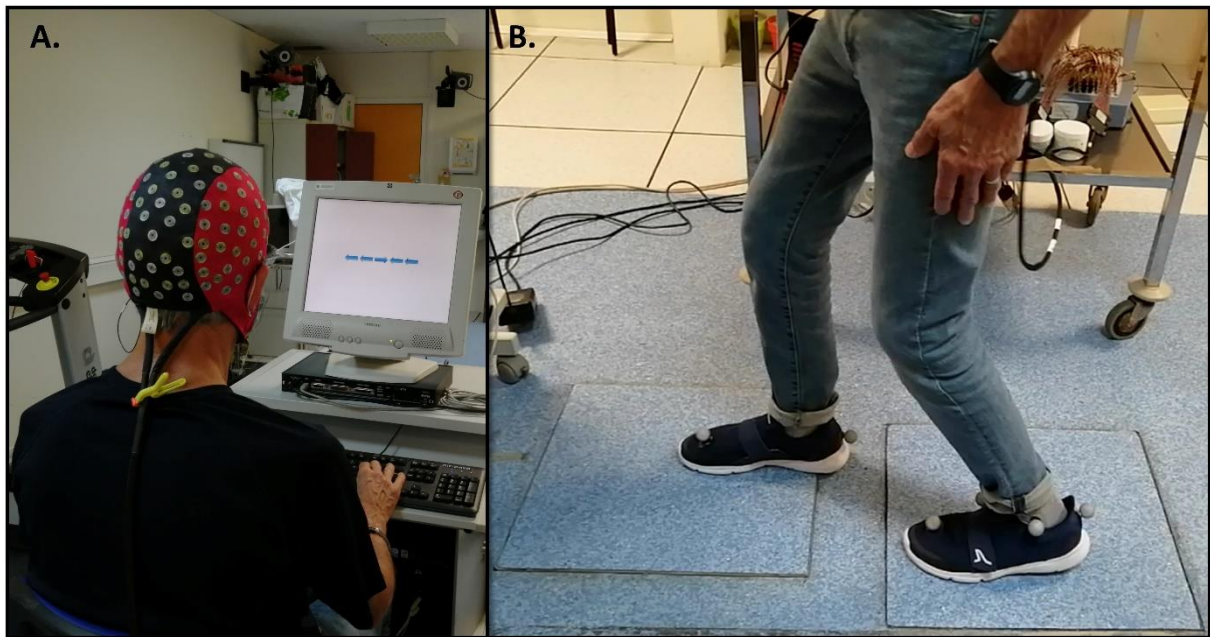
**Figure 8.** Source localization of response-locked ERSPs in beta band throughout a trial of the ANT-INIT. APA onset occurs at 0 ms. Warm colors correspond to ERS, while cold colors correspond to ERD. On the right, only the sources that have a value

superior to 50% of the colorbar maximum are here displayed. C = congruent condition of target; I = incongruent condition of target; Post = posterior; Ant = anterior; L = left; R = right

Under preparation

## 8. Tables and Figures

**Figure 1:**



Under preparation

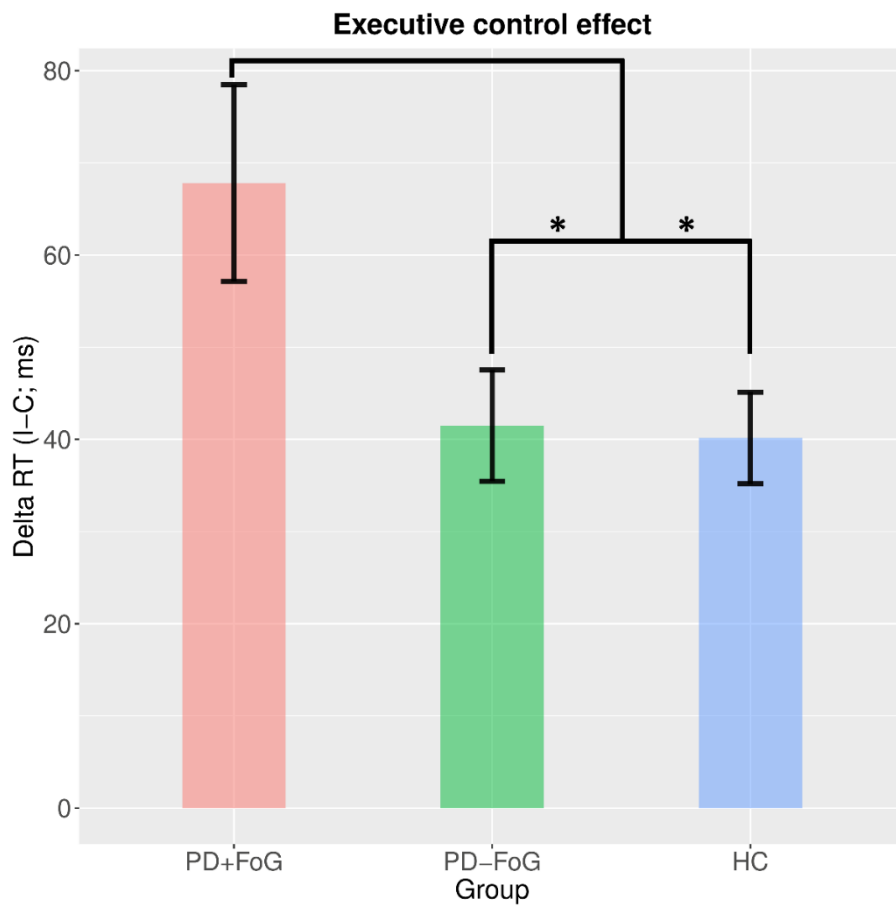


**Table 1:**

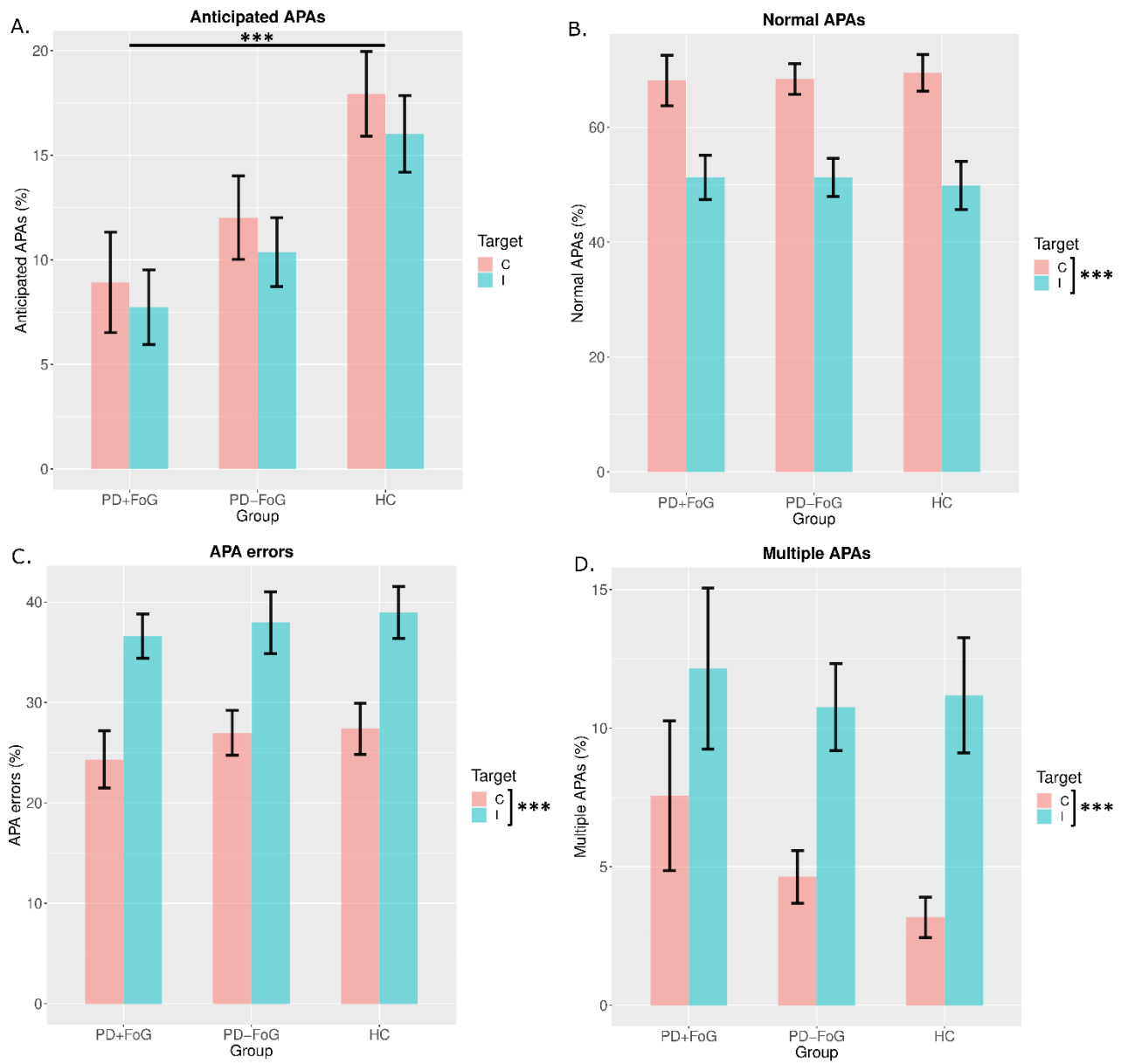
<b>Group</b>	<b>Age</b> (years)	<b>Gender</b> (F/M)	<b>MoCA</b> (/30)	<b>Disease duration</b> (years)	<b>MDS-UPDRS III</b> – Med ON	<b>H&amp;Y – Med ON</b>	<b>LEDD</b> (mg L-Dopa)
<b>PD+FoG</b> (n=15)	65 ± 6	3/12	27 ± 2	10 ± 5	29 ± 12	2 ± 1	1148 ± 612
<b>PD-FoG</b> (n=16)	62 ± 9	10/6	27 ± 2	9 ± 4	23 ± 12	2 ± 1	1025 ± 427
<b>HC</b> (n=15)	59 ± 6	10/5	28 ± 2	/	/	/	/
<b>p-value</b>	0.067	<b>0.018*</b>	0.607	0.483	0.171	0.124	0.526

Under preparation

**Figure 2:**



**Figure 3:**



**Table 2:**

<b>ANT-INIT - EC</b>		<b>Mean ± standard deviation</b>			<b>Group effect</b> (p-value) (a) (b)		<b>Target effect</b> (p-value) (a)	<b>APA type effect</b> (p-value) (a)	<b>Group* Target Interaction effect</b>		<b>Group*APA type Interaction effect</b>		<b>Target* APA type Interaction effect</b> (p-value) (a)	<b>Group*Target* APA type Interaction effect</b>																								
		<b>C - nAPA</b>	<b>C - APAe</b>	<b>C - mAPA</b>					<b>Group* Target Interaction effect</b> (p-value) (a) (b)		<b>Group*APA type Interaction effect</b> (p-value) (a) (b)			<b>Group*Target* APA type Interaction effect</b> (p-value) (a) (b)																								
		<b>I - nAPA</b>	<b>I - APAe</b>	<b>I - mAPA</b>																																		
<b>SET (s)</b>	<b>PD+FoG</b>	1.275 ± 0.182	1.357 ± 0.176	1.483 ± 0.23	<b>0.009**</b>	<b>0.012*</b>	<b>C &lt; I (&lt; 0.001****)</b>	<b>nAPA &lt; APAe (&lt; 0.001****)</b>	0.758	0.757	0.311	0.31	<b>0.001**</b>	<b>C &lt; I: nAPA &lt; APAe (0.011*)</b>	0.753	0.752																						
		1.297 ± 0.188	1.387 ± 0.198	1.401 ± 0.21																																		
	<b>PD-FoG</b>	1.193 ± 0.135	1.296 ± 0.134	1.354 ± 0.185													<b>PD+FoG &gt; HC (0.006**)</b>	<b>PD+FoG &gt; HC (0.009**)</b>	<b>nAPA &lt; mAPA (&lt; 0.001****)</b>	0.447	0.446	0.475	0.479	<b>&lt; 0.001***</b>	<b>C &lt; I: nAPA &lt; APAe (&lt; 0.001****)</b>	<b>C &lt; I: APAe &gt; mAPA (0.007**)</b>	<b>0.018*</b>	<b>0.018*</b>										
		1.215 ± 0.14	1.322 ± 0.123	1.314 ± 0.174																																		
	<b>HC</b>	1.015 ± 0.117	1.119 ± 0.111	1.176 ± 0.087													<b>PD+FoG &gt; HC (&lt; 0.001****)</b>	<b>PD+FoG &gt; PD-FoG (0.072) <sup>(c)</sup></b>											<b>C &lt; I (&lt; 0.001****)</b>	<b>nAPA &gt; APAe (&lt; 0.001****)</b>	0.447	0.446	0.475	0.479	<b>&lt; 0.001***</b>	<b>C &lt; I: nAPA &lt; APAe (&lt; 0.001****)</b>	<b>C &lt; I: nAPA &lt; APAe: PD+FoG &lt; HC</b>	<b>C &lt; I: nAPA &lt; APAe: PD+FoG &lt; HC</b>
		1.036 ± 0.122	1.176 ± 0.101	1.202 ± 0.125																																		
<b>RT (ms)</b>		345.767 ± 63.985	276.667 ± 57.451	301.292 ± 77.016	<b>&lt; 0.001***</b>	<b>&lt; 0.001***</b>	<b>&lt; 0.001***</b>	<b>&lt; 0.001***</b>					<b>&lt; 0.001***</b>	<b>0.018*</b>	<b>0.018*</b>																							
		379.067 ± 81.754	298.733 ± 53.598	266 ± 61.071	<b>PD+FoG &gt; HC (&lt; 0.001****)</b>	<b>PD+FoG &gt; PD-FoG (0.072) <sup>(c)</sup></b>	<b>C &lt; I (&lt; 0.001****)</b>	<b>nAPA &gt; APAe (&lt; 0.001****)</b>	0.447	0.446	0.475	0.479	<b>&lt; 0.001***</b>	<b>C &lt; I: nAPA &lt; APAe (&lt; 0.001****)</b>	<b>C &lt; I: nAPA &lt; APAe: PD+FoG &lt; HC</b>	<b>C &lt; I: nAPA &lt; APAe: PD+FoG &lt; HC</b>																						
		307.25 ± 42.751	244.875 ± 30.041	220.077 ± 55.994																																		

	329.812 ± 55.171	269.156 ± 31.638	227.844 ± 50.946	PD-FoG > HC (0.036*)	PD+FoG > HC (< 0.001***)		nAPA > mAPA (< 0.001***)				C < I: APAE > mAPA (0.021*)	(0.034*) C < I: nAPA < APAe: PD-FoG < HC (0.09*)	(0.036*) C < I: nAPA < APAe: PD-FoG < HC (0.09*)
	262.367 ± 19.631	207.733 ± 17.222	211.192 ± 38.904		PD-FoG > HC (0.037*)		APAE > mAPA (0.009**)						
	258.833 ± 22.907	227.133 ± 24.742	212.667 ± 27.944										
APA duration (ms)	560.3 ± 89.928	725.833 ± 105.356	855.458 ± 152.537				< 0.001***						
	560.367 ± 85.515	749.633 ± 120.842	784.808 ± 131.508	0.068	0.073		nAPA < APAe (< 0.001***)						
	519.594 ± 88.951	692.312 ± 96.774	756.692 ± 144.679			C < I (0.012*)	nAPA < mAPA (< 0.001***)	0.135	0.134	0.406	0.406	0.35	0.84
	522.625 ± 94.967	701.594 ± 92.284	735.969 ± 117.722	PD+FoG > HC (0.061)	PD+FoG > HC (0.067)		nAPA < mAPA (< 0.001***)						
	461.967 ± 42.134	634.7 ± 62.171	630.692 ± 70.202				APAE < mAPA (0.005**)						
	485.167 ± 41.271	667.333 ± 54.502	674.267 ± 87.506										
Swing phase (ms)	363.133 ± 70.235	342.567 ± 60.647	334.792 ± 52.678	0.0099**	0.006**		< 0.001***	0.785	0.784	< 0.001***	< 0.001***	0.73	0.419
	357.867 ± 70.199	340.833 ± 63.017	339.423 ± 67.351	PD+FoG > HC (0.04*)	PD+FoG > HC (0.021*)	C > I (0.025*)	nAPA > APAe (< 0.001***)			nAPA < mAPA: PD+FoG < HC (< 0.001***)	nAPA < mAPA: PD+FoG < HC (< 0.001***)		0.418

	367.344 ± 57.697	350.094 ± 56.973	359.038 ± 64.637	<b>PD-FoG &gt; HC</b> <b>(0.017*)</b>	<b>PD-FoG &gt; HC</b> <b>(0.016*)</b>				<b>nAPA &lt; mAPA:</b> <b>PD-FoG &lt; HC</b> <b>(0.001**)</b>	<b>nAPA &lt; mAPA:</b> <b>PD-FoG &lt; HC</b> <b>(0.001**)</b>				
	363.312 ± 55.069	350 ± 58.962	338.812 ± 51.159						<b>APAe &lt; mAPA:</b> <b>PD+FoG &lt; HC</b> <b>(&lt; 0.001***)</b>	<b>APAe &lt; mAPA:</b> <b>PD+FoG &lt; HC</b> <b>(&lt; 0.001***)</b>				
	282.767 ± 90.53	272.767 ± 86.179	336.423 ± 70.867						<b>APAe &lt; mAPA:</b> <b>PD-FoG &lt; HC</b> <b>(&lt; 0.001***)</b>	<b>APAe &lt; mAPA:</b> <b>PD-FoG &lt; HC</b> <b>(&lt; 0.001***)</b>				
	285 ± 95.534	269.5 ± 83.432	313.533 ± 71.571											
<b>AP size of APA (mm)</b>	14.903 ± 11.218	7.85 ± 8.138	8.927 ± 8.887											
	14.039 ± 11.239	7.981 ± 7.943	7.568 ± 10.083											
	16.731 ± 9.074	8.069 ± 8.297	5.707 ± 9.11	0.486	0.531	<b>C &gt; I</b> <b>(&lt; 0.001***)</b>		0.346	0.348	0.026*	0.025*	<b>C &gt; I:</b> <b>nAPA &lt; APAe</b> <b>(0.042*)</b>	0.704	0.707
	15.068 ± 8.45	5.066 ± 4.428	4.764 ± 5.235							<b>nAPA &gt; mAPA:</b> <b>PD+FoG &lt; HD</b> <b>(0.022*)</b>	<b>nAPA &gt; mAPA:</b> <b>PD+FoG &lt; HD</b> <b>(0.021*)</b>	<b>C &gt; I:</b> <b>nAPA &lt; mAPA</b> <b>(&lt; 0.001***)</b>		
	22.476 ± 13.148	15.205 ± 6.949	13.23 ± 9.504									<b>C &gt; I:</b> <b>APAe &lt; mAPA</b> <b>(0.056)</b>		
	21.852 ± 12.966	10.768 ± 7.422	6.96 ± 8.668											

<b>Lateral COP shift during swing-foot unloading phase (mm)</b>	103.47 ± 22.876	113.987 ± 19.206	114.364 ± 26.042	0.116	0.087	0.05	< 0.001***	0.672	0.669	< 0.001***	< 0.001***	0.814	0.834	
	104.588 ± 19.465	119.85 ± 24.554	101.814 ± 21.529				nAPA < APAe (< 0.001***)			nAPA < APAe: PD+FoG < PD-FoG (0.01*) <sup>(c)</sup>	0.004**			
	104.589 ± 28.967	127.767 ± 30.751	115.715 ± 36.657				nAPA < mAPA (< 0.001***)			nAPA < APAe: PD+FoG < HC (0.002**) nAPA < mAPA: PD+FoG < HC (0.002**)	C > I: nAPA < mAPA (0.023*)			
	103.272 ± 31.136	126.399 ± 31.67	108.273 ± 30.267				APAe > mAPA (< 0.001***)			nAPA < mAPA: PD+FoG < HC (0.028*) nAPA < mAPA: PD+FoG < HC (0.026*)	C > I: APAe < mAPA (0.003**)			
	113.869 ± 30.439	135.517 ± 29.904	132.979 ± 31.053											
	112.491 ± 32.246	138.954 ± 29.582	126.518 ± 37.544											
<b>1<sup>st</sup> step length (mm)</b>	427.082 ± 108.838	428.376 ± 111.535	426.291 ± 114.367	0.973	0.989	0.189	0.046*	0.124	0.124	< 0.001***	< 0.001***	0.245	0.616	0.611
	426.407 ± 108.843	424.671 ± 106.428	413.192 ± 108.685				nAPA < mAPA (0.04*)			nAPA < mAPA: PD+FoG < HC (< 0.001***)	nAPA < mAPA: PD+FoG < HC (< 0.001***)			
	419.353 ± 90.301	421.896 ± 90.301	410.438 ± 102.612				APAe < mAPA (0.056)			nAPA < mAPA: PD-FoG < HC (0.003**) APAe < mAPA: PD-FoG < HC (0.004**)				
	420.458 ± 90.126	420.836 ± 91.314	418.341 ± 90.357							APAe < mAPA: PD-FoG < HC (0.003**) APAe < mAPA: PD-FoG < HC (0.004**)				

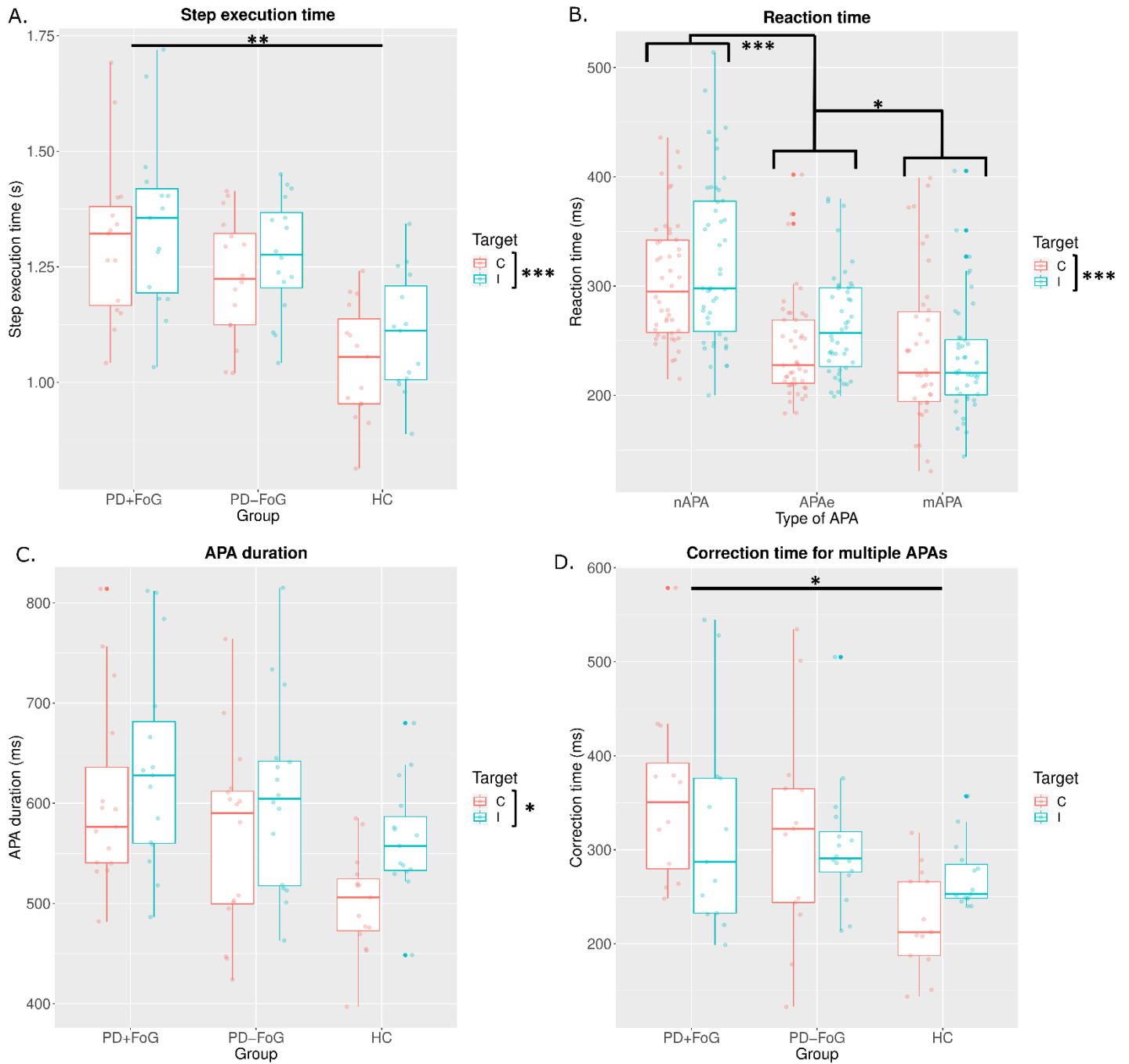
	397.028 ± 137.242	406 ± 124.388	463.662 ± 92.589							PD+FoG < HC ( <b>&lt; 0.001***</b> )	PD+FoG < HC ( <b>&lt; 0.001***</b> )			
	397.545 ± 129.693	404.398 ± 127.882	447.034 ± 105.102							APAe < mAPA: PD-FoG < HC ( <b>&lt; 0.001***</b> )	APAe < mAPA: PD-FoG < HC ( <b>0.001**</b> )			
<b>1<sup>st</sup> step velocity (m/s)</b>	0.815 ± 0.238	0.845 ± 0.243	0.86 ± 0.275	<b>0.02*</b>	<b>0.02*</b>		<b>&lt; 0.001***</b>							
	0.828 ± 0.241	0.843 ± 0.245	0.824 ± 0.232											
	0.819 ± 0.192	0.846 ± 0.199	0.828 ± 0.216	PD+FoG < HC ( <b>0.047*</b> )	PD+FoG < HC ( <b>0.05*</b> )	0.788	nAPA < APAe ( <b>&lt; 0.001***</b> )	0.917	0.918	0.664	0.665	0.495	0.77	0.772
	0.823 ± 0.19	0.849 ± 0.204	0.862 ± 0.206											
	0.992 ± 0.099	1.011 ± 0.116	1.028 ± 0.122	PD-FoG < HC ( <b>0.045*</b> )	PD-FoG < HC ( <b>0.049*</b> )		nAPA < mAPA ( <b>&lt; 0.001***</b> )							
	0.988 ± 0.096	1.012 ± 0.117	0.989 ± 0.143											
<b>CT for APAe (ms)</b>	173.533 ± 30.5941													
	176.967 ± 31.209													
	170.719 ± 24.435			0.917	0.883	C < I ( <b>0.003**</b> )	/	0.653	0.651	/	/	/	/	/
	175.406 ± 20.698													
	178.233 ± 26.963													
	190.467 ± 27.347													
<b>CT for mAPA (ms)</b>	356.792 ± 94.823			<b>0.015*</b>	<b>0.017*</b>									
	321.731 ± 111.617					0.363	/	0.324	0.324	/	/	/	/	/



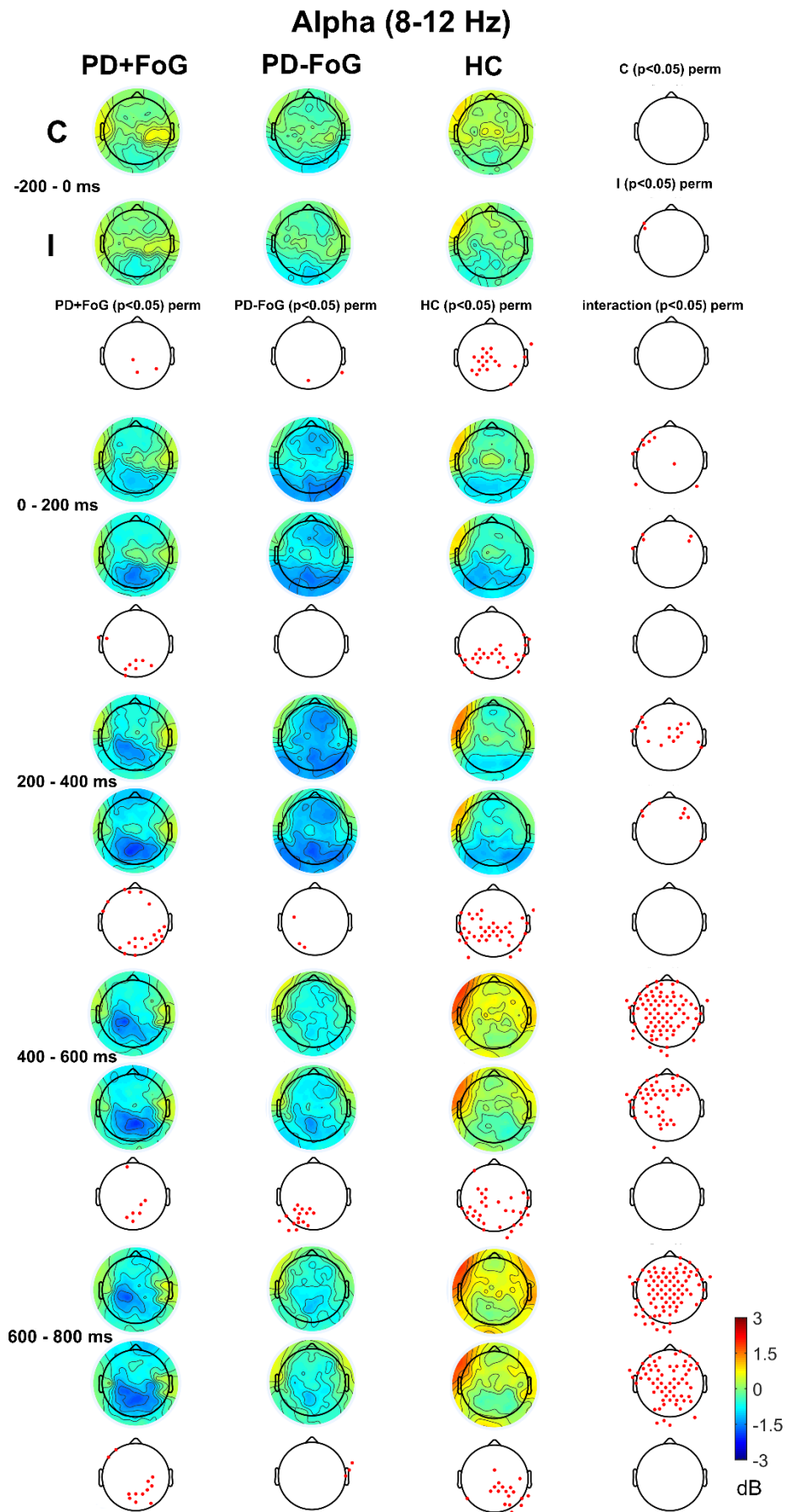
	318.885 ± 115.559	PD+FoG > HC (0.022*)	PD+FoG > HC (0.032*)									
	304.719 ± 68.167											
	225.885 ± 53.67	PD-FoG > HC (0.057)	PD-FoG > HC (0.058)									
	271.333 ± 35.188											

Under preparation

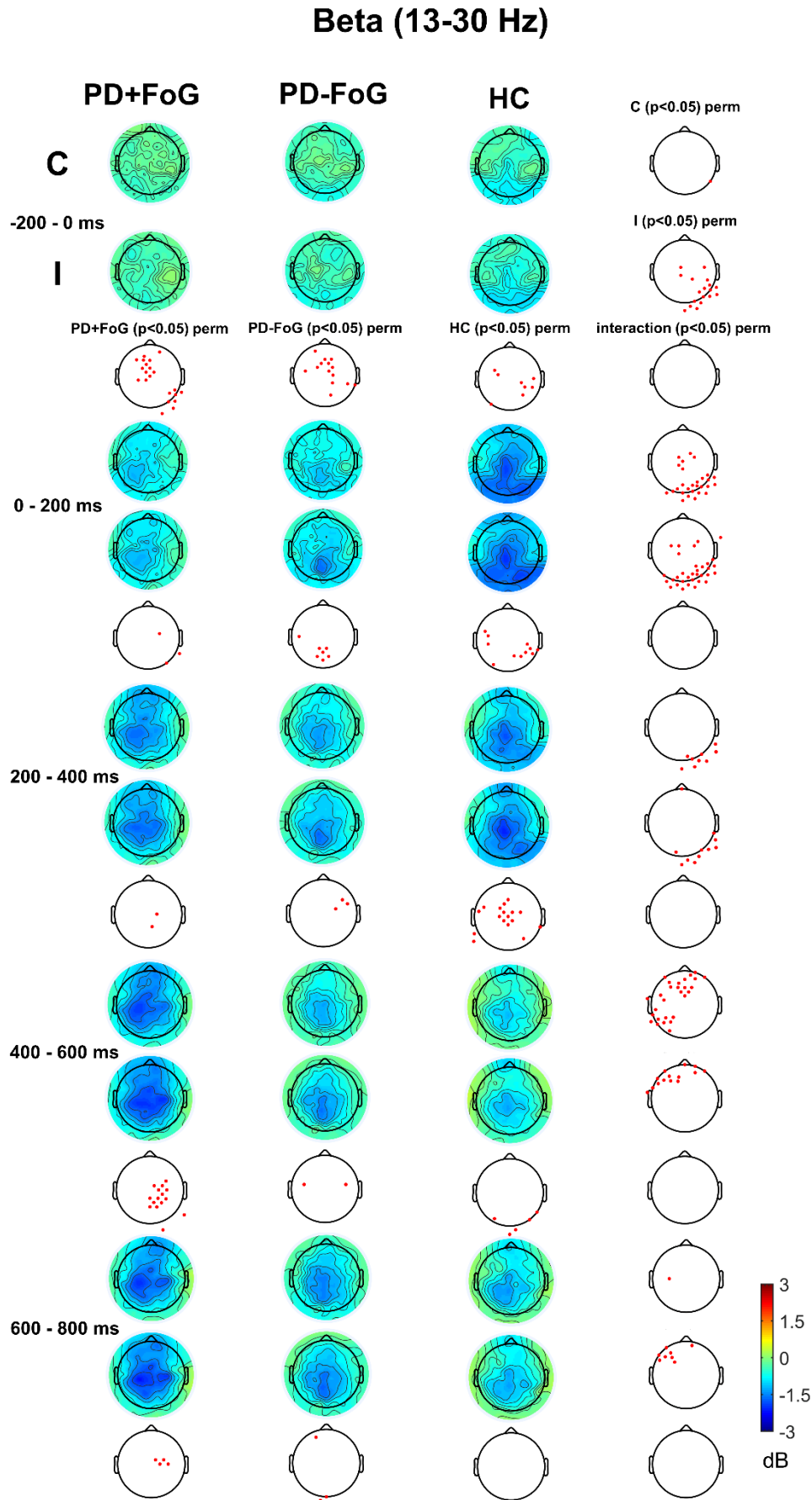
**Figure 4:**



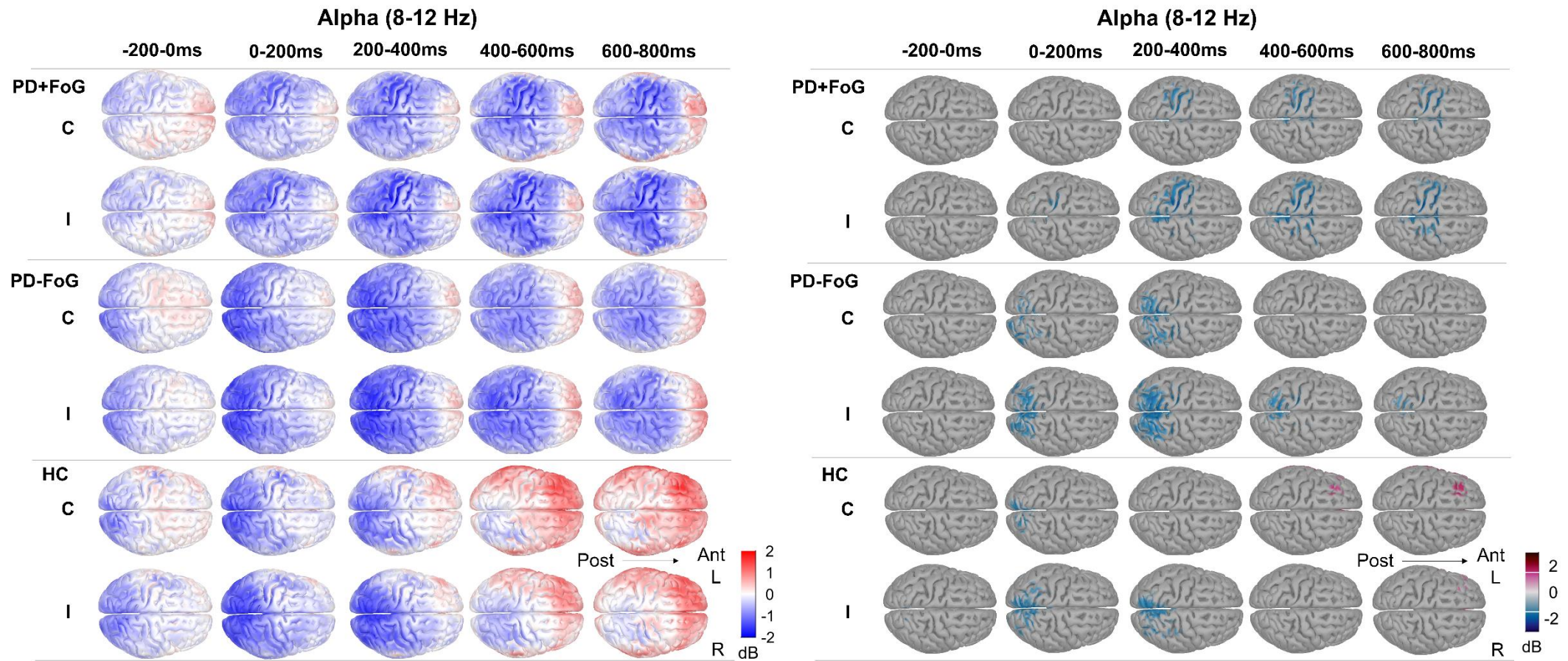
**Figure 5:**



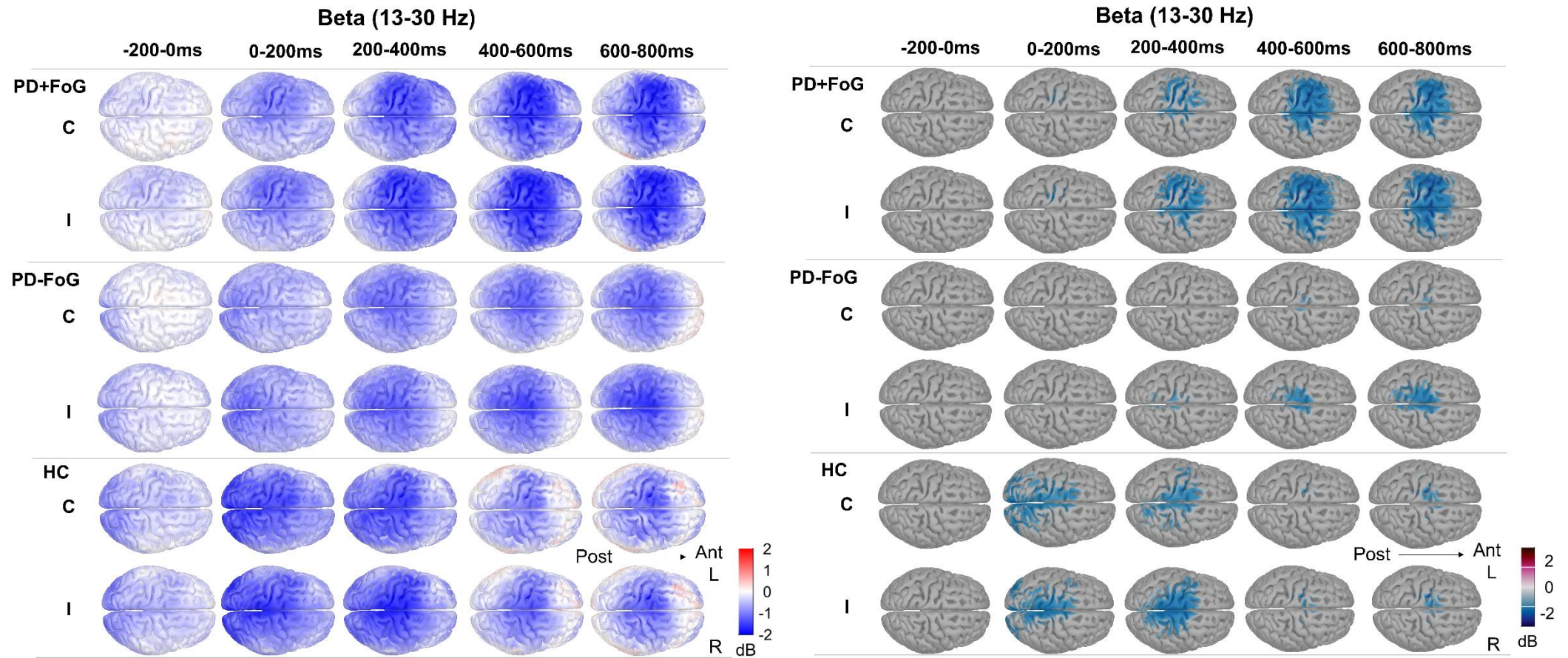
**Figure 6:**



**Figure 7:**



**Figure 8:**



# Etude 5 : Investigation de biomarqueurs du freezing de la marche – Etude électroencéphalographique à l'état de repos (analyse de la connectivité fonctionnelle)

“Functional Networks Underlying Freezing of Gait: A Resting-State Electroencephalographic Study”

**Madli Bayot**, Morgane Gérard, Philippe Derambure, Kathy Dujardin, Luc Defebvre, Nacim Betrouni, Arnaud Delval.

Article soumis.

## Apport personnel

- Enregistrement de la plupart des données.
- Développement des méthodes d'analyse des données et co-traitement (en partie réalisé par Morgane Gérard).
- Co-réalisation des tests statistiques.
- Rédaction et correction du manuscrit suite aux retours des co-auteurs et reviewers.

## Résumé

### Contexte

Le freezing de la marche (FdM) est un syndrome invalidant qui peut apparaître chez les personnes souffrant de la maladie de Parkinson. Malgré son association avec des détériorations motrices, cognitives, limbiques et sensori-perceptuelles, sa pathophysiologie reste incertaine et l'analyse électroencéphalographique de l'état de repos n'a pas encore été effectuée à ce jour dans cette population.

### Objectifs

Nous avons pour objectif de trouver un biomarqueur facilement collectable du FdM pour améliorer sa compréhension et son diagnostic.

### Méthodes

L'électroencéphalographie haute résolution était enregistrée auprès de 18 freezers, 18 non-freezers et 18 contrôles sains pendant une période de repos de 5 minutes avec yeux ouverts et suivie d'une analyse spectrale basique dans l'espace des capteurs ainsi que d'une analyse plus avancée de la connectivité fonctionnelle au niveau des sources.

## **Résultats**

Les freezers présentaient une puissance spectrale relative dans la bande thêta diffuse et plus importante que chez les contrôles. Cette augmentation de puissance tendait à être associée avec de moins bonnes capacités cognitives globales et était significativement corrélée au déficit de contrôle exécutif présent chez les participants freezers. En ce qui concerne la connectivité fonctionnelle à l'état de repos, la force de connexion au niveau du réseau fronto-pariétal gauche était plus importante chez les freezers par rapport aux contrôles dans la bande thêta, était corrélée à la sévérité du freezing et montrait une tendance à être associée avec le déclin du contrôle exécutif.

## **Conclusions**

Les deux types d'analyse électroencéphalographique de l'état de repos semblent utiles et complémentaires pour mieux comprendre le FdM. La connectivité fonctionnelle plus importante au niveau du réseau attentionnel ventral gauche chez les freezers est en concordance avec une supervision excessive du comportement moteur par des stimuli externes à cause d'une dysfonction exécutive, telle que le déficit de contrôle exécutif mis en évidence par l'analyse spectrale. Les conséquences comportementales de cette influence exagérée de l'environnement externe pourraient être des épisodes de FdM. Une étude longitudinale devrait dès lors être réalisée dans le futur.

**Mots-clés :** maladie de Parkinson (MP), freezing de la marche (FdM), état de repos, électroencéphalographie (EEG), analyse spectrale, connectivité fonctionnelle.





# Functional Networks Underlying Freezing of Gait: A Resting-State Electroencephalographic Study

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**Word count:** 3699 words

**Running title:** A resting-state EEG study of freezing of gait

**Keyword:** Parkinson's disease (PD), freezing of gait (FOG), resting state, electroencephalography (EEG), spectral analysis, functional connectivity

**Conflict of Interest:** none

**Funding:** Madli Bayot works on a project that received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 721577. Morgane Gerard received a grant from Lille University for a research year.

## Abstract

### Background

Freezing of gait is a debilitating syndrome that can occur in people with Parkinson's disease. Despite its association with motor, cognitive, limbic and sensory-perceptual impairment, its pathophysiology remains unclear, and resting-state electroencephalography has not been investigated in this population yet.

### Objectives

We aimed to find an easily obtained biomarker of FoG for improving its understanding and diagnosis.

### Methods

High-resolution electroencephalography was recorded in 18 freezers, 18 non-freezers and 18 healthy controls during a 5-min resting-state protocol with eyes open, followed by a basic spectral analysis in the sensor space and a more advanced analysis of functional connectivity at the source level.

### Results

Freezers showed a diffuse higher theta-band relative spectral power than controls. This increased power tended to be associated with worse overall cognition, and was significantly correlated to freezer's deficit in executive control. Concerning resting-state functional connectivity, connectivity strength within a left fronto-parietal network appeared to be higher in freezers than in controls in theta band, to be correlated to freezing severity and to present a trend for an association with executive control decline.

### Conclusions

Both types of resting-state electroencephalography analyses seem useful and complementary for better understanding freezing of gait. The higher connectivity strength within the left ventral attention network in freezers is in line with an excessive guidance of behavior by external cues due to executive dysfunction, such as the executive control deficit emphasized by the spectral analysis. Behavioral consequences of this exaggerate influence of external environment might be freezing of gait episodes.

## Introduction

With a prevalence sometimes exceeding 50% [1–3], freezing of gait (FoG) is a debilitating syndrome occurring in people with Parkinson's disease (PwPD). It is a substantial contributor to falls [4] and is associated with a disabling loss of independence and fear of injury, leading to lower health-related quality of life [5]. In parallel with numerous found risk factors for developing FoG, different pathophysiological models were built for better understanding and characterizing FoG [6,7]. Among them, the interference model and the cognitive model were highly investigated in recent years. In the interference model, the motor, cognitive and limbic neural circuits, with their competing and complementary relationship, are assumed to interfere under dual task due partly to depletion in dopamine neurons [8]. It is complementary to the cognitive model that emphasizes the conflict-resolution deficit, which is related to an unbalance between automaticity and controlled processing in FoG, and its potential behavioral consequences [9]. Further research needs to be undertaken in order to shed light on the pathophysiology of FoG. Analyzing recordings of brain activity during resting state is one possible way nowadays used to physiologically explore this phenomenon, based on the fact that altered resting-state neural activation may reflect underlying neuropathological changes.

At the cortical level, one method for quantitatively analyzing brain activity at rest is the spectral decomposition of the electrical or magnetic signal recorded via electroencephalography (EEG) or magnetoencephalography (MEG). As a matter of fact, spectral analysis of resting-state EEG signals seems promising as an inexpensive, non-invasive and easy to use screening method to identify severity of cognitive impairment in PwPD [10]. Nevertheless, to our knowledge, spectral band power associated with EEG or MEG recordings was neither analyzed in PwPD with FoG (PD+FoG) nor compared with PwPD without FoG (PD-FoG) and healthy controls (HC) so far (see [11] and [12] for a MEG and an EEG review in PwPD).

Besides, functional connectivity of neural networks in PD+FoG during resting state was mainly studied via functional magnetic resonance imaging (fMRI) (see [13] for a systematic review). Despite the direct measurement of brain neural activity, the high temporal resolution of EEG and MEG signals and the routinely use of EEG in clinical practice, less studies about resting-state functional connectivity using EEG or MEG signals in PD are available in the literature (see [12] for an EEG review and [11,14] for MEG reviews). Pathophysiology of FoG was not investigated at rest through EEG or MEG functional connectivity analysis yet.

With the aim of finding an easily obtained biomarker of FoG for improving its understanding, diagnosis and treatment, we performed two different types of analysis on resting-state EEG recordings: (1) a basic spectral analysis in the sensor space, and (2) a more advanced analysis of functional connectivity at the source level. Regarding spectral results, we assumed to observe a more pronounced slowing of resting-state oscillations (increased delta, theta and alpha power, and reduced beta and gamma power) in PD+FoG than in PD-FoG reflecting their more impaired cognition [11,12,15–18]. However, it was more difficult to hypothesize about the spectral pattern underlying their greater motor dysfunction because of inconsistency in the literature [12,16,17]. Concerning brain functional connectivity in PD+FoG, in line with previous fMRI studies, we expected abnormal functional connectivity in frontal networks, brain regions responsible for frontal executive and attention abilities [19–22], but also in posterior rather than in anterior brain areas, especially in the right hemisphere in parieto-occipital networks that are regions responsible for visuospatial abilities [19,23].

## Methods

### Participants

Fifty-four older adult volunteers (18 PD-FoG, 18 PD-FoG and 18 HC) participated in the study after providing their informed written consent. Patients were followed in the movement disorders department of the Lille University Hospital Center. Subjects with a cognitive impairment (i.e., Montreal Cognitive Assessment score or MoCA [24] < 24), a history of medication use that could interfere with attention (neuroleptics or benzodiazepines) or uncorrected visual impairment were excluded. As inclusion criteria, participants had to be able to stand 5 minutes in a row and to walk 10 meters without any help, as well as to understand fairly simple instructions. The study was approved by the local independent ethics committee (CPP Nord-Ouest, Lille, France; reference: 2015-A00013-46).

Demographic and clinical data such as gender and age, medical history and current medication were recorded. Disease duration and levodopa equivalent daily dose (LEDD) [25] were calculated for patients. They were in the ON-state of medication throughout the clinical protocol. In all participants, overall cognition was assessed by the MoCA. The executive control effect, a component of attention that is responsible for conflict resolution, was measured by using the Attention Network Test (ANT) [26]. For the patients, severity of the motor symptoms was assessed by the third part of Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) [27], the Hoehn and Yahr scale [28], and the Freezing of Gait Questionnaire (FOG-Q) [29,30]. Particularly, the third item of FOG-Q was used for the classification of PwPD as PD+FOG or PD-FOG. Medical history as well as the observation of overt FoG episodes during a specific gait trajectory that was thought to trigger FoG [31] also helped to validate the freezing phenotype associated with certain PwPD.

### Resting-state EEG Preprocessing and Analysis

Participants performed a resting-state protocol. More specifically, subjects were asked to stay seated with eyes open for 5 minutes, without staring at something in particular or thinking about anything specifically. During this resting period, brain activity was recorded via high-resolution scalp EEG, that is with an Ag/AgCl 128-scalp-electrode cap (Waveguard, ANT Neuro) positioned according to the 10/05 international system [32]. Data acquisition was performed with ASA software (ANT Neuro), using a sampling frequency of 512 Hz and impedances below 20 k $\Omega$ . Figure 1 summarizes the different steps of EEG data preprocessing and analysis.

A MATLAB toolbox, EEGLAB [33], was used for the preprocessing and the first part of EEG signal analysis. Preprocessing steps were detailed in the Supplementary material file. The first signal processing consisted in a spectral decomposition using a fast Fourier transform with a 4-second Hamming window and without overlapping. The frequency bands of interest were delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz). Higher frequency oscillations (gamma frequency band) were not taken into account because they are difficult to record with scalp EEG due to generators of small volumes [34] and are largely contaminated by muscle activity. Global absolute and relative spectral powers related to each frequency band were observed, as well as in 10 regions of interest (ROIs), according to the cortical projections of the electrodes in Talairach space [35]: right and/or left frontal, temporal, central, parietal and occipital regions (see Figure B.1 in the Supplementary material file).

Functional connectivity matrices at a source level were computed using different MATLAB toolboxes: Brainstorm [36] and EEGNET [37]. We first solved the EEG inverse problem to reconstruct the temporal dynamics of cortical regions, and then measured the functional connectivity between these regions. The weighted Minimum Norm Estimate (wMNE) [38] allowed to solve the inverse problem. Source

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3 signals were then projected on the Desikan-Killiany atlas and its 68 ROIs [81]. Subsequently, matrices  
4 of functional connectivity between the reconstructed sources were computed in theta, alpha and beta  
5 frequency bands via the Phase Locking Value (PLV) method [39]. This measure (ranged between 0 and  
6 1) mirrors interactions between two oscillatory signals through quantification of the phase  
7 relationships. Particularly, it is the modulus of the averaged instantaneous phase differences between  
8 two time series that represent two neural sources, the averaging being first performed over epochs  
9 and then over time points. The obtained connectivity matrices were analyzed either as raw data or in  
10 terms of global topological organization of the network via the graph theory. In the latter case, in order  
11 to remove spurious connections because the brain is not a fully connected network, thresholding of  
12 matrices was performed on the basis of the Efficiency Cost Optimization (ECO) criterion developed by  
13 De Vico Fallani and team [40]. Afterwards, parameters of graph theory were calculated on the  
14 thresholded connectivity matrices: characteristic path length, efficiency, diameter, highest degree,  
15 small-world coefficient, maximal modularity, transitivity and number of components (see Table C.1 in  
16 the Supplementary material file for definitions).  
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19

### 20 **Statistical Analysis**

21  
22 Concerning between-group comparisons of demographic and clinical data, one-way ANOVA was used  
23 for quantitative variables, Chi-square test for gender, and Student's t test or Mann-Whitney U test for  
24 comparing quantitative variables between groups of PwPD, depending on whether general linear  
25 model assumptions were met or not. Normal distribution and homoscedasticity of residuals were  
26 visually inspected, and checked with Shapiro-Wilk and Levene tests. Concerning the executive control  
27 effect, 2x3 repeated measures ANOVA was conducted to determine the existence of an interaction  
28 between group and target condition.  
29  
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31 Regarding the statistical analysis of spectral decomposition, in case of assumptions met, a one-way  
32 ANOVA, followed by Student's t tests with a Bonferroni correction for multiple comparisons, was used  
33 for comparing absolute and relative spectral powers in each band between groups (the between-  
34 subjects factor). The equivalent nonparametric test was the Kruskal-Wallis H test, with Mann-Whitney  
35 U tests as post-hoc tests.  
36  
37

38 The network-based statistic (NBS) approach [41] was used for statistically comparing the functional  
39 connectivity matrices between groups. Indeed, this nonparametric statistical method allows to identify  
40 brain networks associated with a between-group difference. As a first step, we admitted weighted  
41 connections with a between-group statistical test surpassing  $p < 0.001$ , and we then searched for  
42 distinct topological clusters based on sets of the obtained supra-threshold connections for which a  
43 path can be found between any two nodes. Finally, a FWER (family-wise error rate)-corrected p-value  
44 was computed for each cluster by using an ANOVA with permutation testing (1 000 000 permutations),  
45 with group as between-subjects factor and a threshold for statistical significance set to  $p < 0.05$ . Post-  
46 hoc tests were independent Student's t tests with permutation testing and with a Bonferroni  
47 correction for taking multiple comparisons into account. In the context of the topological analysis of  
48 each group's network, similar tests than the ones used for spectral power were performed for  
49 comparing graph parameters between groups.  
50  
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53 Eventually, for frequency bands and ROIs in which PD+FoG presented a significantly different spectral  
54 content compared to PD-FoG or HC (or for differentially connected networks), analysis of correlations  
55 between spectral power (or functional connectivity at each edge) and clinical data (disease duration,  
56 LEDD, MoCA, MDS-UPDRS III and FOG-Q scores) was carried out by calculating Pearson's or Spearman's  
57 correlation coefficients and their level of significance, depending on data distribution. Moreover, a z-  
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score was calculated for the executive control effect. Correlations between this z-score and spectral powers (or edges' functional connectivity) associated with a significant group effect were also tested.

All the above tests except the network-based analysis were carried out thanks to SPSS 16.0. The threshold for statistical significance was set to  $p < 0.05$ .

## Results

### Subjects

There was no significant between-group difference regarding gender, age or overall cognition (Table 1). PD+FoG and PD-FoG did not significantly differ in terms of disease duration, disease severity and medical treatment, but PD+FoG presented a worse executive control than PD-FoG and HC.

### Spectral Analysis

There was no significant between-group difference for absolute spectral power in all frequency bands, but for relative spectral power (see Figure 2). Indeed, PD+FoG exhibited a significantly greater relative spectral power in theta band than HC ( $p = 0.03$ ). In particular, this larger relative theta power was observed in left frontal, right and left temporal, right and left central, and right and left occipital ROIs (see Table D.1 and Figure D.1 in the Supplementary material file for details). The relative theta power in right temporal region was higher in PD-FoG than in HC ( $p = 0.006$ ). They also showed a lower relative beta power in right and left occipital as well as in right central ROIs in comparison with HC. No difference existed between PD+FoG and PD-FoG.

The relative theta power in PD+FoG was not correlated with disease duration, LEDD, motor impairment or freezing severity. However, there was a trend for a negative correlation between the MoCA score and the relative theta power in central ( $r = -0.411$ ,  $p = 0.09$ ), but also right central ( $r = -0.463$ ,  $p = 0.053$ ) and right temporal ( $r = -0.429$ ,  $p = 0.076$ ) ROIs. Particularly, z-score of the executive control effect was significantly positively associated with the relative theta power in the right occipital area ( $r = 0.548$ ,  $p = 0.028$ ). That is, relative spectral power in theta band increased with freezers' dysfunction in executive control.

### Functional Connectivity Analysis

Concerning the topological analysis of functional networks, none of the graph parameters was found to be significantly different between groups, regardless of the frequency band investigated.

When looking at the raw functional connectivity matrices related to theta band, a significant group effect was observed on a network consisting of 20 nodes and 23 edges ( $p = 0.005$ ). More particularly, post-hoc tests emphasized a network composed of 4 nodes and 3 edges with stronger weights in PD+FoG compared to HC ( $p = 0.033$ ). These functional connections represented antero-posterior communications that linked left cortical areas together: the lateral inferior parietal cortex, on the one hand, and the insula or the orbitofrontal cortex, on the other hand (see Figure 3). Furthermore, PD-FoG also exhibited two networks including respectively 15 and 4 nodes connected by means of 17 and 3 edges, and for which the related functional connectivity strength was higher than in HC ( $p = 0.009$  and  $0.033$ , respectively). As seen in Figure 4, the first network was comprised of the medial and lateral temporal, central, medial and lateral parietal, and medial and lateral occipital cortices as well as the limbic lobe (with the left parahippocampal cortex). The second significantly different network, for its part, involved the cingulate cortex and the parahippocampal (i.e., the limbic lobe). No significant between-group differences in terms of functional networks related to alpha and beta bands were observed.

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3 When checking for potential correlations between functional connectivity in theta band and clinical  
4 data associated with PD+FoG, we found significant positive correlations between FOG-Q score, on the  
5 one hand, and the strength of the functional connection between the left inferior parietal cortex and  
6 the left lateral orbitofrontal cortex ( $r = 0.479$ ,  $p = 0.044$ ) as well as between the left inferior parietal  
7 cortex and the left medial orbitofrontal cortex ( $r = 0.495$ ,  $p = 0.037$ ), on the other hand. A trend for an  
8 increase in theta-band insula-lateral inferior parietal cortex connectivity with an increment of z-score  
9 (executive control effect) was also observed ( $r = 0.483$ ,  $p = 0.058$ ).  
10  
11

## 12 Discussion

### 13 Relative Spectral Power in Theta Band Increased with Cognitive Decline in PD+FoG

14 Resting-state spectral analysis resulted in altered relative spectral power in PwPD in comparison with  
15 HC: a diffuse higher theta-band relative spectral power that was correlated to executive control deficit  
16 in PD+FoG and, for PD-FoG, an increased temporal relative spectral power in theta band and a lower  
17 beta-band relative spectral power in occipital and right central regions. These results were consistent  
18 with our hypotheses and outcomes from previous literature [11,15,17,42]: PD patients showed a global  
19 slow-down of oscillatory brain activity during resting-state compared to HC, that is a diffuse increase  
20 of relative theta power in parallel with a decreased relative beta power over the occipital cortex.  
21 Bosboom and colleagues [15] demonstrated that these differential patterns in theta and beta bands  
22 and not for delta and alpha oscillations were particularly characteristic of non-demented PD patients,  
23 as were our patients. Furthermore, in the present study, in comparison with what occurred in PD-FoG,  
24 the observation of a more pronounced increment in relative theta power in PD+FoG with respect to  
25 HC and its trend to increase when the MoCA score decreased (and not when the FOG-Q score  
26 increased) supports the idea that we seem to have found a neural biomarker more related to cognitive  
27 decline than to FoG. Indeed, in previous papers, demented PD patients showed, among other things,  
28 a greater relative theta power all over the scalp during resting state compared to cognitively healthy  
29 PwPD [11,12,15,17,18]. Here, the MoCA score was insignificantly lower in PD+FoG than in PD-FoG,  
30 along with insignificantly longer disease duration and more severe motor impairments for PD+FoG.  
31 These two characteristics of PD (overall cognition decline and motor deficit with the evolution of the  
32 disease) are both linked to the occurrence of FoG in PwPD, and correlate with each other. The presence  
33 of specific cognitive or attentional impairments in PD+FoG is still under debate regarding contradictory  
34 findings obtained so far [43,44]. Besides, elevated relative theta power in the right occipital area was  
35 significantly associated with freezers' impairment in executive control, component of attention that  
36 was – previously [45,46] and in the present study – demonstrated to be worse in PD+FoG compared  
37 to PD-FoG and HC. However, less decrease of relative beta power in posterior regions in PD+FoG than  
38 in PD-FoG with respect to HC was not in line with an effect of the supposed faster progression of  
39 PD+FoG towards cognitive impairment. Even if an increased relative spectral power in the theta band  
40 only was previously found to be related to a decline of motor functions over time in a longitudinal MEG  
41 study with PwPD [16], MDS-UPDRS III and FOG-Q scores did not seem here to explain the higher  
42 relative theta power in PD+FoG. Therefore, the hypothesis of great relative theta power as a biomarker  
43 of an impaired executive control and an earlier cognitive decline in the future for PD+FoG seems more  
44 plausible.  
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### 54 Fronto-parietal Functional Connectivity Strength Increased with FoG Severity

55 Concerning resting-state functional connectivity, connectivity strength within a theta-band fronto-  
56 parietal network appeared to be higher in PD+FoG compared to HC, to positively correlate with FOG-  
57 Q score and to present a trend for an association with the declining executive control. Indeed, several  
58 previous studies have already demonstrated that resting-state fMRI functional connectivity within [47]  
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3 and between [48] brain regions as well as related parameters of graph theory [49], dynamic  
4 connectivity [50] and structural connectivity [51] correlated with ANT performance, highlighting an  
5 intrinsic functional and structural organization of the brain to support attention. The functional  
6 network that significantly differed here in connectivity strength between PD+FoG and HC included  
7 nodes that are part of the ventral attention network, in charge of stimulus-driven reorienting of  
8 attention or “bottom-up attention”: the inferior parietal lobule (including the overlapping  
9 temporoparietal junction), the ventral frontal cortex, and the anterior insula [52–54]. The higher  
10 connectivity strength within this functional network for PD+FoG is in line with an excessive guidance  
11 of behavior by external cues due to executive dysfunction involving response inhibition (or executive  
12 control), divided attention, or switching attention and visuospatial function [55,56]. Behavioral  
13 consequences of this exaggerate influence of external environment may be reflected in the significant  
14 positive correlations between the fronto-parietal edges’ functional connectivity and severity of FoG.  
15 Our results were thus in line with our hypotheses and previous fMRI works. Indeed, PD+FoG showed  
16 reduced functional connectivity within and between brain regions linked to executive functions: within  
17 executive attention (right fronto-parietal) network compared to PD-FoG [19] and between the right  
18 fronto-parietal and executive-control networks in comparison with HC [20]. Moreover, PD+FoG also  
19 presented lower functional connectivity within the right visual network than PD-FoG [19]. These  
20 visuospatial abnormalities would thus impede PD+FoG to use exactly the same strategy of  
21 overdependence on visual cues to control locomotion considering executive deficits as in PD-FoG. They  
22 might instead rely more on the left hemisphere, and particularly on the left ventral attention system  
23 [57]. Contrarily to our findings, Teramoto et al. found a significant relationship between executive  
24 dysfunction in non-demented PwPD and decreased alpha-band EEG coherence between left frontal  
25 and parietal cortices [58].

### 31 **Limitations**

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33 Some limitations exist in this study. Firstly, the assessment of brain activity during a resting-state  
34 protocol with eyes open may have had an impact on the spectral analysis [15]. Comparisons with  
35 previous EEG/MEG results were also less convenient because participants were mostly asked to rest  
36 with eyes closed. However, with eyes open, we assured wakefulness of individuals as well as less ocular  
37 artifacts on the EEG signals. Secondly, the use of a resting-state procedure itself may appear  
38 controversial, since it is not possible to control the subject’s brain activity that is supposed to rest while  
39 not thinking about something in particular. However, this resting-state protocol was chosen in order  
40 to obtain a comparison point with usual fMRI studies and to be generalizable to PD+FoG with more  
41 severe cognitive and motor impairments in the future. The method used here for estimating functional  
42 connectivity, that is the PLV, is often told to be sensitive to volume conduction because this technique  
43 does not remove zero-lag connectivity. Conversely, it was recently reported that PLV-based functional  
44 networks were significantly correlated to fMRI networks during resting state, while it was not the case  
45 for methods that remove zero-lag connections such as Phase Lag Index [59]. Indeed, all zero-lag  
46 connections are not spurious. Finally, it would have been interesting to also record resting-state brain  
47 activity in patients in the OFF-state of medication, since the group differences would have probably  
48 been more intense. Nevertheless, our present results related to the ON-state of medication give insight  
49 into how a dopamine replacement therapy might be improved with a more targeted treatment.

### 54 **Further Perspectives**

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56 On the one hand, a simple EEG spectral analysis at the sensor level allowed to emphasize the impaired  
57 executive control in PD+FoG. On the other hand, studying EEG-based functional connectivity in the  
58 source space highlighted a more connected left fronto-parietal network in PD+FoG than in HC, which  
59 was significantly correlated with the severity of FoG. According to two existing pathophysiological  
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3 models of FoG (the interference model [8] and the cognitive model [9]), this PD symptom might be  
4 closely linked to cognitive impairment in addition to motor deficit. Both types of EEG signal analyses  
5 seem therefore useful and complementary for better understanding the phenomenon. A further step  
6 would be to carry out a longitudinal study with periodic EEG recordings of resting-state brain activity.  
7 We will thus be able to validate or not our assumption that the strength of spectral and functional  
8 connectivity analyses could predict cognitive decline and worsening of FoG episodes in PD+FoG,  
9 respectively. In consequence, causal relationships might be clearer, leading to improved  
10 pathophysiological models of FoG, with new specific biomarkers or targets for therapy.  
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## Authors' Roles

- 1) Research project: A. Conception, B. Organization, C. Execution;
- 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
- 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

Madli Bayot: 1A/B/C, 2A/B, 3A; Morgane Gérard: 2A/B, 3B; Philippe Derambure: 2C, 3B; Kathy Dujardin: 2C, 3B; Luc Defebvre: 2C, 3B; Nacim Betrouni: 2A/C, 3B; Arnaud Delval: 1A, 2C, 3B.

## Financial Disclosures of all authors (for the preceding 12 months)

No author had conflict of interests related to this study.

M. Bayot received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 721577.

M. Gerard received a grant from Lille University for a research year and no other financial disclosure.

P. Derambure, K. Dujardin and A. Delval were employed by French Government (enseignement supérieur) and had no other financial disclosure.

L. Defebvre was employed by French Government (enseignement supérieur), gave consultancies to "Abbvie" and "Orkyn" and earned honoraria for lectures from "UCB" and "Abbvie".

N. Betrouni was employed by INSERM (institut national de la santé et de la recherche médicale), received a grant from PROCOPE Campus France and gave consultancies to LLL France.

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## Tables and Figures Legends

**Figure 1.** Steps of EEG data preprocessing and analysis. LP/HP = low-/high-pass filter; ASR = artifact subspace reconstruction; ICs = independent components; BEM = Boundary Element Method; wMNE = weighted Minimum Norm Estimate; PLV = Phase-Locking Value; ECO = Efficiency Cost Optimization

**Table 1.** Demographic and clinical data characterizing participants (mean  $\pm$  standard deviation).

**Notes.** MoCA = Montreal Cognitive Assessment; MDS-UPDRS III – Med ON = Unified Parkinson's disease Rating Scale, part III, in the ON-state of medication; H&Y scale – Med ON = Hoehn and Yahr scale, in the ON-state of medication; LEDD = Levodopa Equivalent Daily Dose

**Figure 2.** Scalp distribution maps of the relative spectral power in beta, theta, alpha and gamma bands among PF+FOG, PD-FOG and HC

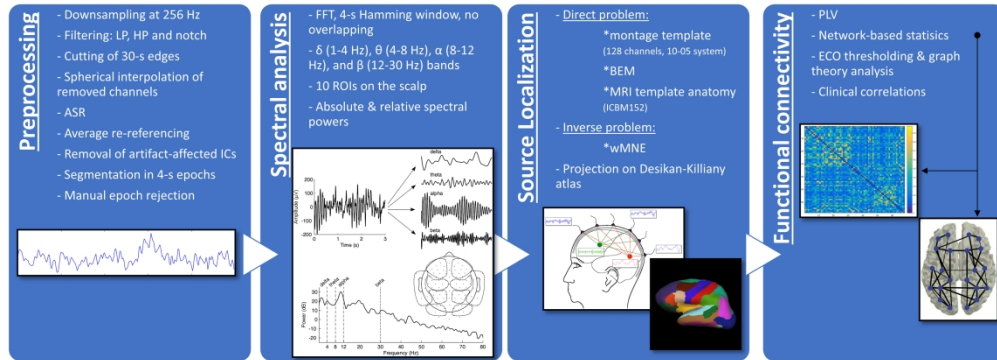
**Figure 3.** Fronto-parietal functional network that presented significantly greater connectivity strength in PD+FoG compared to HC ( $p = 0.033$ ). L = left; inf. = inferior; lat. = lateral; med. = medial; ANT. = anterior; POST. = posterior

**Figure 4.** First (a) and second (b) functional networks with greater connectivity strength in PD-FoG versus HC ( $p = 0.009$ ;  $0.033$ ). R = right; L = left; sup. = superior; inf. = inferior; lat. = lateral; ANT. = anterior; POST. = posterior



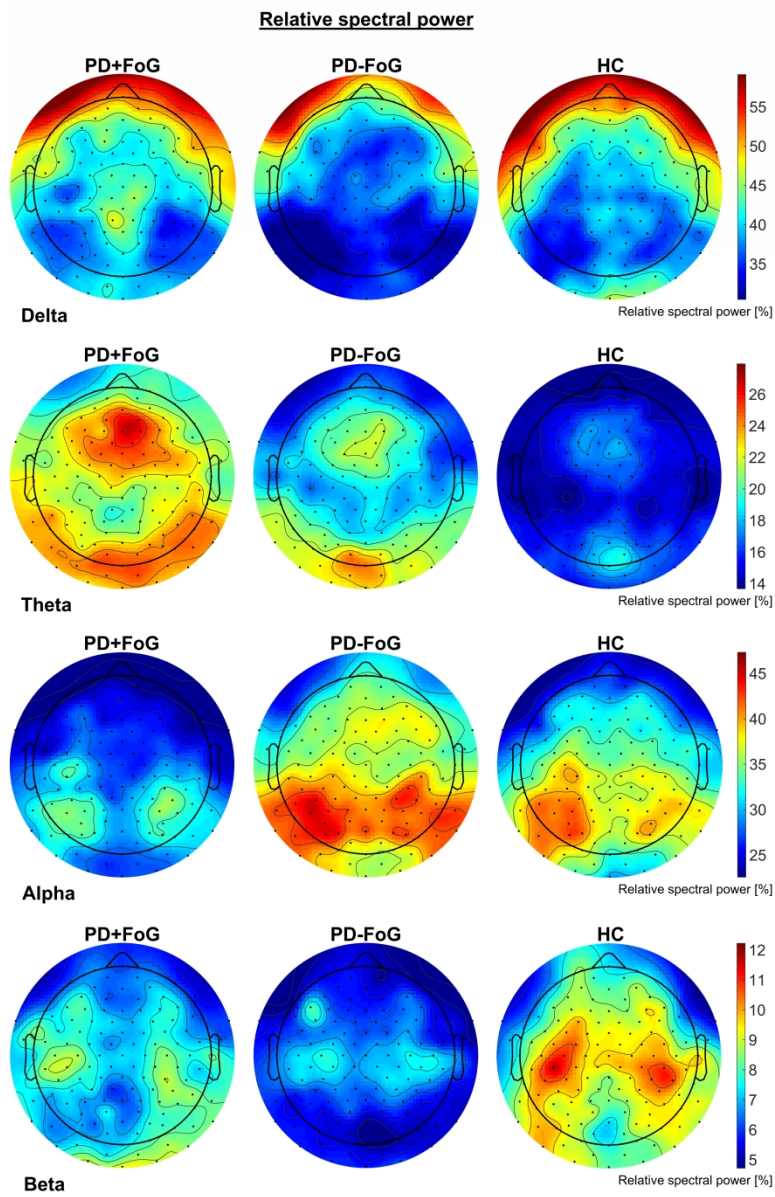
Group	Age (years)	Gender (F/M)	MoCA (/30)	Executive control effect (ms)	Disease duration (years)	MDS-UPDRS III – Med ON (/108)	H&Y – Med ON (/5)	LEDD (mg L-Dopa)
<b>PD+FoG</b> (n=18)	63 ± 8	5/13	26 ± 2	63.531 ± 41.771	10 ± 4	27 ± 13	2 ± 1	1131 ± 600
<b>PD-FoG</b> (n=18)	60 ± 9	8/10	27 ± 2	42.133 ± 20.903	9 ± 4	23 ± 12	2 ± 1	1071 ± 424
<b>HC</b> (n=18)	60 ± 7	8/10	28 ± 2	37.639 ± 16.353	/	/	/	/
<b>p-value</b>	0.49	0.496	0.11	<b>0.027*</b> (Group x Target interaction)	0.435	0.53	0.119	0.723

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Steps of EEG data preprocessing and analysis. LP/HP = low-/high-pass filter; ASR = artifact subspace reconstruction; ICs = independent components; BEM = Boundary Element Method; wMNE = weighted Minimum Norm Estimate; PLV = Phase-Locking Value; ECO = Efficiency Cost Optimization

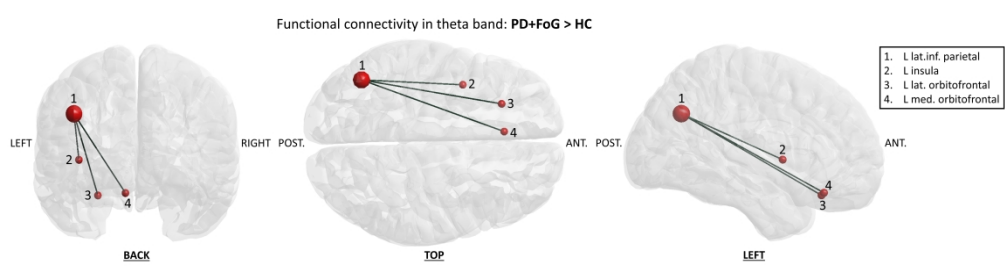
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Scalp distribution maps of the relative spectral power in beta, theta, alpha and gamma bands among PD+FOG, PD-FOG and HC

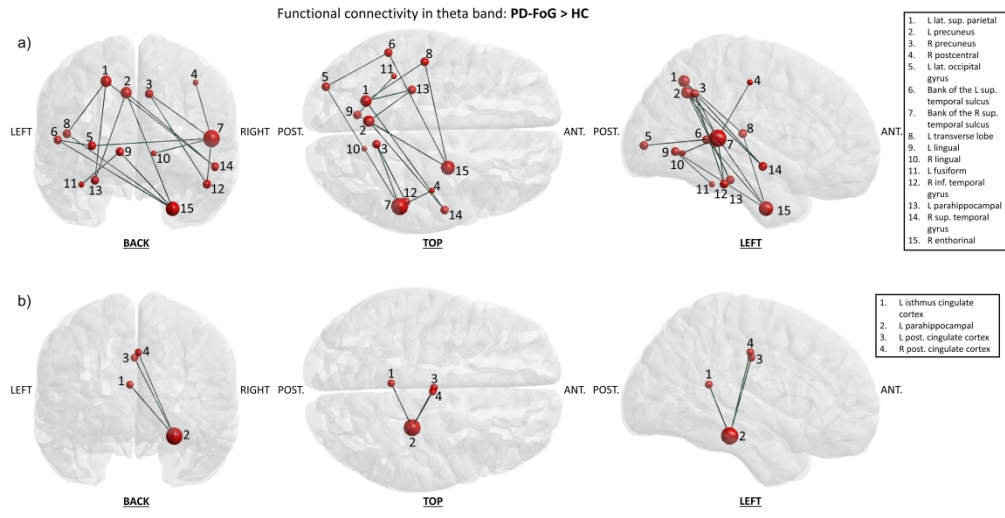
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Fronto-parietal functional network that presented significantly greater connectivity strength in PD+FoG compared to HC ( $p = 0.033$ ). L = left; inf. = inferior; lat. = lateral; med. = medial; ANT. = anterior; POST. = posterior

762x196mm (300 x 300 DPI)



First (a) and second (b) functional networks with greater connectivity strength in PD-FoG versus HC ( $p = 0.009$ ;  $0.033$ ). R = right; L = left; sup. = superior; inf. = inferior; lat. = lateral; ANT. = anterior; POST. = posterior

592x305mm (300 x 300 DPI)

# **Etude 6 : Capacités attentionnelles chez les patients atteints de la maladie de Parkinson et présentant un freezing de la marche – Etude comportementale et électroencéphalographique (analyse de la connectivité fonctionnelle)**

“EEG Functional Connectivity Underpinning Executive Control in Patients with Parkinson Disease and Freezing of Gait”

Morgane Gérard, **Madli Bayot**, Philippe Derambure, Kathy Dujardin, Luc Defebvre, Nacim Betrouni, Arnaud Delval

Article en préparation pour soumission prochaine.

## **Apport personnel**

- Enregistrement de la plupart des données.
- Développement des méthodes d’analyse des données et conseils pour leur traitement.
- Aide à la réalisation des tests statistiques.
- Relecture et correction du manuscrit.

## **Résumé**

### **Contexte**

Le freezing de la marche (FdM) est un symptôme invalidant de la maladie de Parkinson, dont la pathophysiologie reste complexe et doit encore être davantage comprise, car elle implique non seulement des fonctions motrices, mais aussi des dysfonctions cognitives, attentionnelles et exécutives. A ce jour, les réseaux signatures pendant une tâche attentionnelle n’ont pas encore été explorés via analyse de la connectivité fonctionnelle EEG dans cette population.

### **Objectifs**

Notre but était de décrire les spécificités de réseau pendant une tâche attentionnelle chez les patients freezers (MP+FdM), comparés aux patients non freezers (MP-FdM) et contrôles sains.

## Méthodes

Une électroencéphalographie haute résolution a été réalisée chez 15 MP+FdM, 14 MP-FdM et 18 contrôles sains lors de l'Attention Network Test (ANT), une tâche attentionnelle permettant d'étudier le contrôle exécutif. Suite à une étape de localisation de sources, la connectivité fonctionnelle dynamique a été évaluée en utilisant la méthode de la « Phase Locking Value » (PLV). Les valeurs de connectivité fonctionnelles ont ensuite été comparées entre groupes.

## Résultats

Le temps de réaction à la tâche était plus long chez les sujets MP+FdM par rapport aux MP-FdM et contrôles sains et une défaillance du contrôle exécutif a été trouvée chez les sujets MP+FdM. De plus, les MP+FdM différaient des contrôles sains par une connectivité excessive au sein d'un réseau liant les régions orbitofrontale et occipito-temporale dans la bande thêta dans les intervalles de 400-500 ms ( $p = 0,033$ ) et 500-600 ms ( $p = 0,016$ ) après l'apparition de la cible.

## Conclusions

L'augmentation de la connectivité fonctionnelle chez les sujets MP+FdM dans un réseau connectant le réseau visuel et les régions associées aux fonctions exécutives peut indiquer une dépendance plus forte aux paramètres environnementaux afin de compenser leur contrôle exécutif défaillant.

**Mots-clés :** maladie de Parkinson (MP), freezing de la marche (FdM), électroencéphalographie (EEG), connectivité fonctionnelle, Attention Network Test (ANT), contrôle exécutif.





# EEG Functional Connectivity Underpinning Executive Control in Patients with Parkinson Disease and Freezing of Gait

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**Word count:** 3 572 words

**Running title:** A task EEG study of freezing of gait

**Keywords:** Parkinson's disease (PD), freezing of gait (FoG), electroencephalography (EEG), functional connectivity, Attention Network Test (ANT), executive control.

**Conflict of Interest:** none

**Funding:** Madli Bayot works on a project that has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 721577. Morgane Gérard received a grant from the University of Lille for a research internship.

## **Abstract**

### **Background**

Freezing of gait is a disabling symptom of Parkinson's disease (PD), whose pathophysiology remains complex and partly unknown. In addition to motor functions, it also involves cognitive, attentional and executive dysfunctions. Up to now, functional connectivity during an attentional task has not been explored through electroencephalography (EEG) in this population.

### **Objectives**

Our aim was to describe network specificities during an attentional task for patients with freezing of gait (PD+FoG) compared non-freezers (PD-FoG) and healthy control (HC).

### **Methods**

High resolution EEG was recorded in 15 PD+FoG, 14 PD-FoG, and 18 HC when performing the Attention Network Test (ANT). After source localization, functional connectivity was assessed using dynamic Phase Locking Value (PLV), and compared between groups.

### **Results**

Reaction time was longer in PD+FoG than in PD-FoG and HC, and an executive control failure was found in PD+FoG. Moreover, PD+FoG differed from HC by an abnormal connectivity increase in a network connecting orbitofrontal and occipitotemporal regions in the theta band, in the 400-500ms ( $p = 0.033$ ) and 500-600ms ( $p = 0.016$ ) intervals during the task dynamics.

### **Conclusions**

The increased functional connectivity in PD+FoG in a connecting network between visual network and regions attributed to executive functions can indicate higher reliance on environmental features to overcome their executive control impairment.

## Introduction

### Freezing of Gait: Clinical Features and Physiopathological Models

Freezing of gait (FoG) is a frequent and disabling symptom of Parkinson disease (PD), experienced by half the patients with advanced disease. Its prevalence increases with disease duration and it can lead to falls and autonomy loss [1–3]. It is defined as “a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk” [1]. The clinical response to Levodopa being variable regarding FoG, alternative treatments need to be suggested to alleviate this symptom [2–5]. Treatment adaptation will improve thanks to a better understanding of the underlying mechanism through proposed pathophysiological models such as the interference model and the cognitive model. The interference model proposed by Lewis and Barker is based on the « cross-talk » phenomenon [6]. The loss of dopaminergic neurons in basal ganglia in PD results in a limited repertoire of the output nuclei within the motor, cognitive and limbic pathways. This limited reserve of neurotransmitters is sufficient for limited tasks, but in more complex situations such as dual tasks, during which motor, cognitive and limbic compete, this will induce failure by jamming the system, causing FoG with a sudden motor inhibition [6]. Pathological consequences of competition between pathways showed a failure in selecting the relevant input in these patients. PD patients with or without FoG experience cognitive dysfunction, especially when the disease is advanced [7–9]. Although the most frequently altered cognitive domains are executive functions and attention in PD regardless of whether they experience FoG or not [9,10], it was shown that PD patients with FoG (PD+FoG) perform worse in very specific cognitive domains such as flexibility. The cognitive model therefore completes the interference model by adding the idea of a failure in cognitive control in PD+FoG, unlike PD patients without FoG (PD-FoG) who compensate their automaticity loss with stronger cognitive control [11]. This model relies on the results of several neuropsychological studies revealing lower score in PD+FoG patients regarding executive functions, set-shifting, and executive control [12–14], although these deficits could also be related to disease duration [15]. Executive control can be explored by performing a validated attentional task like the Attention Network Test (ANT) ; [16,17], as one of the components described in the three components attention model by Posner and Petersen [18]. We will from now on refer to this model, which will allow to study executive control, which is deficient in PD+FoG patients, whether it be on an OFF-state or an ON-state of medication [19].

### Connectivity Failure in PD and FoG

Studying functional connectivity allows to explore cerebral functions through functional networks. Most connectivity studies in PD populations have focused on motor networks [20] except for a few ones. For instance, Tessitore and collaborators revealed in an fMRI study a decrease in connectivity between visual network and dorsal attention network during resting state in PD+FoG, suggesting a failure in a compensating mechanism involving visual attention in PD+FoG [21]. Furthermore, a task connectivity study recording fMRI during a walking simulation in PD+FoG enlightened specific network patterns associated with freezing severity and compensating situations. Severity of the freezing episode was associated with dorsal attention network connecting limbic network nodes instead of cerebellar nodes in a compensating walking situation, reinforcing the hypothesis of cross-talk discussed above [22]. Connectivity studies using MEG or EEG are scarce and very few concern patients with PD. An evolution towards more random networks in theta band have been shown in PD in a resting state MEG study, a pattern which is also found in other degenerative diseases, such as Alzheimer’s disease, and evoke a less optimal network organization [23]. During encoding in a working

memory task [24], dysfunctions in memory networks but also in the dorsal attention network are present in PD patients. The latter, also called top-down attention network, underlies goal-directed attention, as opposed to the ventral attention network, or bottom-up attention network, underlying stimulus-driven attention [25–27]. During the execution of the ANT, a greater activation within the dorsal attention network is associated with executive control effect in PD, that might reflect the need for more attentional resources in PD for the same task [28]. However, to our knowledge, no study has yet explored the nature of cerebral networks abnormalities through EEG/MEG functional connectivity during an attentional task in PD+FoG patients.

## **Objective**

The objective of this study was to determine whether functional connectivity is altered during a visual attentional task in PD+FoG, in comparison with PD-FoG, and healthy subjects (HC).

The emphasis was set on the executive control measured via the ANT, which is specifically altered in PD+FoG. By consequence, alterations in the executive and attention networks are expected in patients with FoG compared to the other groups.

## **Methods**

### **Population**

We included 47 adult subjects (15 PD+FoG, 14 PD-FoG and 18 HC), after retrieving informed written consent. All patients were followed in the Department of Neurology of Lille University Hospital Center. Subjects with a score at the Montreal Cognitive Assessment score (MoCA) < 24 [29], medication involving benzodiazepines or neuroleptics, or an uncorrected visual deficit were excluded. Subjects included had to be able to walk 10 meters without any technical or human help. The study was approved by the local independent ethics committee (CPP Nord-Ouest, Lille, France; reference: 2015-A00013-46). The following data were recorded for each subject: age, gender, current medication and past medical history, and the score at the MoCA. For patients with PD, we also recorded: levodopa equivalent daily dose (LEDD) [30], Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [31] and especially the third part for motor severity, Hoehn and Yahr scale [32], disease duration, and Freezing of Gait Questionnaire (FOG-Q) [33,34] for FoG severity. PD patients were classified as PD+FoG and PD-FoG according to past medical reports and the third item of the FOG-Q, with the help of freezing trajectory with half-turns [35]. The two patient groups were matched with a group of HC.

### **Task**

Subjects performed a modified version of the ANT in a seated position, looking at a computer screen and answering on a keyboard. The modified ANT is described in Figure 1. Subjects were asked to indicate the direction of a target (i.e., a central arrow pointing either left or right on the screen) by pressing A key on the keyboard for left hand answers, or P key for right hand answers. They were instructed to answer as fast as possible without errors. Each target was flanked with distractors (i.e., flankers), formed by additional arrows on each side of the arrow of interest. The flankers were pointing the same direction as the target in the congruent condition or the opposite direction in the incongruent condition (see [36] for a more detailed paradigm). In this study, we focused on executive control. Therefore, only congruent and incongruent conditions were compared, as the difference between

response time for each condition gives the effect of executive control [16]. All patients were in ON-state of medication.

Reaction time (RT), omission rate and error rate were recorded. The 20 first trials served as training and were excluded from the analyses. Trials with RT shorter than 100 ms were rejected because considered as anticipated starts. Trials with response errors were also excluded. Median RT were assessed in each target condition for each subject.

### **Recording and Preprocessing**

High resolution scalp EEG (128 electrodes) was recorded for all subjects during the attentional task (Waveguard, ANT Neuro). The electrodes were positioned according to the 10-05 system and the EEG signal was recorded with the ASA software (ANT Neuro), with a sampling frequency of 512 Hz while keeping impedances below 20 k $\Omega$ . Preprocessing was performed using EEGLAB toolbox on MATLAB software [37]. The signal was down-sampled at 256 Hz, then filters were applied to keep the bandwidth as [0.5-100Hz]. A 50 Hz notch filter was applied to the signal to remove line noise. Flat signal electrodes and aberrant signal electrodes were semi-automatically removed, then spherically interpolated, with a maximum of interpolated electrodes of 10%. Transient large amplitude artefacts were removed with the Artifact Subspace Reconstruction (ASR) method [38,39]. An average reference was applied. Stationary artefacts were removed using an Independent Component Analysis (ICA) (with the Infomax algorithm [40]) followed by a semi-automatic rejection of components with artefacts, with the help of ICLabel toolbox [41], a highly-trained component classifier. The final manual rejection targeted the non-neurological sources (such as muscle, eye movement, heart), with a maximal amount of rejected components fixed at 20. The remaining signal was segmented in target-locked epochs, each epoch representing one trial of the ANT, starting 1500 ms before the target appearance, and ending 1700 ms after. All epochs were classified as in congruent or in incongruent condition of target. Each epoch was visually inspected and epochs containing remaining artefacts were manually rejected.

### **Source Localization and Functional Connectivity**

Epochs were used as inputs for the step of source localization with Brainstorm toolbox on MATLAB [42]. The inverse problem was resolved by using first the Boundary Element Method (BEM) [43,44] for the head modelling, and by then applying the weighted Minimal Norm Estimation method (wMNE) [45,46], before projecting the source signal on the 68 regions of interest (ROIs) of the Desikan-Killiany atlas [47].

Functional connectivity matrices were constructed for each condition within each subject, in three frequency bands: theta (4-8 Hz), alpha (8-12 Hz) and beta (12-30 Hz). The dynamic Phase Locking Value (PLV) method was used [48]. PLV is a method for measuring phase relationships between oscillatory signals, such as EEG. In our case, it allowed to determine functional connectivity between ROIs. Dynamic PLV allows the construction of a 3D matrix giving a connectivity value for each pair of ROIs at every time point. For visualization, a threshold was set on the matrices via the Efficacy Cost Optimization (ECO) method, a more physiological approach for thresholding than a simple cut-off [49]. Thereafter, matrices were averaged over 100-ms intervals, resulting in six 100-ms time-interval matrices from 0 ms (target appearance) to 600 ms (HC median reaction time). The interval matrices were averaged by group within each condition (C and I) and shown as graphs via the EEGNET toolbox on MATLAB [50].

## Statistical Analyses

Demographic, clinical and scoring variables between groups were analyzed on SPSS. The normality and homoscedasticity of residuals were assessed visually and by means of the Shapiro-Wilk tests. Qualitative variables were compared with a Chi-square test. Quantitative variables with normal distribution and homoscedasticity of residuals were compared using one-way ANOVA with group as between-subjects factor, and either a Student's t-test (normal distribution) or a Mann-Whitney U test (non-normal distribution) in PD patients.

Executive control effect was assessed via the ANT. Median reaction time was calculated for each subject, and compared thanks to a repeated-measures 2x3 ANOVA with the group as between-subject factor and the target condition as within-subject factor. A Bonferroni correction was applied for post-hoc analyses.

Functional connectivity matrices were compared via Network Based Statistics (NBS), a MATLAB toolbox developed specifically for network comparison [51]. Non-thresholded matrices were used, after having been averaged within 100-ms intervals between 0 ms and 600 ms, and by group within each target condition. NBS is a tool developed to minimize family-wise error rate when comparing every connection in a graph, inducing multiple comparison. As first step, all connections (connectivity values) were compared using a manually thresholded test statistic, giving a set of supra-threshold links, which are then organized into identified graph structures called components. We fixed the first statistical threshold at  $< 0.001$  in this study. The found components were compared in a second step between groups and target conditions, the test (an ANOVA with permutation testing) being significant for  $p < 0.05$ . For post-hoc analyses, we applied a Bonferroni correction.

## Results

### Population

Forty-seven subjects were included and analyzed (15 PD+FoG, 14 PD-FoG and 18 HC). Subjects from all three groups did not differ in age, gender, or cognitive function. Patients with PD did not differ in disease severity, disease duration, and LEDD. Demographic and clinical data are reported in Table 1.

### Executive Control Effect on the RT

Response time differed between groups ( $p = 0.012$  ; PD+FoG:  $620 \pm 56$  ms in congruent condition and  $685 \pm 85$ ms in incongruent condition ; PD-FoG:  $609 \pm 69$  ms in congruent condition and  $650 \pm 67$  ms in incongruent condition; HC:  $563 \pm 65$  ms in congruent condition and  $601 \pm 63$  ms in incongruent condition; post-hoc test: PD+FoG > HC, with  $p = 0.011$ ), between target conditions (congruent < incongruent :  $p < 0.001$ ), and an interaction between groups and target conditions was shown (PD+FoG > PD-FoG and PD+FoG > HC;  $p = 0.023$ ). Executive control effect on RT is shown on Figure 2. Accuracy was satisfactory for all three groups, with an omission rate reaching less than 2%, and an error rate amounting to less than 4% in both target conditions.

### Network Dynamics during Visual Attentional Task

After thresholding, functional connectivity matrices were shown as graphs. The time course was represented as 100-ms time intervals, from 0 ms (target presentation) to 600 ms (mean reaction time in HC). Visually, the network dynamics in theta band for HC seemed clear, with a reinforcement of posterior connections at 100-200 ms, and an even more manifest reinforcement of anterior

connections after 400 ms. For PD groups, the network dynamics in theta band was much less marked. Network dynamics in theta band are presented in Figure 3. For network dynamics in alpha and beta bands, it was very unclear, and so in any group.

### **Network Dynamics Comparison**

Functional connectivity matrices were compared between groups and according to target conditions. In theta band, NBS revealed a between-group difference in the 300-400 ms interval, in a fronto-temporal network ( $p = 0.019$ ). Post-hoc analysis revealed that connectivity was increased in the PD-FoG group compared to HC (5 connections,  $p = 0.03$  after correction). In the 400-500 ms interval, a between-group difference was also observed in a left fronto-temporo-occipital network ( $p = 0.013$ ). Post-hoc analysis revealed that connectivity was increased in the PD+FoG group compared to HC (4 connections,  $p = 0.033$  after correction). In the 500-600 ms interval, a between-group difference was also found, in a large network with left predominance ( $p = 0.006$ ). Post-hoc analysis revealed an increased connectivity for PD+FoG compared to HC, in two distinct networks, the first being a ventral fronto-temporo-occipital network (5 connections,  $p = 0.016$  after correction) and the second an inter-hemispheric parieto-temporo-frontal network (5 connections,  $p = 0.016$  after correction). A similar pattern was noticed in the significantly different network in the 400-500 ms interval and the first significantly different network in the 500-600 ms interval, with an increased connectivity for PD+FoG compared to HC. This particular network is presented in Figure 4.

In alpha band, a between-group difference was observed in the 300-400 ms interval only, in an inter-hemispheric parieto-frontal and parieto-temporal network (7 connections,  $p = 0.023$ ). Post-hoc analysis revealed that connectivity was increased in PD-FoG compared to HC in the same network (7 connections,  $p = 0.012$  after correction). In beta band, no significant difference was found between groups. In all three frequency bands, no difference was found between target conditions, and no interaction was found. No difference was found between PD+FoG and PD-FoG in any frequency band.

### **Discussion**

PD+FoG showed deficit in executive control during a visual attention task. This outcome is consistent with results found in the literature [19]. On a cortical network level, no distinction was made between PD+FoG and PD-FoG. PD+FoG showed an increase in functional connectivity in theta band during a visual attentional task, within fronto-temporo-occipital networks, with left predominance, compared to matched healthy controls in the same conditions. The differences only appeared quite late in the cognitive process from target presentation to motor response, after 400 ms. The consistent network with increased functional connectivity in PD+FoG at 400-500 ms and 500-600 ms intervals implied some regions of interest involved in visual and attentional networks. To our knowledge, no previous study about EEG functional connectivity during an attentional task is available to confront those results in a population made of PD+FoG patients. fMRI studies give hints about the functions hosted in the abnormal networks found. The abnormal network differentiating PD+FoG connected the cuneus and inferior temporal regions such as the fusiform area within the visual network. The cuneus is involved in processing visual information, including during a visual attention task like presented by Yang and collaborators [52]. Inferior temporal regions cited above, fusiform and middle temporal gyrus, are associated with the ventral visual pathway, also named “what” pathway, involved in the identification of the shape and nature of a visual information [53]. Excessive connectivity within this pathway during a visual attention task might reflect a mechanism developed to overcome interpretation difficulties in

this population. Another interesting point was the existing connection between said visual nodes, and orbitofrontal cortex, associated with executive functions [54,55]. Orbitofrontal cortex is a key region in executive functions, and it is thought to play an essential role in behavior and decision-making. Encountering excessive connectivity between this node and visual network in the abnormal network in the very end of the cognitive process, just before motor response, may reflect a compensating mechanism for changes in the decision-making process during a visual attention task in PD+FoG. On the other hand, Fan et al. have described in fMRI a network resulting from the executive control component of ANT [56]. This fMRI network involves fusiform regions, anterior and posterior cingular regions, left lateral temporal region and left lateral frontal region [56]. Of those nodes, we found in the present study the fusiform regions within the abnormal network described. Hypothesis can be made that the dysfunction in executive control in PD+FoG might generate a compensating mechanism through excessive connectivity with visual network. Indeed, in daily life, PD patients use environmental cues to facilitate their mobility, namely when the situation contains conflicting information. PD+FoG have been shown to rely more on visual information than healthy subjects [57]. Environmental cueing has been proven efficient in improving gait among PD and is now part of many reeducation programs [58,59]. A higher dependence on environment could explain the improvement of gait by cueing, but also its worsening during double-tasking condition [60]. Increased connectivity within connections between nodes described in either executive control network or executive function cortex, with environment information processing (visual network here) might reflect a stronger dependence on environment in PD+FoG for the same task.

In spite of this description and proposed hypotheses, some reservation can be argued. Some nodes involved in the abnormal network presented are also described in attention networks in fMRI studies. Orbitofrontal node and the banks of the superior temporal sulcus node showed in the abnormal network can also stand for ventral frontal region and the temporo-parietal junction described in the ventral attention network, or bottom-up attention network [61–63]. The hypothesis could also be made that stronger connections between stimulus driven attention networks and visual network in PD+FoG reflects higher attentional demands in these individuals during a visual attention task. Yet, the attentional task should mostly involve the dorsal attention network, or top-down attention network, as long as the attention is supposed to be goal-driven (following the instructions) and not stimulus-driven. A hypothesis stating that a stronger dependence is expected on bottom-up attention during a task needing mostly goal-driven attention seems unlikely, unless the mechanism is at the contrary a causal increase of connectivity inducing the patients to be more easily distracted from the task by irrelevant features. Moreover, the ventral attention network is described as essentially lateralized on the right hemisphere, whereas the abnormal network shown here is lateralized on the left hemisphere when concerning the temporo-parietal junction. This right junction is believed to carry an important role in detecting a “mismatch” between pre-established models and the processed environmental stimuli. Conversely, the same region, but on the left side, is more consistently involved, regardless of the “mismatch” or “match” status [64,65].

## Limitations

First of all, functional connectivity was measured in an ON-state among PD patients. It is admitted in the literature that levodopa can induce change in connectivity, and a partial reversibility of resting state connectivity abnormalities have been observed [66]. It has to be acknowledged that the networks described here are not physiological abnormalities in the strict sense of the term but abnormalities



remaining despite levodopa. Some pathological changes might have been underestimated. However, the ANT needed a motor response and could not be performed in an OFF-state, and PD patients were therefore matched on their LEDD to minimize this bias. Secondly, EEG provides low spatial resolution and even using a source localization step, some imprecision remains on the nodes' localization. This is the reason why only cortical sources were studied, given that EEG spatial resolution for cortical sources is much better than for subcortical sources.

## **Conclusion**

Excessive functional connectivity was shown in theta band between nodes involved in executive functions, including executive control, and visual network nodes, in PD+FoG compared to HC. A deficiency in executive control among PD+FoG was specifically found, assessed thanks to the standard ANT. However, no network difference was shown between PD+FoG and PD-FoG during the same task. The hypothesis of a compensatory mechanism was proposed to account for the network abnormalities found in PD+FoG, with a stronger dependence on the environment. Those results reinforce the necessity of combining motor reeducation with sensorimotor and cognitive reeducation in PD+FoG.

Under preparation

## **Authors' Roles**

- 1) Research project: A. Conception, B. Organization, C. Execution;
- 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
- 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

Morgane Gérard : 1A/B/C, 2A/B, 3A ; Madli Bayot : 1A/B/C, 2A/B, 3B ; Prof Philippe Derambure : 2C, 3B ; Prof Kathy Dujardin : 2C, 3B ; Prof Luc Defebvre : 2C, 3B ; Nacim Betrouni : 2A/C, 3B ; Prof Arnaud Delval : 1A, 2C, 3B.

## **Financial Disclosures of all Authors (for the preceding 12 months)**

No author had conflict of interests related to this study.

M. Gerard received a grant from Lille University for a research year and no other financial disclosure.

M. Bayot received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 721577.

P. Derambure, K. Dujardin and A. Delval were employed by French Government (enseignement supérieur) and had no other financial disclosure.

L. Defebvre was employed by French Government (enseignement supérieur), gave consultancies to "Abbvie" and "Orkyn" and earned honoraria for lectures from "UCB" and "Abbvie".

N. Betrouni was employed by INSERM (institut national de la santé et de la recherche médicale), received a grant from PROCOPE Campus France and gave consultancies to LLL France.

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Under preparation

## Tables and Figures Legends

**Figure 1.** Description of the modified Attention Network Test

**Table 1.** Demographic and clinical data characterizing the 3 groups (mean  $\pm$  standard deviation).

**Notes.** F/M = Number of female/male in each group; MoCA = Montreal Cognitive Assessment; MDS-UPDRS III: Movement Disorders Society Unified Parkinson Disease Rating Scale part III; LEDD = Levodopa Equivalent Daily Dose

**Figure 2.** Executive control effect during the ANT: Mean DRT by group (ms) and 95% confidence interval. DRT = delta response time (for each subject: median reaction time in incongruent condition of target - median reaction time in congruent condition of target)

**Figure 3.** Network dynamics in theta band: graph construction for visualization of dynamic functional connectivity during the ANT by 100-ms intervals; C = congruent condition; I = incongruent condition; R = right; L = left; Ant = anterior; Post = posterior

**Figure 4.** Functional networks with greater connectivity strength in PD+FoG versus HC in 400-500 ms ( $p = 0.033$ ) and 500-600 ms ( $p = 0.016$ ) time intervals in theta band. 1 = right medial orbitofrontal cortex; 2 = right cuneus; 3 = banks of the left superior temporal sulcus; 4 = left fusiform; 5 = left middle temporal gyrus; 6 = left and right entorhinal cortex; in blue: visual network nodes; in light green: node associated with the executive control network in fMRI studies; in dark green: node associated with executive functions; In red: ventral attention network nodes

Under preparation



## Tables and Figures

Figure 1:

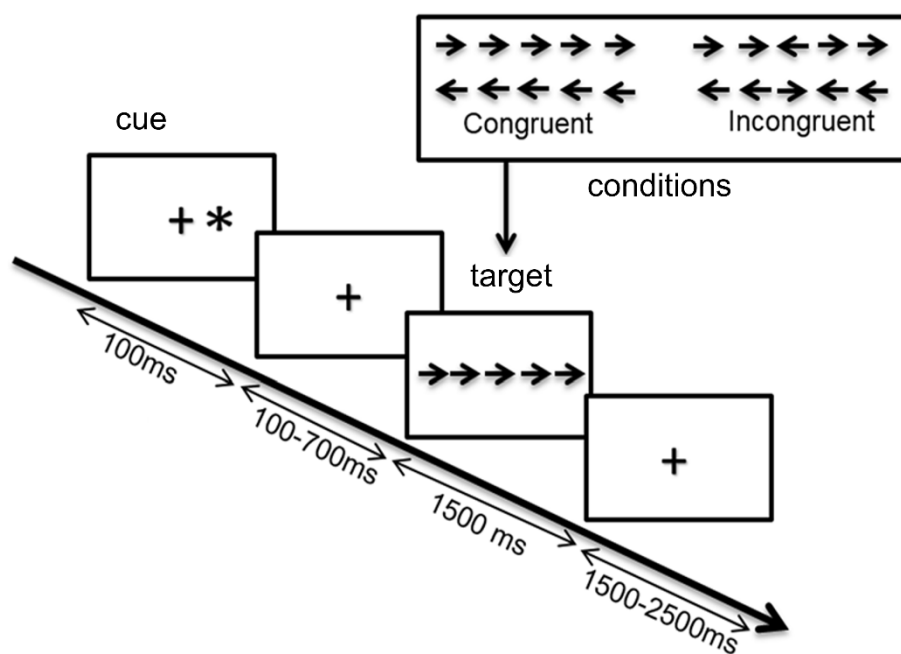
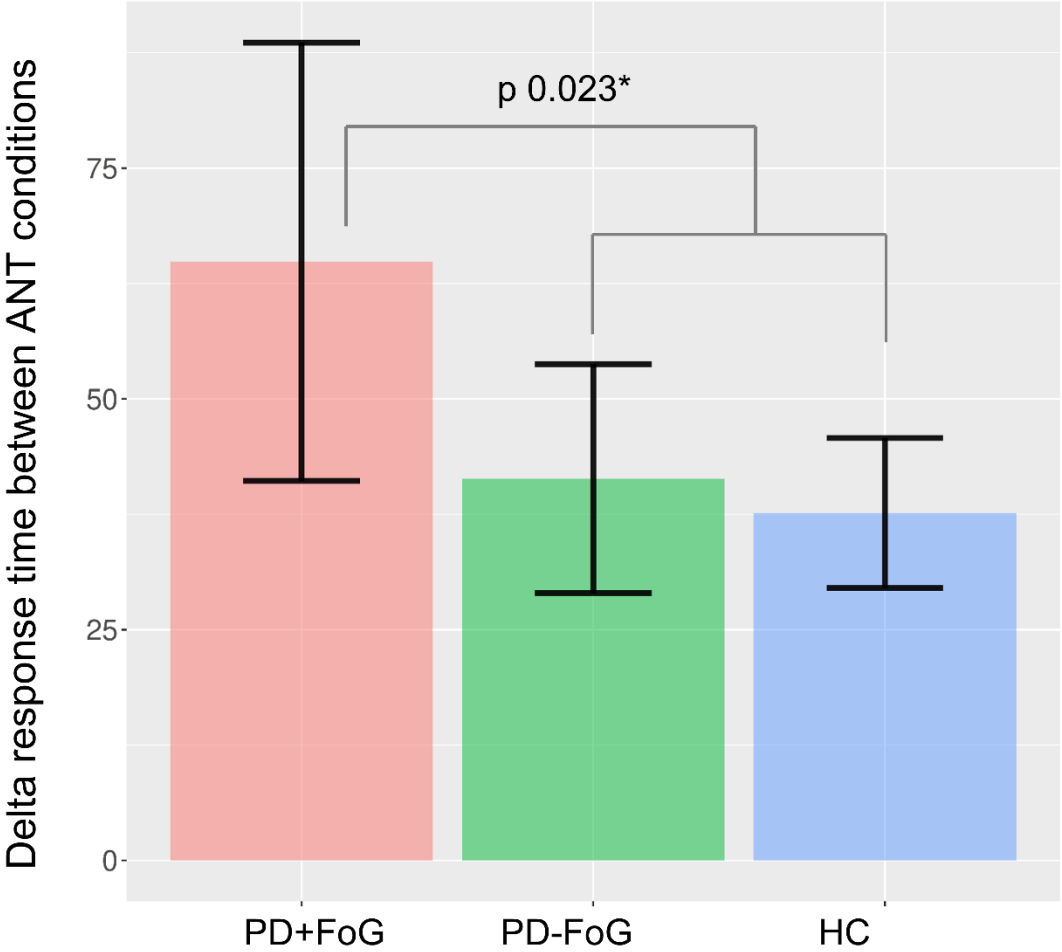


Table 1:

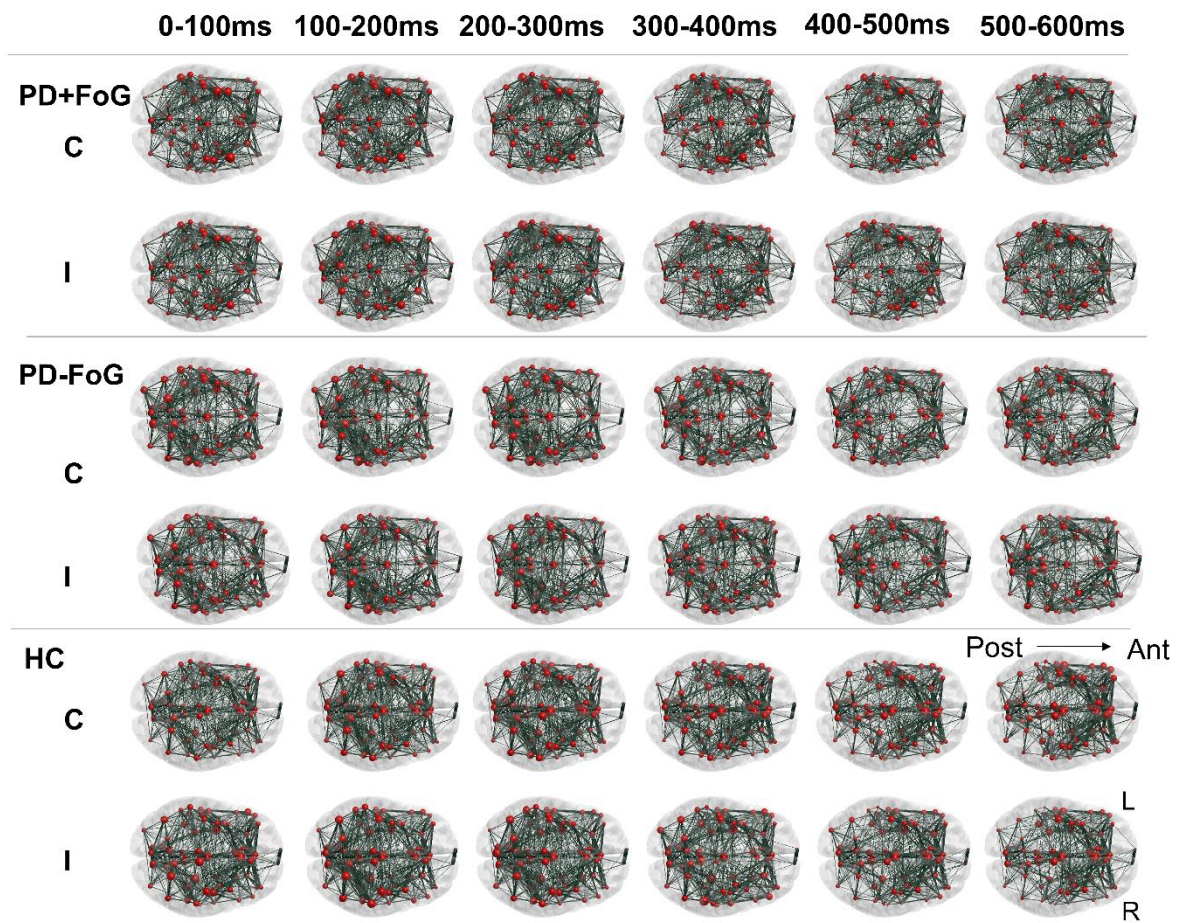
	PD+FoG (N=15)	PD-FoG (N=14)	HC (N=18)	p value
Sex (F/M)	4/11	7/7	8/10	0.100
Age (years)	63±8	61±9	60±7	0.712
MoCA	26±2	27±2	28±2	0.114
Disease duration (years)	9±4	9±4	/	1.000
MDS-UPDRS III	26±13	21±9	/	0.336
LEDD	757±406	931±298	/	0.349

Figure 2:



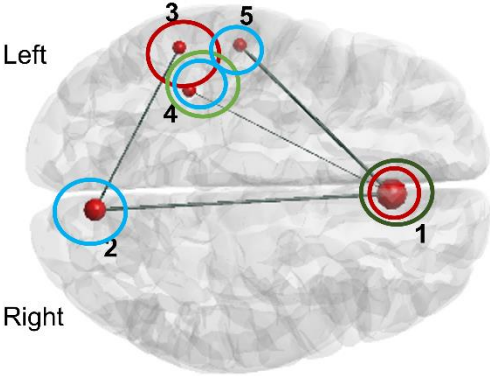
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Figure 3:

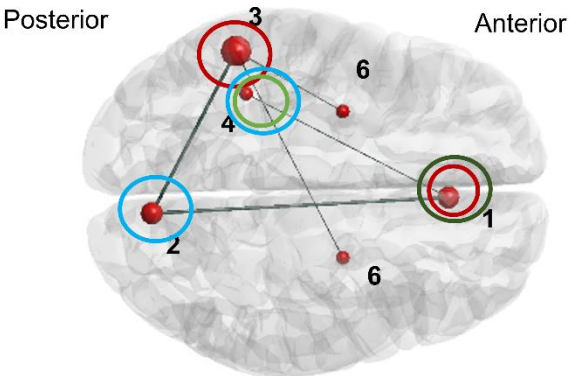


Under review

Figure 4:



[400 - 500ms]  
PD+FoG > HC p 0.033



[500 - 600ms]  
PD+FoG > HC p 0.016

Under preparation

# Point sur l'étude PACTE-I

## 1. Contexte général

L'étude PACTE-I porte sur la « Potentialisation des capacités cognitives chez le sujet âgé par l'association du méthylphénidate et de l'entraînement cognitif : Essai de preuve de concept en double aveugle versus placebo » (*méthylPhenidAte and Cognitive Training in Elderly* ou PACTE-I en abrégé). Cette recherche clinique est menée au sein de l'unité INSERM 1172 (troubles cognitifs, dégénératifs et vasculaires) avec intervention de plusieurs acteurs :

- Centre d'Investigation Clinique (CIC) 1403-PT (plurithématique);
- Service de pharmacologie médicale;
- Service de neurophysiologie clinique ;
- Service de rééducation fonctionnelle ;
- Service de neuroradiologie.

Au sein du service de neurologie clinique, nous nous intéressons particulièrement aux effets du méthylphénidate (MPH) couplé à un entraînement cognitif structuré sur l'interaction attention/contrôle moteur chez les personnes âgées lors de l'initiation de la marche en situation de double tâche.

## 2. Contexte scientifique

Le vieillissement normal s'accompagne d'une diminution de la performance cognitive, touchant notamment les fonctions attentionnelles (Harada et al., 2013). Par la suite, cela peut évoluer vers des troubles cognitifs légers (*mild cognitive impairment* ou MCI), qui n'induisent pas directement une perte d'autonomie, mais représentent eux-mêmes un facteur de risque d'évolution vers une démence (Annoni et al., 2016). Or, l'impact fonctionnel associé à la démence est important: baisse significative de l'autonomie et de la qualité de vie des patients et de leur entourage, augmentation de la morbi-mortalité et important coût socio-économique lié à la prise en charge des individus (Wimo et al., 2017). Par ailleurs, le potentiel de plasticité cérébrale et les mécanismes neuronaux associés tendent à diminuer avec l'âge (Burke and Barnes, 2006). Des études de l'état de repos en IRMf (Hafkemeijer et al., 2012; Ferreira and Busatto, 2013) ont mis en évidence une réduction de la connectivité fonctionnelle chez le sujet sain âgé. Cette réduction affecte principalement les réseaux de la saillance, du mode par défaut et de l'exécutif central, réseaux impliqués dans les fonctions attentionnelles et

exécutives. Finalement, étant donné que la marche associe des processus moteurs et également attentionnels (Yogev-Seligmann et al., 2008), les déficits de l'équilibre et de la marche sont eux aussi omniprésents chez les personnes âgées et représentent un fardeau énorme du point de vue personnel, professionnel et au niveau des soins de santé.

Dans ce contexte, l'un des enjeux majeurs actuels est de retarder l'éventuelle évolution vers la démence et l'une des stratégies possibles serait d'exploiter le potentiel de plasticité cérébrale subsistant. A cette fin, différentes voies ont été explorées, notamment le renforcement de l'activité physique, l'amélioration de la nutrition, la mise en place d'entraînements cognitifs ou la prescription de psychostimulants (Dresler et al., 2013). Dans le cadre de PACTE-I, nous nous sommes plus particulièrement intéressés à l'impact de l'entraînement cognitif et des psychostimulants sur les fonctions cognitives et le contrôle moteur.

D'une part, l'entraînement cognitif, ou programmes d'exercices de stimulation des fonctions cognitives, semble mener à une amélioration de fonctions telles que l'attention, la mémoire de travail et les fonctions exécutives, ainsi qu'à l'amélioration de l'accomplissement des tâches quotidiennes chez les sujets âgés (Martin et al., 2011; Reijnders et al., 2013; Rebok et al., 2014). Sur le plan de la plasticité cérébrale, ces entraînements auraient pour impact l'augmentation de la connectivité fonctionnelle et du débit sanguin cérébral au niveau des réseaux du mode par défaut et de l'exécutif central (Chapman et al., 2015). Un entraînement cognitif permet également de ralentir la dégradation de l'équilibre et améliore la marche en double tâche chez les sujets âgés sains (Smith-Ray et al., 2015).

D'autre part, le MPH est un stimulant du système nerveux central qui, une fois ingéré, bloque les transporteurs présynaptiques de la dopamine et, dans une moindre mesure, de la noradrénaline, et empêche ainsi la recapture de ces neurotransmetteurs par le neurone présynaptique. Les concentrations extracellulaires de catécholamines augmentent donc, notamment au niveau du striatum et du cortex préfrontal. Ces régions sont fortement impliquées dans les fonctions attentionnelles et exécutives (Volkow et al., 2001). Cela amène donc le sujet à un état d'alerte si l'on se réfère à la courbe en U inversée de la relation dose-réponse entre la quantité de catécholamines libérées et les capacités préfrontales. Globalement, les différentes études s'étant intéressées au sujet ont démontré que le psychostimulant avec le profil de sécurité le mieux établi est le MPH. Sur le plan cognitif, des études ont montré l'amélioration de certaines fonctions cognitives (i.e., mémoire de travail, vitesse de traitement de l'information, et attention) après administration de MPH à des volontaires sains (Linszen et al., 2014). En ce qui concerne la plasticité cérébrale, une prise unique de

MPH permettrait d'augmenter la connectivité fonctionnelle au sein de réseaux impliqués dans les fonctions attentionnelles et exécutives (Mueller et al., 2014). Par ailleurs, plusieurs scientifiques (Ben-Itzhak et al., 2008; Shorer et al., 2013) ont également démontré un impact positif de la MPH sur le risque de chute, l'équilibre et la marche chez les personnes âgées, spécifiquement dans le cas de conditions complexes de double tâche qui requièrent un contrôle exécutif plus important. Une potentielle application supplémentaire pourrait aussi voir le jour comme traitement pour la maladie de Parkinson lui a également été découvert, étant donné que le MPH semble améliorer les symptômes axiaux présents chez les patients parkinsoniens (Moreau et al., 2012; Devos et al., 2013).

À ce jour, les études traitant des effets de l'entraînement cognitif ou du MPH sur la cognition, la plasticité cérébrale et la motricité présentent certaines limites :

- une faible puissance statistique (effectifs peu nombreux) ;
- les populations ciblées, qui incluent soit des jeunes adultes, soit une population pathologique ;
- le design des entraînements cognitifs étudiés (hétérogénéité des entraînements, absence de condition contrôle, absence d'évaluation à distance de l'intervention) ;
- et le traitement par MPH prodigué en prise unique.

### **3. Principaux objectifs et hypothèses**

L'objectif de PACTE-I est de déterminer comment l'association d'un entraînement cognitif structuré et d'un traitement par MPH en faible dose et en cure courte agit sur l'attention visuo-spatiale, sa relation avec le contrôleur moteur (i.e., l'initiation du pas dans le cas de la présente étude) et sur la plasticité cérébrale chez des volontaires sains âgés de 55 à 75 ans. Les méthodes de mesure utilisées permettent l'évaluation objective d'une interaction entre comportements moteur et attentionnel via la réalisation du paradigme ANT-INIT (utilisé dans l'étude précédente et décrit ci-avant) et via l'examen des réseaux mis en jeu sur le plan cortical.

Cette étude se focalise, dans un premier temps, sur l'état du contrôle exécutif après traitement chez les personnes âgées et son impact sur leur capacité à initier le pas. Le critère d'évaluation principal est la modification du temps de préparation et d'exécution du pas en situation de résolution de conflits. Par la suite, d'autres données comportementales liées à la préparation du pas (APAs et leurs caractéristiques) et à son exécution sont évaluées, de même, pour les composantes attentionnelles d'alerte et d'orientation. Simultanément, des enregistrements EEG haute densité sont réalisés afin de mieux comprendre les mécanismes neuronaux à la base des déficits de la marche en situation de

double tâche et observer d'éventuels changements au niveau de ces mécanismes suite à l'intervention. Concernant les données EEG, les objectifs primaires sont l'investigation des PE ainsi que l'analyse temps-fréquence des données. Dans un second temps, la localisation de source et la connectivité fonctionnelle basée sur les données EEG sont prévues.

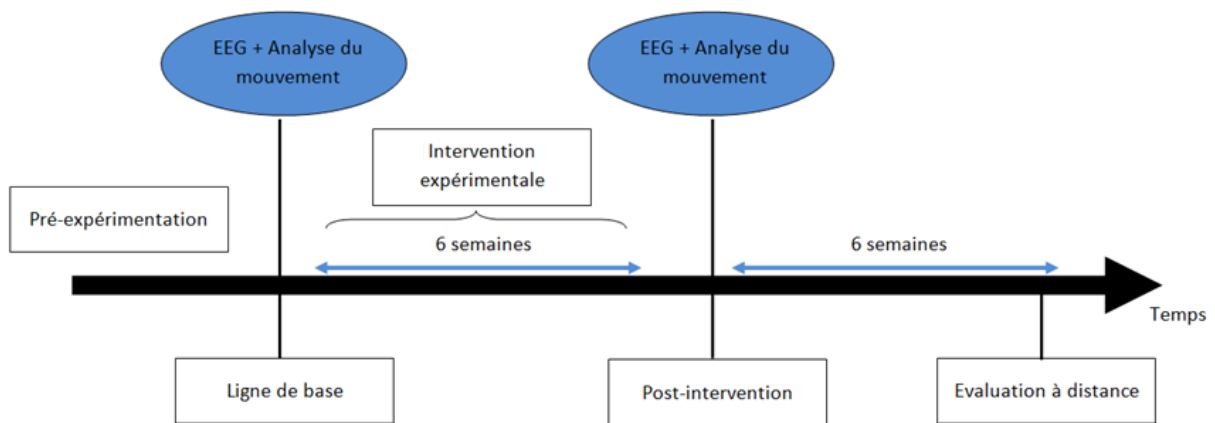
Sur base des résultats de Cohen et collègues qui ont mis en évidence un nombre d'APAs erronés plus important reflétant un défaut d'inhibition chez les personnes âgées comparées aux plus jeunes (Cohen et al., 2011), le résultat principal attendu est une diminution du taux d'APAs erronés chez les participants suivant un traitement au MPH - couplée ou non à un entraînement cognitif structuré - par rapport à ceux qui recourent à un placebo. De même, en guise de résultats secondaires, nous nous attendons à une amélioration de la performance globale de la marche chez les individus âgés traités au MPH et éventuellement entraînés cognitivement : diminution du temps de réaction et de la durée des APAs, et amélioration de l'exécution du pas dans sa globalité (vitesse, latence et longueur).

Plus largement, les conséquences espérées sont une amélioration de la qualité de vie des personnes âgées via l'amélioration de la réalisation de tâches écologiques et une réduction des coûts thérapeutiques. En effet, le MPH, grâce à sa faculté d'améliorer symptomatiquement les capacités attentionnelles du sujet, permettrait à ce dernier de tirer davantage profit d'un entraînement cognitif. De plus, l'action du MPH sur la plasticité cérébrale engendrerait un effet persistant à long terme. C'est pourquoi, dans la présente étude, le traitement est prodigué en cure courte et de faible dose. Plus tard, si l'efficacité de ce nouveau concept est prouvée, l'objectif serait de tester, au cours de plus grandes études de phase III de validation, ses bienfaits chez des patients ayant des troubles cognitifs précédant une démence ou chez des patients ayant des troubles moteurs comme les personnes atteintes de la maladie de Parkinson et éventuellement du freezing de la marche.

#### **4. Design expérimental**

Notre étude porte sur 120 volontaires sains âgés de 55 à 75 ans. Le recrutement des participants est réalisé à partir de la liste des volontaires sains du CIC du CHU de Lille. Le design expérimental est représenté sur la Figure 11.





*Figure 11* Design expérimental de l'étude PACTE-I

Une phase pré-expérimentale est mise en place afin de contrôler l'absence d'éventuels biais. Différents types de biais peuvent être caractérisés : une pathologie neurologique ou psychiatrique chronique sévère, des troubles cognitifs associés à une baisse d'autonomie, des contre-indications à l'IRM, ou encore des troubles visuels et/ou auditifs non-corrigés pouvant interférer avec la passation des évaluations. De plus, parmi d'autres critères de non-inclusion, les sujets ne présenteront pas d'antécédents personnels et/ou familiaux de tics moteurs et syndrome de Gilles de la Tourette, d'anomalies cardiaques, d'hypersensibilité au MPH ou à tout autre constituant du produit, ou de pathologie motrice susceptible d'interférer avec l'expérimentation en cours. Toute dépendance préexistante aux médicaments, aux drogues ou à l'alcool, toute consommation d'un ou plusieurs psychotropes ou produits apparentés et certains traitements concomitants à la prise de MPH comme les sympathomimétiques alpha sont également proscrits.

En ligne de base (V1), les sujets inclus sont assignés à un groupe d'intervention spécifique. En effet, cette étude pilote se veut comparative, randomisée et contrôlée en quatre bras composés chacun de 30 participants :

- groupe 1 : entraînement cognitif structuré et prise de MPH à raison d'une dose faible de 0,3 mg/kg/jour;
- groupe 2: entraînement cognitif structuré et prise d'un placebo;
- groupe 3: pseudo-entraînement au travers d'une vidéo de documentaires suivie d'un quizz sur les connaissances acquises (entraînement cognitif non-structuré) et prise de MPH en faible dose;
- groupe 4: pseudo-entraînement cognitif et prise d'un placebo.

Il s'agit donc d'un essai de preuve de concept comparant ces quatre groupes parallèles en double aveugle. L'intervention expérimentale s'étend sur 6 semaines, avec 12 séances d'entraînements cognitifs structurés ou non-structurés d'une durée d'1h30 (2 fois par semaine pendant 6 semaines). Chaque groupe expérimental est comparé au groupe contrôle.

## 5. Intervention personnelle

La doctorante est intervenue à plusieurs niveaux, pour :

- L'amélioration, le développement et l'implémentation des méthodes d'acquisition et d'analyse des données sur les sujets ;
- La réalisation des tests en ligne de base (V1) et après intervention expérimentale (V2) : analyse mouvement via système d'analyse vidéo tridimensionnelle du mouvement avec plateformes de force intégrées, et enregistrement EEG afin d'évaluer les performances au paradigme ANT standard et couplé à l'initiation du pas (ANT-INIT) ;
- La passation, pour les activités de recherche d'un collègue, d'un test de Go-NoGo avec feedback, avec enregistrement EEG simultané.

## 6. Etats des lieux et problèmes rencontrés

L'objectif initial d'inclusion de 120 sujets âgés sains d'ici à la fin de la thèse n'a pas pu être rempli, à cause d'un retard initial dans l'inclusion des sujets (après environ un an de démarrage de thèse), et une exclusion de nombreux sujets ne répondant pas aux critères d'inclusion (i.e., « screening failures »). Ces difficultés ont été renforcées en fin de doctorat par la crise COVID-19, qui a entraîné l'arrêt de 5 expérimentations en cours (V1 déjà réalisée sur les sujets) et empêché toute inclusion supplémentaire au vu des risques sanitaires encourus. Globalement, plusieurs membres du CHU de Lille ont été impliqués dans l'étude et la doctorante n'a donc pas eu de contrôle sur les inclusions.

Depuis 2018, 51 personnes ont été reçues durant l'étape pré-expérimentale visant la validation ou non du recrutement selon les critères d'inclusion et d'exclusion, 30 sujets ont été inclus et évalués (V1 ou V1+V2), dont 1 a été exclu aux sorties de la V1 et 5 n'ont été testés qu'au cours de la V1 pour cause d'interruption de l'étude clinique jusqu'à nouvel ordre. Au total, seuls 24 sujets ont pu réaliser le protocole complet (V1 + V2), avec les 6 semaines de traitement.

# **Chapitre 4.**

## **DISCUSSION GÉNÉRALE**

# 1. Résultats principaux et validation des hypothèses

Tout d'abord, nous avons pu confirmer l'hypothèse selon laquelle l'attention peut moduler l'activation corticale (liée à la préparation motrice) pendant l'initiation de la marche chez les adultes jeunes sains. Pour la première fois, les caractéristiques corticales de la modulation attentionnelle (à travers l'ANT) pendant l'initiation du pas ont été évaluées (**Etude 2**). Nous avons observé que la charge attentionnelle ne modifie pas les MRCPs, mais que les DLE dans les bandes alpha et bêta étaient modifiées par une variation de modalité de l'indice (alerte) ou de la cible (contrôle exécutif). Ces oscillations corticales ont des conséquences directes sur la préparation du mouvement, avec soit un effet sur le temps de réaction, soit sur la durée de la phase de préparation.

Concernant les relations existant entre posture, APA et exécution du premier pas (**Etude 3**), chez les personnes âgées saines comme chez celles atteintes de la MP avec ou sans FdM, un important déplacement en arrière du CdP pendant l'APA permettait de réaliser un pas rapidement, grâce à la propulsion efficace du CdM vers l'avant (comme trouvé précédemment par (Brenière et al., 1987)). Au sein des sujets avec la MP, la taille ML des APAs (et par extension, la largeur de la posture au repos ou le déplacement latéral du CdP lors de la phase de décharge du membre oscillant) était utilisée pour contrôler la longueur et la vitesse du premier pas. Contrairement aux résultats de Brenière et collaborateurs (Brenière et al., 1987), de plus longs APAs n'étaient pas corrélés à une vitesse plus importante du premier pas, car il s'agissait souvent de la conséquence d'APAs multiples et ce type d'APAs peut être préjudiciable pour la vitesse du premier pas. Dans ce contexte, la durée de la phase de décharge du membre oscillant semble plus intéressante à analyser : elle aide à contrôler la longueur du premier pas chez les sujets sains et la rapidité du premier pas chez les patients MP-FdM. Cette durée de la phase de décharge, significativement plus longue chez les freezers comparés aux autres groupes, pourrait consister en une stratégie d'équilibre dans la direction ML, renforçant la stratégie de positionnement ML initial du CdP vers le pied d'appui. En effet, les sujets avec la MP ont montré un basculement de la position initiale du CdP avant le démarrage des APAs vers le pied d'appui, alors que les contrôles sains plaçaient initialement le CdP davantage vers le pied oscillant. Chez les MP+FdM, au plus le CdP était positionné vers le pied d'appui, au plus leur premier pas était lent et court en longueur. Ce positionnement ML initial du CdP caractéristique pourrait être une stratégie compensatoire pour contrer l'instabilité posturale présente chez les patients MP+FdM.

L'hypothèse émise par notre équipe selon laquelle le contrôle postural altéré au repos chez les MP+FdM pourrait influencer sur les faibles performances motrices observées dans ce groupe lors du

processus d'initiation de la marche (APAs et/ou l'exécution du premier pas) est donc bien vérifiée. Cependant, nous n'avons pas retrouvé la même position moyenne du CdP juste avant l'initiation de la marche que celle mesurée lors d'un enregistrement du contrôle postural au repos (sans initiation du pas ou autre tâche motrice qui suit) (Schlenstedt et al., 2016). Effectivement, ces enregistrements de la posture au repos révélaient une position moyenne du CdP davantage vers les talons chez les MP+FdM par rapport aux MP-FdM et contrôles, alors que nous n'avons pas trouvé de différence en ce qui concerne la position moyenne AP du CdP juste avant le début des APAs. Il semblerait donc que l'étude de la posture au repos ne soit pas pertinente pour la compréhension des épisodes de freezing apparaissant lors de l'initiation de la marche.

La **quatrième étude** a permis d'étudier la combinaison de deux potentiels facteurs contextuels qui provoqueraient le FdM, à savoir : la capacité de résolution de conflit (ou contrôle exécutif) et l'initiation de la marche. Selon les résultats de la littérature, l'étude de facteurs contextuels, par rapport aux études longitudinales et aux études des facteurs associés au FdM, sont celles qui fournissent les nouvelles connaissances les plus pertinentes quant aux mécanismes sous-tendant le FdM (Ehgoetz Martens et al., 2020). Ce genre d'études sont effectivement celles qui apportent le plus d'évidence directe avec le moins de facteurs confondants. Toutefois, dans le cadre de la passation de l'ANT-INIT, nous n'avons pas aperçu d'épisodes de FdM comme attendus, ce qui aurait apporté une évidence directe de l'influence de l'interaction attention-initiation de la marche sur le déclenchement d'épisodes de freezing. Cette absence d'épisode de freezing peut en partie s'expliquer par le caractère non écologique de la tâche et sa complétion en hôpital. Comme alternative, nous nous sommes donc intéressés à la modulation des APAs par la charge attentionnelle. Les caractéristiques de ces ajustements posturaux de préparation motrice sont, en effet, connues pour être associées à l'apparition d'épisodes de freezing (comme c'est le cas pour les APAs multiples). Les étudier permet de répondre à notre question initiale, mais de manière un peu moins directe, donc critiquable.

Les hypothèses émises n'ont donc pour la plupart pas été validées :

- Du point de vue des conséquences comportementales de l'interaction entre attention et motricité :
  - Aucun épisode de freezing n'a été observé. Les patients étant testés sous médication pour pouvoir effectuer correctement la tâche, peu d'épisodes de freezing étaient toutefois attendus.

- Malgré qu'une défaillance du contrôle exécutif chez les MP+FdM par rapport aux MP-FdM et aux contrôles ait été retrouvée, ce déficit attentionnel n'a pas eu d'impact spécifique sur les paramètres de préparation et d'exécution du pas. L'effet du contrôle exécutif était effectivement le même, quel que soit le groupe, sur le TEP et ses sous-composantes, sur les paramètres spatiaux des APAs et sur l'exécution du pas. Seul un ralentissement significatif de la préparation et exécution du pas a été observé chez les patients MP par rapport aux sujets âgés sains, avec des valeurs intermédiaires pour les MP-FdM mais sans se différencier significativement des MP+FdM.
- Une des possibles explications pour ce manque d'interaction entre groupes et conditions de cible est le taux d'APAs multiples qui était plus élevé en condition non congruente qu'en condition congruente, mais qui était similaire parmi les groupes. Cette observation va, à nouveau, à l'encontre des hypothèses posées.
- L'analyse de la synchronisation et de la désynchronisation des oscillations corticales tout au long de la tâche reflétaient assez bien ce qui était observé au niveau comportemental, c'est-à-dire une diminution de l'intensité de la DLE alpha/bêta chez les patients MP par rapport aux contrôles, et une DLE plus tardive et prolongée chez les MP+FdM.

Pour **l'étude n°5**, il a été démontré que :

- D'un côté, une simple analyse spectrale du signal EEG dans l'espace des électrodes a permis de mettre l'accent sur le contrôle exécutif déficitaire chez les patients MP+FdM.
- D'un autre côté, étudier la connectivité fonctionnelle basée sur l'EEG dans l'espace des sources a mis en lumière un réseau fronto-pariétal gauche davantage connecté dans la bande thêta chez les patients MP+FdM que chez les contrôles sains, qui était significativement corrélé à la sévérité du FdM.

Dans cette étude, les hypothèses émises ont été confirmées et infirmées de la façon suivante :

- Même si l'on a trouvé précédemment (Olde Dubbelink et al., 2013a) qu'une puissance spectrale plus élevée seulement dans la bande thêta était liée à un déclin des fonctions motrices au cours du temps, les scores MDS-UPDRS III et FOG-Q ne semblaient pas expliquer ici la plus grande puissance relative thêta chez les patients MP+FdM. Dès lors, l'hypothèse

d'une grande puissance relative thêta comme biomarqueur d'un contrôle exécutif déficitaire et d'un déclin cognitif futur pour les patients freezers semble plus plausible.

- Les conséquences comportementales de la dépendance excessive à l'environnement externe pourraient être reflétées dans les corrélations significativement positives entre la connectivité fonctionnelle des connexions fronto-pariétales et la sévérité du FdM. Nos résultats entrent donc en concordance avec nos hypothèses et des études IRMf précédentes. En effet, les patients MP+FdM montraient une connectivité fonctionnelle réduite dans et entre les régions du cerveau liées aux fonctions exécutives : au niveau du réseau (fronto-pariétal droit) de l'attention exécutive en comparaison avec les MP-FdM (Tessitore et al., 2012) et entre les réseaux fronto-pariétal droit et du contrôle exécutif en comparaison avec les sujets sains (Bharti et al., 2019a).
- Les anomalies visuospatiales empêcheraient les sujets MP+FdM d'utiliser exactement la même stratégie de sur-dépendance aux indices visuels pour contrôler la locomotion en prenant compte de leurs déficits exécutifs, comme chez les patients MP-FdM. Ils pourraient plutôt compter davantage sur l'hémisphère gauche et particulièrement sur le système attentionnel ventral gauche (Doricchi et al., 2010).
- Contrairement à nos résultats, Teramoto et al. ont trouvé une relation significative entre la dysfonction exécutive chez les patients MP non déments et une cohérence atténuée dans la bande alpha entre les cortex frontal et pariétal gauches (Teramoto et al., 2016).

Finalement, dans le cadre de **l'étude n°6**, lors de la réalisation de l'ANT standard, une connectivité fonctionnelle excessive anormale a été trouvée dans la bande thêta entre les nœuds impliqués dans les fonctions exécutives, y compris le contrôle exécutif, et des nœuds du réseau visuel chez les MP+FdM comparés aux contrôles sains. Une déficience du contrôle exécutif spécifique chez des MP+FdM a été observée et évaluée à l'aide de l'ANT. Cependant, aucune différence de réseau n'a été mise en évidence entre les patients MP+FdM et MP-FdM pendant la même tâche. L'hypothèse d'un mécanisme compensatoire a été proposée pour expliquer les anomalies du réseau trouvé chez les patients MP+FdM, avec une plus grande dépendance envers l'environnement.

## 2. Discussion

Différentes thématiques communes aux études réalisées dans le cadre de cette thèse sont discutées dans la présente section : la nature des APAs erronés et des APAs multiples, l'hypothèse cognitive dans

le cadre de la pathophysiologie du FdM ainsi que les substrats corticaux sous-tendant l'ANT et l'ANT-INIT.

## **2.1. APAs erronés ou multiples : vers des processus physiologiques ?**

Contrairement à nos attentes, nous avons retrouvé le même taux d'APAs erronés ou multiples chez les patients âgés sains que chez les patients MP, d'autant plus dans la condition de cible non congruente que congruente. Nous nous attendions effectivement à retrouver des APAs erronés chez les personnes âgées et davantage dans une situation de conflit, les APAs erronés étant liés un déficit de la fonction inhibitrice (Cohen et al., 2011; Sparto et al., 2013). Cependant, au vu des déficits cognitifs plus sévères chez les patients MP et spécifiquement chez les MP+FdM, un taux d'APAs erronés plus important chez les patients parkinsoniens était supposé. Par ailleurs, nous nous attendions également à apercevoir des APAs multiples, APAs caractéristiques relativement couramment observés lors de l'initiation de la marche chez les patients MP (en « ON » ou en « OFF ») comparés aux contrôles, et chez les MP+FdM plus particulièrement, ayant donné naissance à une hypothèse de couplage altéré entre préparation et exécution motrice (Jacobs et al., 2009b). Les études ayant quantifié le taux d'APAs multiples au sein des patients MP ne parvenaient pas toutes à différencier les MP+FdM des MP-FdM : Plate et al. (Plate et al., 2016) (en "ON", plus en condition de marche auto-générée que commandée par un stimulus visuel), Cohen et al. (Cohen et al., 2017) (en "OFF", marche initiée par stimuli visuels), Delval et al. (Delval et al., 2014a) (en "OFF", marche commandée par un stimulus auditif) ; alors que d'autres bien : Delval et al. (Delval et al., 2014a) (en "OFF", marche auto-commandée), Jacobs et al. (Jacobs et al., 2009b) (en "ON" et "OFF", pas compensateurs). Toutefois, toutes ces études s'accordaient sur le fait que les sujets sains appariés en âge (donc population qualifiée d'âgée) présentaient significativement moins d'APAs multiples que les patients, à l'exception de Cohen et al. qui n'ont pas trouvé de différence significative concernant le taux d'APAs multiples mais uniquement un début du pas plus tardif en cas d'APAs multiples chez les patients MP (sans distinction due au caractère de freezing). Ils mettaient donc en évidence plutôt une difficulté des patients MP pour libérer l'inhibition. Cohen et collègues ont été les seuls à étudier de manière différenciée APA erronés et APAs multiples, sans trouver de différences significatives au niveau de l'impact de tels APAs sur la préparation et l'exécution du pas (Cohen et al., 2017).

Nous nous intéressons donc à la nature de ces APAs erronés et multiples qui, au départ semblaient de nature pathologique, mais qui pourraient en fait être un processus physiologique car aperçus dans la condition de cible non congruente aussi bien que congruente, ainsi que chez les jeunes, plus âgés et



malades. Cependant, leur nature pourrait être différente en fonction de la population étudiée et de la complexité de l'initiation motrice. La nature des APAs multiples pourrait également être distincte de celle des APAs erronés.

Dans le cadre de nos investigations, les APAs erronés et multiples étaient significativement plus fréquents en condition de cible entourée de distracteurs non congruents comparés aux distracteurs congruents. De plus, les APAs multiples étaient initiés significativement plus précocement que les APAs erronés, qui étaient à leur tour plus précoces que les APAs normaux. Cela s'explique par le fait que ce genre d'APAs (erronés et multiples) reflèterait des déficits dans l'inhibition de la réponse, mis davantage en évidence dans le cas d'une cible entourée de distracteurs non congruents (i.e., dans le contexte d'une situation conflictuelle). Le TR plus précoce en cas d'APAs multiples ou erronés et donc davantage en condition de cible non congruente est illustré par la DLE bêta plus précoce dans cette situation de conflit.

Dans le cas des APAs erronés, le fait que ce type d'APAs était également présent lors d'essais en condition de cible congruente et était associé, dans cette condition, à un TR significativement plus court que pour les essais avec cible entourée par des distracteurs non congruents porte à croire que les APAs erronés sont, en partie, liés à une précipitation à répondre. Ainsi, l'apparition d'APAs erronés serait, entre autres, associée au souhait de réaliser la tâche rapidement (équivalent à une stratégie « posture second » en théorie des doubles tâches) : le sujet initierait l'APA dans une direction aléatoire, avant discrimination complète de la cible, en se reposant sur sa faculté à pouvoir corriger cette mauvaise direction donnée à l'APA au cours de la phase de préparation motrice. Les sujets sains comme parkinsoniens, mettaient plus de temps pour ajuster leur programme moteur dans la situation avec conflit à résoudre par rapport à la condition de cible congruente, effet du contrôle exécutif sur le temps de correction en cas d'APAs erronés similaire parmi les groupes.

Par ailleurs, les sujets âgés sains semblent davantage utiliser cette stratégie de priorisation de la vitesse sur la stabilité posturale par rapport aux patients MP. En effet, premièrement, les sujets âgés contrôles se différencient des patients de par un taux d'APAs anticipés significativement plus important. Deuxièmement, l'effet du contrôle exécutif sur le TR était d'autant plus élevé lors d'essais avec APAs erronés par rapport aux APAs normaux et multiples. Plus particulièrement, l'effet du contrôle exécutif sur le TR entre les essais avec APAs erronés et ceux avec APAs normaux était significativement plus important chez les sujets âgés sains par rapport aux patients MP (et particulièrement en comparaison aux MP+FdM). Autrement dit, en cas d'APA normal, les contrôles présentaient un TR quasi similaire

vis-à-vis d'une cible avec distracteurs congruents ou non congruents, alors qu'en cas d'APA erroné, leur TR en condition de cible congruente était significativement plus court qu'en présence de distracteurs non congruents. A contrario, les patients MP montraient, déjà lors d'essais avec APA normal, un TR plus long en cas de cible entourée de distracteurs non congruents par rapport à la condition de cible congruente, témoignant de la difficulté plus importante pour la discrimination de ces cibles en situation de conflit. Mises toutes ensemble, ces observations pourraient donc expliquer les taux d'APAs erronés similaires entre groupes, malgré que les APAs erronés des sujets sains seraient davantage liés à la précipitation alors que ceux des patients parkinsoniens seraient davantage associés à une défaillance du contrôle exécutif pour résoudre un conflit. Une meilleure compréhension des stratégies de priorisation permettrait une meilleure interprétation des APAs erronés. Le taux de précision lié à l'ANT-INIT étant assez élevé, il n'est pas possible en l'état de quantifier la stratégie de priorisation.

Les APAs multiples, quant à eux, sont également plus fréquents en condition de conflit, mais sans différence de TR entre condition conflictuelle ou non. Ils semblent juste être associés à un TR assez précoce. La nature des APAs multiples (comprenant plus de deux APAs, en comparaison aux APAs erronés) reste plus complexe à déterminer. Il s'agirait d'une mise en suspens de la phase de préparation motrice afin d'empêcher une exécution trop rapide du mouvement. Par exemple, dans le cas des APAs initiés dans la bonne direction mais multiples, il pourrait s'agir d'un état d'attente volontaire, le temps de résoudre le conflit lié à la cible et ses distracteurs. Contrairement aux APAs erronés, la levée d'inhibition n'est pas plus simple dans une condition de cible que dans une autre mais paraît, par contre, plus évidente chez les contrôles sains que chez les patients parkinsoniens et particulièrement, par rapport aux MP+FdM qui étaient significativement plus lents en termes de temps de correction suite à des APAs multiples. Dans le contexte des APAs multiples, les freezers présentaient donc, comme dans l'étude récente de Cohen et collaborateurs (Cohen et al., 2017), une défaillance pour la libération de l'inhibition en comparaison aux contrôles.

Finalement, alors que les APAs erronés et multiples ne semblent pas spécifiquement liés à la MP, l'absence d'APAs est majoritaire chez les patients MP par rapport aux contrôles. Bien que peu observée durant le paradigme de l'ANT-INIT (**Etude n° 4**), l'absence d'APAs n'était pas du tout associée aux sujets âgés contrôles comparés aux patients. Lors d'une marche auto-commandée (**Etude n° 3**), davantage d'essais sans APAs ont été observés et majoritairement chez les MP+FdM. L'intérêt pourrait se porter sur ce type d'APA dans des investigations futures concernant les mécanismes pathophysiologiques derrière le phénomène de FdM. Par ailleurs, l'analyse du couplage entre posture initiale, phases de

préparation et phase d'exécution du processus d'initiation de la marche semble intéressante à poursuivre pour une meilleure compréhension du freezing de la marche.

## **2.2. Atteintes attentionnelles : spécifiques du freezing de la marche ?**

Tout au long de cette thèse, l'hypothèse cognitive du FdM (Vandenbossche et al., 2012) est remise en question.

En effet, deux études de facteurs associés au FdM ont été réalisées : une analyse de la connectivité fonctionnelle EEG au repos ainsi qu'une étude de l'ANT standard assis, au niveau comportemental et de l'activité corticale, avec un intérêt particulier pour l'étude de la composante attentionnelle qu'est la résolution de conflit. Les patients présentant du FdM, appariés en tout point avec les patients MP-FdM sauf en genre, ont montré un déficit significatif du contrôle exécutif par rapport aux patients MP-FdM et aux sujets contrôles. Cependant, en utilisant le score de sévérité motrice comme covariable, la différence significative entre les patients freezers et non freezers en ce qui concerne leur capacité à résoudre un conflit disparaissait. De plus, via l'analyse de la connectivité fonctionnelle EEG durant l'ANT, nous avons pu constater que les patients freezers se différenciaient des sujets contrôles dans la bande thêta et compensaient ce déficit attentionnel en recourant à un réseau composé de régions appartenant aux réseaux du contrôle exécutif, des fonctions exécutives, mais également attentionnel ventral et visuel. Encore une fois, aucune différence significative n'était observée entre MP+FdM et MP-FdM. Au niveau de la connectivité fonctionnelle de repos, nous retrouvions le même genre de résultats, avec une connectivité fonctionnelle amplifiée dans la bande thêta chez les MP+FdM comparés aux contrôles au niveau d'un réseau comprenant des régions appartenant au réseau attentionnel ventral. Nous avons donc, à nouveau, affaire à une stratégie de compensation de l'attention endogène déclinante par l'attention exogène chez les patients freezers, sans distinction significative avec les patients MP-FdM. Forts de ces résultats, il ne semble donc pas y avoir une association directe entre FdM et contrôle exécutif, étant donné la participation de la progression de la maladie dans le déclin cognitif ainsi que dans l'incidence du FdM. La distinction entre freezers et non freezers pourrait ainsi représenter une séparation artificielle face à un phénomène qui pourrait plutôt être vu comme un continuum (Nutt et al., 2011).

Toutefois, une association indirecte entre le déclin du contrôle exécutif dû à la progression de la maladie et les épisodes de freezing doit encore être testée à travers une étude de facteurs contextuels, à savoir une tâche de résolution de conflit et l'initiation de la marche. En dehors du ralentissement

moteur observé chez les patients MP par rapport aux contrôles (sans distinction entre patients sur base du caractère freezer), nous n'avons pas pu mettre en évidence de différence inter-groupe quant à l'impact de la charge attentionnelle sur l'initiation du premier pas. Une possible solution est la lenteur globale des patients MP qui a pu amoindrir les différences entre gestions de situations conflictuelles et sans conflit dans cette population. Une autre explication pourrait provenir du caractère non écologique de la tâche. Quoiqu'il en soit, une étude ultérieure incluant un panel de patients MP plus hétérogène (et donc plus ressemblant à la population globale des patients parkinsoniens), avec des profils cognitifs différents par exemple, permettrait de valider ou non nos observations. Nous saurions ainsi avec plus de certitude si le déclin cognitif dû à la progression de la MP et le FdM, dont l'incidence augmente avec l'évolution de la maladie, se développent de manière indépendante en parallèle ou s'ils interagissent l'un avec l'autre (Morris et al., 2020).

### **2.3. Substrats corticaux lors de l'ANT versus l'ANT-INIT**

Finalement, en ce qui concerne les substrats corticaux sous-tendant l'initiation du pas sous une charge attentionnelle, ils étaient similaires à ceux trouvés lors d'une tâche d'attention visuo-spatiale avec réponse par appui manuel (autrement dit, lors de l'ANT standard). En effet, dans le cadre d'une analyse complémentaire réalisée au cours de la thèse de doctorat, une étude de localisation des sources des PSLE liées à la cible lors de l'ANT standard assis a été effectuée. Au cours de l'ANT-INIT et de l'ANT standard, l'activation de régions corticales identiques a été mise en évidence : une ERS thêta frontale mésiale et temporale, une ERD alpha au niveau du cortex pariéto-occipital et une ERD bêta au niveau du cortex sensorimoteur (un peu plus latéralisée dans le cas des mouvements manuels). Cela permet de montrer que des substrats sous-corticaux sont également impliqués dans le déclenchement de la marche, comme précédemment démontré (cf. Section *Initiation de la marche – Substrats neuronaux* du Chapitre 1).

## **3. Limites**

Dans le cadre de l'étude n°2 qui a permis de valider le paradigme ANT-INIT auprès de sujets jeunes et sains, mais également dans le cadre des études ultérieures réalisant une étude EEG durant ce même paradigme, la principale limite s'est située au niveau du nombre réduit d'essais pour certaines conditions d'indice combiné au nombre peu élevé de participants, ce qui a pu affaiblir la fiabilité des résultats. Dans tous les cas, pour y remédier, pour chaque sujet, les potentiels évoqués d'intérêt ont clairement été observés. L'effet de l'orientation (indice spatial valide – indice central) n'a pas pu être

mis en évidence, que ce soit sur les TR durant notre version de l'ANT standard ou sur le TEP dans le cadre de l'ANT-INIT. Une étude annexe (dont les résultats ne sont pas montrés ici) nous ont permis de comprendre que notre version de l'ANT, comparée à la version classique de Fan et al. (Fan et al., 2002), permettait moins de mettre en évidence les processus attentionnels dirigés vers un stimulus qui composent également la composante attentionnelle qu'est l'orientation. Avec nos indices spatiaux positionnés centralement à gauche ou à droites, nous évaluons plutôt l'orientation endogène.

Pour **l'étude n°3**, les principales limites identifiées étaient, d'une part, les différences entre patients MP en termes de durée d'évolution de la maladie et, d'autre part, le temps d'intervalle court avant l'initiation de la marche, qui ne permettait pas d'investiguer la position du CdP pendant une posture de repos très étendue.

Pour **l'étude n°4**, les différences entre patients MP en termes de genre (significative) et sévérité des symptômes moteurs (tendance) représentaient une limite à leur comparaison objective sur le seul critère du FdM. L'appariement en termes de performance cognitive globale est aussi sujet à débat, car cela n'est pas le reflet de la réalité : le FdM apparaît relativement tard dans l'évolution de la maladie et donc, les fonctions cognitives observées chez les freezers sont, sans émettre de supposition quant à son lien avec le FdM, tout naturellement globalement empirées chez ces patients. L'évaluation en état « ON » peut également être remise en cause dans le cadre de l'analyse des mécanismes neurophysiologiques sous-tendant l'interaction attention-motricité chez les MP+FdM, mais était nécessaire pour la réalisation de la tâche. La tâche ANT-INIT n'est, de surcroît, pas une tâche écologique, ce qui peut en partie expliquer nos résultats allant à l'encontre de nos hypothèses. Finalement, l'absence de différence significative entre freezers et non freezers, dans le contexte de l'investigation de l'interaction attention-initiation de la marche, mais aussi concernant l'exploration de la connectivité fonctionnelle EEG au repos et durant la réalisation de l'ANT standard, remet en question la dichotomie entre freezers et non freezers, pour l'utilisation d'un spectre continu démarrant avec un FdM absent jusqu'à un FdM sévère, qui serait davantage proche de la réalité (Nutt et al., 2011).

En lien avec **l'étude n°5** réalisée à l'état de repos, certaines limites avaient aussi été évoquées, notamment :

- Le protocole d'évaluation d'un état de repos avec yeux ouverts, qui a pu avoir un impact sur l'analyse spectrale (Bosboom et al., 2006) et rendait la comparaison plus difficile avec des études précédentes (*ndlr.* réalisées souvent avec yeux fermés).
- L'utilisation d'une procédure à l'état de repos, où il est matériellement impossible de contrôler l'activité cérébrale des sujets et, dès lors, le repos du sujet sensé ne penser à rien en particulier.
- L'utilisation de la méthode PLV pour estimer la connectivité fonctionnelle, alors qu'elle est considérée comme sensible à la conduction volumique.
- La possibilité et l'intérêt à enregistrer l'activité cérébrale à l'état de repos des patients en médication « OFF ».

D'autres limitations identifiées dans le cadre de l'**étude n°6** peuvent être synthétisées comme suit :

- La connectivité fonctionnelle a été mesurée en état de médication « ON » chez les patients MP. La lévodopa peut induire un changement dans la connectivité et une réversibilité partielle des anomalies de connectivité à l'état de repos a été observée (Schneider and Alcalay, 2020). Il est important de mentionner que les réseaux décrits ne sont pas des anomalies physiologiques dans le sens strict du terme, mais des anomalies restent malgré la lévodopa. Certains changements pathologiques ont donc pu être sous-estimés. Cependant, l'ANT nécessitait une réponse motrice et ne pouvait donc être réalisé dans l'état « OFF », pour certains patients. Les patients MP étaient dès lors appariés suivant leur dose équivalente quotidienne de lévodopa afin de minimiser le biais.
- L'EEG offre une faible résolution spatiale et même en utilisant une étape de localisation de sources, quelques imprécisions persistent sur la localisation des nœuds. C'est la raison pour laquelle seules les sources corticales étaient étudiées, étant donné que la résolution spatiale EEG pour les sources corticales est nettement meilleure que pour les sources sous-corticales.

## 4. Perspectives

Sur les questions de posture à l'état de repos précédant la marche, les résultats de l'**étude n°3** font ressortir le fait que les MP+FdM pourraient bénéficier d'un entraînement ciblé sur la posture initiale avant le processus d'initiation de la marche avec, pour conséquence, un potentiel effet sur les performances de l'initiation motrice (phases de préparation et exécution). Une étude intermédiaire sur une cohorte avec un meilleur appariement des caractéristiques des populations MP+FdM et MP-

FdM et avec un plus grand nombre d'essais d'initiation de marche auto-commandée permettrait la généralisation de ces résultats.

Dans le cadre de **l'étude n°4** mettant en avant un déficit du contrôle exécutif chez les MP+FdM, mais sans impact spécifique sur l'initiation du pas, il serait intéressant de poursuivre cette analyse via le paradigme de l'ANT-INIT en incluant un échantillon de patients freezers un peu plus proche de la population globale, c'est-à-dire en y incluant des profils MCI et éventuellement déments. Cela nous permettrait de comprendre mieux les liens entre FdM, attention, initiation de la marche et cognition globale. Cette étude est en cours de réalisation.

**L'étude n°5** identifie les perspectives suivantes :

- A l'avenir, une étape supplémentaire serait de réaliser une étude longitudinale avec des enregistrements EEG périodiques de l'activité cérébrale à l'état de repos. Nous serons donc à même de valider ou non notre hypothèse suivante : les analyses spectrale et de la connectivité fonctionnelle pourraient prédire respectivement le déclin cognitif et la détérioration des épisodes du FdM chez les patients MP+FdM.
- En conséquence, les relations causales pourraient être plus claires, amenant à des modèles pathophysiologiques du FdM améliorés, avec de nouveaux biomarqueurs ou de nouvelles cibles spécifiques pour le traitement.

Pour **l'étude n°6**, les perspectives sont les suivantes : nécessité de combiner la rééducation motrice avec rééducation sensorimotrice et cognitive chez les patients MP+FdM.

Globalement, même si certains points nécessitent d'être éclaircis via des analyses ultérieures exploratoires, l'interaction entre attention et initiation de la marche a clairement pu être mise en évidence tout au long de cette thèse et ce, via notre paradigme de l'ANT-INIT. Une perspective est donc tout naturellement de poursuivre avec des essais thérapeutiques qui visent à moduler les capacités cognitives via la combinaison d'un traitement par MPH et d'un entraînement cognitif structuré, pour directement améliorer les fonctions cognitives globales (dont l'attention) et indirectement les performances motrices. Pour ce faire, comme mentionné, un essai thérapeutique est en cours de réalisation chez les sujets âgés sains (PACTE-I) et devrait être décliné à l'avenir dans des populations avec pathologie neurodégénérative (MP, MP+FdM, etc).





# **Chapitre 5.**

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# **Chapitre 6.**

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## **Annexe 2 – Matériel supplémentaire lié aux études**

### **Etude 1.2 – Supplementary material**

Can Dual Task Paradigms Predict Falls Better than Single Task? – A Systematic Literature Review

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Article accepté dans *Neurophysiologie Clinique Clinical / Neurophysiology*.



## Supplementary Material

### A. Search Strategies Among the Different Databases

Table A.1 Search strategies (keywords and filters) related to the different databases used. In bold: MeSH Terms; \* for terms with end-truncation; TS = topic; TITLE-ABS-KEY = document title-abstract-keyword.

Database	Keywords & filters - <i>Gait</i>	Keywords & filters - <i>Gait initiation</i>	Keywords & filters - <i>Posture</i>	Keywords & filters - <i>Turning</i>
Pubmed/Cochrane CENTRAL	(locomotion OR walking OR gait) AND (accidental falls OR faller) AND (aged OR aging) AND (dual task* OR dual-task* OR cognition OR attention), Filters: English, Humans, from 2013 - 2020	(gait initiation OR step initiation) AND (accidental falls OR faller) AND (aged OR aging) AND (dual task* OR dual-task* OR cognition OR attention), Filters: English, Humans, from 2013 - 2020	(posture OR postural balance OR standing position) AND (accidental falls OR faller) AND (aged OR aging) AND (dual task* OR dual-task* OR cognition OR attention), Filters: English, Humans, from 2013 - 2020	(turns) AND (accidental falls OR faller) AND (aged OR aging) AND (dual task* OR dual-task* OR cognition OR attention), Filters: English, Humans, from 2013 - 2020
Scopus	(TITLE-ABS-KEY("accidental falls") OR TITLE-ABS-KEY("faller")) AND ( TITLE-ABS-KEY("aged") OR TITLE-ABS-KEY("aging")) AND ( TITLE-ABS-KEY("cognition") OR TITLE-ABS-KEY("attention") OR TITLE-ABS-KEY("dual task*") OR TITLE-ABS-KEY("dual-task*")) AND ( TITLE-ABS-KEY("locomotion") OR TITLE-ABS-KEY("walking") OR TITLE-ABS-KEY("gait")) AND NOT (TITLE-ABS-KEY("Parkinson") OR TITLE-ABS-KEY("Alzheimer") OR TITLE-ABS-KEY("stroke") OR TITLE-ABS-KEY("multiple sclerosis") OR TITLE-ABS-KEY("diabet*") OR TITLE-ABS-KEY("training")) AND ( LIMIT-TO ( SRCTYPE,"j" ) ) AND ( LIMIT-TO ( DOCTYPE,"ar" ) ) AND ( LIMIT-TO ( SUBJAREA,"MEDI" ) OR LIMIT-TO ( SUBJAREA,"HEAL" ) OR LIMIT-TO ( SUBJAREA,"NEUR" ) OR LIMIT-TO ( SUBJAREA,"MULT" ) ) AND ( LIMIT-TO ( PUBYEAR,2020) OR LIMIT-TO ( PUBYEAR,2019) OR LIMIT-TO ( PUBYEAR,2018) OR LIMIT-TO ( PUBYEAR,2017) OR LIMIT-TO ( PUBYEAR,2016) OR LIMIT-TO ( PUBYEAR,2015) OR LIMIT-TO ( PUBYEAR,2014) OR LIMIT-TO ( PUBYEAR,2013) ) AND ( LIMIT-TO ( LANGUAGE,"English" ) )	(TITLE-ABS-KEY("accidental falls") OR TITLE-ABS-KEY("faller")) AND ( TITLE-ABS-KEY("aged") OR TITLE-ABS-KEY("aging")) AND ( TITLE-ABS-KEY("cognition") OR TITLE-ABS-KEY("attention") OR TITLE-ABS-KEY("dual task*") OR TITLE-ABS-KEY("dual-task*")) AND ( TITLE-ABS-KEY("gait initiation") OR TITLE-ABS-KEY("step initiation")) AND NOT (TITLE-ABS-KEY("Parkinson") OR TITLE-ABS-KEY("Alzheimer") OR TITLE-ABS-KEY("stroke") OR TITLE-ABS-KEY("multiple sclerosis") OR TITLE-ABS-KEY("diabet*") OR TITLE-ABS-KEY("training")) AND ( LIMIT-TO ( SRCTYPE,"j" ) ) AND ( LIMIT-TO ( DOCTYPE,"ar" ) ) AND ( LIMIT-TO ( SUBJAREA,"MEDI" ) OR LIMIT-TO ( SUBJAREA,"HEAL" ) OR LIMIT-TO ( SUBJAREA,"NEUR" ) OR LIMIT-TO ( SUBJAREA,"MULT" ) ) AND ( LIMIT-TO ( PUBYEAR,2020) OR LIMIT-TO ( PUBYEAR,2019) OR LIMIT-TO ( PUBYEAR,2018) OR LIMIT-TO ( PUBYEAR,2017) OR LIMIT-TO ( PUBYEAR,2016) OR LIMIT-TO ( PUBYEAR,2015) OR LIMIT-TO ( PUBYEAR,2014) OR LIMIT-TO ( PUBYEAR,2013) ) AND ( LIMIT-TO ( LANGUAGE,"English" ) )	( TITLE-ABS-KEY ( "accidental falls" ) OR TITLE-ABS-KEY ( "faller" ) ) AND ( TITLE-ABS-KEY ( "aged" ) OR TITLE-ABS-KEY ( "aging" ) ) AND ( TITLE-ABS-KEY ( "cognition" ) OR TITLE-ABS-KEY ( "attention" ) OR TITLE-ABS-KEY ( "dual task*" ) OR TITLE-ABS-KEY ( "dual-task*" ) ) AND ( TITLE-ABS-KEY ( "posture" ) OR TITLE-ABS-KEY ( "postural balance" ) OR TITLE-ABS-KEY("standing position")) AND NOT ( TITLE-ABS-KEY ( "Parkinson" ) OR TITLE-ABS-KEY ( "Alzheimer" ) OR TITLE-ABS-KEY ( "stroke" ) OR TITLE-ABS-KEY ( "multiple sclerosis" ) OR TITLE-ABS-KEY ( "diabet*" ) OR TITLE-ABS-KEY ( "training" ) ) AND ( LIMIT-TO ( SRCTYPE,"j" ) ) AND ( LIMIT-TO ( DOCTYPE,"ar" ) ) AND ( LIMIT-TO ( SUBJAREA,"MEDI" ) OR LIMIT-TO ( SUBJAREA,"HEAL" ) OR LIMIT-TO ( SUBJAREA,"NEUR" ) OR LIMIT-TO ( SUBJAREA,"MULT" ) ) AND ( LIMIT-TO ( PUBYEAR,2020) OR LIMIT-TO ( PUBYEAR,2019) OR LIMIT-TO ( PUBYEAR,2018) OR LIMIT-TO ( PUBYEAR,2017) OR LIMIT-TO ( PUBYEAR,2016) OR LIMIT-TO ( PUBYEAR,2015) OR LIMIT-TO ( PUBYEAR,2014) OR LIMIT-TO ( PUBYEAR,2013) ) AND ( LIMIT-TO ( LANGUAGE,"English" ) )	( TITLE-ABS-KEY ( "accidental falls" ) OR TITLE-ABS-KEY ( "faller" ) ) AND ( TITLE-ABS-KEY ( "aged" ) OR TITLE-ABS-KEY ( "aging" ) ) AND ( TITLE-ABS-KEY ( "cognition" ) OR TITLE-ABS-KEY ( "attention" ) OR TITLE-ABS-KEY ( "dual task*" ) OR TITLE-ABS-KEY ( "dual-task*" ) ) AND ( TITLE-ABS-KEY ( "turns") ) AND NOT ( TITLE-ABS-KEY ( "Parkinson" ) OR TITLE-ABS-KEY ( "Alzheimer" ) OR TITLE-ABS-KEY ( "stroke" ) OR TITLE-ABS-KEY ( "multiple sclerosis" ) OR TITLE-ABS-KEY ( "diabet*" ) OR TITLE-ABS-KEY ( "training" ) ) AND ( LIMIT-TO ( SRCTYPE,"j" ) ) AND ( LIMIT-TO ( DOCTYPE,"ar" ) ) AND ( LIMIT-TO ( SUBJAREA,"MEDI" ) OR LIMIT-TO ( SUBJAREA,"HEAL" ) OR LIMIT-TO ( SUBJAREA,"NEUR" ) OR LIMIT-TO ( SUBJAREA,"MULT" ) ) AND ( LIMIT-TO ( PUBYEAR,2020) OR LIMIT-TO ( PUBYEAR,2019) OR LIMIT-TO ( PUBYEAR,2018) OR LIMIT-TO ( PUBYEAR,2017) OR LIMIT-TO ( PUBYEAR,2016) OR LIMIT-TO ( PUBYEAR,2015) OR LIMIT-TO ( PUBYEAR,2014) OR LIMIT-TO ( PUBYEAR,2013) ) AND ( LIMIT-TO ( LANGUAGE,"English" ) )
Web of Science	TS=(gait OR walking OR locomotion) AND	TS=(gait initiation OR step initiation) AND	TS=(posture OR postural balance OR	TS=(turns) AND TS=(accidental falls OR

	TS=(accidental falls OR faller) AND TS=(aged OR aging) AND TS=(dual-task* OR dual task* OR cognition OR attention) AND LANGUAGE: (English) - <i>Indexes=SCI-EXPANDED, CPCI-S, BKCI-S, ESCI</i> <i>Timespan=2013-2020</i>	TS=(accidental falls OR faller) AND TS=(aged OR aging) AND TS=(dual-task* OR dual task* OR cognition OR attention) AND LANGUAGE: (English) - <i>Indexes=SCI-EXPANDED, CPCI-S, BKCI-S, ESCI</i> <i>Timespan=2013-2020</i>	standing position) AND TS=(accidental falls OR faller) AND TS=(aged OR aging) AND TS=(dual-task* OR dual task* OR cognition OR attention) AND LANGUAGE: (English) - <i>Indexes=SCI-EXPANDED, CPCI-S, BKCI-S, ESCI</i> <i>Timespan=2013-2020</i>	faller) AND TS=(aged OR aging) AND TS=(dual-task* OR dual task* OR cognition OR attention) AND LANGUAGE: (English) - <i>Indexes=SCI-EXPANDED, CPCI-S, BKCI-S, ESCI</i> <i>Timespan=2013-2020</i>
<b>Google Scholar</b>	Anywhere in the article, with all of the words: (locomotion walking gait) (accidental falls faller) (aged aging) (cognition attention dual task dual-task) and without the words: -training; articles in English and dated between 2013 and 2020	Anywhere in the article, with all of the words: (gait initiation step initiation) (accidental falls faller) (aged aging) (cognition attention dual task dual-task) and without the words: -training; articles in English and dated between 2013 and 2020	Anywhere in the article, with all of the words: (posture postural balance standing position) (accidental falls faller) (aged aging) (cognition attention dual task dual-task) and without the words: -training; articles in English and dated between 2013 and 2020	Anywhere in the article, with all of the words: (turns) (accidental falls faller) (aged aging) (cognition attention dual task dual-task) and without the words: -training; articles in English and dated between 2013 and 2020

## B. Detailed Table of Systematic Reviews

Table B.1 Systematic reviews that have assessed in the last 12 years the power of dual-task walking in predicting risk of falls in healthy older adults.

Authors	Description of the systematic review	Electronic databases & Search terms used for literature search	Inclusion and exclusion criteria	Involved population	Motor & Concurrent cognitive tasks	(1) Is DT performance/DT-related change predictor (or discriminator) of falling? (2) Is the DT-related predictive strength superior compared to the ST-related one? (Yes/No/Inconclusive/Not addressed)
Zijlstra et al., 2008 [80]	<p>7 prospective and 9 retrospective data collection of falls; Retrospective study periods: from 6 to 12 months, prospective follow-up periods: from 3 to 12 months.</p> <p>Studies in common with the other reviews: 6 ([12,36,43,62,71,72]) with [9], 5 ([12,43,63,64,72]) with [35], 4 ([12,43,62,72]) with [17], 2 ([64,72]) with [49], 1 ([12]) with [53], 2 ([12,64]) with [75].</p>	<p><u>Search terms:</u> (MeSH key terms are the bold ones): (1) (gait OR walking OR locomotion OR musculoskeletal equilibrium OR posture) (2) #1 AND (aged OR aged, 80 and over OR aging) (3) (cognition OR attention OR cognitive task(s) OR attention task(s) OR DT(s) OR double task paradigm OR second task(s) OR secondary task(s)) (4) #2 AND #3 (5) #4 AND humans</p> <p><u>Databases:</u> PubMed, EMBASE, CINALHL, AMED, PsycINFO and Cochrane</p>	<p><u>Inclusion criteria:</u> (1) population: older adults (mean age ≥ 65 years); (2) assessment tool: DT combining gait or other balance task with a cognitive task; (3) design: prospective or retrospective data collection of falls; (4) papers focusing on measures of the ability to predict future falls or to discriminate between fallers and non-fallers for both tasks during DT performance as well as for the single balance and cognitive task; (5) classification of fallers and non-fallers based on actual fall events.</p> <p><u>Exclusion criteria:</u> Individual abstracts, review articles, studies evaluating sitting balance performance, case studies, letters to the editor and studies with subjective scoring system for the assessment of DT performance.</p> <p><i>Dates of publication: up to 2006</i></p>	<p>Only 6 retrospective studies and 2 prospective studies include from 30 to 380 healthy older people (mean age ≥ 65 years) without a specific pathology or medical condition.</p>	<p><u>Motor task:</u> Straight walking, quiet stance with different surface and sensory conditions, walking tasks including transfers and turns (e.g., TUG). <u>Measures:</u> postural sway, speed, gait measures. <u>Cognitive task:</u> - <b>Verbal fluency tasks:</b> sentence completion, animals or professions naming; - <b>Discrimination and decision-making tasks:</b> Judgment of Line Orientation, phoneme monitoring, Stroop's colored words test, auditory choice reaction time task; - <b>Mental tracking/working memory tasks:</b> backward counting, serial subtractions/additions, remembering a shopping list, listening to a text and answering multiple-choices questions; - <b>Reaction time task:</b> simple auditory reaction time. <u>Measures:</u> speed and accuracy.</p>	<p><b>(1) Yes &amp; (2) Inconclusive:</b> In most cases, specificity and predictive values of the DT were moderate or high whereas sensitivity was low. Moreover, while one retrospective [19] and one prospective [4] study reported similar odds ratios for DT compared to ST and an additional retrospective study [62] showed that ST and DT have similar value for discriminating between fallers and non-fallers, two other prospective studies [11,72] suggested an added value of DT conditions over ST regarding prediction of falls. However, any conclusion could not be made because of incomplete comparisons of single and dual walking/balance tasks, and due to the global heterogeneity of the studies.</p>

<p>Beauchet et al., 2009 [9]</p>	<p>Systematic review including 15 studies: 3 retrospective studies and 12 prospective ones;</p> <p>Retrospective study periods: from 6 to 12 months, prospective follow-up periods: from 50 days to 12 months.</p> <p>Studies in common with the other reviews: 6 ([12,36,43,62,71,72]) with [80], 8 ([7,8,10,12,21,40,43,72]) with [35], 12 ([7,8,10,12,21,40,43-45,62,65,72]) with [17], 4 ([7,8,40,72]) with [49], 4 ([7,8,10,12]) with [53], 2 ([8,12]) with [75].</p>	<p><b>Search terms:</b></p> <p>MeSH terms: “accidental fall” and “aged” or “aged, 80 and over” combined with the terms “DT”, “dual tasking”, “gait”, “walking”, “fall” and “falling”</p> <p><b>Databases:</b></p> <p>English and French Medline and Cochrane library</p>	<p><b>Inclusion criteria:</b> observational studies, retrospective or prospective data collection of falls, number of falls and motor performance under ST and DT as outcomes measures, subjects with mean age of 65 and older, and provided enrolment methods, exact procedures of dual tasking and discriminative or predictive values of falls.</p> <p><i>Dates of publication: from March 1997 to April 2008</i></p>	<p>From 30 to 380 subjects per study;</p> <p>Older adults and frail older adults with mean age of 65 and older.</p> <p><b>Note:</b> In some studies, some subjects exhibit cognitive impairment, dementia, stroke or previous stroke, lower limb neuropathy, depression, or pain in lower limb.</p>	<p><b>Motor task:</b></p> <p>Various DT conditions with <b>walking</b> as main task, some walking tasks including transfers and <b>turns</b> (e.g., TUG).</p> <p><b>Measures:</b> walking time, stop walking, coefficient of variation of stride time variability, walking speed.</p> <p><b>Concurrent task:</b></p> <ul style="list-style-type: none"> <li>- <b>Mental tracking/working memory tasks:</b> backward counting, reciting alternate letters from the alphabet, simple calculations;</li> <li>- <b>Verbal fluency tasks:</b> conversation, recitation of names of animals and professions, or alphabet;</li> <li>- <b>Discrimination and decision-making tasks:</b> visuospatial decision task;</li> <li>- <b>Motor tasks:</b> carrying a glass of water.</li> </ul> <p><b>Measures:</b> increase backward counting performance.</p>	<p><b>(1) Yet &amp; (2) Not addressed:</b></p> <p>Despite few conflicting reports probably because of limited sample sizes, study samples heterogeneity, too short follow-up periods or lack of standardization in DT paradigms and outcomes measures, most involved studies (and the pooled odds ratio) showed that DT-related changes are significantly associated with an increased risk of falling in older adults.</p>
<p>Hsu et al., 2012 [35]</p>	<p>Systematic review including 25 studies, with 16 DT studies: 7 prospective studies and 9 cross-sectional ones;</p> <p>Prospective follow-up periods: from 6 months to 2 years.</p> <p>Studies in common with the other reviews: 5 ([12,43,63,64,72]) with [80], 8 ([7,8,10,12,21,40,43,72]) with [9], 9 ([7,8,10,12,21,29,40,43,72]) with [17], 7 [7,8,29,40,42,64,72]) with</p>	<p><b>Search terms:</b></p> <p>Search and MeSH terms: cognition, executive functions, DT, and falls</p> <p><b>Databases:</b></p> <p>MEDLINE, Pubmed, and EMBASE</p>	<p><b>Exclusion criteria:</b></p> <p>studies that did not examine specific cognitive processes (e.g., only measured global cognitive function), intervention studies that focused on improving cognitive function or reducing falls, protocol studies, studies that did not include falls or falls risk, any case report or case series studies, and samples which included those with significant neurodegenerative disease (e.g., Alzheimer’s disease).</p> <p><i>Dates of publication: from 1948</i></p>	<p>From 27 to 380 subjects per DT study;</p> <p>Adults aged 60 years or older from community-dwelling, senior housing facility, residential care, and geriatric rehabilitation hospital.</p> <p><b>Note:</b> In some studies, some subjects exhibit mild/moderate cognitive</p>	<p><b>Motor task:</b></p> <p>Physical performance task, such as <b>walking</b> (including sometimes transfers and <b>turns</b>), <b>maintaining stability</b> under various conditions, or lower limb maximal strength test.</p> <p><b>Measures:</b> walking speed, mean walking time, swing time average, gait variability, stride time variability, swing time variability, postural recovery, postural stability, maximal isometric leg strength.</p> <p><b>Cognitive task:</b></p> <ul style="list-style-type: none"> <li>- <b>Mental tracking/working</b></li> </ul>	<p><b>(1) Yes &amp; (2) Inconclusive:</b></p> <p>Most studies found a strong association between DT performance on the one hand, and falls or falls risk on the other hand. However, over 16 DT studies, one study [10] found a positive association between better DT performance and falls, whereas another study [7] did not find any predictive power of DT performance regarding falls (based on a multiple logistic regression model) unlike ST performance, and a third study [12] observed a similar predictive strength for DT performance as for ST performance.</p>

	[49], 5 ([7,8,10,12,29]) with [53], 3 ([8,12,64]) with [75].		to May 3, 2011	impairment, dementia, stroke or previous stroke, lower limb neuropathy, depression, or pain in lower limb.	<b>memory tasks:</b> counting backwards, serial subtraction, reciting alternate letters of the alphabet, simple and complex calculations; <b>-Verbal fluency tasks:</b> conversation, sentence completion, recitation of names of animals and professions, or alphabet; <b>- Discrimination and decision- making tasks:</b> auditory choice reaction time task, visuospatial decision task, perceptual matching/judgment of line orientation, listen to a text and phoneme monitoring; <b>- Reaction time task:</b> reaction time on push-button task. <u>Measures:</u> auditory choice reaction time, accuracy in backward counting, number of correct calculations.	
Chu et al., 2013 [17]	Systematic review including 2 retrospective studies and 13 articles using a prospective design; Retrospective study periods: from 6 to 12 months, prospective follow-up periods: from 29.6 ± 25.9 days to 2 years.  Studies in common with the other reviews: 4 ([12,43,62,72]) with [80], 12 ([7,8,10,12,21,40,43– 45,62,65,72]) with [9], 9 ([7,8,10,12,21,29,40,43,72]) with [35], 7 ([7,8,29,40,54,72,77]) with	<b>Search terms:</b> (MeSH key terms are the bold ones): <b>(aged OR aged 80 and over OR elderly OR frail elderly) and (gait[s] OR walking OR ambulation OR locomotion) and (accidental fall[s] OR fall[s]) and (attention OR cognition OR DT[s] OR attention task[s] OR cognitive task[s] OR secondary task[s] OR double task paradigm)</b>  <b>Databases:</b> Medline, PubMed, CINAHL, Cochrane Central Register of Controlled Trials and	<b>Inclusion criteria:</b> DT paradigm used to discriminate fallers and non- fallers or to predict falls; ground walking as the postural task of the DT paradigm; and mean age of 60 years or older for the sample.  <b>Exclusion criteria:</b> dissertation theses, review articles or conference abstracts; articles that focused on a single population with a specific diagnosis, such as stroke or arthritis; intervention studies; and articles that did not report discriminative or predictive values of falls.  <i>Dates of publication: up to May 2011</i>	From 30 to 380 subjects per DT study;  Adults aged 60 years or older from senior housing facilities, inpatients, and community- dwelling elderly.  <b>Note:</b> In some studies, some subjects exhibit cognitive impairment, dementia, stroke or previous stroke, lower limb neuropathy, depression, or pain in lower limb.	<b>Motor task:</b> Straight walking tasks, turn walking and TUG.  <u>Measures:</u> walking time, walking speed, coefficient of strike time variation, swing time variability, mean step width, number of stop walking.  <b>Concurrent task:</b> <b>- Mental tracking/working memory tasks:</b> counting backwards, serial subtraction, reciting alternate letters of the alphabet, simple calculations; <b>- Verbal fluency tasks:</b> conversation, recitation of names of animals and professions, or alphabet; <b>- Discrimination and decision- making task:</b> visuospatial decision	<b>(1) Yes &amp; (2) Not addressed:</b>  Contrary to verbal fluency tasks and manual tasks, mental tracking tasks were the only type of concurrent tasks related to a significant odds ratio, thus to a significant predictive strength for falls.  Besides, the complexity of a specific concurrent task needs to be appropriately chosen for the studied population in order to obtain similar odds ratio independently from the subjects.  Finally, the biggest limitation of the review is the substantial heterogeneity between studies.



	[49], 7 [[7,8,10,12,29,54,77]] with [53], 3 [[8,12,54]] with [75].	PsycINFO			task; - <b>Reaction time task:</b> reaction time on push-button task; - <b>Motor tasks:</b> carrying a glass of water/coffee cup and saucer/tray with a ball. <u>Measures:</u> reaction time, accuracy, speed.	
Menant et al., 2014 [49]	Systematic review and meta-analysis; 30 articles (11 prospective studies and 19 retrospective studies) and 33 samples; Follow-up periods: from 4 to 24 months.  Studies in common with the other reviews: 2 [[64,72]] with [80], 4 [[7,8,40,72]] with [9], 7 [[7,8,29,40,42,64,72]] with [35], 7 [[7,8,29,40,54,72,77]] with [17],  5 [[7,8,29,54,77]] with [53], 8 [[6,8,20,54,57,58,64,78]] with [75].	<u>Search terms:</u> (MeSH key terms are the bold ones): 1. <b>gait</b> OR <b>walking</b> OR locomotion 2. falls OR <b>accidental falls</b> OR falling OR faller 3. <b>aged</b> OR <b>aged, 80 and over</b> OR aging OR ageing 4. DT* OR D-T* OR cognition OR attention 5. #1 AND #2 AND #3 AND #4 <u>Databases:</u> PubMed, Ovid MEDLINE, EMBASE, PsycINFO, CINAHL, Scopus and Cochrane Central Register of Controlled Trials	<u>Inclusion criteria:</u> studies which evaluated gait at self-selected speed under ST and DT conditions in older people to either: (1) predict falls, or (2) discriminate between fallers and non-fallers based on retrospective data collection. <u>Exclusion criteria:</u> exclusion if: (1) individual abstracts, case studies or reviews; (2) focus on patient groups (e.g., PD, stroke, etc.) other than cognitive impairment; (3) participants' mean age less than 65 years or all participants younger than 60 years old; (4) the walking task not involving time or gait speed as an outcome; (5) not a cognitive task as the secondary task; (6) subjective scoring systems to assess DT performance; (7) publications in languages other than Dutch, English, French or German. <i>Dates of publication: from 2008 to February 2013</i>	From 11 to 1308 participants per sample; Mean age ≥ 65 years or participants older than 60 years; Community-dwellers, outpatients from a geriatrics department, participants from senior housing facilities or intermediate care hostels, and geriatrics and Alzheimer's care unit inpatients; 12 studies with a small percentage or all of the subjects having cognitive impairments; 16 studies with slow walkers (< 1 m/s).	<u>Motor task:</u> Straight line <b>walking</b> including sometimes a <b>turn</b> . <u>Measures:</u> walking speed. <u>Cognitive task:</u> Each study comprised one, two or more types of secondary cognitive tasks: mainly <b>mental tracking/working memory tasks</b> (counting backwards, reciting alternate letters from the alphabet, serial subtraction, addition/subtraction) and <b>verbal fluency tasks</b> (enumeration of animal names, enumeration of words starting with a specific letter) and, to a lesser extent, <b>discrimination and decision-making tasks</b> (auditory Stroop task, listening to a randomized audio sequence for "X" and repeating the letter aloud).	<u>(1) Yes &amp; (2) No*:</u> Gait speed did not have a significantly better predictive value for falls in a DT compared to a ST paradigm, but both paradigms were equivalent in discriminating fallers from non-fallers based on gait speed assessments.  Moreover, the latter results stayed invariant when only prospective falls studies/ subgroups of people with fast gait speed, slow gait speed or with cognitive impairment/ a specific type of concurrent task (mental tracking tasks vs. verbal fluency tasks)/ studies with straight line walking were taken into account.  *This answer needs to be taken into account with caution. Indeed, due to a majority of retrospective designs for the reporting of fall history and the analysis of mean difference (an appropriate statistical measure for discriminative ability), it is rather the discriminative power of DT performance (compared to the one of ST) that has been assessed, instead of its predictive value.
Muir-Hunter and Wittwer, 2016 [53]	10 articles with prospective cohort studies that lasted at least 1 year and were based on 7 independent samples.	<u>Search terms:</u> MeSH subject terms and keywords: "accidental falls, falling, prospective studies,	<u>Inclusion criteria:</u> (1) sample participants aged ≥ 60 years; (2) prospective cohort design with a duration of at least 1 year; (3) samples	From 100 (with 98% of subjects available for assessment at the end of the study) to	<u>Motor task:</u> Main tasks included <b>walking</b> (combining sometimes transfers and <b>turns</b> ), <b>quiet stance</b> and <b>stepping reaction responses</b> in	<u>(1) Yes &amp; (2) Inconclusive:</u> Although most studies reported DT performance related to falls, 3 of them [8,29,51] showed a stronger association between DT performance and future fall risk

	<p>Studies in common with the other reviews:  1 ([12]) with [80],  4 ([7,8,10,12]) with [9],  5 ([7,8,10,12,29]) with [35],  7 ([7,8,10,12,29,54,77]) with [17],  5 ([7,8,29,54,77]) with [49],  4 ([8,12,51,54]) with [75].</p>	<p>aged, aged80 and over, elderly, aging, gait, postural balance, DT, cognition and attention"  <b>Databases:</b>  MEDLINE, Pubmed and EMBASE</p>	<p>comprised community-dwelling individuals alone; (4) "falls" as the primary study outcome, including "any fall", "recurrent falls" and "injurious falls", and the association between the DT test and future fall risk evaluated in statistical analysis; (5) DT assessment detailed explicitly in the methods section ; (6) reported inclusion and exclusion criteria and demographic information; and (7) confounding factors reported and used in multi-variable regression analysis to generate adjusted risk estimates.   <i>Dates of publication: from January 1998 to September 2013</i></p>	<p>1038 participants included in each study;  Community-dwelling participants aged ≥ 60 years.</p>	<p>standing.  <b>Measures:</b> number of steps, number of complete stops, mean velocity, mean and variability of walking time, swing time, step length, step width and double support time, amplitude and time of COP during step initiation, amplitude of COP during quiet stance.  <b>Concurrent task:</b>  - <b>Mental tracking/working memory tasks:</b> counting backwards, serial subtraction;  - <b>Verbal fluency tasks:</b> recitation of names of animals or professions;  - <b>Discrimination and decision-making task:</b> Stroop test;  - <b>Motor tasks:</b> carrying a cup and saucer/tray/tray with a cup and saucer/tray with a ball.  <b>Measures:</b> accuracy, speed (e.g., number of names per minute, number of enumerated figures).</p>	<p>than with ST, while 2 additional studies [12,48] did not find any added predictive value for falls in a DT compared to a ST paradigm and 2 others [7,66] even assigned a better predictive power to ST performance. All the studies in favor of the superiority of the DT included a straight (or up and down a hall) walking task. The ones that rather highlighted the use of ST for fall prediction involved respectively a straight walking task, a fast walking and returning task, measures of maximal postural sway during quiet standing under DT conditions and the assessment of stepping reaction responses in standing during a DT situation.</p>
<p>Wollesen et al., 2019 [75]</p>	<p>Systematic review and meta-analysis including 15 and 11 studies respectively, 6 of the 15 studies presenting a prospective design;  Retrospective study periods: from 1 to 24 months, prospective follow-up periods: from 12 to 66 months.   Studies in common with the other reviews:  2 ([12,64]) with [80]  2 ([8,12]) with [9],  3 ([8,12,64]) with [35],  3 ([8,12,54]) with [17],</p>	<p><b>Search terms:</b>  1. "Age" or "old\$" or "elder\$" or "aged" or "advanced age" or "senior\$" or "geriatric\$" or "eldest" or "aging" or "gerontic" or "faller\$" or "fear of falling"  2. "corresponding task\$" or "coupled task\$" or "dual task\$" or "dual task paradigm\$" or "secondary task" or "conflicting task" or "task prioritisation" or "inattentional</p>	<p><b>Inclusion criteria:</b>  (1) population: older adults (mean age ≥ 60 years) with a previous fall; (2) DT paradigm used to discriminate fallers from non-fallers; (3) primary motor task: straight over ground walking at self-selected speed; (4) outcome measures: gait measurements during both ST- and DT-performance or the DT effect on gait performance (more than one gait cycle); (5) clear description of the DT situation; (6) report of adequate data to calculate effect sizes either from descriptive or inferential</p>	<p>From 16 to 1350 healthy older people (mean age between 67 and 87 years) included in each study.</p>	<p><b>Motor task:</b>  Straight over ground walking at self-selected speed.  <b>Measures:</b> cadence, walking speed, gait variability, walking time, stride length, step length, stride length CV, stride time, step time, stride time CV, single-support time/phase, double-support time/phase, stride width, step width, stride width CV, number of strides, number of steps, stance time, swing time, average swing time, swing time variability CV, STV, ML RMS, AP RMS, standardized ML RMS, standardized AP RMS, COP path, min COP velocity, mean COP velocity, median COP velocity,</p>	<p><b>(1) Yes &amp; (2) No*:</b>  The meta-analysis revealed significant mean difference between fallers and non-fallers for both ST and DT gait speed, with a reduced performance for fallers. However, no significant mean difference in DTC on gait speed or on the cognitive task performance (considering or not the cognitive task domain) was observed between fallers and non-fallers. Only trends for higher decrements in gait speed for fallers compared to non-fallers under DT conditions, as well as increased DTC in fallers for verbal fluency and motor DT were showed.   *This answer needs to be taken into account with caution. Indeed, due to a majority of retrospective designs for the reporting of fall</p>

	<p>8 ([6,8,20,54,57,58,64,78]) with [49], 4 ([8,12,51,54]) with [53].</p>	<p>blindness" 3. "gait" or "step length" or "cadence" or "step count" or "step width" or "stance time" or "swing time" or "single support time" or "stride time" or "stride width" or "stride length" or "gait line" or "maximum force forefoot" or "maximum force midfoot" or "maximum force heel" or "double support time" or "gait speed" or "stride speed" or "motion" or "movement\$" or "motor\$" or "locomotion" or "walking" or "balance" or "posture" not "slipping" (not "perturbation") 4. "cognitive" or "neurocognitive" or "cognition\$" or "executive" or "processing" or "spatial" or "visuospatial" or "memory" or "reaction\$" or "speed" or "decision-making" or "mental" or "attention" or "cognitive-motor" or "motor-cognitive" or "reaction\$" or "planning" or inhibition 5. Combination of 1 and 2 and 3 and 4 <u>Databases:</u></p>	<p>statistics; (7) inclusion of interventional studies if the DT effect on gait at baseline if reported. <u>Exclusion criteria:</u> (1) population with brain injuries or diagnosed cognitive decline, physical impairments (e.g., using a cane or walker) or chronic diseases such as multiple sclerosis or PD; (2) studies with a secondary analysis of previous reported results; (3) publications in languages other than English and German. <i>Dates of publication: from 1946 (MEDLINE)/1806 (PsycINFO)/1974 (EMBASE) to 2019 (Week 20)</i></p>		<p>symmetry index, impulse (foot strike to first peak, min to second peak, second peak to foot off, foot strike), stride frequency, stride regularity, number of complete stops. <u>Cognitive task:</u> - <b>Verbal fluency tasks:</b> recitation of letters of the alphabet, animals or professions (starting or not with a specific letter), enumeration of words starting with a specific letter; - <b>Discrimination and decision-making tasks:</b> Stroop task, clock task; - <b>Mental tracking/working memory tasks:</b> backward counting, listening and answering questions; - <b>Motor tasks:</b> carrying a cup/glass/tray.</p>	<p>history and the analysis of mean difference (an appropriate statistical measure for discriminative ability), it is rather the discriminative power of DT performance (compared to the one of ST) that has been assessed, instead of its predictive value. Here, there is no additional benefit of DT walking as a measurement to discriminate fallers from non-fallers compared to ST walking.</p>
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		MEDLINE, PsycINFO and EMBASE				
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### C. Detailed Table of Results from the Systematic Literature Review Regarding Walking Dual Tasks

**Table C.1 Articles regarding walking dual tasks that were included in the systematic literature review.** Abbreviations: y. = years; F = females; M = males; # = number; GDS = Geriatric Depression Scale; HR = hazard ratio; OR = odds ratio; CI = confidence interval; MMSE = Minimal Mental State Examination; SPPB = Short Physical Performance Battery; POMA = Performance Oriented Mobility Assessment; PPV = Positive Predictive Value; NPV = Negative Predictive Value; 6MWT = Six Minute Walk Test; BESTest = Balance Evaluation Systems Test; CT = cognitive task; MT = motor task; AP = anteroposterior; ML = mediolateral; PCA = Principal Component Analysis; AUC = Area Under the Curve; CoV = coefficient of variation; PFC = prefrontal cortex; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; PPA = Physiological Profile Assessment; TMT = Trail Making Test; IconFES = Iconographical-Fall Efficacy Scale; MSIT = Multi-Source Interference Task; EF = executive function.

Authors	Population	Falls	Dual-task paradigm & discriminative/predictive analysis	(1) Do DT-related changes or DT performance discriminate fallers from non-fallers? (2) Are DT-related changes or DT performance predictors of falling? (3) Is the DT-related predictive strength superior compared to the ST-related one? (Yes/No/Inconclusive/Not addressed)	Risk of bias via QUIPS tool (High H, Moderate M, Low L risk of bias)
Ayers et al., 2014 [5]	646 community-dwelling older adults: 337 fallers (80.5 ± 5.4 y.; 219 F; Blessed score: 1.7 ± 1.5; normal walking velocity: 94.3 ± 22.7 cm/s) and 309 non-fallers (79.2 ± 5.5 y.; 176 F; Blessed Score: 1.7 ± 1.6; normal walking velocity: 95.8 ± 22.6 cm/s); <u>Inclusion criteria:</u> aged 70 years-old and older, living in the community; <u>Exclusion criteria:</u> severe auditory or visual loss, inability to ambulate, institutionalization, people with significant cognitive impairment (Blessed Score > 6).	<b>Prospective study;</b> Mean follow-up of 2.6 years with annual clinical, cognitive and mobility assessments and telephone interviews at baseline and every 2-3 months to assess function and falls; → Fallers = (# of falls ≥ 1) during the follow-up period; Definition of a fall: “unintentionally coming down to the floor or a lower level not due to a major intrinsic or extrinsic event” [67].	<u>Motor task:</u> <b>walking</b> 4.6 m at normal pace (+ 0.914 m from either end of the walkway edge) <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> reciting alternate letters of the alphabet <u>Instructions:</u> “pay equal attention to walking and talking” <u>Independent variables &amp; analysis:</u> gait variables at baseline: velocity, cadence, step length, swing, stance, double support, step time variability, swing time variability; (PCA &) Cox proportional hazards models → HR (95% CI)	<u>(1) Not addressed, (2) Yes &amp; (3) Yes:</u> In a Cox proportional hazard model adjusted for gender, age and education, <b>step length in DT condition</b> was the only individual gait parameter that predicted falls, being <b>shorter</b> in fallers compared to non-fallers (HR = 0.989, 95% CI = 0.98-0.99, p = 0.034). In Cox proportional hazard models adjusted for gender, age, education, illness index, prescription medicines, GDS, Blessed Score, chair rise test, clinical gait abnormalities, baseline prevalence of previous falls, normal velocity during ST and normal stride length variability during ST, <b>poorer performance in the DT “pace” domain (including DT velocity and step length)</b> remained a significant predictor of falls (HR = 1.312, 95% CI = 1.11-1.55, p = 0.002). The inclusion of the two last confounding variables allowed concluding for an <b>incremental validity of DT over ST walking assessment in the prediction of falls.</b> However, DTC measured as change in gait velocity between DT and ST conditions did not predict falls. <u>Limitations:</u> difficult generalization to older adults who are institutionalized or with cognitive impairments.	1) M (exclusion criteria missed neurological diseases) 2) L 3) L 4) L 5) L 6) L → Low risk of bias
Hirashima et al., 2015 [30]	92 volunteers from a community senior club: 16 fallers (78.1 ± 5.6 y.; 13 F; MMSE: 28.1 ± 1.6; TUG: 8.3 ± 1.1 s) and 76 non-fallers (74.9 ±	<b>Prospective cohort study;</b> Over a follow-up period of 12 months using monthly postal surveys and	<u>Motor task:</u> <b>walking</b> 60 m (10 m walkway with 3 returns) at usual speed <u>Concurrent cognitive task:</u>	<u>(1) Yes, (2) Yes &amp; (3) Not addressed:</u> Fallers and non-fallers were not significantly different in terms of walking time during ST and DT. There is no significant influence of age on the incidence of injurious	1) L 2) L 3) L

	<p>5.3 y.; 65 F; MMSE: 28.1 ± 1.7; TUG: 8.4 ± 1.5 s);</p> <p><u>Inclusion criteria:</u> aged 65 years-old and older, living independently in the community, ability to walk approximately 500 m without a cane;</p> <p><u>Exclusion criteria:</u> MMSE &lt; 25, neurological and/or orthopedic disorders, previous operations on the spine and/or lower extremities.</p>	<p>telephone calls;</p> <p>→ Fallers = (injured because of falls or # of falls ≥ 2);</p> <p>Definition of a fall: “accidental contact of any body part, except for the plantar, with a low area such as the floor or the ground”[23].</p>	<p><b>discrimination and decision-making task:</b> not stepping on the unequal lines</p> <p><u>Independent variables &amp; analysis:</u></p> <p>time and number of missteps recorded every 20, 40 and 60 m;</p> <p>for group (fallers vs. non-fallers) comparisons at baseline: unpaired t-tests or Mann-Whitney U tests + for comparison between misstep and non-misstep groups and between age groups: Kaplan-Meier survival curves and log-rank tests</p>	<p>falls or more or equal to 2 falls.</p> <p>However, fallers and non-fallers significantly differed in terms of the presence of missteps at 40 m and 60 m (p = 0.041 and 0.035, respectively). Subjects who had made <b>missteps during the DT test with an extended walking distance of ≥ 40 m</b> were significantly more likely to be fallers (p = 0.042 at 40 m and p = 0.038 at 60 m, as results of the log-rank tests).</p> <p><u>Limitations:</u> No direct comparison between ST and DT concerning sensitivity and specificity of predicting falls, unclear inter-rater reliability of the DT test.</p>	<p>4) L</p> <p>5) L</p> <p>6) L</p> <p>→ Low risk of bias</p>
<p>MacAulay et al., 2015 [46]</p>	<p>416 relatively healthy and cognitively intact older adults, 67.5% female, primarily Caucasian, with normal or corrected vision: 81 fallers (69.6 ± 6.81 y.; initial MMSE: 29.47 ± 0.87; initial SPPB: 11.04 ± 1.4) and 312 non-fallers (70.13 ± 6.62 y.; initial MMSE: 29.25 ± 1.02; initial SPPB: 11.02 ± 1.19);</p> <p><u>Inclusion criteria:</u> aged 60 years-old and older;</p> <p><u>Exclusion criteria:</u> GDS ≥ 6; a history of neurological or untreated health conditions that might cause cognitive impairment.</p>	<p>Longitudinal (<b>prospective</b>) study;</p> <p>Structured clinical interview after 1 year in order to obtain participant’s fall history for the past year;</p> <p>→ Fallers = (# of falls ≥ 1);</p> <p>Definition of a fall: “times that individuals unexpectedly lost their balance and unintentionally came unto rest on the ground, floor or other object; events in which participants were able to regain their balance did not count as a fall (e.g., tripping but catching oneself before falling onto the floor)” [41].</p>	<p><u>Motor task:</u></p> <p>straight <b>walking</b> at normal everyday walking speed</p> <p><u>Concurrent cognitive task:</u></p> <p><b>mental tracking/working memory task:</b> spelling a word of 5 letters in length backwards aloud</p> <p><u>Independent variables &amp; analysis:</u></p> <p>stride length, step time → average stride length and step time scores;</p> <p>mixed-design repeated measures ANCOVAs for group differences during ST and DT at both time points + partial correlations</p>	<p><u>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</u></p> <p>Fallers exhibited <b>shorter stride length</b> than non-fallers within both walking task conditions (<b>ST and DT</b>), even when sex, age and height were controlled (F(1,405) = 15.8, p &lt; 0.001).</p> <p>There was <b>no significant interaction between group and task conditions on gait stride length</b>.</p> <p>Shorter strides during DT at follow-up were predicted by worse executive attention/processing speed performance 1 year before (r = 0.24, p &lt; 0.001).</p> <p><u>Limitations:</u> too specific sample (generally college educated participants, predominantly white, with a higher proportion of females), time frame limited to 1-year, potential unreliability of retrospective clinical interview after one year.</p>	<p>1) L</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) L</p> <p>6) L</p> <p>→ Low risk of bias</p>
<p>Gimmon et al., 2016 [26]</p>	<p>160 older adults: 61 fallers (79.4 ± 5.7 y.; 49 F; MMSE: 28.19 ± 1.53; POMA total score: 26.09 ± 2.15) and 99 non-fallers (81.5 ± 5 y.; 69 F; MMSE: 27.9 ± 1.65; POMA total score: 26.69 ± 1.69);</p> <p><u>Inclusion criteria:</u> aged 65</p>	<p>Participants asked to <b>retrospectively</b> recall fall events during the past year;</p> <p>→ Fallers = (# of falls ≥ 1);</p> <p>Definition of a fall: “an event which results in a</p>	<p><u>Motor task:</u></p> <p>narrow path <b>walking</b> test = walking at a comfortable pace within a 6 m long narrow path</p> <p><u>Concurrent cognitive tasks:</u></p> <p>3 <b>mental tracking/working memory tasks:</b> reciting the days of the week backwards, reciting the months of the year backwards, serial-5 subtraction loudly</p>	<p><u>(1) Yes, (2) No &amp; (3) No:</u></p> <p><b>Trial velocity during ST</b> remained significantly <b>slower</b> in fallers compared to non-fallers, even after the gait parameter was adjusted for age, sex and fear of falling (F = 11.498, p &lt; 0.001). Therefore, trial velocity during ST was identified as a potential identifier of falls.</p> <p>There was no significant interaction between group and task. Indeed, among both groups, gait speed decreased during DT. However, <b>no</b></p>	<p>1) L</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) L</p> <p>6) L</p>

	<p>years-old and older, ability to walk independently, MMSE &gt; 24;</p> <p><u>Exclusion criteria:</u> serious visual impairment, severe cardio-vascular disease, terminal diseases, Menier and substantial pain, and severe gait impairment due to focal lower limb muscle weakness or palsy, lower limb amputation or joint arthrodesis, or neurological diseases.</p>	<p>person coming to rest inadvertently on the ground or other lower level, regardless of whether an injury was sustained" [68].</p>	<p>from 100 to 50</p> <p><u>Instructions:</u></p> <p>"to walk at their comfortable pace without stepping outside the narrow path" and "to perform both tasks as best as they can"</p> <p><u>Independent variables &amp; analysis:</u></p> <p>number of steps during each trial, trial time, trial velocity, ML instability (i.e., number of step errors), and number of cognitive task errors during ST (sitting) and DT;</p> <p>2-way ANOVA (with group as between-subjects factor and with repeated measures on the within-subject factor that is task) + 2-way ANCOVA (group as between-subjects factor and adjustment by age, sex and fear of falling) + AUC/validity, sensitivity, specificity and PPV related to ROC curve in ST and DT</p>	<p><b>added value of DT condition over ST condition in identification of fallers</b> has been showed.</p> <p>Predictive abilities: <b>ST trial velocity</b> <math>\geq 0.78</math> m/s vs. DT trial velocity <math>\geq 0.46</math> m/s: sensitivity: 77.5% vs. 70.2%; specificity: 57.4% vs. 55%; AUC/validity: 0.69 (<b>p = 0.002</b>) vs. 0.62 (p = 0.067); PPV: 53.9% for ST gait speed.</p> <p><u>Limitations:</u> small sample size, retrospective study, cognitive task not reflecting a realistic life performance, ST condition can be perceived as a motor-motor DT.</p>	<p>→ Low risk of bias</p>
<p>Howcroft et al., 2016 [32,33]</p>	<p>100 community-dwelling older adults: 24 fallers (76.3 <math>\pm</math> 7 y.; 11 F; 6MWT distance: 446.6 <math>\pm</math> 101.4 m) and 76 non-fallers (75.5 <math>\pm</math> 6.6; 45 F; 6MWT distance: 455.8 <math>\pm</math> 102.4 m);</p> <p><u>Inclusion criteria:</u> aged 65 years-old and older, living in the community;</p> <p><u>Exclusion criteria:</u> cognitive disorder, inability to walk for 6 minutes without an assistive device.</p>	<p><b>Retrospective</b> study;</p> <p>Classification of fallers and non-fallers based on 6-month retrospective fall occurrences;</p> <p>→ Fallers = (# of falls <math>\geq 1</math>);</p> <p>Definition of a fall: [68].</p>	<p><u>Motor task:</u></p> <p>walking 7.62 m</p> <p><u>Concurrent cognitive task:</u></p> <p><b>verbal fluency task:</b> saying words starting with A, F or S</p> <p><u>Independent variables &amp; analysis:</u></p> <p>gait velocities for ST and DT trials; temporal, impulse and COP path-related variables from measurements performed via pressure-sensing insoles; descriptive statistics, temporal features, FFT quartile, ratio of even to odd harmonics (REOH) and maximum Lyapunov exponent (MLE) as accelerometer-derived parameters;</p> <p>a) for each variable: mixed-design ANOVA test, with a 2-factor within-subject walking condition (ST,DT) and a 2-factor between-subjects faller status condition (faller, non-faller); post-hoc tests for comparing walking conditions: Wilcoxon Signed-Rank test or paired t-test; post-hoc tests for comparing faller status conditions: Mann-Whitney U test, independent t-test or Welch's t-test;</p> <p>b) 3 classifier models: multi-layer perceptron neural network, naive Bayesian, support vector machine; model evaluation → accuracy, specificity, sensitivity, PPV, NPV, F1 score, Matthew's Correlation</p>	<p><b>(1) Yes. (2) Yes &amp; (3) No:</b></p> <p>a) Regarding pressure-sensing insole measures, for both DT and ST gait data, no significant differences were found between fallers and non-fallers. Concerning accelerometer-derived parameters, fallers showed significantly <b>greater head posterior standard deviation</b> (p = 0.025) <b>and decreased posterior pelvis AP REOH</b> (p = 0.023) <b>during ST</b>, and <b>greater posterior pelvis vertical MLE</b> (p = 0.017) <b>during DT gait</b>.</p> <p>b) In the context of models of wearable-sensor based fall-risk classification in older adults, <b>ST sensor-based gait assessment models outperformed models based on DT walking</b> or clinical assessment data.</p> <p><u>Limitations:</u> retrospective fall occurrence as the criterion for classification → potential inaccurate recall of falls + potential changes to gait patterns.</p>	<p>1) H (no reporting of global cognitive function - even if self-reported cognitive disorder was an exclusion criterion - or potential neurological disorders, and no baseline comparison of demographic data between fallers and non-fallers)</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) L</p> <p>6) L</p> <p>→ Moderate risk of bias</p>

			Coefficient → ranking method		
Johansson et al., 2016 [37]	<p>1390 fairly healthy community-dwelling older adults aged 70 years (684 F; MMSE: F → 28.5 ± 1.6 vs. M → 28.3 ± 1.7; no significant differences between F and M when objectively measured 7-day total physical activity): over 1350 → 148 fallers (88 F);</p> <p><u>Inclusion criteria:</u> sample representing the general population → residence in the Umea municipal area and age of exactly 70 years-old at the time of testing.</p>	<p><b>Prospective</b> study; Self-reported fall data by telephone 6 and 12 months after examination; → Fallers = (# of falls ≥ 1); Definition of an incident low-energy fall: “unexpected event in which participants came to rest on the ground” [28].</p>	<p><u>Motor task:</u> <b>walking</b> 8.6 m at preferred pace (+ 1 m ahead of the walkway) (+ walking at fast speed only under ST condition) <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> counting backward from 100 in increments of 1 <u>Independent variables &amp; analysis:</u> in ST and DT, CoV for: step/stride width, step/stride length, step/stride time, stance time, swing time, stride velocity, double support time; Student’s t-tests, multiple logistic regression models</p>	<p><b>(1) Yes, (2) Yes &amp; (3) Yes:</b> During the normal-speed trial, no differences in gait variability were detected between fallers and non-fallers, whereas <b>step width, step length, step time and stance time variability</b> were significantly <b>greater</b> in fallers <b>during the fast-speed trial</b> (p = 0.01, 0.02, 0.03 and 0.01, respectively). Nevertheless, <b>during DT</b>, fallers exhibited significantly <b>increased variability for step width, step length, stride length, step time, stance time, stride time, stride velocity and swing time</b> in comparison with non-fallers (p = 0.002, 0.004, 0.01, 0.005, 0.02, 0.02, 0.002 and 0.007, respectively). Moreover, in an adjusted logistic regression model (covariates: sex, physical activity, education level, smoking, cardiovascular disease, diabetes, MMSE, gait speed), <b>step width variance from the DT trial</b> represented an <b>independent predictor</b> of incident falls (OR = 1.09, 95% CI = 1.02-1.17, p = 0.01), <b>as well as other gait parameters under DT</b>. <u>Limitations:</u> limited generalization of the findings to other age groups, potential familiarization with the gait measurement system, difficulties of asking to recall falls.</p>	<p>1) M (no demographic characteristics directly related to fallers and non-fallers, but to females and males, and poor inclusion and exclusion criteria, even if population’s description was quite exhaustive) 2) L 3) L 4) L 5) L 6) L → Low risk of bias</p>
Pelosi et al., 2016 [55]	<p>31 older adults: 17 fallers (73.4 ± 4.2 y., 10 F, MoCA score: 26.4 ± 1.6) and 14 age-matched non-fallers (72.1 ± 4.9 y., 5 F, MoCA: 28.3 ± 2);</p> <p><u>Inclusion criteria:</u> age between 60 and 85 years, ability to walk for 5 min unassisted;</p> <p><u>Exclusion criteria:</u> clinical diagnosis of dementia or other severe cognitive impairment (MMSE &lt; 24), psychiatric co-morbidity, history of stroke or other neurologic disorders.</p>	<p>Cross-sectional (<b>retrospective</b>) study; Self-reported falls over the previous 6 months; → Fallers = (# of falls ≥ 2).</p>	<p><u>Motor task:</u> <b>walking</b> in a corridor at a comfortable speed for 1 min <u>Concurrent cognitive task:</u> <b>verbal fluency task:</b> talking <u>Independent variables &amp; analysis:</u> for ST, DT and proportionate difference (DTC in %): gait speed; repeated measures ANOVA with group as between-subjects factor and task (ST and DT) as within-subject factor + post-hoc t-tests with Bonferroni correction for multiple comparisons</p>	<p><b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b> <b>Gait speed</b> was significantly <b>lower</b> in fallers than in non-fallers <b>during ST and DT</b> (p = 0.003 and 0.005). Unlike non-fallers, fallers significantly <b>reduced their gait speed under DT gait with respect to normal gait</b> (p = 0.022). <u>Limitations:</u> cholinergic activity was evaluated at rest (sitting position) and SAI is reduced in muscles involved in a specific motor task during movement, no plan to test whether anticholinergic drugs may improve cholinergic activity in the faller population.</p>	<p>1) L 2) L 3) M (no clear description of the concurrent cognitive task) 4) M (no formal definition of falls) 5) L 6) L → Moderate risk of bias</p>
Freire Júnior et al., 2017 [22]	<p>62 community-dwelling older adults: 27 fallers (67.96 ± 5.7 y.; 26 F; MMSE: 25, 95% CI 23.5-26.5; BESTest: 84.07 ± 9.43) and 35 non-fallers (67.97 ± 4.82 y.; 24 F; MMSE: 26.57, 95% CI 25.63-27.52; BESTest: 88.77 ± 7);</p>	<p><b>Retrospective</b> study; Questionnaire about the history of falls in the 6 months preceding the assessment day; → Fallers = (# of falls = 1); Definition of a fall: [28].</p>	<p><u>Motor task:</u> <b>walking</b> 8 m at self-selected speed (+ 1 m before the electronic carpet and 1 m after) <u>Concurrent tasks:</u> - <b>verbal fluency task:</b> naming animals without repeating names - <b>motor task:</b> transferring a coin from one pocket</p>	<p><b>(1) No, (2) Not addressed &amp; (3) Not addressed:</b> There were significant effects of the task (increased stride time and reduced gait speed, cadence and single support time under both DT conditions compared to ST, <b>decreased step length under both DT conditions compared to ST but with a larger reduction for CT, increased stride time variability in CT compared to MT and ST</b>), but <b>neither significant main effects of the faller status nor significant interaction effects between group and walking condition</b>.</p>	<p>1) M (exclusion criteria missed neurological diseases) 2) L 3) L 4) L 5) M (no covariates)</p>



	<p><u>Exclusion criteria:</u> inability to walk without help from others, severe impairment of balance, presence of cognitive impairment identified by MMSE (exclusion if MMSE score: <math>\leq 13</math> for illiterate elderly, <math>\leq 18</math> for people with 1-7 years of education, <math>\leq 26</math> for people with 8 years or more of education).</p>		<p>to the other</p> <p><u>Instructions:</u> “do not prioritize either task”</p> <p><u>Independent variables &amp; analysis:</u> for ST, DT and proportionate DTC (<math>((DT_{walking} - ST_{walking})/ST_{walking}) \times 100</math>): gait speed, cadence, stride time, step length, single support time, stride time CoV;</p> <p>2-way repeated-measure ANOVAs (group as between-subjects factor and task as repeated measure, Bonferroni post-hoc tests); Mann-Whitney tests or independent Student’s t-tests for comparing DTC between groups</p>	<p>Regarding <b>DTC</b>, no significant differences between groups were observed, whereas <b>significant differences in step length</b> were found between tasks: <b>CT &gt; MT</b>, <math>p = 0.0003</math> in <b>non-fallers</b> and <math>0.036</math> in <b>fallers</b> (the <b>same for stride time variability in non-fallers</b>, <math>p = 0.016</math>).</p> <p><u>Limitations:</u> fallers had experienced only one fall over the past 6 months, performance on the concurrent cognitive and motor tasks were not measured → no information concerning strategy of task prioritization that might discriminate fallers from non-fallers.</p>	<p>taken in to account in the statistical analyses)</p> <p>6) L → Moderate risk of bias</p>
<p>Vergheze et al., 2017 [73]</p>	<p>166 high-functioning older adults (<math>74.5 \pm 6.07</math> y.; 85 F; RBANS: <math>91.56 \pm 12</math>): 71 fallers (34 with # of falls &gt; 1) and 85 non-fallers;</p> <p><u>Inclusion criteria:</u> community-residing adults, aged 65 years-old and older;</p> <p><u>Exclusion criteria:</u> presence of dementia, inability to walk, active neurologic or psychiatric disorders severe enough to interfere with study assessments, presence of major visual or hearing loss, recent or planned surgical procedures restricting walking, disability, need for assistance or assistive devices to walk, presence of clinical gait abnormalities.</p>	<p><b>Prospective</b> cohort study; 50-month follow-up period (mean follow-up: <math>33.9 \pm 11.9</math> months), annual interviews based on a standardized questionnaire during in-person visits and phone calls every 2 to 3 months;</p> <p>Definition of a fall: “unintentionally coming down on the floor or to a lower level not as a result of a major intrinsic or extrinsic event” [39].</p>	<p><u>Motor task:</u> <b>walking</b> at normal pace on an electronic walkway (for 3 continuous loops consisting of 6 straight segments and 5 turns)</p> <p><u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> recitation of alternate letters of the alphabet (under ST: for 30 seconds while standing)</p> <p><u>Instructions:</u> “to pay equal attention to both tasks to minimize task prioritization”</p> <p><u>Independent variables &amp; analysis:</u> gait stride velocity, correct letter rate per minute; Andersen-Gil extension of the Cox model (hazard ratios), adjusted for age, sex, education, comorbidity count, RBANS score, <math>HbO_2</math> levels during normal walking and cognitive ST conditions, Digit Symbol Substitution test score, walking velocity and correct letter rate during DT (+ models where subjects with slow gait, with instrumental activity limitations, with fall history before baseline were excluded)</p>	<p><b>(1) Not addressed, (2) Yes &amp; (3) Yes:</b></p> <p><b>Higher PFC activation levels on fNIRS during DT predicted falls</b> (HR = 1.32, 95% CI = 1.01-1.7) and this association remained significant when controlling for all the covariates.</p> <p>However, PFC activation during both motor and cognitive ST, as well as gait velocity and letter rate during DT were not significantly associated with risk of falls.</p> <p><u>Limitations:</u> focus limited to PFC analysis, very mild clinical signs and possibility that this compensatory brain activity do not occur in later clinical stages (associated with gait abnormalities), negotiating turns might be more cognitively demanding, observational study does not allow to report real causality.</p>	<p>1) M (no demographic characteristics directly related to fallers and non-fallers)</p> <p>2) L 3) L 4) L 5) L 6) M (no p-values reported) → Moderate risk of bias</p>
<p>Caetano et al., 2018 [13]</p>	<p>50 healthy community-dwelling older adults: high-risk of falling group (<math>n=22</math>; <math>77 \pm 8</math> y.; 16 F) and low-risk of falling group (<math>n=28</math>; <math>72 \pm 4</math> y.; 18 F);</p> <p><u>Inclusion criteria:</u> aged 65</p>	<p><b>Retrospective</b> study; Classification as fallers and non-fallers based on falls experienced in the past 12 months and on the PPA</p>	<p><u>Motor task:</u> gait adaptability test (GAT) → <b>walking</b> over a 6-m path at self-selected speed under 4 conditions: while avoiding an obstacle, stepping onto close or far targets, or walking without any stimulus on the pathway</p>	<p><b>(1) Yes, (2) Yes &amp; (3) No:</b></p> <p>In adjusted logistic regression models, <b>at least one stepping error in the single GAT and reduced GAT velocity in both ST and DT conditions</b> were found to <b>discriminate</b> low- from high-risk of falling groups (<math>\chi^2 = 5.966</math>, <math>p = 0.015</math>; <math>t_{48} = 3.552</math>, <math>p = 0.001</math>; <math>t_{48} = 3.88</math>, <math>p &lt; 0.001</math>) and to be <b>independent predictors of high risk of falling</b>.</p>	<p>1) H (no reporting of a global cognitive score, even if dementia was an exclusion criterion)</p> <p>2) L 3) L</p>

	<p>years-old and older, living independently in the community, cognitive ability to follow instructions, relatively healthy;</p> <p><u>Exclusion criteria:</u> dementia, acute or terminate illness, progressive neurodegenerative diseases, major psychiatric illnesses, color-blindness or untreatable visual impairment, inability to walk independently, recent surgery affecting mobility.</p>	<p>score;</p> <p>→ High fall-risk group = (history of multiple falls and/or PPA score <math>\geq 1.5</math>);</p> <p>Definition of a fall: [41].</p>	<p><u>Concurrent cognitive task:</u></p> <p><b>mental tracking/working memory task:</b> serial-3 subtraction from a two-digit number</p> <p><u>Independent variables &amp; analysis:</u></p> <p>GAT errors, velocity of the stride preceding the target/obstacle;</p> <p>independent sample t-tests, Mann-Whitney-U tests or Chi-square tests + binary logistic regression (with covariates such as TMT, IconFES, quadriceps strength and age) + AUC of ROC curves</p>	<p>The <b>association between ST GAT errors and fall risk</b> (OR 3.54, 95% CI 0.67-18.65) was <b>mediated by impaired EF</b>, while the <b>association between GAT velocity and fall risk in ST</b> (OR = 1.69, 95% CI = 0.62-4.62) <b>and DT</b> (OR = 2.01, 95% CI = 0.75-5.37) situations was <b>mediated by high concern about falling, weak quadriceps strength and impaired EF</b>.</p> <p>However, <b>GAT under DT condition did not provide greater predictive power of fall risk over ST GAT</b> (<math>\chi^2 = 0.09</math>, <math>p = 0.76</math>, for ROC curves comparison).</p> <p><u>Limitations:</u> GAT might be perceived as a DT in itself, the performance of the cognitive task was not measured → no information about strategy of task prioritization that might discriminate fallers from non-fallers, retrospective aspect of the study.</p>	<p>4) L</p> <p>5) L</p> <p>6) L</p> <p>→ Moderate risk of bias</p>
<p>Callisaya et al., 2018 [15]</p>	<p>424 older adults (77.8 <math>\pm</math> 6.4 y.; 234 F; RBANS: 93.5 <math>\pm</math> 12.6; mean normal gait speed: 98.3 <math>\pm</math> 23 cm/s);</p> <p><u>Inclusion criteria:</u> aged 65 years-old and older, participation in the longitudinal Central Control of Mobility in Aging (CCMA) study;</p> <p><u>Exclusion criteria:</u> dementia, inability to walk, severe neurological or psychiatric conditions, major visual or auditory loss, receiving hemodialysis, recent or planned surgery that would interfere with assessments or restrict walking.</p>	<p><b>Retrospective study;</b></p> <p>Participants were asked if they had fallen in the past year;</p> <p>→ Fallers = (# of falls <math>\geq 1</math>).</p>	<p><u>Motor task:</u></p> <p>walking on a computerized mat (457.2 cm long) at normal walking speed</p> <p><u>Concurrent cognitive task:</u></p> <p><b>mental tracking/working memory task:</b> recitation of alternate letters of the alphabet starting with the letter 'A'</p> <p><u>Instructions:</u></p> <p>“to pay equal attention to both the walking and talking tasks to avoid task prioritization effects”</p> <p><u>Independent variables &amp; analysis:</u></p> <p>ST and DT normal walking speed;</p> <p>Spearman’s correlation coefficients related to relationships between mobility measures and prior falls + multivariable linear regression, adjusting for age and gender, between clinic-based mobility measure and each community risk factors (including prior falls) in separate models + final models including each significant mobility measures in the same model</p>	<p><b>(1) Not addressed, (2) Yes &amp; (3) No:</b></p> <p>Prior falls were significantly correlated with ST normal walking speed (<math>r = -0.19</math>, <math>p &lt; 0.001</math>), DT walking speed (<math>r = -0.13</math>, <math>p &lt; 0.01</math>), maze delay (<math>r = 0.12</math>, <math>p &lt; 0.05</math>), time for ascending stairs (<math>r = 0.21</math>, <math>p &lt; 0.001</math>) and time for descending stairs (<math>r = 0.16</math>, <math>p &lt; 0.001</math>).</p> <p><b>In separate regression models</b>, falls in previous year were significantly associated with <b>slower DT walking speed</b> (OR = 0.99, 95% CI = 0.98-0.99, <math>p &lt; 0.5</math>), <b>ascending</b> (OR = 1.49, 95% CI = 1.21-1.84, <math>p &lt; 0.05</math>) <b>and descending stairs</b> (OR = 1.25, 95% CI = 1.07-1.45, <math>p = 0.002</math>).</p> <p>However, in the <b>final model</b>, only time for ascending stairs (OR = 1.33, 95% CI = 1.05-1.68, <math>p = 0.02</math>) remained significant, the pseudo <math>R^2</math> for the model being 5%, with ascending stairs contributing 81.7% of 5%.</p> <p><u>Limitations:</u> no objective measurements of community performance, self-reported measures were subject to recall or reporting bias, cross-sectional study → inability to make causal inferences, other gait parameters to be included (e.g., gait variability), small explained variance for some outcomes.</p>	<p>1) M (no demographic characteristics directly related to fallers and non-fallers)</p> <p>2) L</p> <p>3) H (no formal definition of fall and, number of falls and subjects who had fallen were not reported)</p> <p>4) L</p> <p>5) L</p> <p>6) M (no complete reporting of the statistical analyses)</p> <p>→ Moderate risk of bias</p>
<p>Commandeur et al., 2018 [18]</p>	<p>42 community-dwelling older adults: 27 fallers (75.9 <math>\pm</math> 3.3 y.; 19 F; MMSE: 28.5 <math>\pm</math> 1.6) and 15 non-fallers (75.8 <math>\pm</math> 3.4 y.; 6 F; MMSE: 28.5 <math>\pm</math> 1.1);</p> <p><u>Exclusion criteria:</u> physician-diagnosed dementia, recent</p>	<p><b>Retrospective study;</b></p> <p>Self-reported falls over the previous 12 months;</p> <p>→ Fallers = (# of falls <math>\geq 1</math>);</p> <p>Definition of a fall: “if the participant came to rest on a lower surface as a result</p>	<p><u>Motor task:</u></p> <p>walking there and back (10 ST and 10 DT walking passes) at a self-selected preferred speed along a 6.4 m instrumented walkway (+ 1.5 m prior to and beyond the end of the mat)</p> <p><u>Concurrent cognitive task:</u></p> <p><b>mental tracking/working memory task:</b> serial-7</p>	<p><b>(1) Not addressed, (2) Yes &amp; (3) Not addressed:</b></p> <p>Among the 11 measures kept after PCA, 5 gait measures were sufficient for retrospectively classifying fallers and non-fallers with 92.3% sensitivity, 66.7% specificity and a total model classification of 82.9%: stride time difference, stride width difference, stride length difference, stride width variability difference and stride velocity variability difference. <b>Larger stride length difference and stride time</b></p>	<p>1) L</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) L</p> <p>6) L</p>

	major illness or a neurological, sensory, or mobility impairment that would impede participation, MMSE $\leq$ 24, non-fluent in English.	of a loss of balance”.	subtraction aloud from a randomly generated three-digit number <u>Independent variables &amp; analysis:</u> mean and variability (SD) of DT scores and DTC (difference scores between ST and DT gait trials) for variables included in 4 sub-domains: length, width, timing and velocity; remove of highly collinear and theoretically redundant measures within each domain + PCA + backward stepwise binary logistic regression + Hosmer-Lemeshow test	<b>difference significantly and uniquely contributed to the increase of fall risk</b> ( $p = 0.042$ and $0.047$ , respectively, within the logistic regression model). These DTC gait measures outperformed traditional clinical tests of strength, mobility and balance, and physiological assessments. <u>Limitations:</u> retrospective study.	→ Low risk of bias
Halliday et al., 2018 [27]	27 older adults: 12 fallers ( $76.25 \pm 3.19$ y.; 8 F) and 15 non-fallers ( $75.93 \pm 3.41$ y.; 7 F); <u>Inclusion criteria:</u> healthy, living in the community; <u>Exclusion criteria:</u> self-report of a physician-diagnosed major medical illness with residual motor or sensory deficits (e.g., PD, stroke, heart disease, dementia, cancer, brain tumor), severe sensory impairment, drug or alcohol abuse, history of inpatient psychiatric treatment, significant cognitive impairment (MMSE < 24), English as a second language.	<b>Retrospective study;</b> Follow-up period: the two-years leading up to the first study visit; → Fallers = (# of falls $\geq$ 1); Definition of a fall: “any instance in which the participant came to rest involuntarily on a lower surface (e.g., ground or floor).	<u>Motor task:</u> <b>walking</b> at self-selected, normal walking speed along a 6.4 m instrumented walkway (+ 1.5 m before and after the mat ended) → 10 passes * total recorded walking distance of about 6.1 m <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-7 subtraction from a given three-digit starting number <u>Independent variables &amp; analysis:</u> mean and CoV: swing time, step length; Student’s t-tests (measures of effect size) + logistic regression analysis	<u>(1) Yes, (2) Yes &amp; (3) Yes:</u> <b>Mean step length, step length CoV and swing time CoV</b> were significantly <b>larger</b> in fallers compared to non-fallers in <b>DT</b> ( $t(23) = 1.95, 3.05$ and $2.1, p < 0.05, < 0.01$ and $< 0.05, d = 0.758, 1.178$ and $0.786$ , respectively), and not in ST. <b>Step length variability in DT</b> showed a <b>significant effect within the logistic regression model</b> (OR = 1.163, 90% CI = 1.019-1.328, $p = 0.03$ , on tailed). <u>Limitations:</u> optical array limited to coverage of a portion of the frontal cortex, MSIT with fNIRS relatively unprecedented in the literature, relatively liberal definition of fall status, participants did not undergo clinical assessment for MCI, small sample size, retrospective study.	1) M (existing exclusion criterion MMSE < 24, but no reporting of MMSE scores or other measure of global cognitive functions) 2) L 3) L 4) L 5) L 6) M (no description of methodology concerning statistical analyses within a dedicated section) → Moderate risk of bias
Howcroft et al., 2018 [31,34]	75 community-dwelling older adults: 28 fallers ( $75 \pm 8.2$ y.; 14 F) and 47 non-fallers ( $75.3 \pm 5.5$ y.; 30 F); <u>Inclusion criteria:</u> aged 65 years-old and older, without a fall in the 6 months before evaluation, living in the community; <u>Exclusion criteria:</u> self-reported cognitive disorder, inability to walk for 6 min without an	<b>Prospective study</b> (and comparison with retrospective studies from the same group [32,33]); → Fallers = (# of falls $\geq$ 1 during the 6-month follow-up period); Definition of a fall: [68].	<u>Motor task:</u> <b>walking</b> 7.62 m <u>Concurrent cognitive task:</u> <b>verbal fluency task:</b> saying words starting with A, F or S <u>Independent variables &amp; analysis:</u> as in [32,33]: gait velocities for ST and DT trials; temporal, impulse and COP path-related variables from measurements performed via pressure-sensing insoles; descriptive statistics, temporal features, FFT quartile, REOH and MLE as accelerometer-derived	<u>(1) Yes, (2) Yes &amp; (3) No:</u> a) During both ST and DT, gait velocity was not shown to be significantly different between fallers and non-fallers. On the contrary, <b>for DT gait</b> , fallers had significantly <b>lower stance AP COP path CoV</b> ( $p = 0.046$ ) and <b>AP FFT first quartile for the head accelerometer</b> ( $p = 0.011$ ) compared to non-fallers, whereas, <b>during ST</b> , fallers showed significantly <b>lower ML FFT first quartile for the left shank accelerometer</b> ( $p = 0.045$ ) as well as <b>lower superior maximum acceleration for the right shank accelerometer</b> ( $p = 0.041$ ). Gait differences between fallers and non-fallers were dependent on retrospective or prospective faller identification → more interest of using data based on prospective fall occurrence to be part of a	1) H (no reporting of global cognitive function - even if self-reported cognitive disorder was an exclusion criterion - or potential neurological disorders, and no baseline comparison of demographic data between fallers and non-fallers)

	assistive device.		parameters; a) as in [32]; b) as in [33] + predictive accuracy of the top 10 ST and top 10 DT models → repeated random sampling	successful clinical fall risk assessment protocol compared to measures based on retrospective fall occurrence.  b) Although the <b>best overall models were based on DT walking</b> (for the best one: accuracy = 57%, sensitivity = 43%, specificity = 65%), the <b>comparison between ST- and DT-gait-based models did not reveal a clearly superior gait assessment for fall-risk prediction</b> (similar accuracies for the top ST- and DT-gait-based models).  <u>Limitations:</u> performance of cognitive task not measured → no information about task prioritization → potential masking of faller and non-faller gait differences, 7.62 m walking trial may be not enough reflective of everyday walking, larger number of variables in the analysis increases the potential Type 1 errors.	2) L 3) L 4) L 5) M (no covariates taken in to account in the statistical analyses) 6) L → Moderate risk of bias
Minet et al., 2018 [50]	322 older women: 117 fallers from the falls clinic, 99 fallers (79 [76-85] y.; MMSE: 27 [25-29]) and 106 non-fallers (80 [75-86] y.; MMSE: 28 [26-29]) from the community; <u>Inclusion criteria:</u> women, aged 65 years-old and older; <u>Exclusion criteria:</u> not mobile enough to transfer from bed to chair with or without help.	Observational case-control ( <b>retrospective</b> ) study; Self-reported questionnaire to assess falls history over 1 year; → Once only faller and recurrent fallers (> 1 fall); Definition of a fall: [41].	<u>Motor task:</u> 4-meter <b>walking</b> test at preferred walking speed <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-3 subtractions <u>Independent variables &amp; analysis:</u> for ST and DT: gait speed; for differences between groups: 1-way ANOVAs or Kruskal-Wallis tests, and then post-hoc independent t-tests or Mann-Whitney tests	<b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b> <b>Under both ST and DT, gait speed</b> was significantly <b>slower</b> in fallers compared to non-fallers from the community (p < 0.001). However, gait speed was not significantly different between community-dwelling once only fallers and recurrent fallers. <u>Limitations:</u> self-reported falls questionnaires.	1) M (poor inclusion and exclusion criteria such as cognitive impairment and neurological diseases) 2) L 3) L 4) L 5) M (no covariates taken in to account in the statistical analyses) 6) L → Moderate risk of bias
Gillain et al., 2019b [24,25]	96 community-dwelling older adults: 35 fallers (69 [67-76] y.; 17 F; MoCA: 27 [26-29]; SPPB: 10 [9-11]) and 61 non-fallers (70 [67-74] y.; 31 F; MoCA: 28 [26-29]; SPPB: 11 [10-12]); <u>Inclusion criteria:</u> aged 65 years-old and older, living independently at home, ability to understand French and to provide written informed consent; <u>Exclusion criteria:</u> history of fall(s) in the previous year, use	Longitudinal ( <b>prospective</b> ), observational study; 2-year follow-up, using personal falls diaries and phone calls every 3 months; → Fallers = (# of falls ≥ 1); Definition of a fall: [41].	<u>Motor task:</u> <b>walking</b> at self-selected comfortable speed (+ walking at self-selected fast speed) <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-7 subtraction from 100 <u>Independent variables &amp; analysis:</u> for both ST, DT, proportionate differences (DTC and fast walking improvement): gait speed, stride length, stride frequency, stride symmetry, stride regularity, and minimum toe clearance MTC (mean, median, minimum, SD, variance, CoV, delta1 = max - mean, delta2 = mean - min);	<b>(1) Yes, (2) Yes &amp; (3) Inconclusive:</b> Compared to non-fallers, fallers had <b>lower gait speed during fast walking ST</b> (p = 0.035), <b>shorter stride length during normal speed and fast walking ST</b> (p = 0.035 and 0.01, respectively) and <b>higher symmetry DTC</b> (p = 0.022). Among the discriminative variables, <b>symmetry DTC was the only one significantly related to the risk of falls</b> (OR = 1.018, 95% CI = 1.002-1.033, p = 0.027). The obtained model included symmetry DTC, stride length in fast walking ST, stiffness, mean MTC in normal speed walking ST, MTC CoV DTC, MTC variance and mean MTC in fast walking ST, delta1 MTC in DT and gender. Regarding its performances, this model was related to an accuracy of 84%, a sensitivity of 80%, a specificity of 87%, a PPV of 78%, a NPV of 88%, an AUC related to ROC curve of 0.84, and an area	1) L 2) L 3) L 4) L 5) L 6) L → Low risk of bias

	<p>of a walking aid, gait disorders and/or increased fall risk related to neurological or osteoarticular disease, dementia, hip or knee prosthesis in the previous year, pain when walking, acute respiratory or cardiac illness (&lt; 6 months), recent hospitalization (&lt; 3 months), untreated or uncontrolled comorbidities, use of neuroleptic and sedative drugs (except sleeping pills), and presence of a cardiac pacing device.</p>		<p>1-way ANOVAs or Kruskal-Wallis tests + binary logistic regression analysis + supervised machine learning algorithm (J48 classifier) → accuracy and sensitivity</p>	<p>under the Precision Recall Curve of 0.83.  <u>Limitations:</u> small sample size, with non-fallers that were more numerous than fallers → it led to a first classification node of the model that identified non-fallers (because chosen as the attribute that allows the classification of higher number of people), while the aim of the present study was to identify fallers → the results obtained were limited by the volume of available data associated with prospective fall risk, as it was the case for the last classification node; no external validation of the classification model in an independent sample that was different from the one used to develop the model.</p>	
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**D. Detailed Table of Results from the Systematic Literature Review About Dual Tasks Involving Gait Initiation**

**Table D.1** Articles about dual tasks involving gait initiation that were included in the systematic literature review. Abbreviations: y. = years; F = females; M = males; # = number; OR = odds ratio; RR = risk ratio; CI = confidence interval; MMSE = Minimal Mental State Examination; RDST = Rapid Dementia Screening Test; EF = executive function; RT = reaction time.

Authors	Population	Falls	Dual-task paradigm & discriminative/predictive analysis	<p>(1) Do DT-related changes or DT performance discriminate fallers from non-fallers?</p> <p>(2) Are DT-related changes or DT performance predictors of falling?</p> <p>(3) Is the DT-related predictive strength superior compared to the ST-related one?</p> <p>(Yes/No/Inconclusive/Not addressed)</p>	Risk of bias via QUIPS tool (High H, Moderate M, Low L risk of bias)
Callisaya et al., 2016 [14]	<p>124 older adults: 27 single fallers (71.3 ± 5.3 y.; 13 F), 20 multiple fallers (73.5 ± 9 y.; 11 F) and 77 non-fallers (70.2 ± 6.6 y.; 29 F);</p> <p><u>Inclusion criteria:</u> aged between 60-85 years-old, randomly selected from the Southern Tasmanian electoral roll;</p> <p><u>Exclusion criteria:</u> resident of a nurse home, inability to walk without the use of gait aid, any contraindications to having an MRI scan, suffering from PD or dementia.</p>	<p><b>Prospective study;</b></p> <p>Falls questionnaire sent every 2 months for 12 months + falls calendar + follow-up with a phone call;</p> <p>→ Fallers = (# of falls ≥ 1) (single fallers or multiple fallers);</p> <p>Definition of a fall: [41].</p>	<p><u>Motor task:</u> <b>starting walking</b> in response to a buzzer activated at random times</p> <p><u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> 3-serial subtraction</p> <p><u>Independent variables &amp; analysis:</u> time from stimulus to first lateral movement, transfer time (from first lateral movement to toe off of the leading foot), swing time (from toe off to foot contact), overall GI time from stimulus to leading foot contact;</p> <p>log multinomial regression with adjustment for age and sex, and then also for physiological and cognitive fall risk factors</p>	<p><b>(1) Not addressed, (2) Yes &amp; (3) No:</b></p> <p>There was no association between GI time (or any of its components) and single falls over 12 months.</p> <p><b>Slower overall GI time under ST and DT</b> (ST: RR = 1.28, 95% CI = 1.03-1.58; DT: RR = 1.14, 95% CI = 1.02-1.27), <b>swing time under DT</b> (RR = 1.44, 95% CI = 1.08-1.94) and <b>slower time to first lateral movement under ST</b> (RR = 1.9, 95% CI = 1.23-2.94) <b>increased the risk of multiple falls.</b></p> <p>However, <b>GI under DT did not increase the discrimination of multiple fallers over ST condition:</b> slower time to first lateral movement under ST showed the strongest association with multiple falls.</p> <p><u>Limitations:</u> performance of the concurrent cognitive task was not recorded, which did not provide any information concerning strategy of task prioritization and did not allow comparing sensitivity with other types of DT; heels spaced by 6 cm may have influenced stability for some subjects.</p>	<p>1) H (no global cognition score reported even if dementia was an exclusion criterion, and no statistical comparisons on demographic characteristics at baseline)</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) L</p> <p>6) M (no p-values reported)</p> <p>→ Moderate risk of bias</p>

### E. Detailed Table of Results from the Systematic Literature Review About Dual Tasks Involving Postural Control

**Table E.1 Articles about dual tasks involving postural control that were included in the systematic literature review.** Abbreviations: y. = years; F = females; M = males; # = number; IRR = incidence rate ratio; CI = confidence interval; MMSE = Minimal Mental State Examination; SPPB = Short Physical Performance Battery; POMA = Performance Oriented Mobility Assessment; BESTest = Balance Evaluation Systems Test; AP = anteroposterior; ML = mediolateral; PCA = Principal Component Analysis; RMS = root mean square; RT = reaction time.

Authors	Population	Falls	Dual-task paradigm & discriminative/predictive analysis	(1) Do DT-related changes or DT performance discriminate fallers from non-fallers? (2) Are DT-related changes or DT performance predictors of falling? (3) Is the DT-related predictive strength superior compared to the ST-related one?  (Yes/No/Inconclusive/Not addressed)	Risk of bias via QUIPS tool (High H, Moderate M, Low L risk of bias)
Kang et al., 2013 [38]	717 relatively healthy community-dwelling older adults (77.9 ± 5.3 y.; 458 F; MMSE: 27.1 ± 2.6; 90 subjects with BBS ≤ 45); 131 outdoor fallers, 137 indoor fallers, 129 fallers with both outdoor and indoor falls and 320 non-fallers;  <u>Inclusion criteria:</u> aged 70 years-old and older, from the Boston area, living in the community, ability to walk 6 m and to communicate in English;  <u>Exclusion criteria:</u> cognitive impairment (MMSE ≤ 18), terminal disease, severe hearing or vision loss.	<b>Prospective</b> study; Falls monitored using a monthly mail-in calendar over 6-36 months and telephone interviews; → Fallers = (# of falls ≥ 1); Definition of a fall: [39]; Characterization into indoor (i.e., falls in one's own home, someone else's home, other buildings and other enclosed spaces like transportation vehicles) and outdoor falls (i.e., falls in outside stairs, gardens, yards, sidewalks, streets, curbs, parking lots, etc).	<u>Motor task:</u> <b>quiet standing</b> barefoot with eyes open for 30 s <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-3 subtraction from 500 (individual adaptation of the task in case of difficulty) <u>Instructions:</u> "to prioritize standing and look forward" <u>Independent variables &amp; analysis:</u> In AP and ML directions, during ST and DT: COM RMS, postural stiffness, postural damping; negative binomial regression models, with the number of falls for a given period as dependent variable and model adjustments by the time spent either indoor or outdoor and clinical variables that were associated with both prospective falls and the biomechanical variable	<u>(1) Not addressed, (2) Yes &amp; (3) No:</u> <b>Only AP COM RMS was significantly smaller in non-fallers</b> compared to fallers (p = 0.015).  <b>Greater postural stiffness and damping were associated with lower outdoor fall risks.</b> Furthermore, <b>greater COM RMS was associated with higher indoor falls</b> (IRR ranges = 1.4-1.66, p < 0.05), whereas <b>greater damping in the AP direction was related to lower rates of indoor falls</b> (IRR = 0.65, 95% CI = 0.42-0.99, p = 0.044). Except for the last predictor, the associations of postural measures with indoor and outdoor fall rates were invariant by direction (AP vs. ML) and by condition (ST vs. DT).  Therefore, <b>measuring postural control under DT did not improve fall prediction.</b> <u>Limitations:</u> lack of a feedback mechanism in the inverted pendulum model used, instruction of prioritization of the standing task while looking forward.	1) M (no demographic characteristics directly related to fallers and non-fallers, and a neurological disorder was not an exclusion criteria) 2) L 3) L 4) L 5) L 6) M (p-values and statistical variables are plotted but not all clearly reported) → Moderate risk of bias
Maranesi et al., 2015 [47]	130 older adults: 45 infrequent fallers (79 ± 6 y.; 26 F; MMSE: 25 ± 3; POMA, gait score = 11; POMA, balance score = 13), 18 frequent fallers (81 ± 6 y.; 16 F; MMSE: 25 ± 3; POMA, gait score = 10; POMA, balance score = 14) and 67 non-fallers	<b>Retrospective</b> study; Last year fall history; → Infrequent fallers = 1 or 2 falls, frequent fallers ≥ 2 falls.	<u>Motor task:</u> <b>quiet standing</b> with eyes open and closed on both a firm and a compliant surface during 30 s <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-7 subtraction (performed while standing with eyes open on a firm surface)	<u>(1) Yes but..., (2) Not addressed &amp; (3) Not addressed:</u> <b>Postural DT on a firm surface</b> and related posturographic parameters ( <b>RANGE-AP, MVELO-AP and MVELO-ML</b> ) were significantly <b>different between non-fallers and frequent fallers</b> , while <b>RANGE-AP</b> was also found to be significantly <b>different between infrequent and frequent fallers.</b>  <b>However, performing postural ST with eyes open on a compliant</b>	1) M (poor inclusion and exclusion criteria) 2) L 3) L 4) M (no formal definition of a fall) 5) M (covariates not

	<p>(79 ± 5 y.; 38 F; MMSE: 26 ± 3; POMA, gait score = 11; POMA, balance score = 14);</p> <p><u>Inclusion criteria:</u> cognitive ability;</p> <p><u>Exclusion criteria:</u> diagnosed dementia.</p>		<p><u>Independent variables &amp; analysis:</u></p> <p>MDIST-AP (mean distance-AP, average AP distance from the mean COP) , MDIST-ML, RDIST-AP (RMS distance-AP), RDIST-ML, RANGE-AP (maximum distance between 2 points of the AP time series), RANGE-ML, MVELO-AP (average velocity of the COP in the AP direction), MVELO-ML, AREA-SW (estimation of the area enclosed by the COP path per unit of time), MFREQ-AP (frequency of a sinusoidal oscillation with an average value of MDIST-AP and a total path length of total excursions-AP), MFREQ-ML, pfap-50 (frequency below which 50% of the power spectral density of the AP times series is found), pfml-50, pfap-95, pfml-95, MD (mean distance fixed radius = mean spatial distance between 2 consecutive peaks of the sway density curve calculated with relative radius), MP (mean duration of the peaks of the sway density curve calculated with relative radius);</p> <p>for group differences: Kruskal-Wallis tests and post-hoc comparisons with Wilcoxon Rank Sum tests + PCA for each task → Kruskal-Wallis test</p>	<p><b>surface and using PCA-derived parameters allowed to discriminate between non-fallers and (infrequent and frequent) fallers and between infrequent fallers and frequent fallers.</b> Indeed, the parameter derived from the first principal component (PC1) was significantly different between all pairs of groups (<math>p &lt; 0.01</math>). For this task, PC1 involved posturographic parameters concerning the AP variation in COP displacement: MDIST-AP, RDIST-AP, RANGE-AP.</p> <p><u>Limitations:</u> retrospective study, acquisition of only a single trial for each test condition, use of only one force platform instead of two.</p>	<p>taken in to account in the statistical analyses)</p> <p>6) M (no reporting of exact p-values) → Moderate risk of bias</p>
<p>Westlake et al., 2016 [74]</p>	<p>23 older adults: 12 fallers (70 ± 5 y.; MMSE = 29) and 11 non-fallers (69 ± 4 y.; MMSE = 30);</p> <p><u>Exclusion criteria:</u> significant musculoskeletal, vestibular or neurological impairments, MMSE score &lt; 24 (suggestive of dementia).</p>	<p><b>Retrospective study;</b></p> <p>Falls history over the last year;</p> <p>→ Fallers = (# of falls ≥ 1);</p> <p>Definition of a fall: [39].</p>	<p><u>Motor task:</u></p> <p>maintaining <b>postural stability</b> under 2 different perturbation conditions (“quickly grab one handrail and do not take a step”): predictable and unpredictable</p> <p><u>Concurrent cognitive tasks:</u></p> <p>- <b>verbal fluency task:</b> associated verb generation as quickly as possible after having heard a noun that was read by a staff member</p> <p>- <b>mental tracking/working memory task:</b> 1-back verb generation task</p> <p><u>Instructions:</u></p> <p>“not to prioritize one task over the other (i.e., balance vs. cognitive) once the perturbation occurred”</p> <p><u>Independent variables &amp; analysis:</u></p> <p>RT (time from the onset of platform perturbation to initial arm response), movement time (time from initial arm response to handrail contact), grasp error frequency, direction of grasp, errors in verb</p>	<p><b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b></p> <p>The only significant difference between older adult fallers and non-fallers concerned <b>grasp errors under both DT conditions</b>, with a <b>higher amount of errors</b> in fallers compared to non-fallers (verb generation: <math>t(21) = 9.31</math>, <math>p = 0.03</math>; 1-back verb generation: <math>t(21) = 9.64</math>, <math>p = 0.013</math>). A longer movement time under both DT conditions was observed in fallers in comparison with non-fallers, but this difference was not significant.</p> <p><u>Limitations:</u> retrospective fall data, only a lateral reach response induced from stationary standing while perturbations occur from multiple directions during dynamic walking.</p>	<p>1) M (some missing information like gender, and no statistical comparisons on demographic characteristics at baseline)</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) M (covariates not taken in to account in the statistical analyses)</p> <p>6) L</p> <p>→ Moderate risk of bias</p>



			generation; 2-way (3 groups x 4 conditions) repeated measures ANOVA with condition as the repeated factor and Tukey-Kramer post-hoc tests, or Kruskal-Wallis tests and Dunn's multiple comparison post-hoc tests		
Rinaldi et al., 2017 [59,60]	30 older adults: 15 fallers (70.1 ± 5.1 y.; 15 F; MMSE: 27 ± 3.2; Mini-BESTest: 19 ± 2.6) and 15 non-fallers (71.8 ± 5.8 y.; 15 F; MMSE: 28 ± 1.3; Mini-BESTest: 27.3 ± 1.6); <u>Inclusion criteria:</u> right-handed, normal or corrected-to-normal vision, no neurological /musculoskeletal disorder that would affect task performance; <u>Exclusion criteria:</u> cognitive impairment (MMSE < 24), ability to walk without assistance.	<b>Retrospective study;</b> 12-month follow-up period prior to data collection; → Fallers = (# of falls ≥ 1); Definition of a fall: [39].	<u>Motor task:</u> <b>walking</b> at self-selected speed (also perform as ST) (or <b>postural control:</b> performing the concurrent task while staying stationary → in [60]) <u>Concurrent task:</u> <b>motor task:</b> to reach and grasp a dowel with the right hand and without contacting the obstacles and knocking down the support, under different difficulty levels: stable (SB) and unstable (UB) bases without obstacles, stable base with obstacles at short (SSD) and long (SLD) distances, and unstable base with obstacles at short (USD) and long (ULD) distances <u>Instructions:</u> "to walk at their self-selected speed and to continue walking when grasping the dowel" <u>Independent variables &amp; analysis:</u> frequency of occurrence of: different joint couplings: right-left shoulder and right shoulder-right hip, different movement directions: flexion/extension and adduction/abduction, different patterns of coordination: in-phase, anti-phase, left and right shoulder phase and right hip phase; for group differences: 1-way ANOVAs + repeated measures 3-way ANOVAs (groups x conditions [grasping conditions or ST versus DT] x strides [stride at the moment of dowel contact and one stride before contact]) + ANCOVA for differences in gait phases (double or single support, ipsilateral or contralateral) used according to grasping difficulty, with walking speed as covariate + post-hoc tests with Bonferroni adjustments	<b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b> In a previous study from the group using the same dataset but other sort of analyses [60], <b>step width</b> (p = 0.003) and <b>step duration</b> (p = 0.03) were <b>greater</b> in fallers than in non-fallers. Furthermore, <b>step velocity</b> was <b>lower</b> in fallers compared to non-fallers, in <b>step at dowel contact</b> (p ≤ 0.0001). Moreover, fallers exhibited a <b>greater reduction in AP COM velocity</b> than non-fallers (p ≤ 0.0001), while they presented a <b>minimum AP COM velocity significantly earlier</b> than non-fallers <b>before dowel contact</b> (p = 0.004). <b>AP and ML margins of dynamic stability</b> were <b>greater</b> for fallers than for non-fallers (p = 0.022 and ≤ 0.001, respectively). Finally, concerning the prehension task, in comparison with non-fallers, fallers showed a <b>greater movement time</b> (p = 0.046) and <b>temporal difference between right heel contact and reaching onset</b> (p = 0.002), and <b>lower peak wrist velocity</b> (p = 0.0001), <b>time-to-peak grip aperture</b> (p = 0.002) only <b>during walking DT, peak grip aperture velocity during postural DT</b> (p = 0.042) and <b>time-to-peak grip aperture velocity</b> (p = 0.007). → <b>Generalized slowing down in movement performance in fallers.</b> Here (in [59]), <b>mean walking speed during both ST and DT</b> was significantly <b>lower</b> in fallers compared to non-fallers (p = 0.014 and 0.001, respectively). Fallers presented a <b>higher frequency of grasping the dowel in double support</b> in comparison with non-fallers, whereas <b>non-fallers</b> showed a <b>greater frequency of dowel grasping using a contralateral single support.</b> → <b>Greater decoupling between walking and prehension in fallers.</b> <u>Limitations:</u> level of difficulty of the manual task potentially not high enough to elicit modifications in interlimb coordination, subjects that were free to choose their walking speed.	1) L 2) L 3) L 4) L 5) L 6) M (all the p-values related to post-hoc tests were not clearly reported) → Low risk of bias
Zhou et al., 2017 [79]	738 older adults: 460 fallers (78.1 ± 5.5 y.; 292 F; SPPB: 9.3 ± 2.6) and 278 non-fallers (77.9 ± 5.3 y.; 178 F; SPPB: 9.4 ± 2.4); <u>Inclusion criteria:</u> aged 70	<b>Prospective study;</b> Over a follow-up period of 48 months using monthly falls calendar and follow-up interviews;	<u>Motor task:</u> <b>quiet standing</b> barefoot with eyes open for 30 s <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-3	<b>(1) Yes, (2) Yes &amp; (3) Yes:</b> Fallers exhibited <b>lower AP postural sway complexity</b> (measured by multiscale entropy) <b>under both ST and DT</b> in comparison with non-fallers (p = 0.007 and 0.002, respectively), while there were no differences in terms of sway speed, sway area, AP path length and	1) H (existing exclusion criterion MMSE ≤ 18, but no reporting of MMSE scores or other

	<p>years-old and older, ability to walk 6 m without personal assistance (walking aids permitted);</p> <p><u>Exclusion criteria:</u> cognitive impairment (MMSE <math>\leq</math> 18), terminal disease, severe hearing or vision loss.</p>	<p>→ Fallers = (# of falls <math>\geq</math> 1);</p> <p>Definition of a fall: “unintentionally coming to rest on the ground or other lower level, not as a result of an overwhelming external hazard or a major intrinsic event”.</p>	<p>subtraction from 500 (individual adaptation of the task in case of difficulty)</p> <p><u>Independent variables &amp; analysis:</u></p> <p>AP postural sway complexity metric, sway speed, sway area, AP path length;</p> <p>for differences between fallers and non-fallers as well as between quintiles of the continuous postural sway complexity: ANOVAs and Student’s t-tests + negative binomial regression with involvement of covariates → IRR</p>	<p>SPPB score.</p> <p>In negative binomial analyses with covariate adjustments, <b>AP complexity of postural sway during ST and DT was independently negatively associated with the incidence of future falls</b> (ST: IRR = 0.98, 95% CI = 0.96-0.99, <math>p = 0.02</math>; DT: IRR = 0.98, 95% CI: 0.97-0.99, <math>p = 0.02</math>). Unlikely, sway speed, sway area, AP path length and SPPB score did not significantly predict future falls rate.</p> <p><b>During ST</b>, older adults in the <b>quintile 1</b> had a significantly <b>higher falls rate than those in quintiles 4 and 5</b> (<math>p &lt; 0.01</math>), whereas, <b>during DT</b>, those in <b>quintiles 1,2 and 3 of complexity presented higher fall rates than those in quintiles 4 and 5</b> (<math>p &lt; 0.04</math>).</p> <p><b>In the DT condition</b>, older adults in the <b>lower quintiles of complexity (quintiles 1, 2 and 3) experienced significantly more falls during the follow-up</b> (IRRs = 1.48, 1.42 and 1.44, 95% CI = 1.04-1.99, <math>p &lt; 0.03</math>) <b>compared to those in the highest quintile of complexity (quintile 5)</b>.</p> <p><b>DT postural sway complexity</b>, with its particular sensitivity, was a <b>better predictor of future falls risk than ST postural sway complexity</b>.</p> <p><u>Limitations:</u> postural sway complexity only analyzed in AP direction.</p>	<p>measure of global cognitive functions, and no exclusion criterion such as neurological disease)</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) L</p> <p>6) L</p> <p>→ Moderate risk of bias</p>
<p>Santos et al., 2018 [61]</p>	<p>30 older women: 15 fallers (79 <math>\pm</math> 6 y.; 26 F; MMSE : 25 <math>\pm</math> 3; POMA, gait score = 11; POMA, balance score = 13) and 15 non-fallers (81 <math>\pm</math> 6 y.; 16 F; MMSE : 25 <math>\pm</math> 3; POMA, gait score = 10; POMA, balance score = 14) ;</p> <p><u>Inclusion criteria:</u> 65 years-old and older, ability to walk without the help of others or walking aids, (gender was not an inclusion criterion);</p> <p><u>Exclusion criteria:</u> visual impairments not corrected by eyeglasses or contact lenses, severe neuromuscular, musculoskeletal or cardiopulmonary disorders, dysfunction of the dominant upper limb, low cognition (MMSE &lt; 24).</p>	<p><b>Retrospective study;</b></p> <p>6-month follow-up period;</p> <p>→ Fallers = (# of falls <math>\geq</math> 1).</p>	<p><u>Motor task:</u></p> <p><b>walking</b> (also perform as ST) or <b>postural control</b> (performing the concurrent task while staying stationary)</p> <p><u>Concurrent task:</u></p> <p><b>manual task:</b> grasping, transporting and placing the dowel as close as possible to the center of the target, with 4 different levels of difficulty according to target distance (short versus long distance) and target size (target of either 8 or 12 cm)</p> <p><u>Independent variables &amp; analysis:</u></p> <p>variables related to the analysis of dowel position relative to target center: radial error, constant error (target center position - dowel center) in AP and ML directions; variables related to the analysis of dowel transport: duration of transport, peak wrist velocity during dowel transport, time to peak wrist velocity adjusted to the duration of transport; variables related to gait analysis: AP and ML margin of dynamic stability at dowel contact and release;</p> <p>Student’s t tests for independent samples + for dowel position and transport: 4-way (group x task x distance x diameter) ANOVAs with repeated measures; for gait variables: 2 4-way (group x task x</p>	<p><u>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</u></p> <p><b>During ST walking, step length</b> was significantly <b>smaller</b> in fallers compared to non-fallers (<math>p = 0.004</math>).</p> <p>Addition of a manual task did not affect gait stability of fallers but they underperformed in this manual task of grasping, transporting and placing a dowel. Indeed, fallers were <b>less accurate</b> (significantly <b>larger AP constant error</b>, particularly <b>for the walking DT combined with the 8-cm target</b>; <math>F(1,28) = 6.395</math>, <math>p = 0.017</math>) and <b>slower (during the postural DT and for the long distance</b> in comparison with the walking DT and short distance, respectively; <math>p \leq 0.0001</math>) <b>in the dowel-positioning task</b> than were non-fallers.</p> <p><u>Limitations:</u> sample composed only of women, task that is not as close to everyday activities as others could be, force applied on the dowel not quantified, different simple manual tasks not assessed.</p>	<p>1) M (only women)</p> <p>2) L</p> <p>3) L</p> <p>4) M (no formal definition of a fall)</p> <p>5) M (covariates not taken in to account in the statistical analyses)</p> <p>6) L</p> <p>→ Moderate risk of bias</p>

			distance x diameter) MANOVAs with repeated measures + post-hoc analysis with Bonferroni adjustment		
Uiga et al., 2018 [70]	<p>78 older adults: 34 fallers (69 ± 3.52 y.; 29 F; MMSE: 29.03 ± 0.98) and 36 non-fallers (68.89 ± 3.7 y.; 28 F; MMSE: 29.23 ± 1.11);</p> <p><u>Exclusion criteria:</u> physical or neurological impairment, static visual acuity worse than 20/40, use of walking aids, Cantonese version of MMSE &lt; 24/30 that would not reflect normal cognition.</p>	<p><b>Retrospective study;</b></p> <p>Falls history over the last 2 years;</p> <p>→ Fallers = (# of falls ≥ 1);</p> <p>Definition of a fall: “any fall for which a participant was clearly able to identify a timeframe, venue and mechanism”.</p>	<p><u>Motor task:</u></p> <p>1-minute <b>quiet standing</b></p> <p><u>Concurrent cognitive task:</u></p> <p><b>discrimination and decision-making task:</b> tone-counting task → monitoring and subsequently reporting the number of high-pitched tones presented via computer speakers</p> <p><u>Instructions:</u></p> <p>“to prioritize the balancing task”</p> <p><u>Independent variables &amp; analysis:</u></p> <p>COP measures of postural stability: ellipsoidal area (85.35%), average velocity, SD of ML axis (SD-ML), SD-AP, ML sample entropy (SampEn-ML), SampEn-AP, ML detrended fluctuation analysis (DFA-ML), DFA-AP, tone-counting accuracy;</p> <p>for group differences: 2 (task) x 3 (group, which also included a group of young adults) multivariate repeated measures ANOVAs separately for traditional COP variables and for complexity-based COP variables + univariate ANOVA for group differences in tone-counting accuracy + Bonferroni corrected pairwise comparisons</p>	<p><b>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</b></p> <p>Regarding traditional COP sway variables, there was a significant effect of group on balance performance (F(8,228) = 4.02, p &lt; 0.001), with <b>greater area of sway</b> (p &lt; 0.001), <b>SD-ML</b> (p = 0.006) and <b>SD-AP</b> (p = 0.007) in fallers compared to non-fallers. Particularly, under DT condition, group difference was particularly significant for area of sway. A significant effect of task condition on balance performance was also found (F(4,114) = 4.06, p = 0.004), with less average sway velocity (p &lt; 0.001) and less SD-AP (p = 0.043) under DT in comparison with ST. However, <b>no significant interaction between task condition and group</b> was observed.</p> <p>Concerning complexity-based COP sway variables, there was no significant group effect (older adults fallers versus non-fallers) on such kind of variables, a significant effect of task condition but with non-significant results to post-hoc tests, and no interaction between group and task condition.</p> <p>Moreover, no significant difference between older adult fallers and non-fallers was found for mean tone-counting accuracy.</p> <p><u>Limitations:</u> quiet standing is a relatively easy task, healthy and active older adults → lack of generalization in the old population.</p>	<p>1) M (no statistical comparisons on demographic characteristics at baseline)</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) L</p> <p>6) L</p> <p>→ Low risk of bias</p>

**F. Detailed Table of Results from the Systematic Literature Review About Dual Tasks Involving Turns**

**Table F.1 Articles about dual tasks involving turns that were included in the systematic literature review.** Abbreviations: y. = years; F = females; M = males; # = number; OR = odds ratio; CI = confidence interval; MMSE = Minimal Mental State Examination; POMA = Performance Oriented Mobility Assessment; RDST = Rapid Dementia Screening Test; AUC = Area Under the Curve.

Authors	Population	Falls	Dual-task paradigm & discriminative/predictive analysis	<p>(1) Do DT-related changes or DT performance discriminate fallers from non-fallers?</p> <p>(2) Are DT-related changes or DT performance predictors of falling?</p> <p>(3) Is the DT-related predictive strength superior compared to the ST-related one?</p> <p>(Yes/No/Inconclusive/Not addressed)</p>	Risk of bias via QUIPS tool (High H, Moderate M, Low L risk of bias)
<p>Muhaidat et al., 2014 [52]</p>	<p>62 independently ambulant community-dwelling older adults: 13 fallers (82 ± 12 y.; 9 F; MMSE: 29 ± 3; POMA: 26 ± 7) and 49 non-fallers (75 ± 11.5 y.; 32 F; MMSE: 29 ± 2; POMA: 28 ± 2);</p> <p><u>Inclusion criteria:</u> aged 65 years-old and older, living in the community, able to speak and understand English, able to travel to the assessment laboratory, MMSE ≥ 24, able to maintain their feet together and adopt the semi-tandem stance of the 4-test balance scale for 10 s</p> <p><u>Exclusion criteria:</u> use of walking frames and uncorrected visual or hearing impairments.</p>	<p><b>Prospective study;</b></p> <p>6-month follow-up validation cohort study, with monthly falls' diaries and telephone interviews;</p> <p>→ Fallers = (# of falls ≥ 1); + falls in the previous year.</p>	<p>8 dual-task tests and 1 triple-task test, with <b>straight walking with or without obstacles, walking with turns and stair descent</b> as motor tasks and <b>motor, verbal fluency, mental tracking/working memory, and discrimination and decision-making tasks</b> as concurrent tasks:</p> <ul style="list-style-type: none"> <li>- straight walking and visuospatial clock task;</li> <li>- walking with turns and naming animals;</li> <li>- walking with turns and counting backwards in 3s;</li> <li>- avoiding stationary obstacles and naming animals;</li> <li>- avoiding a moving obstacle and carrying a cup;</li> <li>- timed Up &amp; Go (TUG) and carrying a cup;</li> <li>- stair descent and naming animals;</li> <li>- walking while talking complex;</li> <li>- straight walking, visuospatial clock task, and carrying a cup</li> </ul> <p><u>Instructions:</u></p> <p>“to walk at their preferred speed and to perform both tasks as well as they could”</p> <p><u>Independent variables &amp; analysis:</u></p> <p>for ST, DT, proportionate and absolute differences: walking time, performance speed (total answers/second), accuracy (errors/total answers); random forest classification analysis (mean decrease in accuracy, mean decrease in Gini impurity, out-of-bag error rate) + binary logistic regression for the top 5 variables</p>	<p><b>(1) Not addressed, (2) Yes &amp; (3) Inconclusive:</b></p> <p>18 (36.7%) of the non-fallers and 10 (76.9%) of the fallers had an history of falls in the previous year (p = 0.01).</p> <p>This multivariate analysis <b>failed to identify a useful predictive tool, but gave an indication regarding the most useful variables in predicting falls in a multivariate analysis; that is, time for avoiding a moving obstacle in ST and DT while carrying a cup, time required to perform the walking task in the triple-task test, time for TUG in DT, and absolute difference for TUG time between ST and DT.</b></p> <p><b>For these 5 variables,</b> the ORs obtained with binary logistic regression were all <b>statistically significant</b> (OR = 1.29, 1.22, 1.12, 1.23, 0.61; 95% CI = 1.11-1.54, 1.07-1.41, 1.03-1.24, 1.1-1.41, 0.43-0.81; p = 0.002, 0.004, 0.01, 0.001, 0.002).</p> <p>Moreover, in terms of the form of DT outcomes, absolute difference could be a better predictor of falls than the proportionate difference.</p> <p><u>Limitations:</u> small sample size while large number of variables, short follow-up period, and participation of subjects in exercise classes.</p>	<p>1) M (no information regarding comorbidities; e.g., a neurological disorder)</p> <p>2) L</p> <p>3) L</p> <p>4) M (no formal definition of a fall)</p> <p>5) L</p> <p>6) L</p> <p>→ Moderate risk of bias</p>

<p>Ansai et al., 2016 [1]</p>	<p>67 community-dwelling older adults: 24 fallers (80-85 y.; 18 F; MMSE = 24) and 43 non-fallers (80-83 y.; 27 F; MMSE = 27);</p> <p><u>Inclusion criteria:</u> aged 80 years-old and older, living in the community (non-institutionalized), sedentary, ability to walk alone either with or without a cane;</p> <p><u>Exclusion criteria:</u> walking with a walker, cognitive, neurological and skeletal muscle disorders that prevent walking correctly, MMSE score below the designated educational level cut-off minus one standard deviation.</p>	<p>Cross-sectional (<b>retrospective</b>) study;</p> <p>Self-report of falls over the past 3 months;</p> <p>→ Fallers = (# of falls ≥ 1);</p> <p>Definition of a fall: “an event which results in a person coming to rest inadvertently on the ground or floor or other lower level and other than as a consequence of the following: sustaining a violent blow; loss of consciousness; sudden onset of paralysis; or an epileptic seizure” [16].</p>	<p><u>Motor task:</u></p> <p><b>TUG test (walking, turning and transfers)</b></p> <p><u>Concurrent tasks:</u></p> <ul style="list-style-type: none"> <li>- <b>mental tracking task/working memory task:</b> repeating days of the week in reverse order;</li> <li>- <b>motor task:</b> grasping a drinking filled with water</li> </ul> <p><u>Independent variables &amp; analysis:</u></p> <p>for both cognitive and motor DT-TUG tests: completion time, number of steps, occurrence of poured water, number of correct and incorrect answers, number of correct answers to time spent ratio, number of total answers to time spent ratio; Spearman product-moment correlation coefficient + Mann-Whitney tests or Chi-square tests</p>	<p><u>(1) Yes, (2) Not addressed &amp; (3) Not addressed:</u></p> <p>Most balance and DT variables were significantly correlated.</p> <p>While fallers did not show differences on balance tests in comparison with non-fallers, they <b>took significantly more time and steps during both TUG tests with cognitive</b> (p = 0.013 and 0.057, respectively) <b>or motor concurrent task</b> (p = 0.037 and 0.039).</p> <p><u>Limitations:</u> small sample size, absence of a random sampling, non-prospective analysis of falls, lack of certain gait variables such as step variability.</p>	<p>1) L 2) L 3) L 4) L 5) L 6) L → Low risk of bias</p>
<p>Ponti et al., 2017 [56]</p>	<p>36 community-dwelling healthy older adults: 18 fallers (75.25 ± 8.2 y.; 15 F; MMSE: 23.75 ± 3.93) and 18 non-fallers (70.94 ± 6.69 y.; 10 F; MMSE: 26.46 ± 4.35);</p> <p><u>Inclusion criteria:</u> aged 60 years-old and older, ability to stand up from a chair with arms without other person’s help and to walk independently without aid device, eutrophic;</p> <p><u>Exclusion criteria:</u> amputation and/or use of lower limb prosthesis or other device that modifies the gait pattern, neurological or muscular disease, any condition listed it Charlson Comorbidity Index, obesity, presence of any important risk factor that compromises safety, according to the evaluator.</p>	<p><b>Retrospective</b> study;</p> <p>Participants questioned about their history of falls over the past year;</p> <p>Definition of a fall: “come to inadvertently get in the soil or in other lower level, excluding intentional position changes to lean on furniture, walls or other objects” [76].</p>	<p><u>Motor task:</u></p> <p><b>TUG test</b></p> <p><u>Concurrent tasks:</u></p> <ul style="list-style-type: none"> <li>- <b>motor task:</b> carrying a cup filled with water (TUG-M)</li> <li>- <b>mental tracking/working memory task:</b> continuous simple subtraction questions (TUG-C)</li> </ul> <p><u>Independent variables &amp; analysis:</u></p> <p>completion time, mean completion time among tasks, number of steps; for the whole signal (containing the 3 TUG tasks), TUG ST, TUG-M and TUG-C: Power Spectral Entropy (PSE), Power Spectrum Peak Frequency (PSPF), Power Spectrum Peak (PSP), Weighted Power Spectrum Peak (WPSP); distance-based features, features fusion;</p> <p>t-tests for group comparisons on traditional TUG parameters + Mann-Whitney U-tests for group comparisons on frequency domain features, and fusion of relevant features + ROC analysis (sensitivity, specificity, AUC, f1-Score)</p>	<p><u>(1) Yes, (2) Yes &amp; (3) Yes:</u></p> <p>Traditional features such as (mean) completion time and number of steps were not significantly different between fallers and non-fallers in any of the versions of TUG test (ST and both DT).</p> <p>Regarding frequency domain features, only <b>lower PSE</b> (p = 0.014), <b>WPSP2</b> (p = 0.022) <b>and WPSP3</b> (p = 0.009) <b>related to TUG-C</b> as well as <b>lower features fusion</b> (p = 0.001), <b>lower PSE</b> (p = 0.029) <b>and PSP</b> (p = 0.014) <b>differences between the whole signal and the TUG-C, lower PSPF difference between TUG and TUG-M</b> (p = 0.049), and <b>lower WPSP difference between TUG-M and TUG-C</b> (p = 0.034) as well as <b>lower distances fusion</b> (p = 0.001) were significantly <b>able to identify fallers from non-fallers</b>.</p> <p>Outcomes from the ROC analysis were consistent with the previously reported results: <b>the extracted frequency and distance-based features had higher values of AUC, f1-Scores, sensitivity and specificity compared to the traditional parameters</b> (e.g., completion times) <b>related to TUG tests</b>. However, the <b>best results were allocated to the fusion of distance-based features</b>, with AUC = 0.84, f1-Score = 0.83, sensitivity = specificity = 0.83 for the probability cut-off point 0.5 with a 95% CI 0.62-0.91.</p> <p>Therefore, both distance-based features and fusion have shown to be interesting methods to improve the results.</p> <p><u>Limitations:</u> sample size, intraclass variability of the data.</p>	<p>1) M (no criterion about global cognitive functions, even if MMSE scores were relatively high) 2) L 3) L 4) L 5) L 6) L → Low risk of bias</p>

<p>Asai et al., 2018 [3]</p>	<p>537 community-dwelling older adults: 103 fallers (77.5 ± 6 y.; 68 F; RDST: 9.5 ± 3.1) and 434 non-fallers (76.5 ± 6.4 y.; 278 F; RDST: 9.6 ± 2.8);</p> <p><u>Inclusion criteria:</u> aged 60 years-old and older, ability to walk independently with or without an assistive device, no physical or social care services from the local government, no self-reported neurological disorders that could affect mobility or balance;</p> <p><u>Exclusion criteria:</u> inability to perform the ST- or DT-TUG, inability to understand the DT method because of severe cognitive impairment, incomplete data on any of the measurements.</p>	<p><b>Retrospective</b> study; Self-administered questionnaire; Definition of a fall: [39].</p>	<p><u>Motor task:</u> <b>TUG</b> test (walking at a comfortable and safe pace)</p> <p><u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-1 subtraction aloud from 100</p> <p><u>Instructions:</u> no instructions given regarding which task to prioritize</p> <p><u>Independent variables &amp; analysis:</u> completion time, last number spoken, backward counting speed ((100-last number counted)/completion time), DTC (sort of proportionate difference, with the mean completion time among ST and DT as divisor); Unpaired t-tests for group comparisons + multivariate logistic regression models with history of falls as dependent variable and with covariates (age, sex, height, weight and RDST score) + final logistic regression model with significant and uncorrelated TUG-related variables + ROC curve → AUC, cut-off value, sensitivity, specificity → classification into 4 fall risk groups and ORs + final logistic regression model applied on well-functioning (ST-TUG score &lt; 7 s), transitional-functioning (ST-TUG score = 7-16 s) and frail groups (ST-TUG score &gt; 16 s)</p>	<p><u>(1) Yes, (2) Yes &amp; (3) Yes – additional value:</u></p> <p>Fallers took significantly <b>longer to complete ST-TUG</b> (p = 0.002) and presented a <b>lower DTC value</b> (p = 0.13) in comparison with non-fallers.</p> <p>Either in separate regression models or in a common regression model, even after adjustment for covariates, <b>ST-TUG score and DTC value were significantly associated with fall history</b> (ST-TUG score: OR = 1.133, 95% CI = 1.029-1.249, p = 0.011, cut-off value = 7.98 s, AUC = 0.58, sensitivity = 46%, specificity = 71%; DTC value: OR = 0.984, 95% CI = 0.968-0.998, p = 0.032, cut-off value = 15.4%, AUC = 0.57, sensitivity = 70%, specificity = 44%). Compared to the other three fall risk groups, a <b>higher proportion of older adults from the fall risk group characterized by a slower ST-TUG score and a lower DTC value reported a history of falls.</b></p> <p>Finally, <b>both above mentioned predictors were similarly significantly associated with falls history in the transitional functioning group</b> (ST-TUG time = 7-16 s; ST-TUG score: OR = 1.198, 95% CI = 1.019-1.408, p = 0.029; DTC: OR = 0.979, 95% CI = 0.958-0.997, p = 0.043), but <b>not in the well-functioning group</b> (ST-TUG score &lt; 7 s).</p> <p><u>Limitations:</u> cross-sectional study → not possible to establish a causal relationship between TUG-related variables and the occurrence of a fall, various potential bias affecting the results (e.g., recall bias due to a fall history obtained via a questionnaire, selection bias because of the relatively healthy lives of the participants, confounding bias such as executive function that can affect both fall risk and DT performance), no assessment of the effects of different concurrent tasks on the TUG test score, no comparison between the predictive validity of the DT-TUG test and the DT gait test.</p>	<p>1) M (no exclusion criterion regarding non-severe cognitive impairment, even if RDST scores were high)</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) L</p> <p>6) L</p> <p>→ Low risk of bias</p>
<p>Toma-Carus et al., 2019 [69]</p>	<p>367 community-dwelling older adults: 96 fallers (78 F/18 M; 71.5 ± 9/73.5 ± 8 y.; Clock Drawing Test score: 19 ± 2/20 ± 1) and 271 non-fallers (179 F/92 M; 70 ± 7/73 ± 8 y.; Clock Drawing Test score: 19 ± 2/19 ± 1);</p> <p><u>Inclusion criteria:</u> aged 65 years-old and older, ability to walk and understand the study protocol by themselves;</p> <p><u>Exclusion criteria:</u> diagnosis of dementia, Parkinson's disease or vertigo, Clock Drawing Test score &lt; 18 (associated with</p>	<p>Cross-sectional (<b>retrospective</b>) study; Fall history over the last year; → Fallers = (# of falls ≥ 1); Definition of a fall: "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects" [76].</p>	<p><u>Motor task:</u> <b>TUG</b> test</p> <p><u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-1 subtraction from 100</p> <p><u>Instructions:</u> "walk as quickly and safely as possible (...), and count as quickly and surely as possible"</p> <p><u>Independent variables &amp; analysis:</u> for TUG-ST and TUG-DT: time spent on the test task accomplishment; for TUG-DT: number of cognitive errors, cognitive stops and motor stops; DTC being a kind of proportionate difference (difference in time spent between TUG-ST and TUG-DT, divided by the</p>	<p><u>(1) Yes, (2) Yes &amp; (3) Yes:</u></p> <p>History of falls was significantly positively correlated to mean TUG-ST and TUG-DT time spent, mean cognitive errors, mean cognitive stops and mean motor stops.</p> <p>Among <b>men</b>, <b>mean TUG-DT time spent</b> (p = 0.014), <b>mean cognitive stops</b> (p = 0.049), <b>mean motor stops</b> (p = 0.023), <b>DTC</b> (p &lt; 0.001), <b>[TUG-DT time + cognitive stops]</b> (p = 0.006) and <b>[TUG-DT time + cognitive stops + cognitive errors]</b> (p = 0.021) were significantly <b>higher</b> in fallers compared to non-fallers. Regarding <b>women</b>, only significantly <b>greater [TUG-DT time + cognitive stops + cognitive errors]</b> (p = 0.045) and <b>mean motor stops</b> (p = 0.024) were found in fallers in comparison with non-fallers.</p> <p>In <b>men</b>, a <b>significant AUC for predicting risk of falls</b> was found for <b>mean TUG-DT time spent</b> (p = 0.014), <b>[TUG-DT time + cognitive stops]</b> (p = 0.006), <b>[TUG-DT time + cognitive stops + cognitive errors]</b> (p = 0.021) and <b>DTC</b> (p &lt; 0.001), whereas it was only for <b>[TUG-DT time +</b></p>	<p>1) L</p> <p>2) L</p> <p>3) L</p> <p>4) L</p> <p>5) L</p> <p>6) L</p> <p>→ Low risk of bias</p>

	cognitive impairment and different types of dementia).		average score between both tasks); [TUG-DT time + cognitive stops], [TUG-DT time + cognitive stops + cognitive errors]; non-parametric Spearman's correlations + Mann-Whitney U tests in both sexes + AUC of ROC curve, cut-off values, sensibility and specificity	<b>cognitive stops</b> ] (p = 0.046) and <b>[TUG-DT time + cognitive stops + cognitive errors</b> ] (p = 0.036) in women. The <b>best predictor</b> (in terms of AUC) was <b>DTC in men</b> (0.764) and <b>[TUG-DT time + cognitive stops + cognitive errors] in women</b> (0.583). <u>Limitations:</u> cross-sectional design limiting the extraction of conclusions about the predictive value of the TUG, small sample size, reliability of the new variables [TUG-DT time + cognitive stops] and [TUG-DT time + cognitive stops + cognitive errors] not tested yet.	
Asai et al., 2020 [4]	649 community-dwelling older adults: 331 young-older adults (60–74 y.), with 78 fallers (72.1 ± 2.9 y.; 53 F; RDST: 10.6 ± 2.5) and 253 non-fallers (71.7 ± 2.8 y.; 164 F; RDST: 11 ± 1.7), and 318 old-older adults (≥ 75 y.), with 97 fallers (80.4 ± 3.6 y.; 69 F; RDST: 9.3 ± 2.9) and 221 non-fallers (80.8 ± 3.9 y.; 139 F; RDST: 9.1 ± 2.9) <u>Inclusion criteria:</u> aged 60 years-old and older, ability to walk independently with or without an assistive device; <u>Exclusion criteria:</u> inability to perform the ST- or DT-TUG, incomplete data on any of the measurements, self-reported neurological disorders that could affect mobility or balance.	Longitudinal observation study ( <b>prospective</b> ) study; 1-year follow-up; Definition of a fall: [39].	<u>Motor task:</u> <b>TUG</b> test (walking at a comfortable and safe pace) <u>Concurrent cognitive task:</u> <b>mental tracking/working memory task:</b> serial-1 subtraction aloud from 100 <u>Instructions:</u> no instructions given regarding which task to prioritize <u>Independent variables &amp; analysis:</u> completion time, last number spoken, backward counting speed ((100-last number counted)/completion time), DTC (sort of proportionate difference, with the mean completion time among ST and DT as divisor); Mann-Whitney U tests + unpaired t-tests + multivariate logistic regression models with covariates (age, sex, height, weight, RDST score at baseline, change in RDST score and comorbidities)	<u>(1) Yes, (2) Yes &amp; (3) Yes – additional value:</u> <b>In young-older adults</b> , fallers took <b>longer to perform ST-TUG</b> in comparison with non-fallers (p = 0.02). <b>Old-older adult fallers</b> , for their part, showed <b>lower DTC</b> than non-fallers (p = 0.005). Regarding <b>predictive power for risk of falls</b> , ST-TUG time was not significantly associated with the occurrence of falls in the follow-up year in young older adults anymore, after controlling for covariates such as RDST and backward counting speed during DT-TUG. However, <b>in old older adults</b> , a <b>longer ST-TUG time</b> (OR = 1.143, 95% CI = 1.018-1.285, p = 0.024) and <b>lower DTC value</b> (OR = 0.981, 95% CI = 0.963-0.999, p = 0.049) were significantly associated with falls occurrence, even after adding RDST at baseline, change in RDST score, backward counting speed during DT-TUG and comorbidities as covariates into the regression model. Therefore, <b>DT may provide an additional value in TUG for predicting falls among old-older adults</b> . <u>Limitations:</u> relatively low follow-up rate (649/987, 66%), potential selection bias, some data regarding falls were not obtained, potential additional confounders, quite easy cognitive task, no other concurrent task tested.	1) M (no exclusion criterion regarding cognitive impairment, even if RDST scores were high) 2) M (relatively low follow-up rate) 3) L 4) L 5) L 6) L → Moderate risk of bias

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## Etude 2 – Supplementary material

A new paradigm to study the influence of attentional load on cortical activity for motor preparation of step initiation

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Article publié dans *Experimental Brain Research*.





## 8 Supplementary Material

### 8.1 Introduction

Next to the previously reviewed alterations of target N200 and P300 with target congruency (see the Introduction section of the main paper), modulations of target P100 and N100 by the presence or absence of a foregoing cue have also been observed (Neuhaus et al. 2010; Williams et al. 2016). Such kind of alterations of target-locked early ERP components would be due to attentional top-down processes representing the amount of information used to direct visual attention. Target P100 amplitude was significantly higher at parietal sites in the no cue condition compared to the situation with a cue as well as when following a central cue compared to a spatial cue according to some authors (Williams et al. 2016), while other scientists observed a reversed orienting effect on target P100 amplitude in the parieto-occipital scalp regions (Galvao-Carmona et al. 2014). As a sign of amplified perceptual discrimination, alerting induced increased amplitude of target N100 over parietal leads (Neuhaus et al. 2010; Williams et al. 2016) whereas target N100 following orienting was enhanced over occipital and parieto-occipital leads (Neuhaus et al. 2010; Williams et al. 2016), though Galvao-Carmona et al. did not find any orienting effect for target N100 (Galvao-Carmona et al. 2014).

Concerning ERSPs associated with the standard ANT, according to Fan et al. (Fan et al. 2007), each attentional network may have a distinct set of oscillations related to its activity. In the context of the alerting and orienting networks, theta-, alpha- and beta-band activity has been shown to decrease at 200-450 ms after the presentation of a neutral cue and corresponds to the usual desynchronisation of electrical activity after a warning. Unlike Fan et al. (Fan et al. 2007), Deiber and colleagues (Deiber et al. 2013) observed a transient increase of theta power after the presentation of a cue. These oscillations known to be significantly phase-locked after the visualisation of a stimulus would contribute to the generation of P100 event-related component (Makeig et al. 2002; Klimesch et al. 2011). During the cue-target interval, ERDs in alpha and beta bands were observed (Deiber et al. 2013) and, as being proportional to the amount of information carried by the cue, these ERDs signal the level of attentional mobilisation prior to target occurrence (Klimesch 1999; Pfurtscheller 1999; Bastiaansen and Brunia 2001; Engel and Fries 2010; Tzagarakis et al. 2010). Concerning target-locked analysis, the executive control network (i.e. incongruent minus congruent target conditions) exhibited a complex time-frequency pattern: an early (<400 ms) increase of a broad-band activity including beta band, followed by a late (>400 ms) decrease of a broad-band activity including theta, alpha and beta bands (Fan et al. 2007). Indeed, Deiber et al. (Deiber et al. 2013) also found, together with a transient ERS in theta power, an ERD in alpha and beta bands after the target presentation, which was more pronounced for incongruent flankers. Furthermore, alerting and orienting effects on target-locked ERSPs have been observed (Fan et al. 2007). Firstly, under no cue and central cue conditions, an early ERS in some frequency components of beta band and

higher frequencies occurred between 100 and 300 ms after target presentation and was related to the orienting processing needed when the target surrounded by flankers appeared on the computer screen. In the case of a spatial cue preceding the target, such an ERS was therefore not seen. Second, a late target-locked ERD in theta-, alpha- and beta-band power was more pronounced under no cue condition compared to central cue and spatial cue conditions because this decrease in power was associated with the alerting status recruited for the target response (Fan et al. 2007).

On the strength of the above reported results for the standard seated ANT, the present section will present a secondary objective of the study: the replication of similar target-locked ERPs and ERSPs in the context of the ANT combined with step initiation.

## **8.2 Material and methods**

### **8.2.1 Target-locked ERPs analysis**

Target-locked ERPs were analysed with the EEGLAB toolbox (Delorme and Makeig 2004), with a baseline interval from 1500 to 1000 ms before target onset, in the context of comparison of target conditions. The time window analysis was from -200 ms before S2 to 1000 ms after. We first analysed ERP scalp distribution maps between 250 and 650 ms. Next, based on the observation of topographic maps of ERPs and according to the well-known topography of such ERP components (Berchicci et al. 2012), P300 wave's characteristics were assessed and collected by grand-averaging over the relevant midline electrode: Pz). P300 peak latencies and amplitudes of all the subjects were compared as a function of the conflict resolution condition (target surrounded by congruent vs. incongruent flankers). The amplitude of potentials was measured as the difference between the maximum peak of the ERP waveform and the mean baseline voltage. Latency was defined as the interval between target presentation and the point of peak amplitude in the time window of the potential. Time window of P300 ranged from 250 to 650 ms after target presentation. On the other hand, when we evaluated the alerting and orienting effects on target ERPs, we used a baseline interval from -200 ms until target presentation in order not to take into account the contingent negative variation which is not analysable because of the variable time interval between cue and target. The time window analysis was from -200 ms before S2 to 800 ms after, and ERP scalp distribution maps between 0 and 300 ms were observed in order to assess and collect N100 wave's features by grand-averaging over the relevant midline electrodes, i.e. Pz and POz (Di Russo et al. 2002, 2003). Finally, potential alerting and orienting effects on N100 peak latencies and amplitudes were evaluated. Time window associated with N100 ranged between 150 and 300 ms after S2. The grand-averaged ERPs were low-pass filtered at 40 Hz for displaying purpose only. It should be noted that N200 and P100 waves were not involved in the comparison between target and cue conditions, respectively, because these types of ERPs were not clearly visible in most individual event-related averages.

After the manual rejection of epochs of EEG data with artefacts, participants showed trials that were distributed as follows (median (first quartile - third quartile)): 125 (112.25 - 134.5) congruent trials, 116.5 (110.25 - 126.5) incongruent trials, and 40.5 (37 - 44.75), 48 (42.5 - 50), 115.5 (106.25 - 124), 39.5 (35.25 - 42) trials corresponding respectively to no cue condition, central cue condition, and both valid and invalid spatial cue conditions.

### **8.2.2 Target-locked ERSPs analysis**

Target-locked ERSP data were also analysed using the EEGLAB toolbox (Delorme and Makeig 2004) with a baseline interval of between 1500 and 1000 ms before target presentation. In order to characterise event-related EEG oscillations such as ERD and ERS in theta (4-7 Hz), alpha (8-12 Hz) and beta (13-30 Hz) bands, we applied a time-frequency analysis using a continuous Morlet wavelet transform, with 2 cycles at the lowest frequency and 7.5 at highest (factor: 0.5), and analysed ERSP scalp distribution maps between 0 and 700 ms after S2.

### **8.2.3 MRCP source localisation**

In order to have a more accurate idea of generators of MRCP, source localisation was performed on response-locked EEG data. To this end, MRI (template) and EEG data were co-registered via identification of the same anatomic landmarks (the left and right pre-auricular points and nasion). A realistic head model was built by segmenting the MRI data with Freesurfer software (Dale et al. 1999). The lead field matrix was then computed for a cortical mesh with 15000 vertices using Brainstorm software (Tadel et al. 2011) and OpenMEEG software (Gramfort et al. 2010). Afterwards, the weighted minimum norm estimate was used to reconstruct the dynamics of the EEG signal's cortical sources, using Brainstorm software. The obtained source matrices were finally averaged over epochs and subjects for each condition of cue and target in order to reflect sources of ERPs, and then averaged in time over a 200-ms time interval before APA onset.

### **8.2.4 Statistical analyses**

By means of EEGLAB toolbox, permutation tests for multiple comparisons were performed on overall ERP and ERSP data with FDR correction. Afterwards, conflict resolution, alerting and orienting effects on specific ERP waveforms at particular scalp sites were assessed by using a Student's t-test or a Wilcoxon's signed rank test (if normality is not observed) on peak amplitude and latency, with SPSS 16.0 software. The threshold for statistical significance was set to  $p=0.05$ .

## 8.3 Results

### 8.3.1 Target-locked ERPs

In Fig. 7, a negative wave (corresponding to target N100) was seen on parietal and occipito-parietal leads. No significant orienting effect was associated with this ERP waveform, but an alerting effect on target N100 wave was observed at Pz and POz (Fig. 8), with a higher N100 amplitude in central cue condition compared to trials without a cue (respectively  $-2.28 \pm 1.81 \mu\text{V}$  vs.  $-2.61 \pm 2.08 \mu\text{V}$  at Pz with  $p=0.005$ , and  $-2.71 \pm 1.87 \mu\text{V}$  vs.  $-3.08 \pm 2.25 \mu\text{V}$  at POz with  $p=0.014$ ).

Besides, the ERP scalp distribution maps between 250 and 650 ms revealed a positive component (corresponding to P300) in the step initiation task (see Fig. 9). Maximum amplitude was measured at Pz for both flanker conditions. The peak latency was significantly longer ( $p=0.002$ ) in trials with incongruent flankers than in trials with congruent flankers, whereas the peak amplitude was not significantly different between target conditions (respectively  $457 \pm 108 \text{ ms}$  vs.  $426 \pm 96 \text{ ms}$  for peak latency, and  $2.66 \pm 2.36 \mu\text{V}$  vs.  $2.88 \pm 2.7 \mu\text{V}$  for peak amplitude).

### 8.3.2 Target-locked ERSPs

Regarding the effect of cues on target-related ERSPs, we noticed an alerting effect but no effect of orientation (see Fig. 10). Indeed, alpha and beta desynchronisations are related to attentional load and particularly warning and, over the somatosensory cortex and the motor cortex, they mirror the preparation phase toward the movement and the movement itself. These ERDs started significantly later in trials without cue compared to trials preceded by a central cue.

As shown in Fig. 11, time-frequency analysis of the alpha band revealed posterior ERD that tended to be more pronounced and lasted significantly longer in trials with incongruent flankers. The posterior suppression of alpha-band oscillatory activity was accompanied by anterior and central enhancements of alpha activity. Time-frequency analysis of the beta band revealed a central-posterior ERD that was also more pronounced and lasted significantly longer for incongruent flankers than for congruent flankers.

### 8.3.3 Localisation of MRCP sources

It was surprising to have observed a maximal BP at parietal leads while this motor potential is supposed to be symmetrically distributed and maximal at the midline centro-parietal area (Shibasaki and Hallett 2006). Thanks to MRCP source localisation averaged over a 200-ms time interval before APA onset (see Fig. 12), we confirmed the location of BP over the sensorimotor cortex, with the supplementary motor area as a potential generator. EEG activity was also found in orbito-frontal and temporal regions as a sign of attentional load.

#### 8.4 Discussion regarding target-locked EEG activity

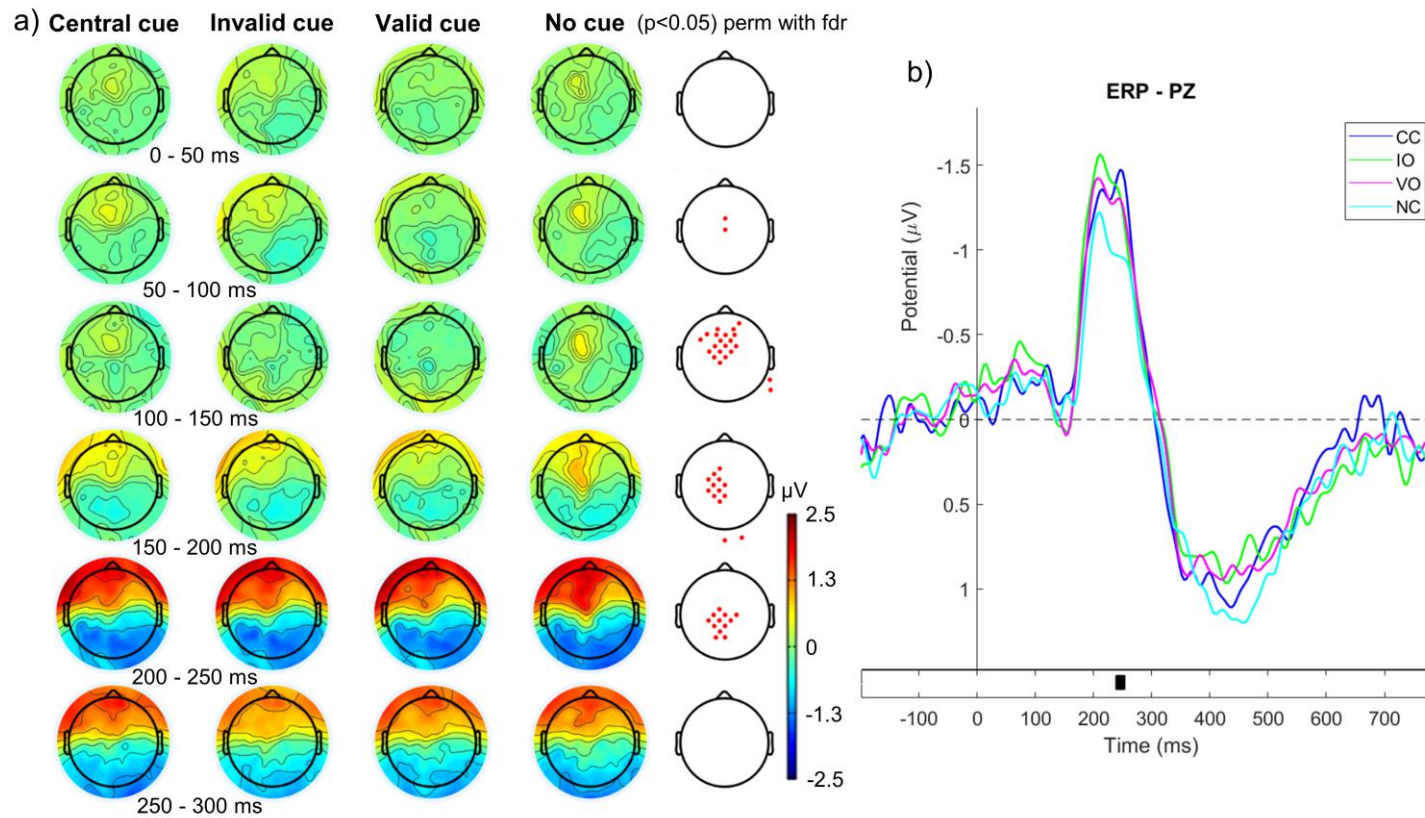
Target-locked ERPs: When mapping the ERPs between 250 and 650 ms after target presentation in a step initiation ANT, we observed a positive wave with a peak amplitude at Pz; this might correspond to the P300 component. An effect of conflict resolution on P300 amplitude was found. A lower P300 amplitude in the presence of incongruent flankers might be accounted for by the greater task difficulty in this condition (Polich 1987; Hagen et al. 2006) and might thus be associated with greater response inhibition (Groom and Cragg 2015). Contradictory results have also already been reported in ERP studies of the standard ANT, with a lower amplitude in incongruent trials in some studies (Neuhaus et al. 2007, 2010; Deiber et al. 2013; Galvao-Carmona et al. 2014) but not in others (Fan et al. 2007; Williams et al. 2016), and with a possible effect of age (Deiber et al. 2013). Furthermore, our analyses revealed target-related latency modulation. Indeed, in ANT combined with step initiation, the P300 peak latency was significantly longer in incongruent trials than in congruent trials. No previous studies of the standard ANT paradigm have reported target-related variations in latency (Fan et al. 2007; Neuhaus et al. 2010; Deiber et al. 2013; Galvao-Carmona et al. 2014) with the exception of Williams et al. and Neuhaus et al. (Neuhaus et al. 2007; Williams et al. 2016), who demonstrated that P300 peak latency was longer for incongruent flankers. The increased latency of P300 wave may mirror the use of more time to evaluate the target surrounded by incongruent flankers (Falkenstein et al. 1994; Verleger et al. 2006). Concerning the influence of cues on target-locked ERPs, we noticed an alerting effect on amplitude target N100, with higher target N100 amplitude over parietal and occipito-parietal electrodes for trials with a central cue compared to situations without any cue. It confirms what Neuhaus et al., Williams et al. and Galvao-Carmona and colleagues found (Neuhaus et al. 2010; Galvao-Carmona et al. 2014; Williams et al. 2016), although no orienting effect on target N100 amplitude was observed in this study unlike (Neuhaus et al. 2010; Williams et al. 2016). This increased target N100 amplitude related to alertness can be interpreted as an amplified perceptual discrimination of the target (Neuhaus et al. 2010) or an enhanced attention to the target (Williams et al. 2016), as N100 enhancement would mirror orienting to and enhanced processing of any input found relevant in a preliminary sensory analysis (Näätänen and Michie 1979).

Target-locked ERSPs: With regard to the ERSP data, we observed posterior alpha-band ERD and an anterior enhancement of alpha activity. This association has previously been described (Pfurtscheller 1999; Bastiaansen and Brunia 2001); alpha oscillatory activity was suppressed in areas engaged in visual attention, and ERS appeared concomitantly in brain regions not involved in stimulus processing or maintenance (Foxe and Snyder 2011; Deiber et al. 2013). In fact, ERS is thought to reflect the active inhibition of cortical regions, whereas ERD is thought to reflect the activation of regions engaged in visuospatial attention or motor execution (Pfurtscheller 1999). As reported in studies investigating the standard seated ANT and carried out by Deiber et al. (Deiber et al. 2013) and Fan et al. (Fan et al. 2007), alpha-band ERD tended to be more pronounced as well as of longer duration in trials with incongruent

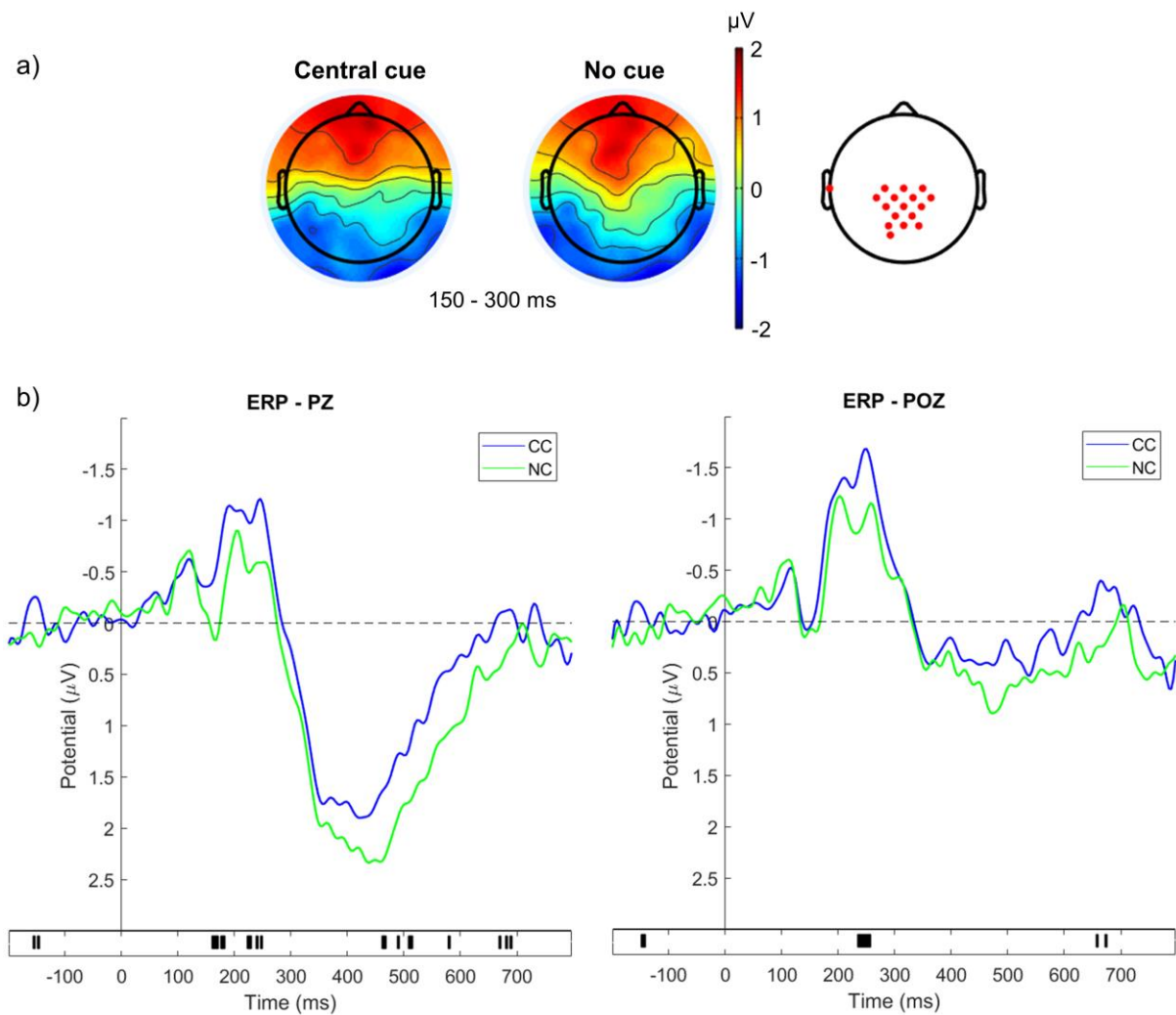
flankers than in trials with congruent flankers - reflecting the greater attentional load. Concerning beta-band oscillations, our results showed central ERD that was more pronounced and lasted longer for incongruent trials than congruent trials in the step initiation ANT (as also reported by Deiber et al. (Deiber et al. 2013)). This reflects the specific participation of areas involved in motor preparation and execution. It is noteworthy that posterior alpha ERD and posterior and central beta ERD occurred around 200 ms after target presentation; this corresponds to movement preparation (the medians - for each subject - of the reaction time in our step initiation ANT ranged from 158 to 269 ms) but is also seen in attentional tasks (Klimesch et al. 2007). The influence of cues on target-locked ERSPs was rarely studied before. We found alpha and beta ERDs over the parietal cortex that started significantly later in trials without cue compared to trials preceded by a central cue, reflecting the increased perceptual discrimination of the target associated with the presence of a cue that was already shown through target-locked ERPs.

## **8.5 Figures**

**Fig. 7 Influence of cue modality on target-locked ERPs.** a) ERP scalp distribution maps between 0 and 300 ms after presentation of the target, for trials with a central cue (first column), an invalid spatial cue (second column), a valid spatial cue (third column) and without cue (fourth column) in the step initiation ANT. Column to the right of ERP scalp distribution maps: significant differences in a permutation test with FDR correction (threshold at  $p < 0.05$ ) are marked as red dots. b) ERPs at Pz for the four kinds of cues. A negative wave (corresponding to N100) was observable. At the bottom, time intervals highlighted in black represent those for which the p-value related to permutation statistics with FDR correction is significant (i.e.  $< 0.05$ ). CC = trials with a central cue; IO = trials with an invalid spatial cue; VO = trials with a valid spatial cue; NC = trials without cue

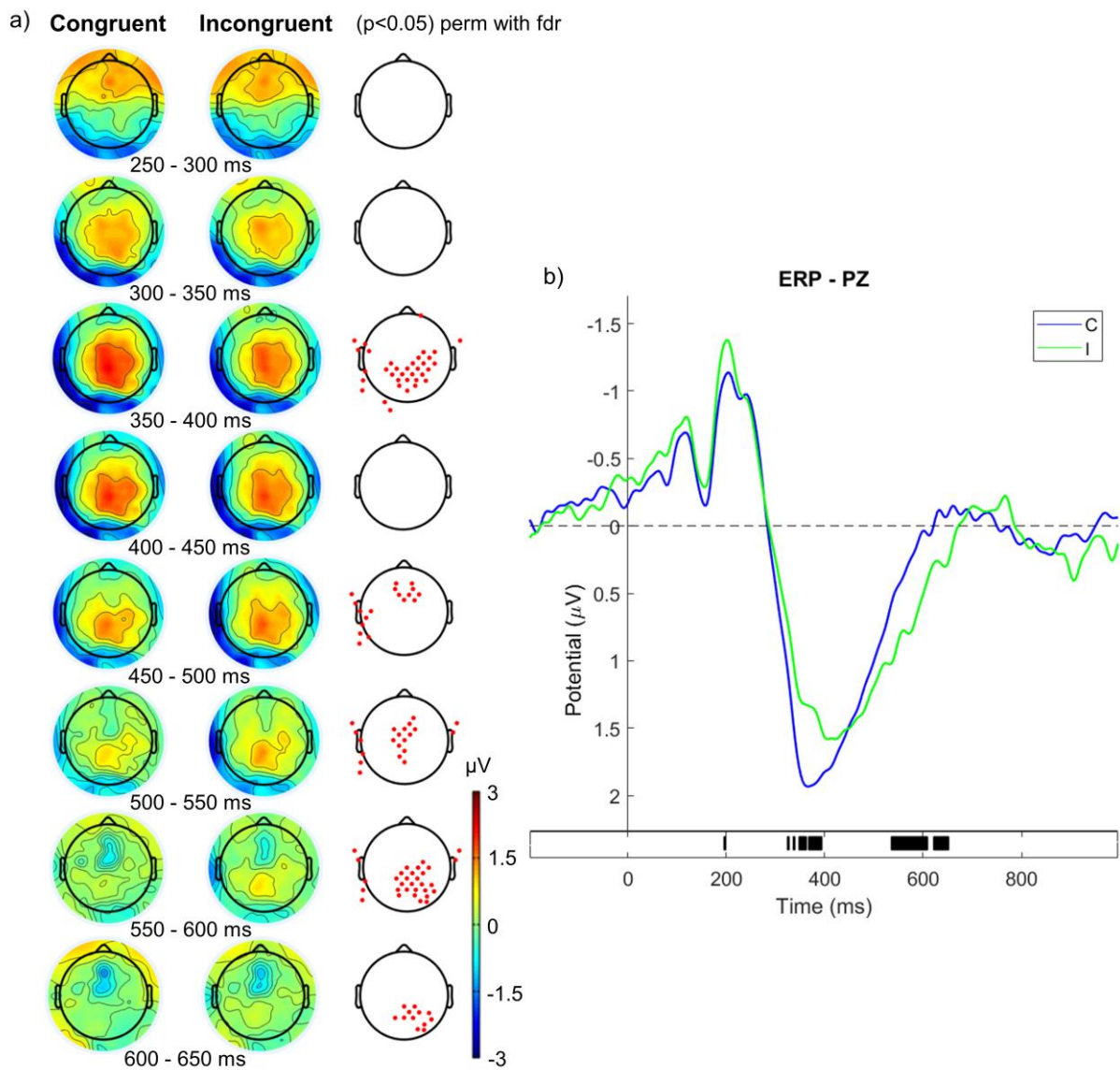


**Fig. 8 Alerting effect on N100.** a) ERP scalp distribution maps between 150 and 300 ms after presentation of the target, for trials with a central cue (CC, first column) and without cue (NC, fourth column) in the step initiation ANT. Column to the right of ERP scalp distribution maps: significant differences in a permutation test with FDR correction (threshold at  $p < 0.05$ ) are marked as red dots. b) ERPs at Pz and POz for trials with a central cue and without cue. A negative wave (corresponding to N100) was observable. At the bottom, time intervals highlighted in black represent those for which the p-value related to permutation statistics with FDR correction is significant (i.e.  $< 0.05$ ). CC = trials with a central cue; NC = trials without cue





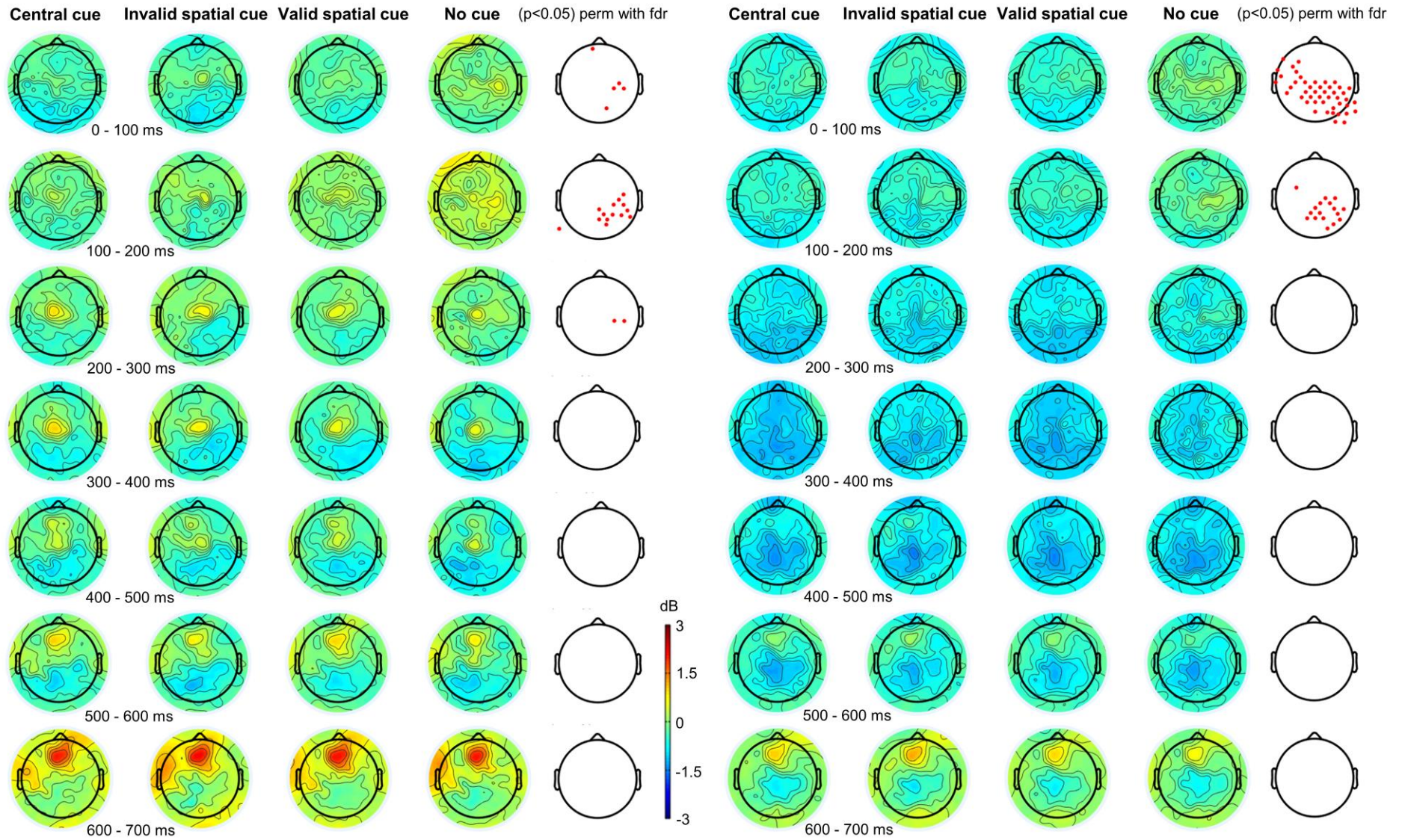
**Fig. 9 Influence of target modality on ERPs.** a) ERP scalp distribution maps between 250 and 650 ms after presentation of the target, for trials with congruent flankers (first column) or incongruent flankers (second column) in the step initiation ANT. Column to the right of ERP scalp distribution maps: significant differences in a permutation test with FDR correction (threshold at  $p < 0.05$ ) are marked as red dots. b) ERPs at Pz. A positive wave (corresponding to P300) was observable. At the bottom, time intervals highlighted in black represent those for which the p-value related to permutation statistics with FDR correction is significant (i.e.  $< 0.05$ ). C = trials with congruent flankers; I = trials with incongruent flankers



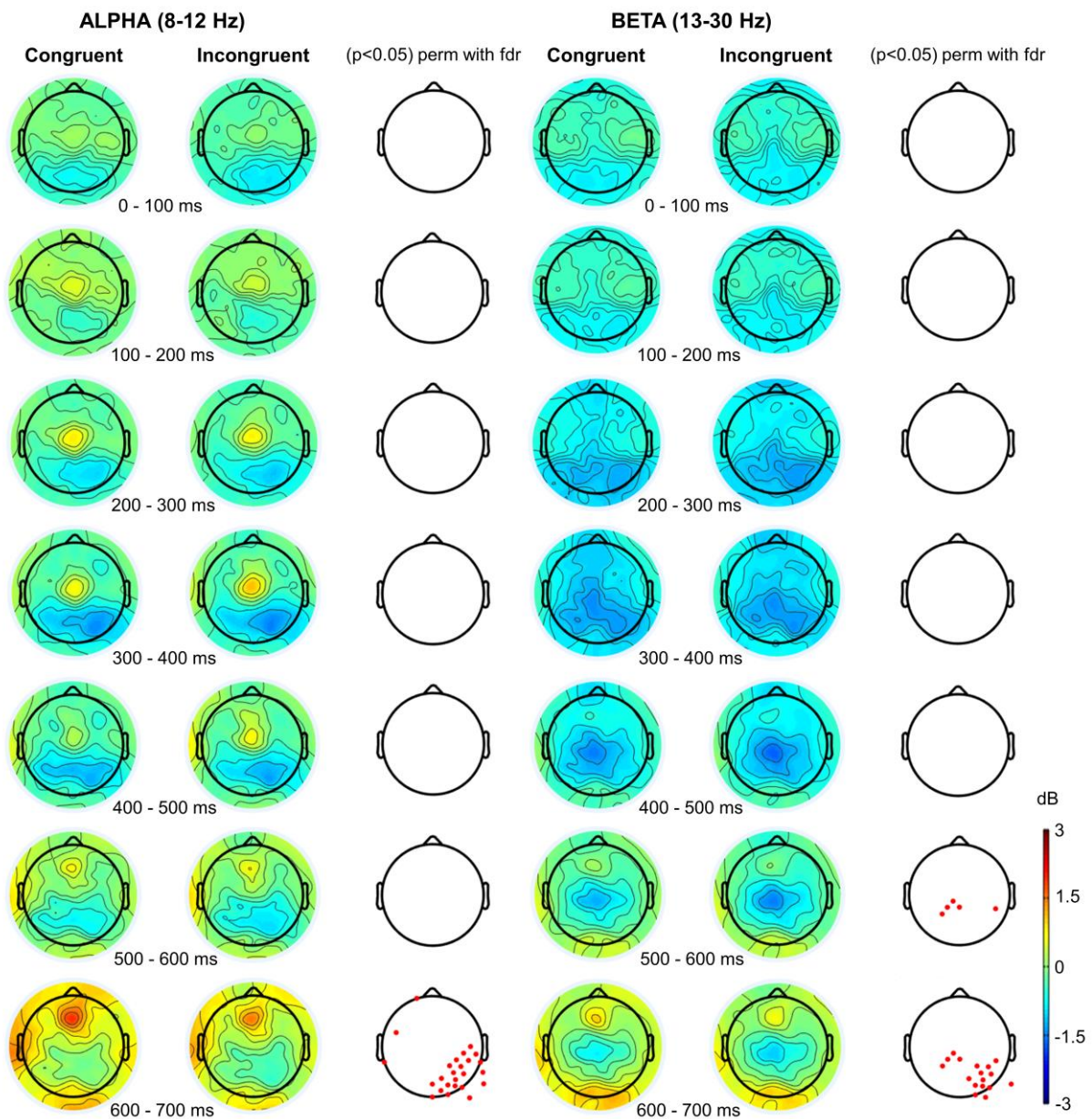
**Fig. 10 Influence of cue modality on target-locked ERSPs.** Target-locked topographic distributions of time-frequency energy (left: in alpha band (8-12 Hz); right: in beta band (13-30 Hz)), corresponding to the four cue conditions (central cue, invalid spatial cue, valid spatial cue and no cue) in the step initiation ANT. Time interval: between 0 and 700 ms after the presentation of the target. ERD is shown in blue and ERS is shown in red. Column to the right of spectral distributions in each frequency band: significant differences in a permutation test with FDR correction (threshold at  $p < 0.05$ ) are marked as red dots

ALPHA (8-12 Hz)

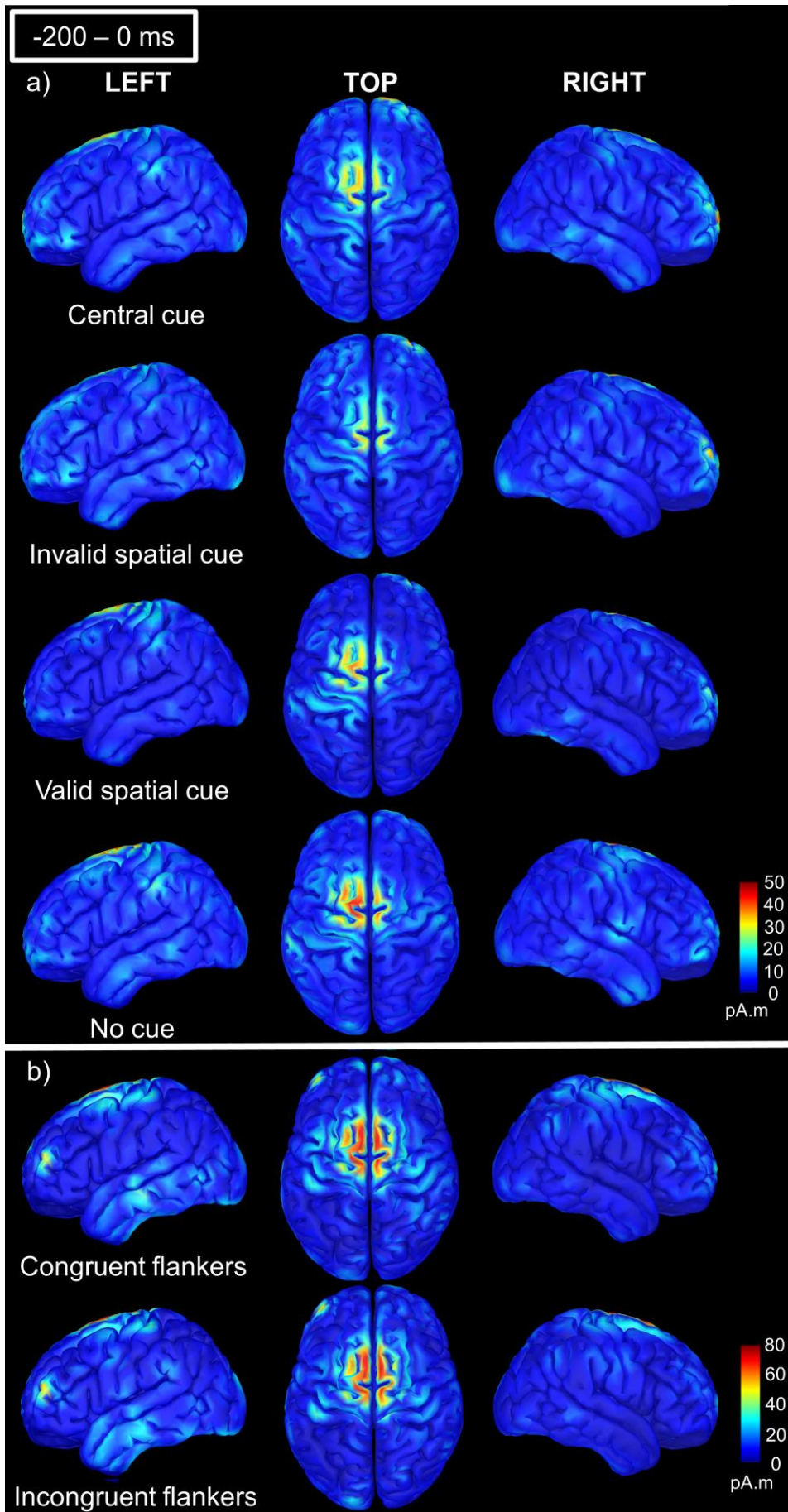
BETA (13-30 Hz)



**Fig. 11 Influence of target modality on target-locked ERSPs.** Target-locked topographic distributions of time-frequency energy (left: in alpha band (8-12 Hz); right: in beta band (13-30 Hz)), corresponding to the two flanker conditions (congruent or incongruent) in the step initiation ANT. Time interval: between 0 and 700 ms after the presentation of the target. ERD is shown in blue and ERS is shown in red. Column to the right of spectral distributions in each frequency band: significant differences in a permutation test with FDR correction (threshold at  $p < 0.05$ ) are marked as red dots



**Fig. 12 Localisation of MRCP sources.** a) Comparison of MRCP source localisation between conditions of cue during a time interval ranging from 200 ms before APA onset to the start of APA. b) Comparison of MRCP source localisation between conditions of target during a time interval ranging from 200 ms before APA onset to the start of APA



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## Etude 3 – Supplementary material

Initial Center of Pressure Position Prior to Anticipatory Postural Adjustments during Gait Initiation in People with Parkinson's Disease with Freezing of Gait

**Madli Bayot**, Arnaud Delval, Caroline Moreau, Luc Defebvre, Clint Hansen, Walter Maetzler, Christian Schlenstedt.

Article en révision dans *Parkinsonism & Related Disorders*.

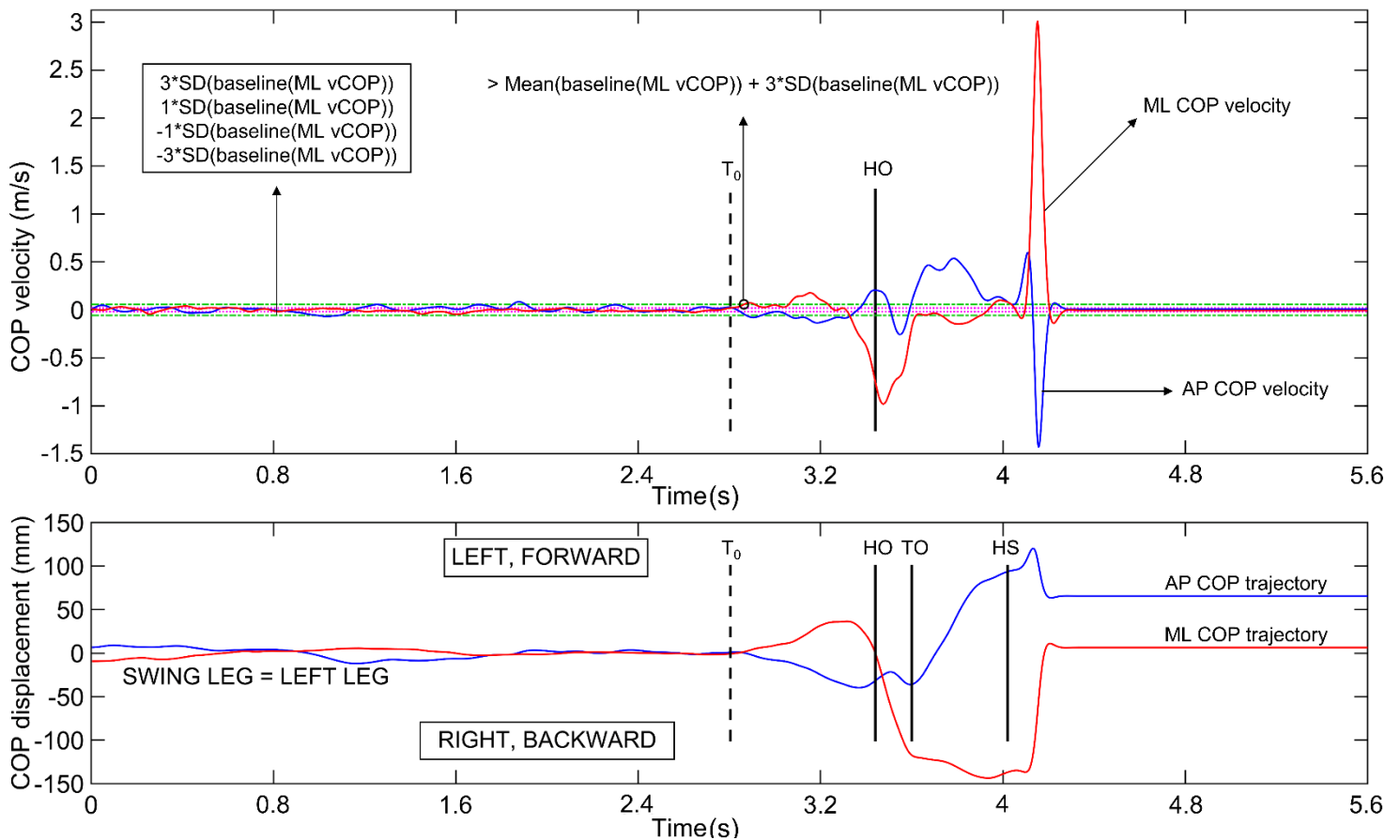


# Supplementary material

## A. Kinetic and kinematic data analysis – detailed version

In order to assess preparation and execution of gait, different spatio-temporal features of the first step were extracted from the data, by using an in-house MATLAB script (The MathWorks, Natick, MA, USA) based on methodologies found in the literature to detect gait events. Data of each trial were plotted and visually checked.

- **Initial mean AP and ML COP positions**, expressed respectively as a percentage of foot length and stance width (Figure 1), were calculated and averaged over 1 s prior to APA onset. Foot length was assessed as the AP distance between points located at mean distance between both toe markers and both heel markers, whereas stance width was the ML distance between the orthogonal projections of the middle points between left/right heel and toe markers on a parallel line passing by the marker at the left/right ankle. Initial mean AP and ML COP positions over 1 s prior to APA onset were measured by reference to the middle point between both heel markers and to the orthogonal projection of the middle point between stepping-foot heel and toe markers on a parallel line passing by the ankle marker, respectively. An initial mean AP/ML COP position at 50% of the foot length/stance width thus corresponds to an averaged centered COP within the basis of support.
- **Heel off (HO)** was defined as the time when the heel velocity in the sagittal plane is equal to or greater than its baseline (mean velocity in the sagittal plane over 1 s after the start of recording) plus 100 mm/s [1,2]. This algorithm method has been shown to be both reliable in comparison to the visual inspection and accurate [1].
- **Toe-off event (TO)** was considered as the time of a local maximum in the vertical velocity component of the heel marker [3].
- Time of a local minimum in the vertical velocity component of the toe marker was detected and linked to **heel strike (HS)** [3].
- **APA onset ( $T_0$ )**, see Figure A.1) was detected as the time when ML velocity of COP exceeds  $mean(baseline) + 1 * standard\ deviation(baseline)$  just before exceeding  $mean(baseline) + 3 * standard\ deviation(baseline)$  [4,5]. The baseline was defined as a time interval from the start of recording until the maximum between 1 s and  $(TO - 2\ s)$ .
- **Duration of APA** was described as the time between  $T_0$  and HO [6,7].
- **ML size of APA** was defined as the maximum COP displacement in the ML direction during APA, relating to the COP position at  $T_0$  [6].
- **Lateral COP shift between  $T_0$  and TO** that can also be described as the lateral COP shift during the unloading of the swing foot ( $COP_u$ ) was also assessed, as well as the **duration of the unloading phase ( $T_u$ )**.
- **AP size of APA** was described as the maximum COP excursion in the AP direction during APA, relating to the COP position at  $T_0$  [6]. It has to be noted that a backward shift of the COP is not always observed in individuals, particularly in PD patients.
- **Length and speed of first step** as well as **swing phase duration** corresponded to the distance covered and speed of the swing leg between TO and HS, and the duration of the step execution phase.



**Figure A.1.** Detection of APA onset based on ML COP velocity.  $T_0$  = APA onset; HO = heel off; TO = toe off; HS = heel strike

## B. Statistical analysis – detailed version

All statistical analyses were conducted in R [8], with the use of ggplot2 [9] package for producing figures. The statistical significance threshold associated with all the tests was  $p < 0.05$ .

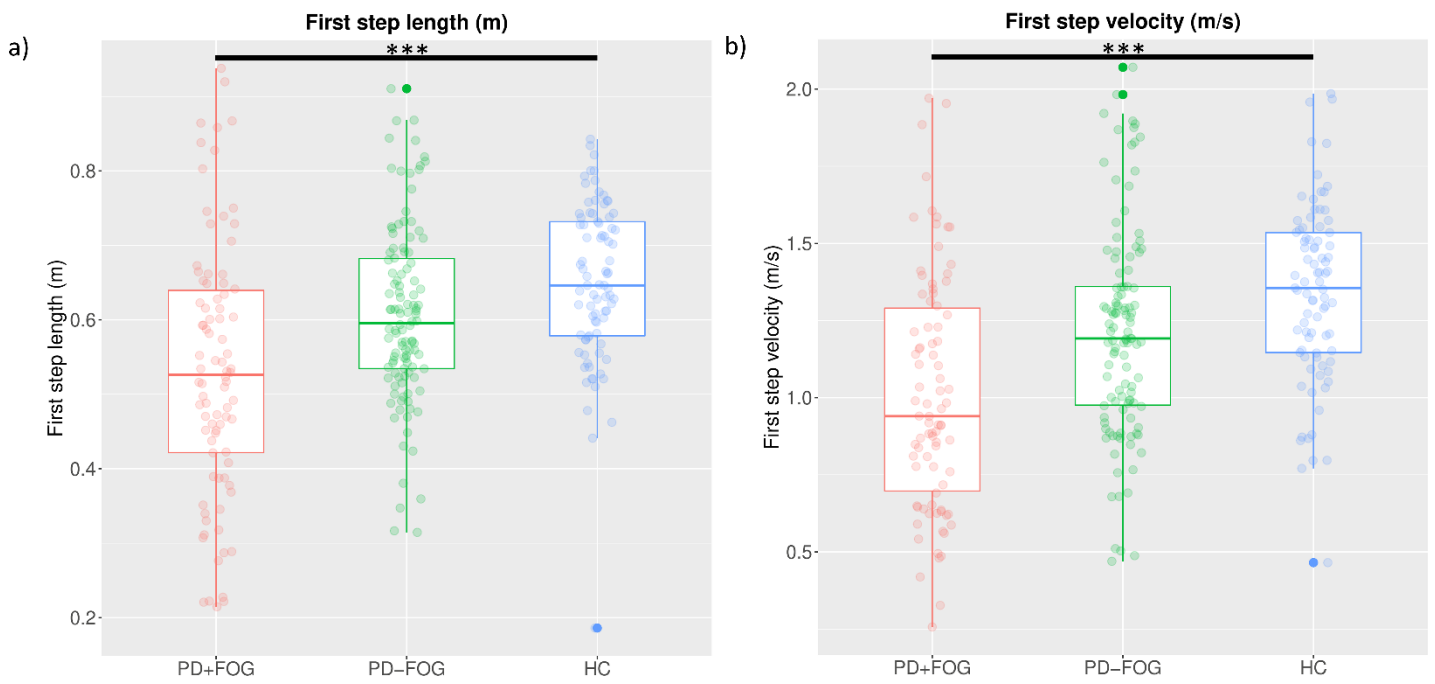
Demographic and clinical data between PD+FOG, PD-FOG and HC were compared with Kruskal-Wallis test, and between PD+FOG and PD-FOG with Mann-Whitney U test. Dichotomous data were compared using Chi-Square test.

Because each participant performed a different amount of trials varying from one to five, differences between groups in terms of initial mean COP position over 1 s prior to APA onset and characteristics of the first step preparation (features of APA) and execution (the step itself) were statistically tested using a linear mixed model (LMM) with group as fixed effect, participant as random effect and stance width as covariate (except for the analysis of the initial mean ML COP position prior to APA onset). In order to control for a significantly different clinical variable between PD+FOG and PD-FOG (i.e. disease duration), a second ANCOVA related to the PD patients only was carried out, based on the same previous LMM but with disease duration as a new covariate. A Tukey correction for post-hoc tests was used to adjust for multiple comparisons. When the assumptions of normal distribution and homogeneity of variances of residuals among groups were violated (assumptions checked mainly visually with a QQ plot/a plot of residual values versus fitted values, followed by Shapiro-Wilk and Levene tests among groups), generalized linear mixed models (GLMM) were used. APA duration (and  $T_0$ ), as a reaction time [10], presented a positively skewed distribution and therefore required to be

tested via a GLMM with inverse gaussian distribution of the data and an inverse link function. The size of APA in AP and ML directions included some zero values while exhibiting a positively skewed distribution. The glmmTMB package was thus useful in order to fit a zero-inflated GLMM [11], with a modified Gamma distribution of the data (skipping checks for zero values and fitting therefore hurdle-Gamma models) and a log link function. In general, the use of lme4 package [12] was necessary for performing (generalized) linear mixed analyses.

Furthermore, in order to investigate the relationships between the initial mean AP/ML COP position over 1 s prior to APA onset, gait preparation and first step execution in each group, repeated measures correlation coefficients were assessed and allowed to determine the common within-individual association for paired measures evaluated in a given population [13]. Based on that, different linear mixed models including uncorrelated features of quiet stance prior to gait initiation and characteristics of APAs as potential predictors of first step length and velocity were the starting point for choosing the best regression model associated with each group by AIC (Akaike's Information Criteria) in a backward stepwise algorithm (R functions used: *lme* from nlme for building LMM, *stepAIC* from MASS for model selection, and *r.squaredGLMM* from MuMIn for obtaining marginal and conditional r-squared). Disease duration was also tested as an independent variable in the regression analysis related to each PD group. The absence of multicollinearity between predictors was confirmed by variance inflator factors that did not exceed 5 [14].

### C. Execution of first step – box plots



**Figure C.1.** Characteristics of first step execution that were significantly different between groups: first step (a) length and (b) velocity. \*\*\* for p-value < 0.001

## D. Correlation analysis

**Table D.1.** Correlations between the initial mean COP position and characteristics of gait preparation and execution. Values represent repeated measures correlation coefficients (p-values); \* p-value < 0.05; \*\* p-value < 0.01; \*\*\* p-value < 0.001. Cells with bold borders represent the common significant associations between two variables (different than first step length and velocity) among groups. Only statistically significant Spearman's correlation coefficients or with a trend toward significance (related p-value < 0.1) are shown

	Group	ML COP position	AP size of APA	ML size of APA	COP <sub>U</sub>	APA duration	T <sub>U</sub>	Stance width	Swing phase duration	First step length	First step velocity
AP COP position	PD+FOG		0.232 (0.071)							<b>-0.33**</b> (0.0099)	
	PD-FOG	<b>0.328**</b> (0.002)	<b>0.348**</b> (0.001)		-0.192 (0.078)						
	HC										
ML COP position	PD+FOG			<b>0.329**</b> (0.009)							-0.247 (0.057)
	PD-FOG				-0.202 (0.063)		<b>-0.296**</b> (0.006)				
	HC			<b>0.317*</b> (0.014)							0.217 (0.098)
AP size of APA	PD+FOG			<b>0.423***</b> ( $< 0.001$ )	<b>0.294*</b> (0.021)				<b>-0.242</b> (0.061)		
	PD-FOG			<b>0.371***</b> ( $< 0.001$ )			-0.19 (0.082)		<b>-0.326**</b> (0.002)		<b>0.276*</b> (0.01)
	HC			<b>0.594***</b> ( $< 0.001$ )					-0.251 (0.055)		
ML size of APA	PD+FOG				<b>0.68***</b> ( $< 0.001$ )		<b>-0.289*</b> (0.024)	<b>0.274*</b> (0.032)			
	PD-FOG				<b>0.573***</b> ( $< 0.001$ )				<b>-0.291**</b> (0.007)	<b>0.308**</b> (0.004)	<b>0.401***</b> ( $< 0.001$ )
	HC				<b>0.474***</b> ( $< 0.001$ )			<b>0.289*</b> (0.026)			
COP <sub>U</sub>	PD+FOG							<b>0.552***</b> ( $< 0.001$ )		0.225 (0.084)	<b>0.314*</b> (0.014)
	PD-FOG						<b>0.345**</b>	<b>0.345**</b>		<b>0.263*</b>	<b>0.246*</b>

	HC					-0.231 (0.079)	(0.001)	<b>0.506***</b> ( $< 0.001$ )		(0.015)	(0.023)
<b>APA duration</b>	PD+FOG										
	PD-FOG										
	HC								<b>-0.269*</b> (0.039)	<b>-0.279*</b> (0.033)	
<b>T<sub>u</sub></b>	PD+FOG							-0.213 (0.099)			
	PD-FOG								<b>0.325**</b> (0.002)		-0.182 (0.096)
	HC								<b>0.315*</b> (0.015)	0.246 (0.06)	
<b>Stance width</b>	PD+FOG									0.216 (0.097)	
	PD-FOG										
	HC										
<b>Swing phase duration</b>	PD+FOG									<b>0.407**</b> (0.001)	<b>-0.534***</b> ( $< 0.001$ )
	PD-FOG										<b>-0.679***</b> ( $< 0.001$ )
	HC										<b>-0.596***</b> ( $< 0.001$ )
<b>First step length</b>	PD+FOG										<b>0.485***</b> ( $< 0.001$ )
	PD-FOG										<b>0.675***</b> ( $< 0.001$ )
	HC										<b>0.663***</b> ( $< 0.001$ )



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## **Etude 4 – Supplementary material**

Is Impaired Executive Control Associated with Abnormal Gait Initiation in Parkinsonian Patients with Freezing of Gait?

**Madli Bayot**, Morgane Gerard, Aurore Braquet, Kathy Dujardin, Céline Tard, Caroline Moreau, Luc Defebvre, Arnaud Delval

Article en préparation pour soumission prochaine.



## Supplementary material

### A. Standard ANT – Demographic and clinical data

**Table A1.** Demographic and clinical data characterizing participants who performed the standard ANT (mean  $\pm$  standard deviation)

<b>Group</b>	<b>Age</b> (years)	<b>Gender</b> (F/M)	<b>MoCA</b> (/30)	<b>Disease duration</b> (years)	<b>MDS-UPDRS III – Med ON</b>	<b>H&amp;Y – Med ON</b>	<b>LEDD</b> (mg L-Dopa)
<b>PD+FoG</b> (n=13)	65 $\pm$ 6	3/10	27 $\pm$ 2	10 $\pm$ 5	29 $\pm$ 13	2 $\pm$ 1	1083 $\pm$ 570
<b>PD-FoG</b> (n=15)	62 $\pm$ 9	10/5	27 $\pm$ 2	9 $\pm$ 4	21 $\pm$ 9	2 $\pm$ 1	1081 $\pm$ 376
<b>HC</b> (n=15)	59 $\pm$ 6	10/5	28 $\pm$ 2	/	/	/	/
<b>p-value</b>	0.098	<b>0.031*</b>	0.709	0.907	0.058	0.105	0.992

Notes. MoCA = Montreal Cognitive Assessment; MDS-UPDRS III – Med ON = Movement Disorder Society-sponsored revision of the Unified Parkinson's disease rating Scale, part III, in the ON-state of medication; H&Y scale – Med ON = Hoehn and Yahr scale, in the ON-state of medication; LEDD = Levodopa Equivalent Daily Dose. \* for p-value < 0.05

## B. Standard ANT – Executive control effect

Table B.1. Executive control effect measured thanks to the standard ANT

Standard ANT - EC	Mean ± standard deviation [C – I]		Group effect (p-value)		Target effect (p-value)	Group*Target Interaction effect (p-value)	
			(a)	(b)	(a)	(a)	(b)
Response rate (% of trials without omission errors)	98.451 ± 1.705	98.02 ± 3.619	<b>0.006**</b>	<b>0.014*</b>	<b>C &lt; I (0.016*)</b>	0.217	0.223
	99.008 ± 1.673	99.317 ± 1.812	PD+FoG = PD- FoG (0.219) <b>PD+FoG &lt; HC (0.006**)</b>	PD+FoG = PD- FoG (0.098) <sup>(c)</sup> <b>PD+FoG &lt; HC (0.011*)</b>			
	99.679 ± 0.458	99.943 ± 0.204	PD-FoG = HC (0.292)	PD-FoG = HC (0.284)			
Accuracy (% of trials without commission errors)	99.562 ± 0.686	96.877 ± 3.967	0.184	0.207	<b>C &gt; I (&lt; 0.001***)</b>	0.164	0.16
	99.398 ± 0.858	96.967 ± 4.802					
	99.625 ± 0.541	99.263 ± 0.903					
RT (ms)	625.5 ± 59.252	693.308 ± 88.487	<b>0.033*</b>	<b>0.026*</b>	<b>C &lt; I (&lt; 0.001***)</b>	<b>0.013*</b>	<b>0.021*</b>
	598.367 ± 75.016	640.633 ± 75.366	PD+FoG = PD- FoG (0.385) <b>PD+FoG &gt; HC (0.029*)</b>	PD+FoG = PD- FoG (0.275) <sup>(c)</sup> <b>PD+FoG &gt; HC (0.022*)</b>			
	570.3 ± 53.654	608.733 ± 58.471	PD-FoG = HC (0.7)	PD-FoG = HC (0.705)			

Notes. EC = executive control; C = condition of target surrounded by congruent flankers; I = condition of target surrounded by incongruent flankers; (a) without covariate taken into account; (b) corrected for gender; (c) corrected for gender and MDS-UPDRS III in ON-state of medication. \* for p-value < 0.05; \*\* for p-value < 0.01; \*\*\* for p-value < 0.001

### C. ANT-INIT: Executive control effect on APA types

Table C.1. Executive control effect on step initiation measured thanks to the ANT-INIT: rate of APA types

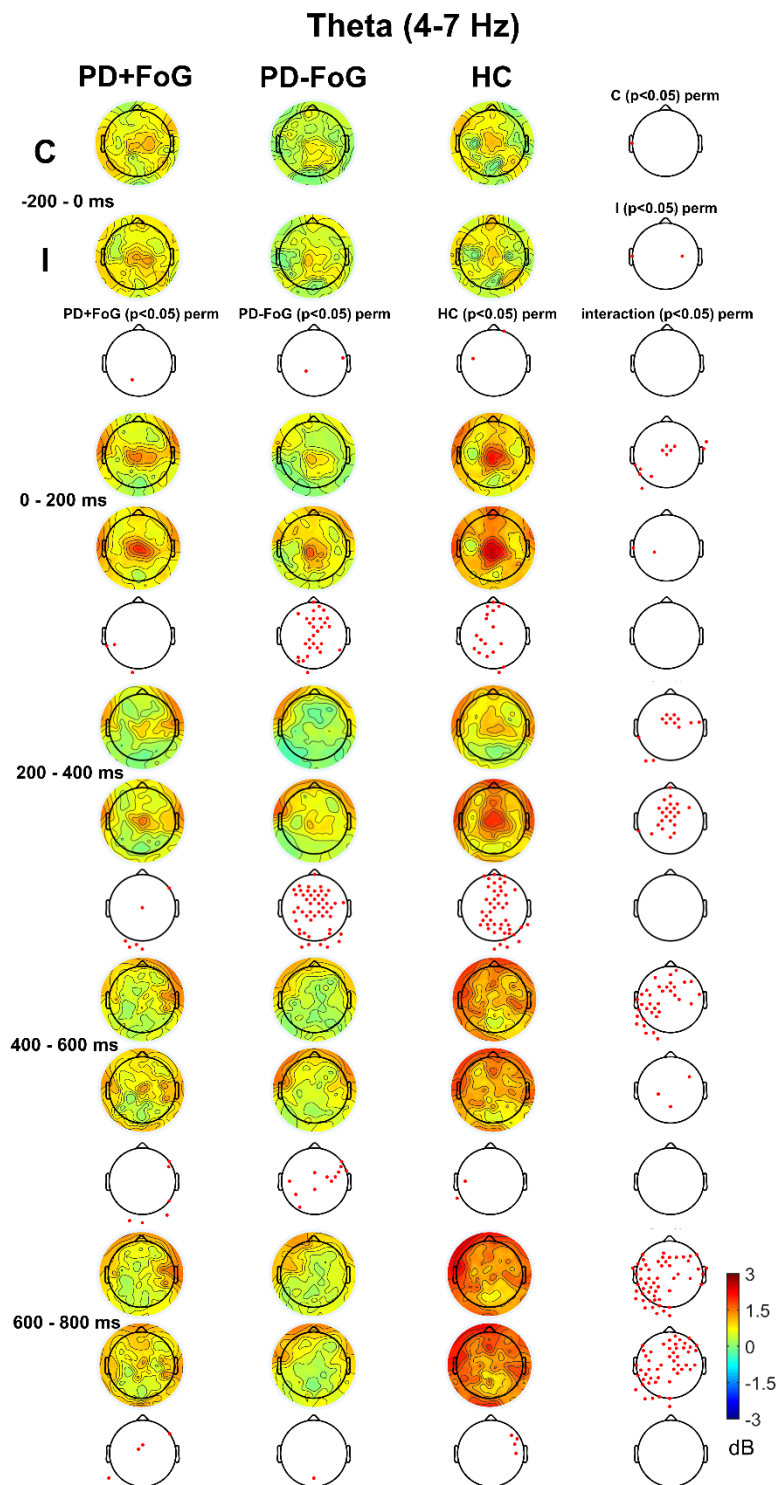
ANT-INIT - EC		Mean ± standard deviation		Group effect (p-value)		Target effect (p-value)	Group*Target Interaction effect (p-value)	
		(a)	(b)	(a)	(b)	(a)	(a)	(b)
		C	I				(a)	(b)
Rate of wrong steps (%)	PD+FoG	2.312 ± 4.128	2.249 ± 4.165	0.297	0.378	0.108	<b>0.032*</b>	<b>0.031*</b>
	PD-FoG	0.921 ± 1.901	2.103 ± 3.765				PD+FoG = PD-FoG (0.129)	<b>C &gt; I in PD+FoG &amp; C &lt; I in PD-FoG (0.047*)<sup>(c)</sup></b>
	HC	0.2 ± 0.348	0.818 ± 1.309				PD+FoG = HC (0.093)	PD+FoG = HC (0.099)
Rate of anticipated steps (%)		8.922 ± 9.319	7.735 ± 6.878	<b>0.001**</b>	<b>0.001**</b>	0.184	0.939	0.939
		12.011 ± 7.966	10.371 ± 6.603	PD+FoG = PD-FoG (0.351)	PD+FoG = PD-FoG (0.402) <sup>(c)</sup>			
		17.933 ± 7.814	16.019 ± 7.125	<b>PD+FoG &lt; HC (&lt;0.001***)</b>	<b>PD+FoG &lt; HC (&lt;0.001***)</b>			
Rate of no APAs (%)		0.885 ± 1.6	0.715 ± 1.108	0.794	0.987	0.769	0.907	0.96
		0.996 ± 0.978	1.049 ± 2.557					
		0	0.059 ± 0.228					
Rate of normal APAs (%)		68.12 ± 17.11	51.234 ± 14.969	0.998	0.994	<b>C &gt; I (&lt;0.001***)</b>	0.782	.0.782
		68.397 ± 10.819	51.286 ± 13.26					
		69.447 ± 12.369	49.86 ± 16.348					
APA errors (%)		24.321 ± 11.056	36.617 ± 8.538	0.667	0.778	<b>C &lt; I</b>	0.81	0.811

	26.97 ± 8.921	37.958 ± 12.304			( <b>&lt;0.001***</b> )		
	27.378 ± 9.93	38.958 ± 10.034					
<b>Multiple APAs (%)</b>	7.558 ± 10.473	12.149 ± 11.238	0.764	0.806	<b>C &lt; I</b> ( <b>&lt;0.001***</b> )	0.227	0.224
	4.633 ± 3.779	10.756 ± 6.261					
	3.174 ± 2.844	11.182 ± 8.029					

**Notes.** EC = executive control; C = condition of target surrounded by congruent flankers; I = condition of target surrounded by incongruent flankers; (a) without covariate taken into account; (b) corrected for gender; (c) corrected for gender and MDS-UPDRS III in ON-state of medication. \* for p-value < 0.05; \*\* for p-value < 0.01; \*\*\* for p-value < 0.001

Under preparation

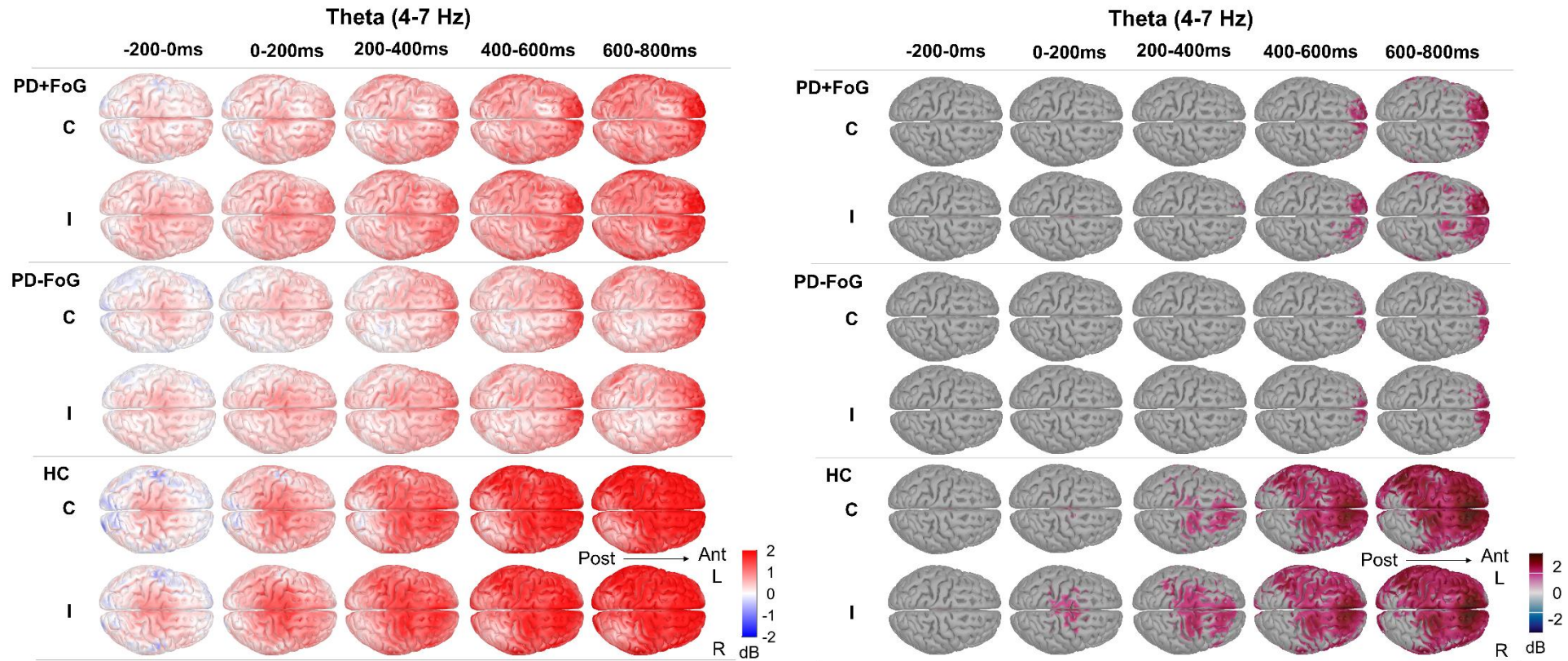
## D. ANT-INIT – Executive control and scalp ERSPs in theta band



**Figure DC.1.** Executive control effect on response-locked ERSPs in theta band over the scalp and throughout a trial of the ANT-INIT. APA onset occurs at 0 ms. Topographic distribution of EEG power, with warm colors corresponding to ERS, while cold colors correspond to ERD. In the column to the right and in the row below spectral distributions, red dots mark significant differences in a permutation test with target condition (column) and group (row) as respective within-subject and between-subject factors, and a statistical significance threshold at  $p < 0.05$ . The intersection between this column and this row show the potential significant interaction existing between target and group. C = congruent condition of target; I = incongruent condition of target



## E. ANT-INIT – Executive control and source localization of theta-band ERSPs



**Figure EP.1.** Source localization of response-locked ERSPs in theta band throughout a trial of the ANT-INIT. APA onset occurs at 0 ms. Warm colors correspond to ERS, while cold colors correspond to ERD. On the right, only the sources that have a value superior to 50% of the colorbar maximum are here displayed. C = congruent condition of target; I = incongruent condition of target; Post = posterior; Ant = anterior; L = left; R = right

## Etude 5 – Supplementary material

Functional Networks Underlying Freezing of Gait: A Resting-State Electroencephalographic Study

**Madli Bayot**, Morgane Gérard, Philippe Derambure, Kathy Dujardin, Luc Defebvre, Nacim Betrouni, Arnaud Delval.

Article soumis.

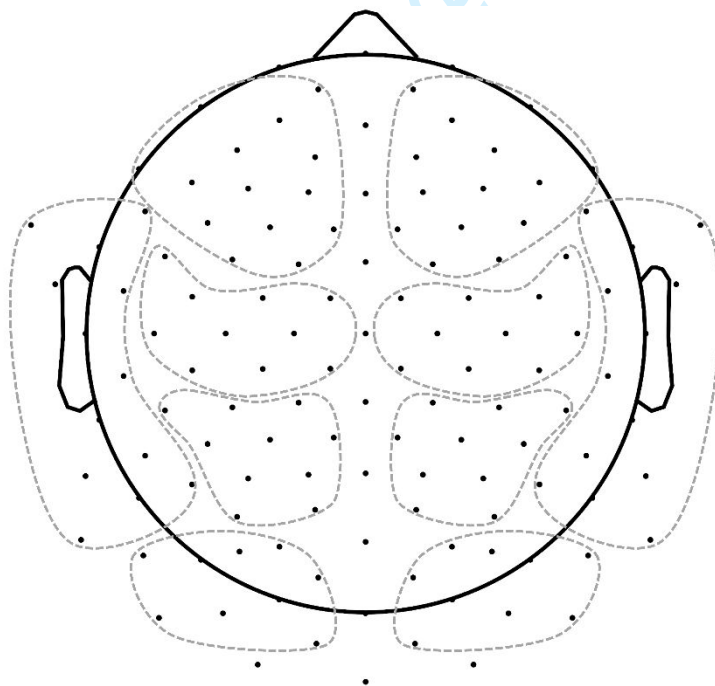


## Supplementary material

### A. EEG preprocessing

Preprocessing of EEG signals was performed via the MATLAB toolbox EEGLAB [24]. After downsampling at 256 Hz, a low-pass filter was first applied to remove the first harmonic of the line noise at 100 Hz, as well as a high-pass filter with a cut-off frequency of 0.5 Hz and a 50-Hz Notch filter to remove baseline drift and line noise, respectively. Secondly, after the removal of the first and last 30 seconds of the signal, only a 4-minute EEG segment of interest was kept. Subsequently, flat electrodes were automatically removed on the basis of a maximum tolerated flatline duration of 5 seconds, while the artifact-affected electrodes were semi-automatically detected (either an electrode correlated at less than a minimum correlation value to a reconstruction of itself based on other channels in a given time window, or a channel with lower- and upper-accepted standard deviation for the related EEG signal). Thereafter, the removed channels (maximum 10%) were spherically interpolated. Transient, non-biological, large-amplitude noise/artifacts were removed thanks to the artifact subspace reconstruction (ASR) method [25,26]. Average reference was then chosen as re-referencing method. Next, constant fixed-source noise/artifacts/signals of stationary data were decomposed via a stationary method: the independent component analysis (ICA), and the Infomax algorithm in particular [27]. ICLabel [28], a highly trained independent component classifier, allowed to automatically select the artifact-affected components (maximum 20) among the components related to the highest percentage of explained variance. A manual confirmation of the components representing non-neural sources followed. We finally segmented the EEG data into 4-second epochs, and a final visual inspection was needed to manually remove epochs containing remaining artifacts. From 26 to 59 4-second EEG segments were associated with each participant.

### B. Spectral analysis of scalp EEG



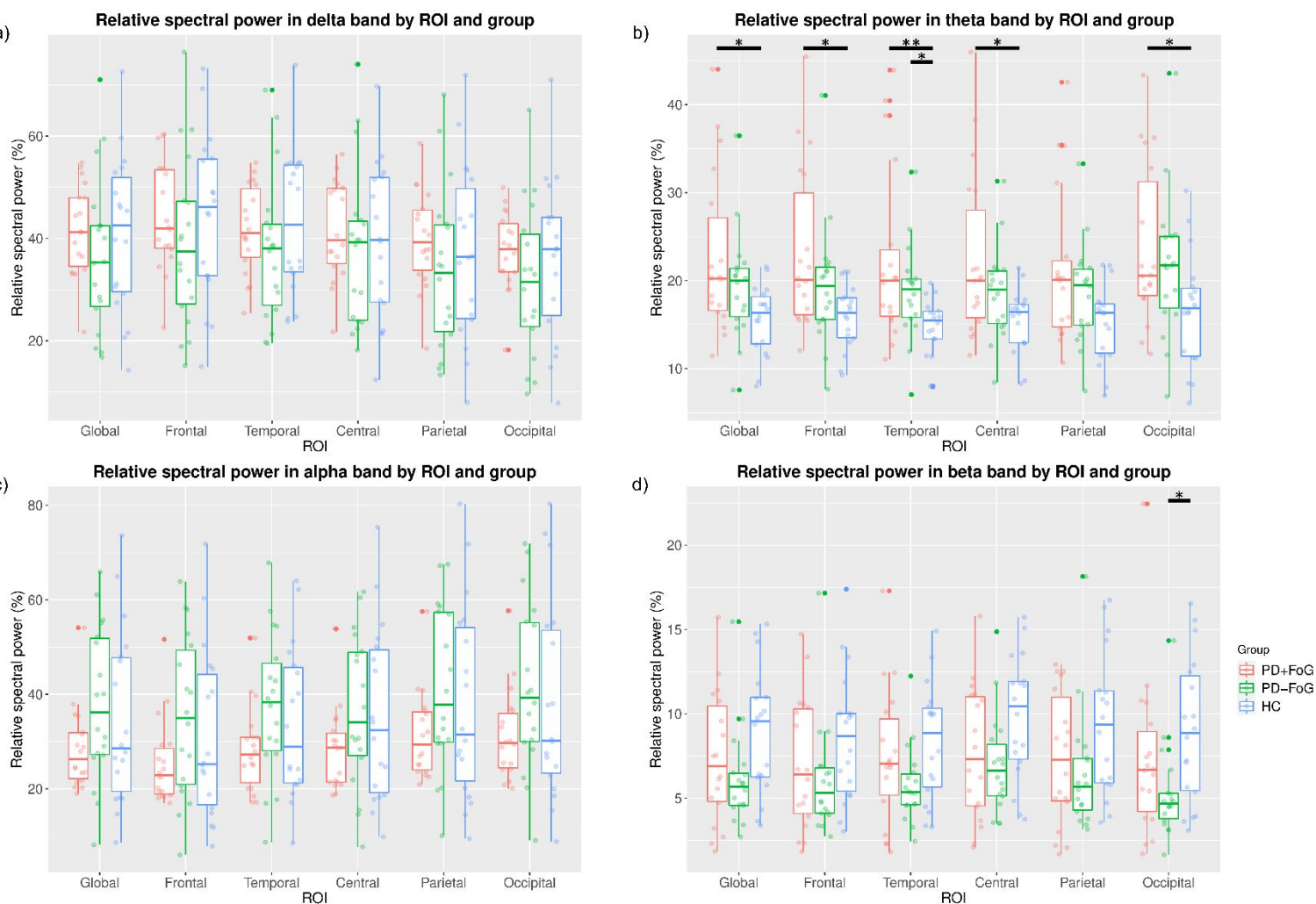
**Figure B.1.** Division of the scalp electrodes into 10 regions of interest (right/left frontal, temporal, central, parietal, and occipital), according to the cortical projections of the electrodes in Talairach space [30]. For more clarity, both mastoid channels have not been drawn on the present figure.

### C. Parameters of graph theory

**Table C.1.** Definitions of graph parameters used in the present study.

<b>Parameter of graph theory</b>	<b>Definition</b>
<i>Characteristic path length</i>	the average shortest path length (number of connecting edges between two nodes, in a binary network) in the network
<i>Efficiency</i>	the average inverse shortest path length in the network, quantifying the global communication of a network or its “global integration”
<i>Diameter</i>	the maximum eccentricity or the largest number of vertices to traverse in order to travel from one vertex to another
<i>Highest degree</i>	the maximum number of links connected to a node of the network
<i>Small-world coefficient</i>	measure of the network randomness via the comparison of clustering (local segregation) and path length (global integration) of a given network with an equivalent random network with the same degree on average
<i>Maximal modularity</i>	the maximal strength of division of a network into modules
<i>Transitivity</i>	ratio of the connected triples of nodes (triangles) to triplets in the network
<i>Number of components</i>	number of groups of nodes for which all pairs of nodes are connected by paths

### D. Spectral analysis - Results



**Figure D.1.** Box plots of relative spectral power in (a) alpha, (b) theta, (c) alpha and (d) beta bands, among different ROIs and in PD+FoG, PD-FoG and HC. \* for p-values < 0.05; \*\* for p-values < 0.01

**Table D.1.** Comparison of absolute (Abs) and relative (Rel) spectral powers between groups. R= right; L= left; \* for p-values < 0.05; \*\* for p-values < 0.01

ROI	Spectral power	Group			F value/ Chi-Square	p-value	Post-hoc tests
		PD+FoG	PD-FoG	HC			
Global	<i>Delta Abs</i> [ $\mu V^2/Hz$ ]	2.435 $\pm$ 2.141	2.363 $\pm$ 1.746	1.996 $\pm$ 1.351	0.135	0.935	/
	<i>Theta Abs</i> [ $\mu V^2/Hz$ ]	1.699 $\pm$ 2.527	1.202 $\pm$ 0.835	0.759 $\pm$ 0.654	3.376	0.185	/
	<i>Alpha Abs</i> [ $\mu V^2/Hz$ ]	1.471 $\pm$ 1.202	2.107 $\pm$ 1.512	1.888 $\pm$ 2.109	3.238	0.198	/
	<i>Beta Abs</i> [ $\mu V^2/Hz$ ]	0.321 $\pm$ 0.21	0.325 $\pm$ 0.225	0.353 $\pm$ 0.262	0.041	0.98	/
	<i>Delta Rel</i> [%]	41.525 $\pm$ 8.942	36.582 $\pm$ 15.196	40.83 $\pm$ 15.386	0.706	0.498	/
	<i>Theta Rel</i> [%]	22.716 $\pm$ 9.189	19.388 $\pm$ 6.215	15.555 $\pm$ 3.954	7.386	<b>0.025*</b>	<b>PD+FoG &gt; HC (0.03*)</b>
	<i>Alpha Rel</i> [%]	28.394 $\pm$ 8.648	37.929 $\pm$ 16.333	34.706 $\pm$ 18.46	3.072	0.215	/
	<i>Beta Rel</i> [%]	7.364 $\pm$ 3.893	6.101 $\pm$ 2.897	8.908 $\pm$ 3.74	5.386	0.068	/
Frontal	<i>Delta Abs</i> [ $\mu V^2/Hz$ ]	2.751 $\pm$ 2.19	2.801 $\pm$ 2.421	2.213 $\pm$ 1.434	0.381	0.826	/
	<i>Theta Abs</i> [ $\mu V^2/Hz$ ]	1.697 $\pm$ 2.35	1.182 $\pm$ 0.849	0.776 $\pm$ 0.614	3.557	0.169	/
	<i>Alpha Abs</i> [ $\mu V^2/Hz$ ]	1.389 $\pm$ 1.276	1.826 $\pm$ 1.176	1.765 $\pm$ 2.259	2.619	0.27	/

	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.312 ± 0.206	0.341 ± 0.256	0.353 ± 0.248	0.325	0.85	/
	<i>Delta Rel</i> [%]	44.288 ± 10.634	39.177 ± 16.739	44.359 ± 16.133	0.73	0.487	/
	<i>Theta Rel</i> [%]	23.307 ± 9.274	19.437 ± 7.063	15.885 ± 3.621	7.658	<b>0.022*</b>	<b>PD+FoG &gt; HC</b> (0.021*)
	<i>Alpha Rel</i> [%]	25.364 ± 9.032	35.318 ± 17.08	31.148 ± 18.123	2.967	0.227	/
	<i>Beta Rel</i> [%]	7.04 ± 3.913	6.068 ± 3.299	8.607 ± 3.885	4.757	0.093	/
Frontal R	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	2.739 ± 2.314	2.775 ± 2.398	2.14 ± 1.379	0.251	0.882	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.679 ± 2.425	1.117 ± 0.814	0.753 ± 0.582	1.889	0.389	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.29 ± 1.226	1.716 ± 1.257	1.724 ± 2.23	2.615	0.271	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.285 ± 0.19	0.343 ± 0.283	0.342 ± 0.249	0.391	0.822	/
	<i>Delta Rel</i> [%]	44.047 ± 10.851	40.181 ± 16.14	44.455 ± 16.205	0.469	0.628	/
	<i>Theta Rel</i> [%]	22.949 ± 9.605	19.271 ± 6.619	15.896 ± 3.698	5.868	0.053	/
	<i>Alpha Rel</i> [%]	25.885 ± 8.973	34.31 ± 16.373	31.032 ± 18.194	1.815	0.403	/
	<i>Beta Rel</i> [%]	7.118 ± 4.232	6.238 ± 3.63	8.617 ± 3.793	4.593	0.101	/
Frontal L	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	2.811 ± 2.227	2.896 ± 2.643	2.337 ± 1.609	0.539	0.764	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.671 ± 2.238	1.235 ± 0.888	0.786 ± 0.63	3.762	0.152	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.481 ± 1.521	1.95 ± 1.24	1.782 ± 2.244	2.852	0.24	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.341 ± 0.261	0.345 ± 0.244	0.361 ± 0.251	0.197	0.906	/
	<i>Delta Rel</i> [%]	44.978 ± 11.213	38.658 ± 17.364	44.629 ± 16.162	0.99	0.379	/
	<i>Theta Rel</i> [%]	23.215 ± 8.953	19.325 ± 7.401	15.647 ± 3.571	9.315	<b>0.009**</b>	<b>PD+FoG &gt; HC</b> (0.009**)
	<i>Alpha Rel</i> [%]	24.76 ± 9.402	36.063 ± 17.79	31.162 ± 18.072	3.719	0.156	/
	<i>Beta Rel</i> [%]	7.047 ± 3.835	5.954 ± 2.985	8.562 ± 3.943	4.356	0.113	/
Temporal	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	3.217 ± 3.298	2.906 ± 2.029	2.753 ± 1.995	0.17	0.918	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	2.348 ± 3.777	1.402 ± 0.992	0.859 ± 0.693	3.435	0.18	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.801 ± 1.449	2.639 ± 2.207	2.104 ± 2.13	3.107	0.211	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.386 ± 0.226	0.369 ± 0.225	0.391 ± 0.261	0.259	0.879	/
	<i>Delta Rel</i> [%]	41.796 ± 8.633	37.81 ± 14.332	43.089 ± 14.113	0.853	0.432	/
	<i>Theta Rel</i> [%]	22.422 ± 9.947	18.694 ± 5.444	14.679 ± 3.333	10.676	<b>0.005**</b>	<b>PD+FoG &gt; HC</b> (0.009**) <b>PD-FoG &gt; HC</b> (0.021*)
	<i>Alpha Rel</i> [%]	28.314 ± 9.061	37.704 ± 15.43	33.91 ± 16.187	3.561	0.169	/
	<i>Beta Rel</i> [%]	7.467 ± 4.063	5.791 ± 2.234	8.321 ± 3.453	2.677	0.078	/
Temporal R	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	3.289 ± 3.556	2.761 ± 2.459	2.813 ± 2.31	0.06	0.971	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	2.248 ± 3.485	1.356 ± 1.024	0.834 ± 0.732	2.501	0.286	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.671 ± 1.356	2.546 ± 2.342	2.015 ± 1.997	2.002	0.368	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.376 ± 0.253	0.362 ± 0.26	0.39 ± 0.273	0.284	0.868	/
	<i>Delta Rel</i> [%]	41.914 ± 7.933	36.823 ± 13.483	43.531 ± 13.958	1.506	0.232	/
	<i>Theta Rel</i> [%]	22.126 ± 9.775	19.368 ± 5.766	14.364 ± 3.215	12.574	<b>0.002**</b>	<b>PD+FoG &gt; HC</b> (0.006**) <b>PD-FoG &gt; HC</b> (0.006**)
	<i>Alpha Rel</i> [%]	28.379 ± 8.683	37.814 ± 14.973	33.628 ± 16.21	3.968	0.138	/
	<i>Beta Rel</i> [%]	7.581 ± 4.101	5.994 ± 2.431	8.476 ± 3.609	4.865	0.088	/
Temporal L	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	3.145 ± 3.133	3.051 ± 1.847	2.692 ± 1.756	0.465	0.793	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	2.448 ± 4.18	1.449 ± 1.07	0.884 ± 0.664	3.281	0.194	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.931 ± 1.751	2.731 ± 2.276	2.192 ± 2.361	1.952	0.377	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.396 ± 0.259	0.377 ± 0.211	0.392 ± 0.258	0.03	0.97	/
	<i>Delta Rel</i> [%]	41.678 ± 10.031	38.797 ± 15.761	42.647 ± 14.648	0.384	0.683	/
	<i>Theta Rel</i> [%]	22.719 ± 10.278	18.021 ± 5.323	14.994 ± 3.576	8.404	<b>0.015*</b>	<b>PD+FoG &gt; HC</b> (0.024*)
	<i>Alpha Rel</i> [%]	28.249 ± 9.866	37.594 ± 16.39	34.191 ± 16.558	2.878	0.237	/
	<i>Beta Rel</i> [%]	7.353 ± 4.191	5.587 ± 2.219	8.167 ± 3.549	4.714	0.095	/
Central	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.784 ± 1.623	1.674 ± 1.357	1.279 ± 0.87	0.681	0.712	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.333 ± 2.219	0.844 ± 0.641	0.547 ± 0.454	2.026	0.363	/

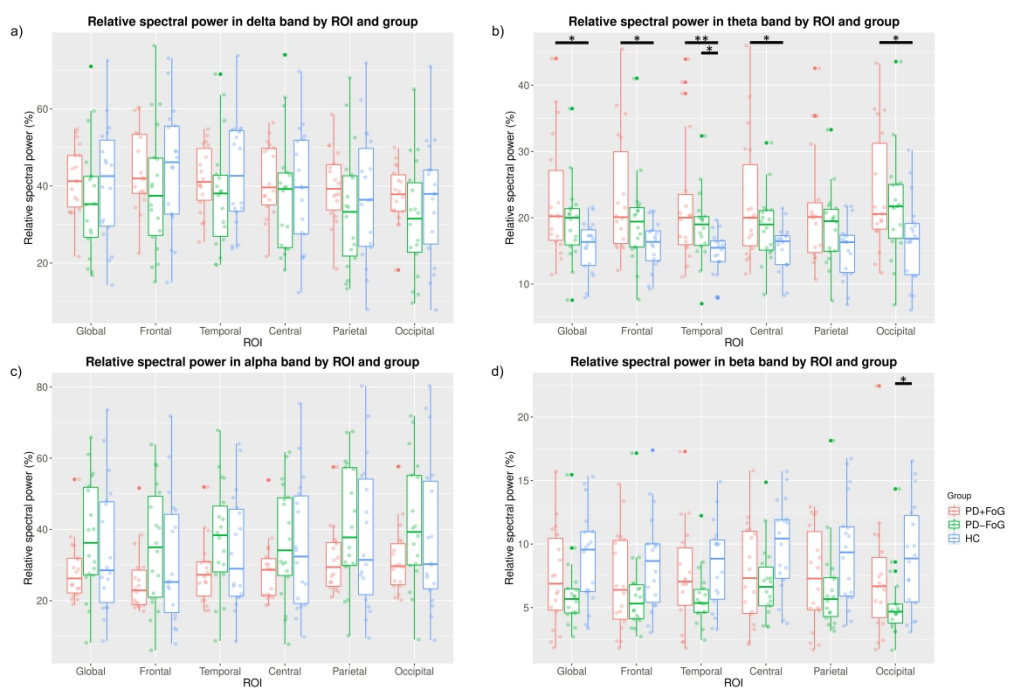
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	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.175 ± 1.165	1.468 ± 1.172	1.472 ± 1.689	1.078	0.583	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.257 ± 0.185	0.289 ± 0.271	0.326 ± 0.307	0.462	0.794	/
	<i>Delta Rel</i> [%]	41.664 ± 9.674	37.824 ± 15.729	39.382 ± 15.448	0.347	0.708	/
	<i>Theta Rel</i> [%]	22.43 ± 9.523	18.582 ± 5.211	15.421 ± 3.569	6.931	<b>0.031*</b>	<b>PD+FoG &gt; HC</b> (0.036*)
	<i>Alpha Rel</i> [%]	28.19 ± 8.748	36.627 ± 16.171	35.382 ± 18.549	2.297	0.317	/
	<i>Beta Rel</i> [%]	7.716 ± 3.967	6.967 ± 2.966	9.815 ± 3.667	3.099	0.054	/
Central R	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.698 ± 1.57	1.478 ± 1.278	1.193 ± 0.821	0.674	0.714	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.23 ± 1.925	0.749 ± 0.623	0.504 ± 0.433	1.241	0.538	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.069 ± 1.05	1.323 ± 1.182	1.411 ± 1.611	0.396	0.82	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.237 ± 0.18	0.257 ± 0.259	0.319 ± 0.306	1.186	0.553	/
	<i>Delta Rel</i> [%]	40.924 ± 9.475	37.741 ± 16.052	38.851 ± 15.269	0.243	0.785	/
	<i>Theta Rel</i> [%]	22.195 ± 9.784	18.502 ± 5.397	15.2 ± 3.497	7.481	<b>0.024*</b>	<b>PD+FoG &gt; HC</b> (0.027*)
	<i>Alpha Rel</i> [%]	29.07 ± 8.711	36.754 ± 16.335	35.978 ± 18.528	1.741	0.419	/
	<i>Beta Rel</i> [%]	7.81 ± 4.046	7.003 ± 3.249	9.971 ± 3.597	6.45	<b>0.04*</b>	<b>PD-FoG &lt; HC</b> (0.039*)
Central L	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.875 ± 1.833	1.862 ± 1.542	1.355 ± 0.95	0.741	0.69	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.461 ± 2.679	0.923 ± 0.706	0.575 ± 0.46	2.567	0.277	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.308 ± 1.503	1.621 ± 1.408	1.501 ± 1.718	1.323	0.516	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.279 ± 0.227	0.319 ± 0.297	0.327 ± 0.283	0.566	0.753	/
	<i>Delta Rel</i> [%]	42.331 ± 10.74	38.019 ± 15.818	39.88 ± 15.631	1.698	0.428	/
	<i>Theta Rel</i> [%]	22.568 ± 9.487	18.524 ± 5.177	15.538 ± 3.675	6.466	<b>0.039*</b>	<b>PD+FoG &gt; HC</b> (0.048*)
	<i>Alpha Rel</i> [%]	27.439 ± 9.334	36.511 ± 16.165	34.906 ± 18.542	2.864	0.239	/
	<i>Beta Rel</i> [%]	7.662 ± 4.048	6.945 ± 2.71	9.675 ± 3.749	2.862	0.066	/
Parietal	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.77 ± 1.903	1.63 ± 1.58	1.485 ± 1.235	0.07	0.965	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.321 ± 2.312	0.894 ± 0.684	0.621 ± 0.565	1.646	0.439	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.303 ± 1.371	1.908 ± 1.709	1.718 ± 1.828	2.482	0.289	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.224 ± 0.169	0.272 ± 0.247	0.321 ± 0.275	0.943	0.624	/
	<i>Delta Rel</i> [%]	39.814 ± 9.479	33.766 ± 15.877	37.353 ± 17.16	0.785	0.462	/
	<i>Theta Rel</i> [%]	21.435 ± 8.915	18.589 ± 5.769	15.157 ± 4.362	4.879	0.087	/
	<i>Alpha Rel</i> [%]	31.4 ± 9.232	41.17 ± 17.284	38.124 ± 20.707	2.644	0.267	/
	<i>Beta Rel</i> [%]	7.351 ± 3.938	6.475 ± 3.59	9.365 ± 4.241	4.889	0.087	/
Parietal R	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.878 ± 2.057	1.753 ± 1.947	1.421 ± 1.15	0.18	0.914	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.226 ± 2.037	0.92 ± 0.725	0.615 ± 0.557	1.254	0.534	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.218 ± 1.239	2.001 ± 1.595	1.825 ± 1.998	2.225	0.329	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.211 ± 0.153	0.272 ± 0.239	0.328 ± 0.273	2.312	0.315	/
	<i>Delta Rel</i> [%]	40.657 ± 9.468	33.198 ± 15.682	36.377 ± 16.988	1.212	0.306	/
	<i>Theta Rel</i> [%]	21.105 ± 8.923	18.554 ± 6.395	14.948 ± 4.536	4.876	0.087	/
	<i>Alpha Rel</i> [%]	31.072 ± 8.903	41.837 ± 17.78	39.285 ± 20.94	3.04	0.219	/
	<i>Beta Rel</i> [%]	7.167 ± 3.871	6.411 ± 3.564	9.389 ± 4.326	4.926	0.085	/
Parietal L	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.659 ± 1.822	1.54 ± 1.386	1.428 ± 1.131	0.07	0.965	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.508 ± 2.913	0.892 ± 0.726	0.617 ± 0.564	1.31	0.52	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.46 ± 1.653	1.911 ± 2.153	1.662 ± 1.907	0.951	0.621	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.246 ± 0.205	0.279 ± 0.274	0.317 ± 0.269	0.731	0.694	/
	<i>Delta Rel</i> [%]	38.021 ± 9.526	33.922 ± 16.425	37.866 ± 17.244	0.443	0.645	/
	<i>Theta Rel</i> [%]	21.932 ± 9.523	18.613 ± 5.597	15.305 ± 4.338	4.844	0.089	/
	<i>Alpha Rel</i> [%]	32.331 ± 9.899	40.915 ± 17.475	37.296 ± 20.625	2.167	0.338	/
	<i>Beta Rel</i> [%]	7.716 ± 4.363	6.55 ± 3.743	9.533 ± 4.322	4.774	0.092	/
Occipital	<i>Delta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	2.21 ± 1.93	2.323 ± 1.812	1.884 ± 1.73	0.707	0.702	/
	<i>Theta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.678 ± 2.13	1.614 ± 1.276	0.96 ± 1.109	4.591	0.101	/
	<i>Alpha Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	1.715 ± 1.19	2.813 ± 2.087	2.544 ± 3.198	3.949	0.139	/
	<i>Beta Abs</i> [ $\mu\text{V}^2/\text{Hz}$ ]	0.394 ± 0.456	0.327 ± 0.23	0.384 ± 0.304	0.329	0.848	/



	<i>Delta Rel [%]</i>	37.524 ± 7.705	31.603 ± 15.02	36.241 ± 15.845	2.113	0.348	/
	<i>Theta Rel [%]</i>	23.833 ± 9.17	21.599 ± 8.113	16.634 ± 6.471	7.307	<b>0.026*</b>	PD+FoG > HC (0.024*)
	<i>Alpha Rel [%]</i>	31.331 ± 9.55	41.509 ± 17.691	38.167 ± 21.364	3.234	0.199	/
	<i>Beta Rel [%]</i>	7.312 ± 4.793	5.289 ± 2.806	8.958 ± 4.324	7.856	<b>0.02*</b>	PD-FoG < HC (0.021*)
Occipital R	<i>Delta Abs [<math>\mu V^2/Hz</math>]</i>	2.272 ± 2.056	2.247 ± 1.611	1.681 ± 1.487	1.401	0.496	/
	<i>Theta Abs [<math>\mu V^2/Hz</math>]</i>	1.637 ± 2.006	1.674 ± 1.23	0.883 ± 0.992	5.345	0.069	/
	<i>Alpha Abs [<math>\mu V^2/Hz</math>]</i>	1.656 ± 1.22	2.843 ± 1.958	2.325 ± 2.877	4.302	0.116	/
	<i>Beta Abs [<math>\mu V^2/Hz</math>]</i>	0.338 ± 0.272	0.367 ± 0.289	0.361 ± 0.271	0.122	0.941	/
	<i>Delta Rel [%]</i>	38.451 ± 7.836	31.036 ± 14.575	35.214 ± 16.892	3.456	0.178	/
	<i>Theta Rel [%]</i>	23.773 ± 8.956	22.356 ± 8.56	16.403 ± 6.492	4.221	<b>0.02*</b>	PD+FoG > HC (0.025*)
	<i>Alpha Rel [%]</i>	30.852 ± 10.044	41.097 ± 17.535	39.322 ± 22.437	3.02	0.221	/
	<i>Beta Rel [%]</i>	6.924 ± 3.858	5.511 ± 3.133	9.061 ± 4.249	7.112	<b>0.029*</b>	PD-FoG < HC (0.03*)
Occipital L	<i>Delta Abs [<math>\mu V^2/Hz</math>]</i>	2.194 ± 1.791	2.517 ± 2.15	2.064 ± 1.963	0.512	0.774	/
	<i>Theta Abs [<math>\mu V^2/Hz</math>]</i>	1.691 ± 2.015	1.671 ± 1.493	1.014 ± 1.12	2.67	0.263	/
	<i>Alpha Abs [<math>\mu V^2/Hz</math>]</i>	1.704 ± 1.313	2.621 ± 2.147	2.601 ± 3.771	4.044	0.132	/
	<i>Beta Abs [<math>\mu V^2/Hz</math>]</i>	0.517 ± 0.814	0.308 ± 0.202	0.387 ± 0.309	0.196	0.907	/
	<i>Delta Rel [%]</i>	37.219 ± 9.823	33.518 ± 15.677	38.671 ± 15.811	0.644	0.53	/
	<i>Theta Rel [%]</i>	24.275 ± 9.364	21.735 ± 8.098	16.94 ± 6.163	6.675	<b>0.036*</b>	PD+FoG > HC (0.051)
	<i>Alpha Rel [%]</i>	30.406 ± 9.913	39.615 ± 17.601	35.608 ± 20.658	2.652	0.265	/
	<i>Beta Rel [%]</i>	8.099 ± 6.142	5.132 ± 2.488	8.781 ± 4.498	7.679	<b>0.022*</b>	PD-FoG < HC (0.039*)

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## **Annexe 3 - Participation à d'autres articles en tant que co-auteur**

### **Motor Preparation of Step Initiation: Error-related Cortical Oscillations**

Arnaud Delval, Aurore Braquet, Nauaman Dirhoussi, **Madli Bayot**, Philippe Derambure, Luc Defebvre, Céline Tard, and Kathy Dujardin.

Article publié dans *Neuroscience*.

DOI : <https://doi.org/10.1016/j.neuroscience.2018.09046>

## Motor Preparation of Step Initiation: Error-related Cortical Oscillations

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**Abstract**—Gait initiation can vary as a function of the available and engaged attentional resources. Conflict resolution can disrupt movement preparation and lead to “errors” in motor programming. These “errors” are physiologically useful by enabling us to adapt our motor behavior to situations with conflicting information. The objective of the present study was to analyze the patterns of cortical activation associated with motor programming errors and the corresponding error corrections. Incongruent flankers around a target arrow were used to trigger errors in anticipatory postural adjustments (APAs) prior to gait initiation; i.e. perturbed motor programming but normal execution. Thirty healthy adults performed a gait initiation task. The event-related potentials (ERPs) and event-related desynchronization (ERD) after target presentation were analyzed according to the presence or absence of an APA error. The ERP was similar in both conditions, except that the Ne and P300 peak latencies were longer for APA errors. Motor programming errors during gait initiation were characterized by longer, less intense low-beta-band ERD over the sensorimotor cortex and alpha ERS followed by stronger alpha ERD during errors. APA errors were associated with a specific alpha/beta oscillation profile over the sensorimotor cortex; these beta oscillations might be sensitive markers of non-conscious motor error and correction monitoring. © 2018 IBRO. Published by Elsevier Ltd. All rights reserved.

**Key words:** cortical activation, gait initiation, posture, inhibition, attention.

### INTRODUCTION

Gait initiation is a motor program characterized by the transition from a static stable stance to a continuously unstable posture during locomotion. The characteristics of gait initiation can vary as a function of the available attentional resources. Indeed, gait initiation can be modulated when the subject is obliged to deal with conflicting information (Uemura et al., 2012). Gait is initiated in two phases: a motor preparation phase (corresponding to anticipatory postural adjustments, APAs) and then an execution phase (corresponding to the time interval between “toe-off” and “heel strike” for the swing leg). During standard gait initiation (i.e. in the absence of external or internal stimuli requiring modulation of the motor program), healthy subjects display a stereotypical APA pattern. Foot-off of the swing leg is preceded by a shift in body weight that displaces the center of pressure

(CoP) backward and toward the swing leg. Next, the CoP is displaced forward and toward the stance leg. Hence, APAs create the conditions required for progression (Brenière and Do, 1991). Furthermore, APAs along the mediolateral axis are predictive of postural stability (McIlroy and Maki, 1999). However, it is known that self-triggered gait initiation is not always preceded by an APA (Delval et al., 2014; Lu et al., 2017). The lack of a lateral or posterior APA was nevertheless infrequent (in 2% of the trials) in healthy elderly controls during externally triggered rapid stepping (Delval et al., 2014). Conversely, the absence of APAs can be frequently observed in patients with freezing of gait and an increased risk of falls (Delval et al., 2014). The occurrence of APA errors can also perturb the gait initiation program by delaying the onset of movement execution (Cohen et al., 2011). This corresponds to the correction of an APA when the initial direction of postural adjustment is not appropriate (for example, when the CoP moves inappropriately toward the stance leg and is then appropriately moved first toward the swing leg and only then toward the stance leg). This APA error corresponds to a motor program error, which is efficiently corrected and prevents incorrect step initiation from taking place. It is known that APA errors are more frequent in conditions modulated by attention (especially in the presence of incongruent stimuli

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**Abbreviations:** APAs, anticipatory postural adjustments; CoP, center of pressure; CRN, Correct-Related Negativity; EEG, electroencephalogram; ERD, event-related desynchronization; ERD/S, event-related (de)synchronization; ERN, Error-Related Negativity; ERPs, event-related potentials; Pe, Positive error-related.

(Uemura et al., 2013) or with invalid cues (Tard et al., 2013)) than in conditions with congruent step initiation stimuli. However, it is not known if and how these APA errors are modulated in the cortex.

Cortical areas involved in gait initiation include the sensorimotor cortex, premotor cortex, basal ganglia and brainstem structures. It was initially suggested that the motor programs underlying the elicitation of gait initiation were stored in subcortical structures, and could be elicited by a startling stimulus or a decision for action (Takakusaki, 2008; Queralt et al., 2010; Delval et al., 2012; Watanabe et al., 2016a). However, studies in patients with focal lesions of the supplementary motor area and studies in patients with Parkinson's disease (Viallet et al., 1992; Gantchev et al., 1996) have shown that APAs can be modulated at the supraspinal level, since the supplementary motor area, the basal ganglia and the pontomedullary reticular formation are linked by neural networks. Moreover, inhibitory repetitive transcranial magnetic stimulation over the supplementary motor area shortens the APA duration for a brief period, i.e. for the first stepping trial after stimulation (Jacobs et al., 2009). The output of this pathway is located in the mid-brain locomotor region (which may correspond in part to the cuneiform nucleus and the dorsal part of the pedunculopontine nucleus), which is connected to limbic structures and the basal ganglia (Pahapill and Lozano, 2000).

Attentional control can modulate gait initiation – either directly by involving brainstem structures (for example, the alert process induced by a loud stimulus can product a start-react effect) or indirectly via a cortical loop that includes more complex attentional networks (Delval et al., 2012; Tard et al., 2013). Cortical movement preparation can be measured through electroencephalogram (EEG) features like event-related potentials (ERPs) and event-related (de)synchronization (ERD/S). In the frequency domain, ERD (mainly in the alpha- and beta-bands) is the cortical marker of movement intention. It has been demonstrated that gait initiation is associated with desynchronization of sensorimotor rhythms related to sensorimotor cortex activation (Pfurtscheller and Andrew, 1999). If the EEG is response-locked (i.e. locked to the motor response), a movement-related cortical potential (MRCP) is present before gait initiation or when imagining gait initiation (Vidailhet et al., 1993, 1995). For the gait initiation task, if the EEG is target-locked, the early ERP components are probably influenced by the different physical characteristics of the stimuli (Rektor et al., 2006) and a posterior P300 can be found, higher in case of stimulus driven attention for example (Tard et al., 2013), whereas late components reflect motor preparation (Hamano et al., 1997). More recently, combined ERP and ERD/S recordings via an EEG brain–computer interface were used to detect gait initiation (Jiang et al., 2015; Sburlea et al., 2015).

ERPs are also used to monitor cognitive control of action. During error recognition, a negativity (named the “Error-Related Negativity” (ERN or Ne)) and then a “Positive error-related wave” (Pe) can be observed (for a review, see Wessel and Aron (2017)). The functional significance of ERN was associated with error detection

(Falkenstein et al., 1991). Alternatively, the ERN was proposed to reflect conflict resolution due to a finding of the “Correct-Related-Negativity” (CRN) (Vidal et al., 2000; Meckler et al., 2011). However, errors during gait initiation are mostly non-conscious and the presence of an ERN or Pe during an APA error in healthy subjects remains uncertain. For example, Watanabe found similar frontal ERN and CRN in trials with or without APA errors during gait initiation (Watanabe et al., 2016b). The significance of these potentials remains discussed. Indeed, it has been demonstrated that the ERN occurs also after “partial errors”, i.e., incorrect activities that are not sufficient to produce overt errors (Carbónnell and Falkenstein, 2006), which is observed during spontaneous correction of APA errors. To date, the cortical areas involved in gait initiation errors have not been extensively studied and the focus was only on Fz, FCz, and Cz (Watanabe et al., 2016b). Indeed, the human sensorimotor system needs to be able to rapidly correct for errors in an ongoing motor command brought about by sudden, unexpected changes in the movement environment (such as conflicting information, for example) (Krigolson et al., 2008). The present study was designed to evaluate the cortical changes induced by these adaptive reactions called APA errors. The study's primary objective was to use a combined ERP and time–frequency analysis to evaluate cortical activation during correct gait initiation (i.e. with no APA errors) and during disturbed step initiation (i.e. with APA errors). Our starting hypothesis was that APA errors would be associated with ERP modulations featuring error-related potentials (for example, error-related negativity/positivity (Ne/Pe) (Falkenstein et al., 2000)) and/or changes in beta-band ERS, for example increased beta ERS, as observed in stop-signal paradigms for movements requiring motor inhibition (Duque et al., 2017). Modulations in lower bands (delta–theta) have also been attributed to error monitoring in children, young and elderly adults (Kolev et al., 2001, 2005; Albrecht et al., 2009).

## EXPERIMENTAL PROCEDURES

### Participants

Thirty healthy adult volunteers (16 females, 14 males; 29 right-handed; mean  $\pm$  standard deviation (SD) age: 39.4  $\pm$  14.2 years) participated in the study after providing written, informed consent. None of the participants had a history of medication use (neuroleptics, benzodiazepines, etc.) or disease (neurological, orthopedic or psychiatric) that could have interfered with gait. The mean  $\pm$  SD Montreal Cognitive Assessment score (Nasreddine et al., 2005) was 28.5  $\pm$  2. Participants with a score of less than 26 out of 30 were excluded. The study was approved by the local independent ethics committee (CPP Nord-Ouest, Lille, France; reference: 2015-A00013-46).

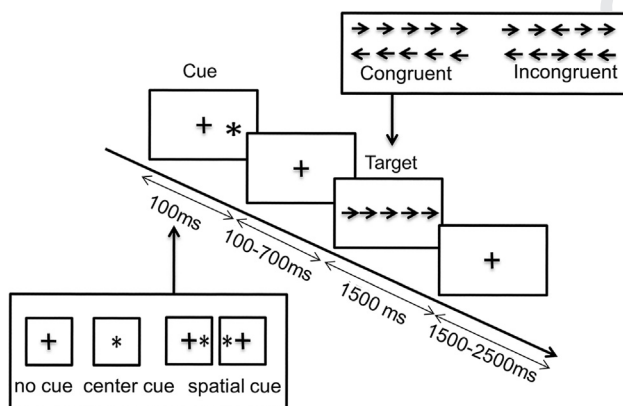
### The experimental setting

The participant was told to stand in a stable, comfortable, natural posture on a force platform, with his/her feet

171 parallel and with a gap of a few centimeters between the  
172 feet. A computer display screen was placed at head  
173 height 1 meter in front of the participant. The attentional  
174 task was an adaptation of the attentional network test  
175 (Fan et al., 2002) (Fig. 1). The participant was instructed  
176 to initiate a forward step after presentation of the visual  
177 target (an arrow pointing to the right or to the left, which  
178 was visible for 1500 ms). If the arrow pointed to the left,  
179 the participant had to initiate gait with the left foot; con-  
180 versely, if the arrow pointed to the right, the participant  
181 had to initiate gait with the right foot. The balance weight  
182 shift between the 2 feet was controlled online (position of  
183 the CoP between the 2 feet visualized by the Nexus soft-  
184 ware). The present study only assessed the condition with  
185 incongruent flankers (i.e. flankers pointing in the opposite  
186 direction to the target arrow), in which the frequency of  
187 APA errors is reportedly higher (Uemura et al., 2013).  
188 Indeed, differences in ERP amplitudes have been  
189 reported between congruent and incongruent conditions  
190 in a similar study design in seated condition (Neuhaus  
191 et al., 2010). A total of 144 incongruent trials (out of a total  
192 of 300) were available for each participant.

193 **Motion analysis**

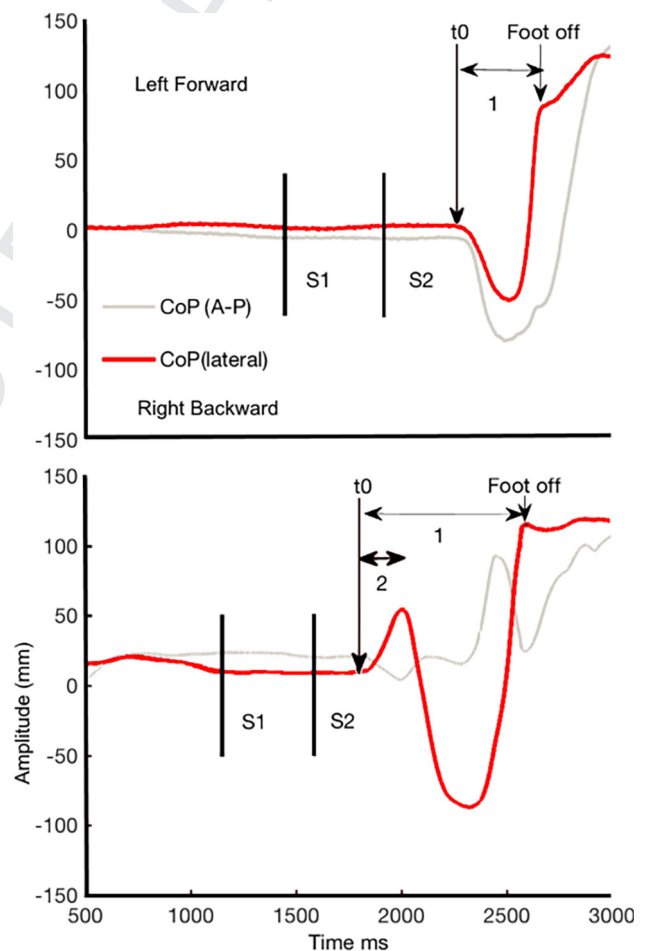
194 Data were collected with a three-dimensional motion  
195 analysis system (VICON 370®, Oxford Biometrics,  
196 Oxford, UK), using eight infrared cameras and a  
197 sampling frequency of 100 Hz. The CoP was measured  
198 with two force platforms (the ORG-5 model from  
199 AMTI®, Watertown, MA, USA) at a sampling frequency  
200 of 1000 Hz. Reflective markers were placed on precise,  
201 reproducible, anatomic landmarks on each foot: the toe



**Fig. 1.** Attentional Network test. A schematic diagram of the attentional task. S1: cue; S2: target. The target appeared for 1500 ms and was surrounded by flankers (four arrows: two on each side) that were either congruent or incongruent. The targets could be preceded by valid or invalid spatial cues, i.e. asterisks indicating (or not) the direction of the arrow. Four blocks of 75 trials were administered. The blocks were separated by short breaks of variable duration. The cue and target conditions were presented in a pseudo-random order: 156 congruent trials, 144 incongruent trials, 49 trials with no cue, 61 trials with a central cue, and 190 trials with a spatial cue (142 valid and 48 invalid cues). Only incongruent trials were analyzed in the present study. The proportion of no cue trials was 16.3%, the proportion of neutral cue trials was 20.3%, the proportion of valid cue trials was 47.3%, and the proportion of invalid cue trials was 16%.

(the head of the second metatarsal), the lateral malleolus, and the heel. The data were then computed by the same operator using an in-house MATLAB® routine (The MathWorks, Natick, MA, USA).

The direction of the APA was considered to be normal if the CoP moved backward and sideways toward the swing foot. Conversely, the direction of the APA was considered to be abnormal (i.e. an APA error) if the CoP moved first toward the stance foot and only then toward the swing foot (see Fig. 2). The reaction time (RT) was defined as the time interval between the appearance of the target (S2) and the beginning of the APA or  $T_0$ . An RT < 100 ms was classified as a false start and was excluded from further analyses. Incorrect starts (i.e. starts with the wrong foot) were also excluded. An in-house MATLAB® routine detected changes in CoP velocity > mean + 3 SD of the baseline period (-1500 to 1000 ms before target stimulus), the experimenter then chose the start of the APAs according to the curves in X and Y axis. Toe-off was detected visually



**Fig. 2.** Normal Anticipatory Postural Adjustments (APA) and APA error. Step initiation with the right foot by a study participant. Top panel: a normal APA, where the center of pressure (CoP) shifts to the swing leg (right) and then to the stance leg (left) (lateral CoP: red line). Bottom panel: an APA error: the CoP shifts toward the stance leg (left) but the trajectory is corrected. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(from the toe marker trajectory in the sagittal plane) and then reported on the CoP curve. It corresponded to the time the CoP shifted forward. The APA duration was assessed by subtracting  $T_0$  from the toe-off time. For APA errors, the correction time was defined as the time interval between  $T_0$  and the sideways corrective shift (i.e. the beginning of the APA in the correct direction).

#### 229 Acquisition of electroencephalographic data

230 The electroencephalogram (EEG) was recorded with an  
231 Ag/AgCl 128-scalp-electrode cap (Waveguard®, ANT  
232 Neuro, Enschede, The Netherlands), positioned  
233 according to the 10/05 international system (Oostenveld  
234 and Praamstra, 2001). Data were acquired with ASA™  
235 software (ANT Neuro), using a 0.01- to 100-Hz band-  
236 pass filter, a sampling frequency of 512 Hz, and impe-  
237 dances below 20 kΩ. The data were pre-processed with  
238 ASA™ software in order to reject ocular artifacts and apply  
239 a 50-Hz notch filter to the recordings. Next, interpolation  
240 was performed for artifact-affected electrodes, with a  
241 maximum interpolation rate of 10% ( $n = 13$ ) for the whole  
242 set of 128 scalp electrodes.

243 The EEG data were then analyzed with Brain Vision  
244 Analyzer 2.0 software (BrainProducts). Muscle artifacts  
245 were manually removed from the EEG layout;  
246 thereafter, we segmented the EEG data into 2500-ms  
247 epochs that were time-locked with respect to target  
248 onset (1500 ms before and 1000 ms afterward). The  
249 median (min–max) number of epochs selected (after  
250 artifact rejection) per participant was 49 (20–98) for APA  
251 errors and 69 (38–107) for normal APAs.

252 *ERP analyses.* ERP were analyzed with the EEGLAB  
253 toolbox (Delorme and Makeig, 2004), using a baseline  
254 from 1500 ms before the target onset to 1000 ms for  
255 target-locked ERP and from 1500 ms before the APA  
256 onset to 650 ms for response-locked ERP. The time win-  
257 dow analysis was from S2 to 1000 ms after target onset.  
258 We first analyzed ERP scalp distribution maps. Next,  
259 the ERP wave's characteristics were assessed and col-  
260 lected by grand-averaging over the main central elec-  
261 trodes (Fz, Cz, Pz).

262 For target-locked ERP, we focused on P300 over Pz.  
263 For response-locked ERP, we analyzed ERN/CRN over  
264 Fz and P300/Pe over Pz. The amplitude of potentials  
265 was measured as the difference between the maximum  
266 peak of the ERP waveform and the mean baseline  
267 voltage (which occurs prior to the stimulus). Latency  
268 was defined as the interval between target presentation  
269 and the point of highest positive amplitude in the time  
270 window of the potential. For target-locked ERP, time  
271 window of P300 ranged from 250 to 500 ms after target  
272 presentation. For response-locked ERP, the time  
273 window of the ERN/CRN ranged from –50 to 200 ms  
274 after APA start and from 0 to 400 ms for the posterior  
275 component.

276 *ERD/ERS analyses.* Time–frequency analysis  
277 requires computing the power spectrum over a sliding  
278 latency window. ERD data were analyzed using  
279 EEGLAB software (Delorme and Makeig, 2004) with a

500-ms baseline (between 1500 and 1000 ms before 280  
the target's appearance, target-locked and response- 281  
locked). To characterize event-related EEG oscillations 282  
like ERD and ERS, we applied a time–frequency analysis 283  
based on a continuous wavelet transform. We used a ver- 284  
sion of sinusoidal wavelets in which the number of cycles 285  
increases slowly with frequency (e.g. 1.5 cycles at 4 Hz, 286  
and 5.6 cycles at 30 Hz) with a window width of 213 sam- 287  
ples (416 ms). This procedure has been described in 288  
(Delorme and Makeig, 2004), and similar approaches for 289  
time windows of around 2500 ms have been described 290  
in (Fan et al., 2007). Time–frequency analyses were per- 291  
formed between 4–7 Hz (the theta-band), 8–12 Hz (the 292  
alpha-band), and 13–30 Hz (the beta-band, divided in a 293  
low-beta-band (13–20 Hz) and a high-beta-band (20– 294  
30 Hz)). 295

*Cortical sources.* A realistic head model was built by 296  
segmenting a template MRI data with Freesurfer 297  
software (Dale et al., 1999). The lead field matrix was 298  
then computed for a cortical mesh with 15,000 vertices, 299  
using Brainstorm software (Tadel et al., 2011) and Open- 300  
MEEG software (Gramfort et al., 2010). The weighted 301  
minimum-norm estimate was then used to reconstruct 302  
the cortical sources (using Brainstorm toolbox (Tadel 303  
et al., 2011)) in the time window corresponding to motor 304  
preparation. 305

#### 306 Statistical analyses

307 Characteristics of APAs were compared using a one-way 308  
ANOVA after checking normality of the distributions. To 309  
evaluate differences in cortical activation (ERPs, ERD/S 310  
and source localization) in trials with an APA error vs. 311  
trials with a normal APA, we used a non-parametric 312  
permutation (randomization) test to obtain the p-value 313  
for each electrode and each time point (for ERP and 314  
ERD/S) and for each source reconstruction. The false 315  
discovery rate (FDR) method was used to correct for 316  
multiple comparisons (Genovese et al., 2002), and 317  
enabled us to determine which electrodes differed 318  
between the two conditions at the different time points 319  
(scalp maps) and to compare ERD/ERS maps between 320  
both conditions. These analyses were performed with 321  
the EEGLAB toolbox (Delorme and Makeig, 2004), which 322  
includes MATLAB statistical routines at this purpose. For 323  
comparisons between source localizations, we used the 324  
scripts included in the Brainstorm toolbox (Tadel et al., 325  
2011)). Peak amplitudes and latencies (for P300 on Pz, 326  
for example) were compared in a t-test (in SPSS 17 for 327  
Windows) after checking the normality of distribution in 328  
a Kolmogorov–Smirnov test. The threshold for statistical 329  
significance was set to  $p < 0.05$  for all analyses.

## 330 RESULTS

### 331 Behavioral data

In trials with incongruent flankers, the APA error rate was 332  
41.0%. 333

*The false start rate.* The false start rate (i.e. 334  
RTs < 100 ms) was 11.9%. These trials were excluded 335

336 from further analysis, since they did not correspond to  
337 APA errors.

338 *The error step rate.* A start with the wrong foot was  
339 rare, since it occurred in only 0.56% of the trials. These  
340 trials were excluded from the analysis because they did  
341 not correspond to correct error monitoring. The low  
342 number of these events prevented us from analyzing  
343 them separately.

344 The mean  $\pm$  SD RT was  $0.27 \pm 0.08$  s for normal  
345 APAs and  $0.23 \pm 0.06$  s for APA errors ( $p < 0.001$ ).  
346 The mean  $\pm$  SD APA duration was longer for APA  
347 errors ( $0.64 \pm 0.13$  s) than for normal APAs ( $0.47$   
348  $\pm 0.10$  s) ( $p < 0.001$ ). The mean  $\pm$  SD correction time  
349 for APA errors was  $0.20 \pm 0.07$  s (i.e.  $0.43 \pm 0.07$  s  
350 after target presentation, on average).

## 351 Erp

352 *Target-locked ERP:* as shown in Fig. 3, the ERP scalp  
353 distribution maps revealed an early anterior component  
354 (N2, see discussion), a late central negative component  
355 (corresponding to preparation of movement) and a  
356 posterior positive component (at the same scalp sites as  
357 the P300). There were no differences in the ERP maps  
358 between the “APA error” and “normal APA” conditions  
359 except for P300 component (see Figs. 3 and 4).

360 The mean  $\pm$  SD P300 peak latency (Pz electrode)  
361 was longer for the APA error condition than the normal  
362 APA condition ( $0.50 \pm 0.08$  s vs.  $0.47 \pm 0.08$  s,  
363 respectively;  $p < 0.01$ ). No differences in P300 peak  
364 amplitude were observed.

365 *Response-locked:* in both APA conditions, early  
366 negativity (in the time window of ERN or CRN)  
367 occurred, later in case of APA error. Late positivity  
368 (P300 or Pe, see discussion) also occurred in both  
369 conditions, later in case of APA error on posterior  
370 regions. The mean  $\pm$  SD ERN/CRN peak latency (Fz  
371 electrode) was longer for the APA error condition than  
372 the normal APA condition ( $0.12 \pm 0.05$  s vs.  $0.08$   
373  $\pm 0.05$  s, respectively;  $p < 0.001$ ). No differences in  
374 peak amplitude were observed. The mean  $\pm$  SD Pe/  
375 P300 peak latency (Pz electrode) was longer for the  
376 APA error condition than the normal APA condition  
377 ( $0.26 \pm 0.07$  s vs.  $0.19 \pm 0.06$  s, respectively;  
378  $p < 0.001$ ). No differences in peak amplitude were  
379 observed.

## 380 ERD data

381 As shown in Figs. 5 and 6, we observed similar theta-  
382 band ERS (between 200 and 600 ms, target-locked;  
383 starting at T0, response-locked) in both conditions.

384 Alpha ERS was significantly more pronounced in trials  
385 with an APA error (starting around 300 ms after S2,  
386 target-locked; during APA, response-locked) and was  
387 followed by a stronger alpha ERD (response-locked).

388 Central beta ERD was observed, starting 200 ms after  
389 S2 (target-locked); or just before T0 (response-locked).  
390 This feature lasted significantly longer over Cz in trials  
391 with an APA error (Fig. 6). Moreover, beta ERD over  
392 the sensorimotor cortex was more attenuated in the low-  
393 beta-band (i.e. 13–20 Hz) than in the high-beta-band

(20–30 Hz) in trials with an APA error (relative to trials  
with a normal APA) in target-locked analysis (Figs. 5  
and 6). We can observe that this beta ERD was present  
during both normal APAs and APA errors but was more  
prolonged (response-locked and target-locked) in case  
of error.

## Cortical sources of changes in the EEG signal during motor programming

Cortical sources in the 0- to 600-ms time interval (target-  
locked) are shown in Fig. 7. Occipital and temporoparietal  
regions were activated at 200 ms, and then the  
sensorimotor cortex and the frontal dorsolateral cortex  
were activated during both normal APAs and APA errors.

## DISCUSSION

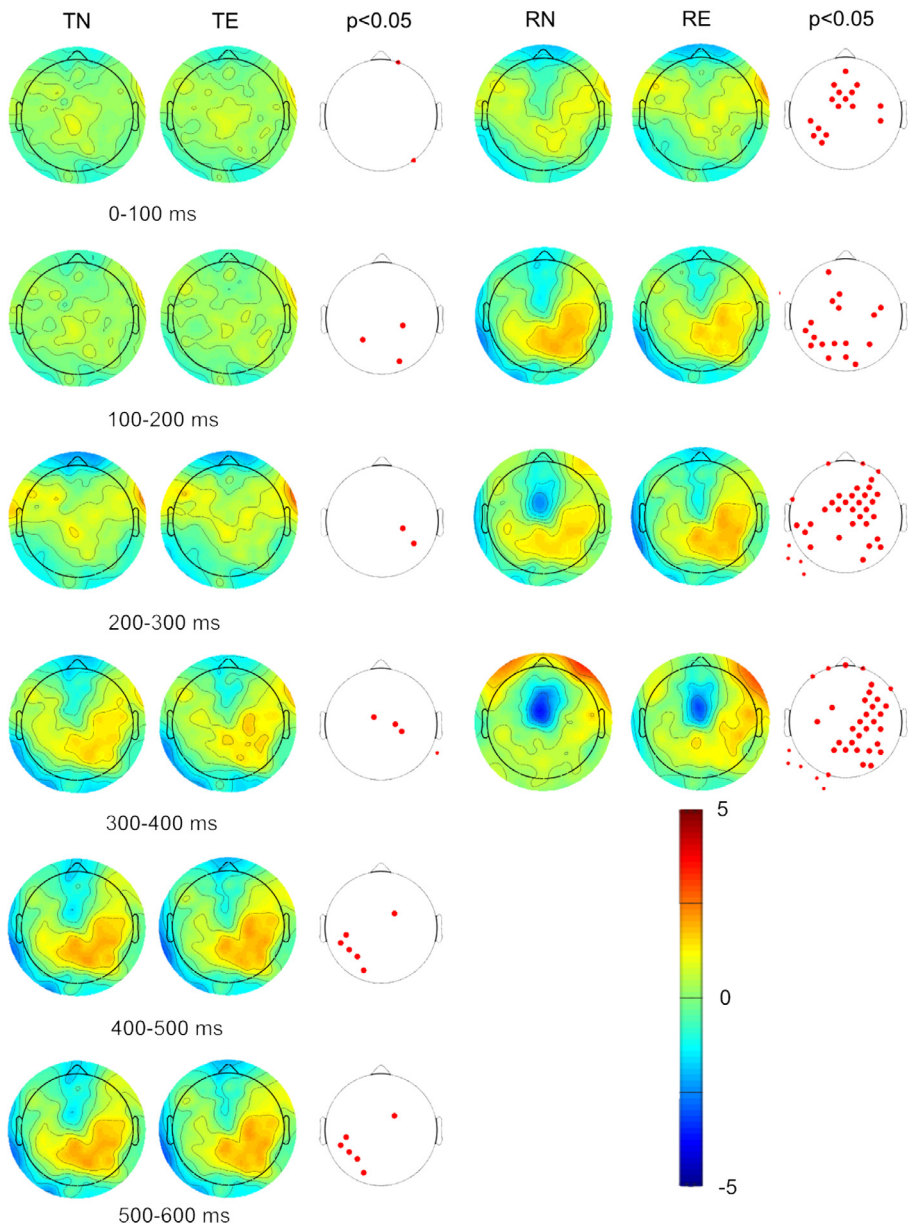
Our present results showed that an error in motor  
programming during gait initiation in healthy subjects  
was not associated with obvious differences in ERPs.  
We only observed a longer P300 peak latency in trials  
with an APA error. However, we observed extended  
beta ERD over the sensorimotor cortex, and more  
pronounced alpha ERS followed by an ERD in trials with  
an APA error.

### Are APA errors low-level errors?

It is known that the motor program can be adjusted during  
APAs. This process might involve rapid, direct  
sensorimotor loops via visual afferences for stimulus  
detection and proprioceptive afferences for the ongoing  
APA. Hence, healthy subjects are able to adjust the  
motor program after it has started by delaying foot lift  
until the correct motor program has been selected.  
Response inhibition – the ability to rapidly cancel an  
action – is a critical component of executive function. In  
gait initiation, response inhibition quickly corrected APAs  
initiated in the wrong direction (around 200 ms after the  
start of the APA error (Tard et al., 2015)). This means that  
subjects can react to the perception of conflicting informa-  
tion and quickly reorient ongoing actions. Many research-  
ers have investigated the neural substrates of behavioral  
inhibition by applying laboratory tasks based on the stop-  
signal paradigm and that require a planned action to be  
stopped (Duque et al., 2017); however, these tasks  
require complete inhibition of the motor program, rather  
than just correction (as in APA errors).

Moreover, the different types of errors described in the  
literature appear to have different neural bases: Hill and  
Raab (Hill and Raab, 2005) first distinguished the correc-  
tion of errors induced externally and internal errors gener-  
ated by the subject itself. Another distinction has been  
made between low-level errors (i.e. non-conscious,  
quickly corrected errors) involving posterior regions of  
the brain, and high-level errors (i.e. conscious errors that  
are not always corrected) involving the medial frontal lobe  
(Krigolson and Holroyd, 2007). The errors in our study  
would be classified as internal, low-level, since the partici-  
pants were not aware of them; although some partici-





**Fig. 3.** Event-related potentials in normal Anticipatory Postural Adjustments (APA) and APA error. Top view of topographic voltage maps for each condition (i.e. a normal APA-N- or an APA error-E-). 0 ms corresponds to either the target presentation (S2), target-locked (T), or to the start of the APAs (response-locked:R). Cold and hot colors correspond to negative and positive ERPs, respectively. Red dots correspond to electrodes with differences between conditions (whatever the direction), as indicated by permutation tests with FDR correction. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

449 pants described “start hesitation” in a few trials, most  
450 were unaware of the quickly corrected motor program.

451 Cortical activations during unexpected events have  
452 recently been reviewed (Wessel and Aron, 2017). Most  
453 of the relevant studies were based on the use of stop-  
454 signal paradigms and fMRI to identify the underlying  
455 motor inhibition system. The right inferior frontal cortex,  
456 pre-supplementary motor area and subthalamic nucleus  
457 (STN) of the basal ganglia are all involved, with down-  
458 stream effects on the pallidum, thalamus, and primary  
459 motor cortex. Indeed, the STN’s role has been empha-

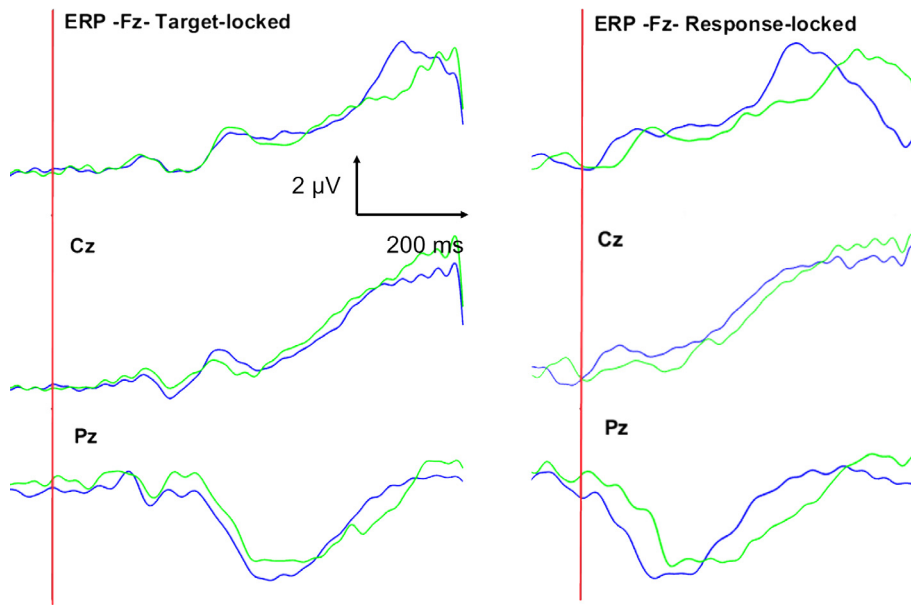
460 sized by several fMRI studies (Aron and Poldrack, 2006; Li  
461 et al., 2008); activity in the STN is greater during both stop successes  
462 and stop errors than in “go” trials,  
463 and greater for stop errors than  
464 for stop successes (Li et al.,  
465 2008). These findings suggest that  
466 the STN has a role in suppressing  
467 thalamocortical output, which  
468 thereby blocks motor response  
469 execution via a hyperdirect path-  
470 way (Aron and Poldrack, 2006).  
471 The mechanisms in our paradigm  
472 were less clear, since error correc-  
473 tion re-oriented a movement rather  
474 than stopping it completely as in  
475 stop-signal paradigms. Subjects  
476 were able to shift their weight  
477 toward the swing leg to correct  
478 the error. This could correspond  
479 to “partial errors”, i.e., incorrect  
480 activities which are not sufficient  
481 to produce overt errors  
482 (Carbonell and Falkenstein,  
483 2006). These latter could produce  
484 both ERN and CRN. However, we  
485 would have expected more ample  
486 negativity over frontal regions in  
487 case of APA errors.  
488  
489

### Cortical markers of error monitoring

490 Evaluating the precise timing of  
491 cortical activations requires  
492 electrophysiological recordings  
493 based on local field potentials or  
494 EEG. It is generally thought that  
495 an anterior component (ERN/Ne)  
496 reflects error inhibition (Kopp  
497 et al., 1996), conflict detection  
498 (Carter et al., 1998) or the  
499 comparison (response checking)  
500 of the neural representation of the  
501 actual (erroneous) response and  
502 the representation of the required  
503 (i.e. correct) response. In our  
504 paradigm, however, successful  
505 error inhibition was followed by a  
506 motor programming correction  
507  
508

509 and then appropriate movement execution. With regard  
510 to response checking, the participant had to recognize  
511 the engaged motor program (the left or right foot) –  
512 usually a non-conscious process – and determine  
513 whether or not it corresponded to the appropriate  
514 response. This process is much the same in APA errors  
515 and normal APAs.

516 We did not observe any differences in the ERN/CRN  
517 amplitudes. The amplitudes of CRN and ERN were also  
518 similar for the stepping task in (Watanabe et al., 2016b)  
519 that used a Simon task to elicit APA errors. They pro-



**Fig. 4.** Event-related potentials in normal Anticipatory Postural Adjustments (APA) and APA error in midline derivations. ERP for Fz, Cz and Pz sites in two conditions: blue: grand average of normal APA vs. green, grand average of APA error. 0 ms corresponds to either the target presentation (S2), target-locked, or to the start of the APAs (response-locked). Target-locked: P300 occurred later in case of APA error. Response-locked: negative components (?Ne and CRN) were observed, later in case of APA error. P300 or Pe occurred later in case of APA error. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

520 posed different interpretations: the more convincing one  
 521 in our opinion is that APA errors are brief, covert, and  
 522 are likely corrected by initiating a step with the appropriate  
 523 leg. As a consequence, ERN amplitude may have  
 524 become smaller because APA errors were not recognized  
 525 as definite errors. Once again, this error is not conscious.  
 526 The late, posterior, positive ERP component observed  
 527 after presentation of the target is more difficult to interpret.  
 528 Considering target-locked responses, the ERP peaked in  
 529 the parietal cortex at about 400 ms (target-locked) and  
 530 100–200 ms (response-locked). It might therefore be a  
 531 P300 component. It is very similar to the response-  
 532 locked posterior component. The latency (but not the  
 533 amplitude) differed according to the presence or not of  
 534 an APA error. The absence of a difference in amplitude  
 535 was not very surprising because P300's amplitude is  
 536 primarily modulated by the stimulus's rarity (as in the oddball  
 537 paradigm). Here, only incongruent targets were considered.  
 538 They elicited a large P300, regardless of the forth-  
 539 coming motor preparation (Neuhaus et al., 2010; Deiber  
 540 et al., 2013). Alternatively, the ERP component might cor-  
 541 respond to Pe. The latter is thought to reflect (i) error cor-  
 542 rection, (ii) a delayed parietal P300 (since it is present in  
 543 correct trials) or (iii) additional error processing or post-  
 544 error processing (for a review, see Falkenstein, 2010).  
 545 Here, the distribution is posterior and not anterior. More-  
 546 over, in our paradigm, there were no amplitude differ-  
 547 ences between trials with and without APA errors. It  
 548 must be borne in mind that the variability in Pe depends  
 549 on error detectability: the larger the difference between  
 550 the representations (i.e. the easier the error is to detect),  
 551 the larger and/or earlier the Pe. There are several possi-

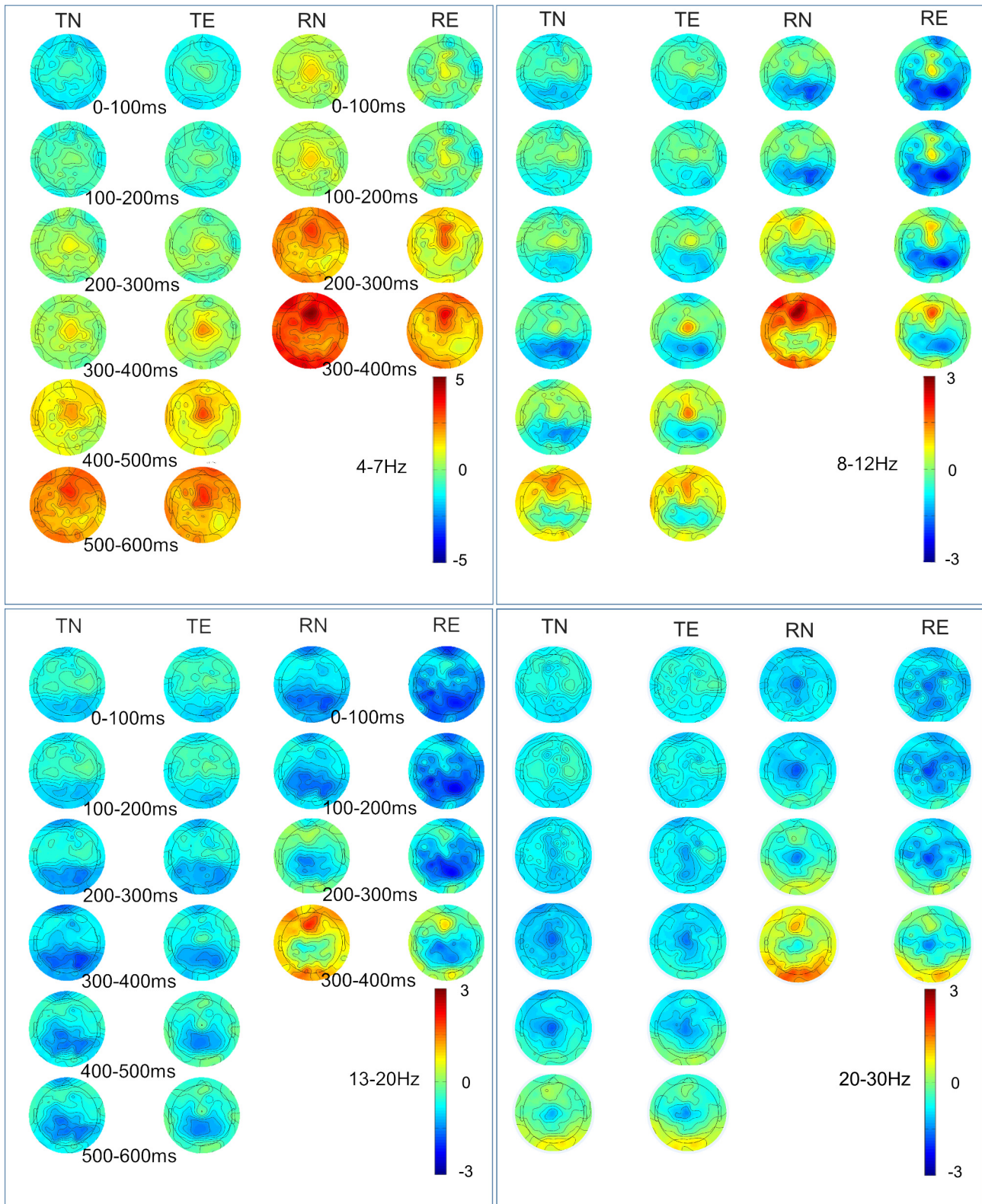
552 ble explanations for the lack of dif-  
 553 ference in the amplitude of Pe. The  
 554 participant was not given any infor-  
 555 mation about APA error monitoring.  
 556 Indeed, both Ne and Pe are  
 557 closely related to conscious percep-  
 558 tion of the error (Nieuwenhuis  
 559 et al., 2001; Charles et al., 2013).  
 560 In fact, in the work by Charles  
 561 et al., the ERN was absent only  
 562 when subjects reported that they  
 563 did not see the target. That was  
 564 not the case in our study since sub-  
 565 jects well identified the target (no  
 566 error of step side).

567 Instructing the participant to  
 568 pay attention (or not) to the error  
 569 stimulus (Ramautar et al., 2006)  
 570 can also amplify the ERP. In  
 571 Ramautar et al.'s study, Pe was  
 572 much more pronounced for per-  
 573 ceived errors than for unperceived  
 574 errors. We suggest that these  
 575 ERPs reflect cognitive processing  
 576 of the stimulus (i.e. incongruent  
 577 flankers surrounding the arrow)  
 578 more than perception of the APA  
 579 error. These scalp ERPs did not  
 580 seem to be relevant for studying  
 581 the non-conscious monitoring of

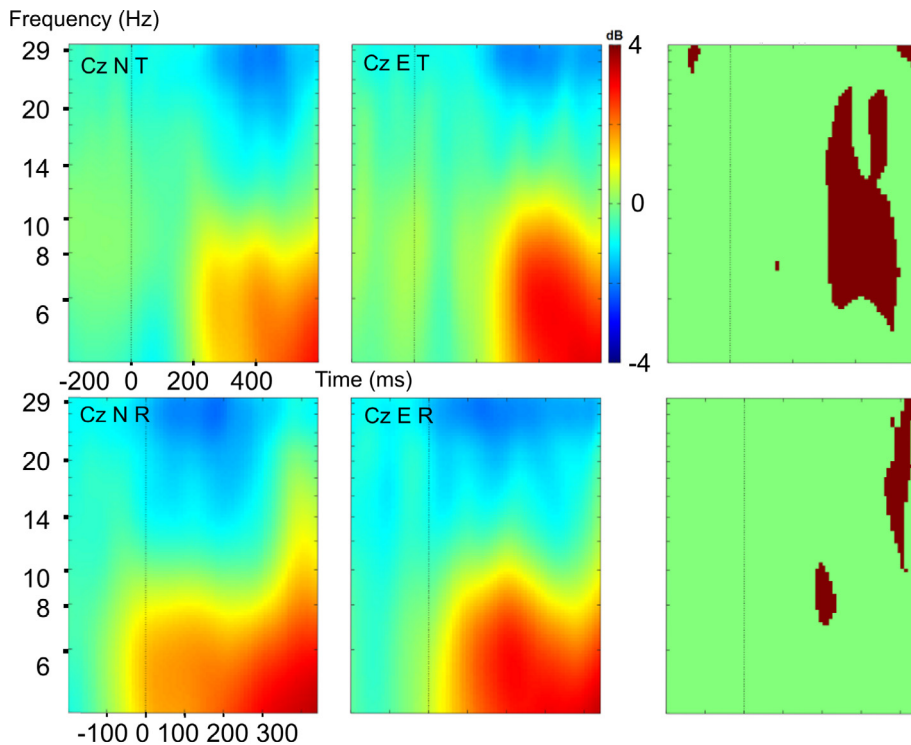
582 an ongoing action, when the error was corrected online  
 583 before the possible erroneous outcome (i.e. initiation with  
 584 the wrong foot). According to Krigolson and Holroyd, the  
 585 P300 component has a role in the online control process  
 586 for low-level errors (Krigolson and Holroyd, 2007). In a  
 587 corrective limb adjustment task using a joystick (in which  
 588 the target's location changed unexpectedly following  
 589 movement onset, in order to elicit errors), the researchers  
 590 concluded that if P300 arises after behavioral changes  
 591 associated with the online control of movement, then it  
 592 cannot be involved in the evaluation of target errors  
 593 (Krigolson et al., 2008). Indeed, the P300 started after  
 594 the participants had begun to adjust their motor output  
 595 to accommodate the target perturbation. Moreover,  
 596 Krigolson and Holroyd did not observe a difference in  
 597 amplitude according to the presence or absence of cor-  
 598 rection. As suggested by Krigolson et al. (Krigolson  
 599 et al., 2008), we hypothesize that P300 reflects the updat-  
 600 ing of an internal model of the movement environment –  
 601 processing of flankers, for example (Donchin and Coles,  
 602 1988).

### Time–frequency analysis and motor programming

603  
 604 Non-phase-locked (induced) changes can be studied in a  
 605 time–frequency analysis, which highlights the cortical  
 606 oscillations related to an external or internal event  
 607 (Rektor et al., 2006). Indeed, motor-related cortical oscil-  
 608 lations are generally assessed by quantifying increases or  
 609 suppressions in spectral power. For example, increases  
 610 in amplitude of the cortical oscillations in the delta-band  
 611 (2–4 Hz) and the gamma (bands 60–200 Hz) are



**Fig. 5.** Event-related desynchronization/synchronization (ERD/ERS) in normal Anticipatory Postural Adjustments (APA) and APA error. Top view of spectral maps (in dB) in the 4–7 Hz, 8–12 Hz, 13–20 Hz and 20–30 Hz bands for normal APAs (N) and APA errors (E). Target-locked (T) and response-locked (R) are shown. 0 ms correspond either to the target presentation or to T0 (start of the APAs). The color at each image pixel indicates the power (in dB) of a given frequency band. Hot colors correspond to an increase in power relative to the baseline, and cold colors correspond to a decrease in power. Theta, alpha ERS were observed in both conditions after target presentation. Beta ERD was observed in both conditions but was more prolonged for APA errors. The low-beta ERD was less intense for APA errors (target-locked only). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 6.** Event-related desynchronization/synchronization (ERD/ERS) in normal Anticipatory Postural Adjustments (APA N) and APA error (E) over Cz. ERD/ERS in the different frequency bands over Cz in trials with a normal APA (N top row) or an APA error (E second row). The line indicates the target presentation time (target-locked: T) or T0 (start of the APAs, response-locked: R). ERD is shown in blue, and ERS is shown in red in dB. We observed alpha ERS during APAs more intense for APA errors, beta ERD during the normal APA and during the APA error. This ERD was longer (target-locked, response-locked) and less intense (target-locked) in the low-beta-band for APA errors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

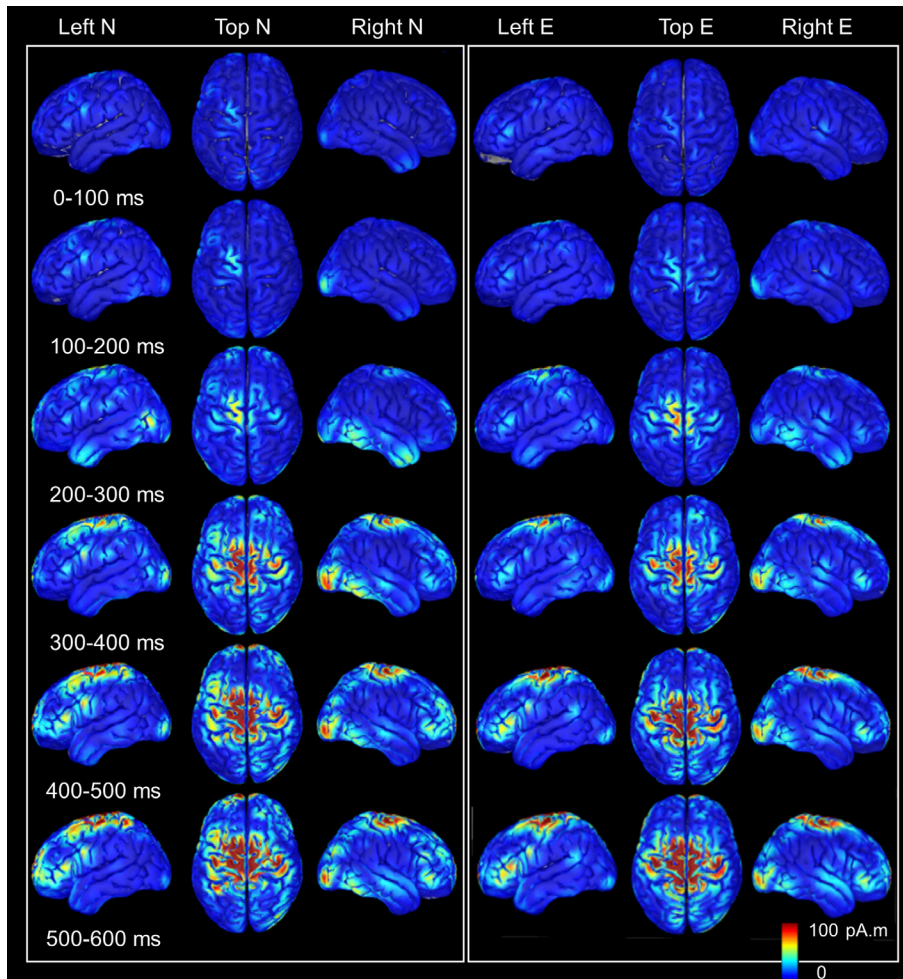
influenced by performance monitoring (theta ERS), error speed processing (posterior alpha ERD) (van Driel et al., 2012). Increasing alpha ERS is supposed to facilitate the goal-directed behavior (Dockree et al., 2007) by reflecting active mechanisms of sensory suppression for irrelevant-task stimulus (Foxe and Snyder, 2011) which could be particularly useful for proper motor execution in case of APA errors triggered by incongruent stimuli. Then, alpha ERD (response-locked) is strongly associated to visual perception and involved in task anticipation to modulate the excitability in human parieto-occipital cortex (Capotosto et al., 2017). Alpha ERD is therefore stronger in trials with APA errors in order to facilitate the modulation of the sensorimotor cortex with stimulus' perception. It signs the further orientation and maintenance of visual attention (posterior predominant, engagement of parieto-occipital areas (Foxe et al., 1998)).

Beta ERD is thought to reflect the activation of regions engaged in visuospatial attention or motor execution (Pfurtscheller and Lopes da Silva, 1999). During tasks requiring attention, significant increases in the delta-, theta- and gamma-bands have been reported during the planning phase and especially during execution. In contrast, alpha, beta and low-gamma power falls after an execution cue (Combrisson et al., 2017). In our paradigm, the occurrence of beta ERD following the appearance of the target was consistent with this pattern. Oscillations in the beta- and gamma-bands during motor preparation have been studied in paradigms that compare successful stops with unsuccessful stops (Swann et al., 2009, 2012). Overall, brief beta ERS is followed by longer beta ERD. The latter is more pronounced in successful stop trials. These findings provide insight into our results – even though our study did not feature successful vs. unsuccessful stops. In trials with APA errors, we observed prolonged beta ERD over the sensorimotor cortex; this probably reflected the fact that movement preparation was longer when an APA error occurred (Cohen et al., 2011). We also observed less intense low-beta ERD during APA errors. In a study evaluating a shifting cognitive task during gait (Wagner et al., 2016), two different beta oscillations were noted: beta ERD (expressing motor execution and motor readiness related to gait movements) and a frontal beta ERS (related to cognitive top-down control on gait). The less intense ERD in the APA error condition might be due to the summation of concomitant ERD

612 observed during both the planning and execution of  
613 movement (Combrisson et al., 2017). The initiation of vol-  
614 untary movements has also been linked to desynchro-  
615 nization of cortical activity in the alpha-band (8–12 Hz)  
616 and the beta-band (13–30 Hz) in electrocorticography  
617 and scalp EEG recordings (and then decrease of ampli-  
618 tude of oscillations in the corresponding frequency band)  
619 over the motor and premotor cortex (Pfurtscheller, 1981;  
620 Neuper et al., 2006).

621 Firstly, we observed theta synchronization and a more  
622 pronounced alpha synchronization in case of error.  
623 Secondly, beta ERD was observed over sensorimotor  
624 cortex.

625 Theta-band ERS is linked to an alert effect (Luu et al.,  
626 2004) and to stimuli monitoring and discrimination (Wang  
627 et al., 2005) engaged in attentional processes (Luu et al.,  
628 2004; Fan et al., 2007; Song et al., 2014). Alpha ERS  
629 (coupled with theta ERS) at the start of APAs was fol-  
630 lowed by stronger posterior alpha ERD in case of APA  
631 error. This particular pattern has been previously  
632 described during different variants of the Simon task dur-  
633 ing errors in an upper limb task (van Driel et al., 2012) and  
634 seems consistent. These patterns according to the vari-  
635 ants of the attentional task (in terms of amplitude, loca-  
636 tion, coupling between different cortical regions) were



**Fig. 7.** Source localization of cortical activity in the 0- to 600-ms time window N: normal APAs; E: APA errors. The source localizations were the same in both conditions.

698 (for movement preparation) and ERS (for the cognitive  
699 load, with a complicated process for conflict resolution  
700 and correction of the engaged motor program). Further-  
701 more, beta frequency oscillations are associated with  
702 the maintenance of the “status quo”, such as holding a  
703 fixed position. In the event of an APA error, the status  
704 quo is disrupted. For example, stabilized gait on treadmill  
705 is characterized by beta-band desynchronization that  
706 lasts for at least 15 steps (Wagner et al., 2016). Here,  
707 the presence of differences in low-beta ERD during an  
708 APA error suggested that the status quo had been dis-  
709 rupted (Engel and Fries, 2010). However, low-beta mod-  
710 ulations have been studied more frequently in cognitive  
711 tasks (including memory tasks) than in motor tasks. Other  
712 spectral properties (such as phase and phase-amplitude  
713 coupling) have also been shown to carry information with  
714 regard to the oscillatory dynamics underlying motor pro-  
715 cesses, and an analysis of these variables might be of  
716 value in studying network dynamics during low-level  
717 errors (Combrisson et al., 2017). There was a contradic-  
718 tion between the findings of ERN and theta/alpha ERD/  
719 S. Contrary to ERP, alpha synchronization appeared in  
720 this study to be more sensitive, probably because of its

time resolution and the relative  
specificity of the different fre-  
quency bands to monitor brief cov-  
ert errors such as APA errors.  
Indeed, previous studies (Kolev  
et al., 2005, 2005; Albrecht et al.,  
2009) found modulations in low-fre-  
quency band (delta, theta) and  
ERN in different paradigms (choice  
reaction task, flankers...) provok-  
ing overt errors in different popula-  
tions but once again, APA errors  
are of different nature.

### Limitations

There is a strong relationship  
between the ERP and ERD/ERS.  
However, ERD and ERS are not  
systematically time-locked to the  
target ERP. Theta- and delta-  
band ERSs correspond most  
closely to N200 and P300,  
respectively (Huster et al., 2013).  
In fact, an increase in the ampli-  
tude of P300 is invariably associ-  
ated with an increase in power in  
the low-frequency bands – as  
observed in the present study.  
Removing or not the ERP signal  
of the time–frequency analysis is  
still subject to debate. In a non-  
presented analysis, we removed  
the ERP signal from the EEG  
before performing event-related  
spectral analysis in the beta-band;  
this enabled us to study the  
induced response alone and not  
the evoked response: no clear dif-

ferences (topographical or statistical maps) were  
observed after the removal.

The attention network task enabled the study of  
different components of attention (Fan et al., 2002). How-  
ever, trials with cues might influence the RTs or the pro-  
portion of pre-APAs (i.e. APAs occurring between the  
cue and the target presentation but not followed by a step,  
with a return to the baseline posture at the moment of tar-  
get presentation (Tard et al., 2015)); however, the propor-  
tions of valid, invalid cued and uncued trials did not differ  
after removal of trials with artifacts. The proportion of no  
cue trials was 17.8% (normal APA) vs. 16.7% (APA error)  
vs 16.3% (before removal of trials with artifacts), the pro-  
portion of neutral cue trials was 19.3% (normal APA) vs.  
18.2% (APA error) vs. 20.3% (before removal of trials with  
artifacts), the proportion of valid cue trials was 47.5%  
(normal APA) vs. 47.4% (APA error) vs. 47.3% (before  
removal of trials with artifacts), the proportion of invalid  
cue trials was 15.4% (normal APA) vs 17.6% (APA error)  
vs. 16% (before removal of trials with artifacts). Further-  
more, we excluded false start trials (i.e. those with an  
RT < 100 ms). The median number of trials by subject /  
condition after removal of artifacts was 49 (20–98) for

781 APA errors and 69 (38–107) for normal APAs. One sub-  
782 ject has a very low number of trials taken into account  
783 but the ERP was clearly identifiable in this particular case.  
784 The subject was thus not excluded.

785 Our present results highlighted a cortical marker of  
786 gait initiation APA errors in healthy subjects. Differences  
787 in sensorimotor activation (reflected by differing alpha/  
788 beta-band ERS/ERD patterns) were observed during  
789 APA errors. It remains to be seen how these cortical  
790 oscillations are influenced by cortical-subcortical loops.  
791 Future research should consider the role of the basal  
792 ganglia (and specifically the STN) in movement  
793 inhibition. In contrast to ERP analysis, time–frequency  
794 methods are useful for monitoring non-conscious errors.  
795 These methods could also be used to monitor motor  
796 programming errors (in patients with dysexecutive  
797 syndrome, for example), and could be implemented in  
798 brain–computer interface algorithms.

### 799 UNCITED REFERENCE

800 [Capotosto et al. \(1991\).](#)

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(Received 5 December 2017, Accepted 29 September 2018)  
(Available online xxx)

# **Cortical Oscillations during Gait: Wouldn't Walking be so Automatic?**

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Article publié dans *Brain Sciences*.

DOI : <https://doi.org/10.3390/brainsci10020090>



Review

# Cortical Oscillations during Gait: Wouldn't Walking be so Automatic?

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Received: 20 January 2020; Accepted: 7 February 2020; Published: 9 February 2020

**Abstract:** Gait is often considered as an automatic movement but cortical control seems necessary to adapt gait pattern with environmental constraints. In order to study cortical activity during real locomotion, electroencephalography (EEG) appears to be particularly appropriate. It is now possible to record changes in cortical neural synchronization/desynchronization during gait. Studying gait initiation is also of particular interest because it implies motor and cognitive cortical control to adequately perform a step. Time-frequency analysis enables to study induced changes in EEG activity in different frequency bands. Such analysis reflects cortical activity implied in stabilized gait control but also in more challenging tasks (obstacle crossing, changes in speed, dual tasks...). These spectral patterns are directly influenced by the walking context but, when analyzing gait with a more demanding attentional task, cortical areas other than the sensorimotor cortex (prefrontal, posterior parietal cortex, etc.) seem specifically implied. While the muscular activity of legs and cortical activity are coupled, the precise role of the motor cortex to control the level of muscular contraction according to the gait task remains debated. The decoding of this brain activity is a necessary step to build valid brain–computer interfaces able to generate gait artificially.

**Keywords:** Gait; EEG; oscillations

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## 1. Introduction

Gait control in natural environments (e.g., passing through a doorway, stepping an obstacle, initiating gait,...) can only be achieved on the basis of proprioception, visual and vestibular signals, and implies cognitive control [1]. These processes occur mainly at cortical and cerebellar levels and compose the voluntary aspect of walking. Measuring brain activity during gait with sufficient temporal resolution can help to determine which brain areas are involved in motor behavior control. Electroencephalography (EEG) presents better temporal resolution than other brain imaging methods to record cortical activation during gait. Indeed, gait is often considered as an automatic activity which can be modified by cortical activations in certain circumstances that necessitate adaptation of gait pattern [2]. Gait is actually composed of repetitive stereotyped gait cycles. Each cycle consists of two phases: following foot contact, the leg is on the ground supporting the gravitational load of the body and propelling the body forwards. This first phase is called the stance phase, with two periods of double contact. Then, during the swing phase, the leg is lifted from the ground by the muscles and is moved against its inertial load. The changeover of relatively similar right and left cycles occurs rhythmically. Animal studies in decerebrate cats suggest that central pattern generators which are responsible for rhythmic movements are located in the spinal cord. Indeed, the spinal cord itself contains neural circuits that, when activated, can coordinate the different muscles to produce locomotor movements [3]. Adaptations of this motor program are necessary

during gait initiation, stops, turns, obstacles, or following changes in the environment. A central network generates essential features of the motor pattern and sensory feedback signals control the system. In mammals, locomotor regions situated in the brainstem can directly activate central pattern generators located in the medulla and are under the control of the basal ganglia, cerebellum and cortex [3]. There is now large evidence of the role of the cerebral cortex in gait control [1]. In fact, numerous interactions exist between motor control of gait and cognition. Some of these interactions, often defined as dual-task interactions, are common in daily life, and involve common situations such as walking while simultaneously talking, texting on a cell phone or thinking about one's shopping list [4,5]. Dual-task walking abilities in humans are at least in part under the control of cortical prefrontal areas [6], but other cortical and subcortical regions are also involved [5].

In order to study cortical activity during real locomotion, EEG appears to be particularly appropriate. Indeed, overall EEG devices have a compact size, are relatively low-cost and easily available. EEG is a non-invasive brain imaging modality and allows a direct assessment of neural activation with a high temporal resolution (in the order of one millisecond). One of the strengths of EEG is thus the possibility to assess brain functioning during online walking and to correlate cortical activation with gait measures given by other devices (video-based motion analysis systems, force insoles, inertial sensors, electromyogram,...) (Figure 1). By comparison, in the context of positron emission tomography (PET) or single photon emission computed tomography (SPECT), metabolic changes occur several minutes after the injection according to the marker used. Spatial resolution of EEG is also better than functional near-infrared spectroscopy. However, PET and SPECT scans present a higher spatial resolution than EEG, while functional magnetic resonance imaging (fMRI) is associated with still better spatial accuracy despite the low temporal resolution related to this neuroimaging modality due to the slowness of changes in blood flow following fast changes in electrical neuronal activity. The main limitation of the use of fMRI, PET, and SPECT scans for analyzing gait-related neural activation remains the required head immobility of the subjects.



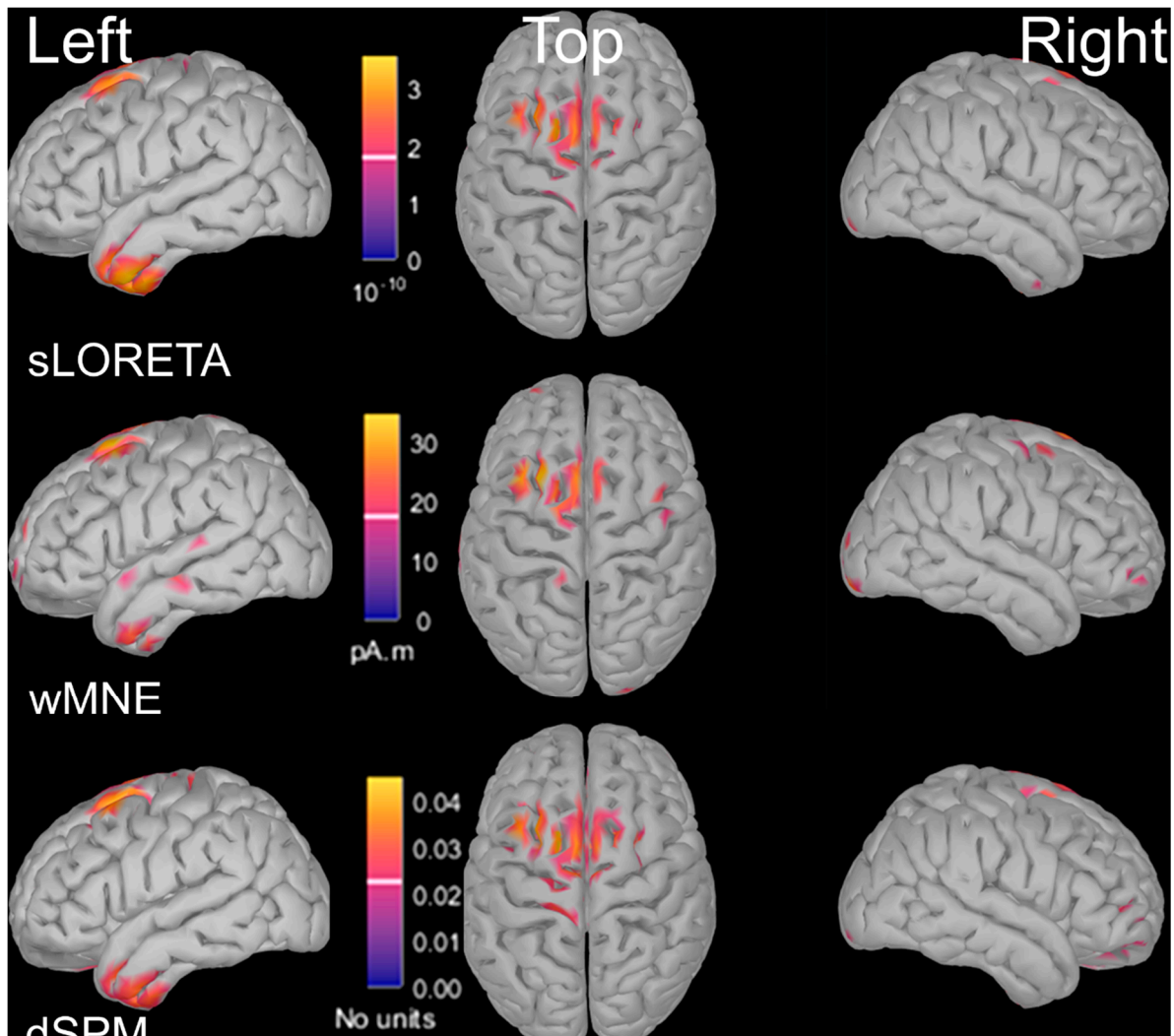
**Figure 1.** EEG recording during treadmill walking in a healthy subject. The EEG system is synchronized with a video-based motion analysis system (retroreflective markers on both feet) that allows recording of the different events (foot off and strike) characterizing gait. Cortical activity was recorded with an Ag/AgCl 128-scalp-electrode cap (Waveguard®, ANT Neuro, Enschede, The Netherlands). Data were acquired with ASA™ software (ANT Neuro).

In this narrative review, after some methodological considerations, we will mainly focus on recent literature regarding EEG spectral changes during gait initiation and stable gait in healthy subjects, restricting this paper to cortical activity. Most recent studies have investigated cortical

oscillations while some of them have also analyzed event-related potentials (ERPs). However, the latter were not within the scope of this paper. Spectral analyses promote a better understanding of the neurophysiology of gait and the role of oscillations in the adaptation of gait to the environment.

## 2. Methodological Considerations

Until recently, several concerns limited the use of EEG during real locomotion. Firstly, spatial resolution of EEG is low compared to PET, SPECT or MRI. Source localization from scalp EEG signals can be used to improve spatial resolution at the cortical level. Sources of EEG activity can be estimated by solving the inverse problem (i.e., identifying the location and calculating the amplitude and orientation of the neural sources that are responsible for the measured EEG data, based on these scalp EEG recordings). These characteristics of a source are adjusted in order to obtain a best fit between the recorded EEG signal and the calculated potentials produced by the source [7]. However, the main limit of this approach is that signals recorded by scalp electrodes mostly result from post-synaptic potentials of cortical neurons or synchronized activity of cortical neurons with deep sources (subcortical nuclei). There is still some disagreement among scientists about the possibility for EEG to record deep sources that are not synchronized with cortical activity [8]. Indeed, source analysis localized the irritative zone in patients suffering from epilepsy with high sensitivity and specificity if EEG signals were recorded with a large number of electrodes (128–256 channels) and if individual MRI was used as head model [9]. Other studies confirmed that a large number of electrodes is necessary to adequately solve the inverse problem (32 electrodes is not enough [10]), for example for a cognitive task (picture naming) [11]. However, the sources in these examples are cortical and, for some authors, subcortical signals are much weaker than cortical activity and deeper sources can be associated with distributed cortical activity [12]. Moreover, although the obvious differentiation between dipolar models with their a-priori assumed fixed number of dipoles and distributed source imaging techniques, the diversity of methods to solve the inverse problem as well as the difficulty of obtaining evidence about the true location of the sources makes it difficult to give any guidelines for the best method to choose. An example of different results of source localization methods during gait initiation is provided in Figure 2. Intracerebral recordings of local field potentials with deep brain stimulation electrodes can also be used to explore profound sources [13–15]. Unfortunately, they can only be performed in patients that require deep brain stimulation to reduce their symptoms.



**Figure 2.** Source localization of EEG signal (4–30 Hz) during gait initiation in a paradigm using cues and flankers (task described in [16]). The signal was averaged over a time interval between 200 and 0 ms before the onset of the anticipatory postural adjustments. Three different methods for source localization were applied on the same EEG dataset (128 electrodes). All three methods showed sources in premotor cortex, supplementary motor area and primary motor cortex. Only sLORETA and dSPM showed sources on left temporal lobe but not wMNE.

Secondly, artefacts caused by movement and muscle activity contaminate EEG signals. Of course, adequate filtering, bad channel repair by interpolation (flat electrodes or with high-amplitude noise), and the selection of epochs uncontaminated by obvious artefacts must be performed [17]. Another possible pre-processing step aims at removing transient, non-biological, large-amplitude noise/artefacts (e.g., abrupt impedance changes due to headset motions) using a non-stationary method based on sliding window principal component analysis: the Artifact Subspace Reconstruction (ASR) method [18]. Despite these essential first steps, two studies [19,20] investigated movement-related artefacts in EEG recordings and found contamination of the EEG data at frequencies from 1 to 150 Hz. As EEG signal frequencies investigated during walking include theta (4–7 Hz), alpha (8–12 Hz), beta 1 (13–20 Hz) beta 2 (20–30 Hz) and gamma (> 30 Hz) bands, these motion artefacts are taken into account in the analysis of cortical activity during gait and should be removed before considering motor-related changes in a power frequency band.

Currently, the most frequently performed method to remove movement-related artefacts used independent component analysis (ICA) [21]. In this context, EEG is assumed to be a linear mixture of non-Gaussian and statistically independent source components that can be separated via ICA,

visually examined, and classified as artefacts or EEG signal components [22]. Therefore, ICA allows to identify EEG sources, regardless of their localization. Once the artefact components have been identified, they can be removed. The remaining EEG signal components can be projected back to the original electrode space. This procedure yields the reconstruction of an artefact-free EEG signal. The number of independent components is equal to the rank of the matrix storing the original EEG signals (i.e., the total number of channels minus the amount of interpolated electrodes). We should note that, in reality, the effective number of statistically independent signals contributing to the scalp EEG is generally unknown. Although some sources correspond to obvious artefacts (e.g., eye blinks, horizontal and vertical eye movements), it is often difficult to determine with certainty whether the component represents cortical signal or not. Localization of the source on a scalp map, the component time course, the component activity power spectrum and an image of collected single-trial data epochs are crucial for identifying the nature of the considered independent component. It has also been proposed to use image processing algorithms on independent components in order to automatically reject EEG artefacts [23]. More generally, researchers can now use (semi-)automated EEG independent component classifiers, including *ICLabel* that proved the best classification accuracy and computational efficiency [24]. These classifiers that were highly trained on components labelled by experts of the field help to eliminate EEG artefacts. Other algorithms that model independent components as equivalent current dipoles can be used to localize neural sources (DIPFIT) [25]. A recent study tested the ability of ICA combined with DIPFIT as a source localization algorithm in order to remove EEG artefacts during treadmill walking (cortical signal blocked by a silicon cap) [26]. ICA and dipole fitting accurately localized 99% of the independent components in non-neural locations. Some authors also propose removal of specific muscular activity such as neck muscle activity that can affect the EEG signal during walking [22,27], by using either ICA or another blind source separation approach called canonical correlation analysis (CCA) [28]. A more general problem remains with analysis in the gamma band since gamma rhythms are generated by small volumes and are thus difficult to record with scalp EEG [29]. Moreover, the gamma band is largely contaminated by muscle activity.

Once the EEG signal is pre-processed, two methods are mainly used for the subsequent analysis step: either ERPs if the EEG signal changes are phase-locked to an event; or time-frequency analysis in order to study induced changes (i.e., time-locked to an event) in EEG activity in different frequency bands. More recently, some groups used brain connectivity methods to study the directed and undirected functional links between different cortical areas [10], mainly during tasks involving upper limb movement [30] or cognitive tasks such as the Stroop task [31] or picture naming [11]. Some studies have also been performed during gait but in pathological conditions, mainly in patients with Parkinson's disease [15].

### 3. Brain Oscillations: Principles of Time-Frequency Analysis

Non-phase-locked (induced) changes can be studied in a time-frequency analysis, which highlights the cortical oscillations related to an external or internal event [32]. EEG signal mainly represents the temporal-spatial summation of post-synaptic potentials from the local neuronal population. Oscillations in a given frequency band are the results of synchronization across neurons [33]. Indeed, motor-related cortical oscillations are generally assessed by quantifying increases (also called event-related synchronizations or ERS) or decreases (event-related desynchronizations or ERD) in spectral power in a given frequency band. Studying these oscillations across time, also called time-frequency analysis, consists in calculating the relative values of the signal power in different physiological frequency bands. The event-related spectrum (averaged over trials or related to a single trial) at each time-frequency point is either divided by the average spectral power in the pre-stimulus baseline period (during which the subject does not move) at the same frequency, or a subtraction of the average baseline power and a division by the standard deviation of the baseline power at the same frequency can be performed. These two models for the pre-stimulus baseline correction of event-related spectral perturbations (ERSPs) are respectively called gain model and additive model, and both are used in EEG studies. The units of ERSP are thus a z-score or a percentage of the average

baseline power, but spectral perturbations can also be expressed as the log value of this percentage [34]. For example, increases in amplitude of the cortical oscillations in delta and gamma bands are observed during both the planning and execution of movement [35]. The initiation of voluntary movements has been linked to desynchronization of cortical activity in alpha and beta bands in electrocorticography and scalp EEG recordings over the motor and premotor cortices [36,37]. We should keep in mind that these oscillations, whatever the considered frequency band, are not specific to movement and have been attributed to numerous cognitive processes such as memory or attention [38,39]. Contrary to ERPs, EEG power changes do not need to be phase- or time-locked to a particular event at each trial (e.g., foot strike, start of the anticipatory postural adjustments for gait initiation). In summary, time-frequency analysis of EEG activity contributes to a better understanding of the neuronal oscillations that underlie information processing in the brain or programming of a movement.

The most frequent pattern before and during movement, whatever its nature, is a decrease of alpha- and beta-band power starting over the sensorimotor cortex. The mu rhythm is of particular interest [40,41]. The latter is defined by activity in the alpha band recorded by scalp electrodes over the sensorimotor cortex during movement. Despite being comprised in the alpha band, the mu rhythm is distinct from alpha rhythm since the latter is recorded occipitally, reacts to eyes opening and is not specifically related to movement [42,43]. It has been firstly described that the mu rhythm reflects synchronized activity in large groupings of pyramidal neurons in the brain's motor cortex [44]. A role of mu rhythm in the mirror neuron system [45] has then been proposed since mu rhythm is also attenuated during observed movements [46]. Despite this specificity, in most publications, it is not distinguished from the alpha rhythm. In the present review, we will use indifferently either alpha power decrease/increase (i.e., alpha ERD/ERS) or mu rhythm increase/decrease (mu ERD/ERS) according to the methodology used in the different articles.

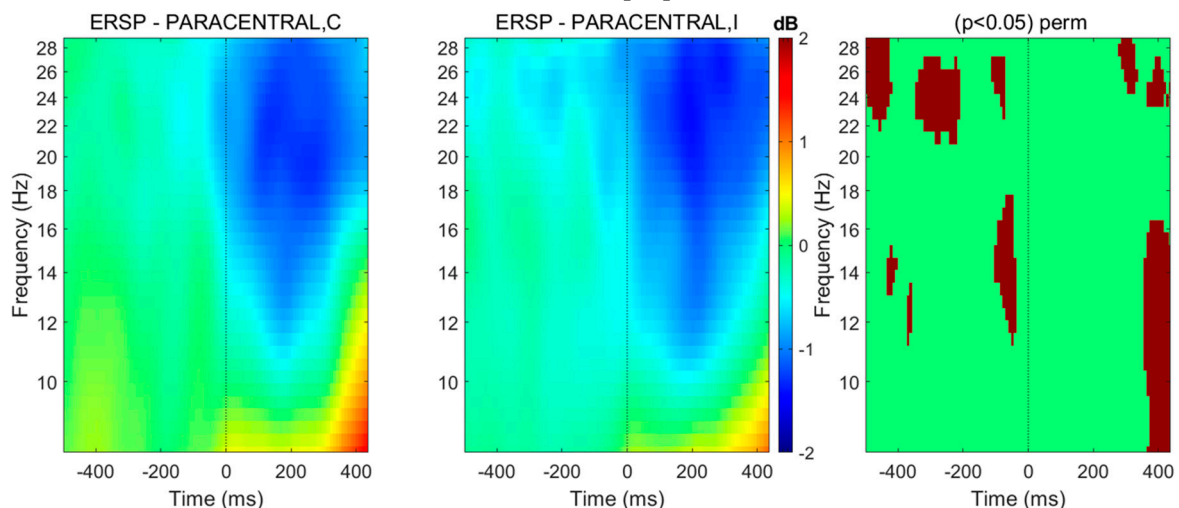
#### 4. Cortical Oscillations during Gait Initiation in Healthy Subjects

Cortical areas involved in gait initiation include the sensorimotor cortex, premotor cortex in link with basal ganglia and brainstem structures. It was initially suggested that the motor programs underlying gait initiation were stored in subcortical structures, and could be elicited by a startling stimulus or a decision for action [1,47–49]. However, studies in patients with focal lesions of the supplementary motor area (SMA) and studies in patients with Parkinson's disease have shown that the motor program can also be modulated at the supraspinal level, with implication of the SMA, the basal ganglia and the pontomedullary reticular formation [50,51]. Moreover, inhibitory repetitive transcranial magnetic stimulation over the SMA shortens the duration of anticipatory postural adjustments for a brief period, i.e., for the first stepping trial after stimulation [52]. As a consequence, cortical activation seems to directly (or via cortico-subcortical loops) modulate the timing of the motor program. The output of this pathway is located in the midbrain locomotor region (which may correspond in part to the cuneiform nucleus and the dorsal part of the pedunculopontine nucleus), which is connected to limbic structures and the basal ganglia [53].

Attentional control can also modulate gait initiation: either directly by involving brainstem structures (e.g., the alerting process induced by a loud stimulus can produce a start-react effect) or indirectly via a cortical loop that includes more complex attentional networks [48,54,55]. Indeed, gait initiation requires more attentional resources than gait [56] and may cause more dual-task interference with an attentional task than steady-state walking does [57]. For instance, errors in motor programming have been exhibited in tasks requiring executive control [16], and particularly in older subjects [58].

It has been demonstrated that gait initiation is associated with the desynchronization of sensorimotor rhythms (alpha and beta bands) related to sensorimotor cortex activation [59]. Alpha and beta ERD are sensitive to the attentional demand, being more ample in case of selective attention required during preparation of movement. Different patterns of alpha/beta ERD during preparation of step initiation according to the attentional demand are also noticed: earlier alpha/beta ERD in case of alert stimulus, more prolonged beta ERD in case of conflicting information [16]. This implies that

alpha and beta ERD during gait initiation are directly modulated by attentional abilities of the subject. This modification of sensorimotor cortex activation has direct consequences on motor commands and could lead, for example, to errors in the motor program (i.e., errors in anticipatory postural adjustments that increase with ageing). During gait, oscillations in lower bands (delta, theta) are more difficult to interpret since they largely overlap with the ERPs locked with the stimulus, leading to high inter-trial coherence (ITC; a quantification of event-related phase modulations locked to an event) [60]. We should also point out that activations over non-motor areas (prefrontal, temporal, etc.) are not specific to gait initiation but are also recorded when the attentional task is coupled, for instance, with button pressing and not with step initiation. They may reflect more adequately the attentional processes than the movement preparation itself. We can give the example of EEG scalp recordings during gait initiation of 30 healthy subjects using a flanker task in Figure 3 (signal locked to the onset of the anticipatory postural adjustments). Some of the data have been previously published in [16]. Subjects had to initiate gait with the leg indicated by the direction of a target arrow that was surrounded by either congruent or incongruent flankers. In this latter case, executive control is necessary to inhibit the incongruent flankers indicating the wrong lateralization. We observed an earlier and more ample alpha/beta ERD in case of incongruent flankers, reflecting the interaction between the executive attentional control and motor preparation.



**Figure 3.** Spectral perturbations related to anticipatory postural adjustment onset located at paracentral lobules (right and left pooled), in case gait initiation is driven by a target surrounded by congruent (C) or incongruent (I) flankers. Using BRAINSTORM toolbox [61], the head model was created from a standard MRI template and the boundary element method was used for calculating the leadfield matrix, whereas cortical sources were reconstructed thanks to weighted minimum-norm estimates before projecting the obtained dipole sources on 68 cortical regions from the Desikan-Killiany atlas. The spectral patterns were averaged over 30 healthy subjects. Spectral distribution among frequency bands from 4 to 30 Hz are shown. Right column: significant differences in a permutation (perm) test (threshold at  $p < 0.05$ ).

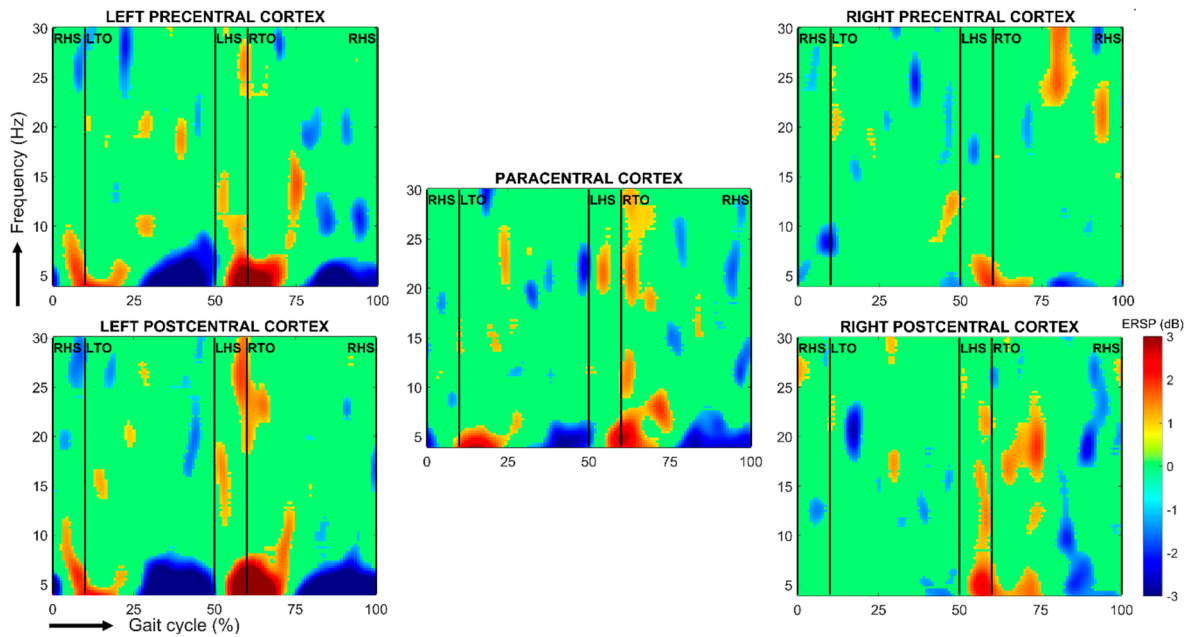
## 5. Cortical Oscillations during Gait in Healthy Subjects

The first proper analyses using methods to avoid artefacts such as ICA as described in the methodological considerations paragraph were conducted on eight subjects during treadmill walking [62]. In this analysis, each gait cycle was expressed in function of the average gait cycle. Significant alpha- and beta-band power increases over sensorimotor cortex and dorsal anterior cingulate cortex occurred during the end of stance, as the leading foot was contacting the ground and the trailing foot was pushing. This demonstrates that, even under steady-speed walking conditions, the cortex shows moment-to-moment adjustments in activity tone. In another study including six subjects walking slowly on a treadmill, the analysis consisted in expressing changes in EEG oscillations during gait according to the EEG activity during standing while fixing a cross on a

computer screen [27]. When looking at changes throughout the gait cycle, a desynchronization occurred in mu and beta bands during the swing phase. Just before heel strike and during the double support phase, increases in mu and beta power were observed. These results were later confirmed ([63], robotic gait with a lokomat versus gait on treadmill) and source analysis [64] revealed that beta ERD is located in central sensorimotor area, which is consistent with somatotopic representation of leg movements [65,66]. This location found with scalp recordings was confirmed during electrocorticographic recordings of leg movements [67]. An example of a scalp EEG recording in one healthy subject by our group is given in Figure 4. Indeed, mu rhythm and beta-band power decreases observed over the central sensorimotor and parietal areas during active walking relative to standing are similar to the desynchronization in mu- and beta-band power observed in the motor system during the preparation and voluntary execution of movements [68]. Beta-band power increases in scalp EEG data are related to movement suppression or more probably to sensorimotor integration of the movement since this synchronization disappears when sensory information is disrupted [69]. Recently, electrocorticographic recordings in two subjects pointed out the precise role of the primary motor cortex (M1) in gait pattern generation [70]. Mu, beta, and gamma oscillations were recorded during steady gait and gait across multiple walking speeds. Only gamma oscillations were consistent in both subjects during the tasks and were directly related to gait speed or gait initiation. Beta modulation was recorded in only one subject. More generally, gamma oscillations in M1 encode for high-level motor control and probably interact with subcortical/spinal networks, which are responsible for low-level motor control. The main limitation of this study was the small number of subjects and the lack of recording of key structures such as the SMA. Indeed, these results have to be compared with those from a study using fMRI and PET scan [71]. The latter study compared imagined locomotion (multiple initiations, stops, changes in speed) that recruits mainly an indirect pathway of modulatory locomotion (via the SMA, basal ganglia and mesencephalic locomotor region) and real locomotion that recruits a direct pathway of steady-state locomotion (M1 that hypothetically drives directly the central pattern generators in this model).

Coupling between the EEG and electromyography (EMG) activity during gait has also been studied. Significant coupling between EEG recordings over the leg motor area and EMG from the anterior tibial muscle (ankle dorsal flexor) was found in the gamma frequency band prior to heel strike, during the swing phase of walking and not during the support phase [72]. In another recent study, cortical power, corticomuscular coherence, and ITC were evaluated. In contrast to the previous study, theta, alpha, beta, and gamma frequencies increased during the double support phase of the gait cycle [73]. The authors concluded that the coherent activity between M1 and muscle would reflect, due to its high ITC, an evoked response. Therefore, an additive response would be evoked during the double support phase. Recently, EEG recorded from the leg area of M1 and EMG recorded from ankle plantar flexor muscles have shown coupled gamma oscillations in the stance phase during treadmill walking [74]. Our group has also demonstrated that either excitatory or inhibitory repetitive transcranial magnetic stimulation of M1 was unable to change the level of activity of the leg muscles during gait contrary to what is observed for simple upper limb movements, suggesting a more complex role of M1 than simply controlling muscle tone during gait [75].





**Figure 4.** Spectral perturbations related to right heel-strike during a stride cycle relative to the full gait cycle baseline over the left and right pre-, para- and postcentral cortices. The subject performed 52 gait cycles on a treadmill. Using BRAINTSTORM toolbox [61], the head model was created from a standard MRI template and the boundary element method was used for calculating the leadfield matrix, whereas cortical sources were reconstructed thanks to weighted minimum-norm estimates before projecting the obtained dipole sources on 68 cortical regions from the Desikan-Killiany atlas. The single-trial spectrograms were linearly time-warped in order to adjust the latencies of right heel-strikes in each epoch and thus to align gait cycles. Finally, a bootstrap test was performed, with  $\alpha = 0.1$ . RHS/LHS: right/left heel-strike; RTO/LTO: right/left toe-off.

## 6. Cortical Oscillations during More Challenging Tasks

In daily life, subjects do not walk slowly on a treadmill but have to adapt their speed, to change their pace, to modify their stride length according to an obstacle or to navigate according to different cues (visual, auditory, etc.). When comparing walking on an incline with walking on level surface, theta power was greater in the anterior cingulate, sensorimotor and posterior parietal clusters during incline walking. It also showed differences in gamma band suggesting that these areas are implied in control of gait in these conditions [76]. Moreover, as stated earlier, cortical activations are directly linked to muscle tone although it is not the main mechanism of control [71], and corticomuscular coherence also differs according to the type of walk, predominating in swing phase during overground walking and in stance phase during ramp walking [77].

Most of the previous studies did not include gait in real-world conditions that involve cognitive processing. For example, when subjects had to adapt their speed (e.g., increasing their gait speed), beta and gamma synchronizations in prefrontal and parietal areas were enhanced, suggesting that executive control of sensorimotor areas was intensified in order to improve speed tracking performance [78]. Furthermore, according to the walking conditions (level ground, ramp ascent, and stair ascent), differences in activation in the posterior parietal cortex or M1 occurred [79]. Alpha and beta ERD was more pronounced at the beginning of gait cycle for more challenging gait conditions. Beta ERD was also larger over posterior parietal cortex.

When walking in synchrony with a series of cue tones, requiring the subject to adapt step rate and length to sudden shifts, beta-band power increases were observed in the medial prefrontal and dorsolateral prefrontal cortex [80]. Once again, the role of such cortical regions in cognitive control of gait was proposed as an explanation of this pattern and Wagner et al. [80] attributed this specific pattern of beta synchronization to cognitive top-down control.

Dual-tasking situations are common in daily life, especially the ones which involve the concurrent performance of a cognitive task and gait [81]. For example, people often send or read a text message while walking. McIsaac et al. [82] have proposed to define dual-tasking as “the concurrent performance of two tasks that can be performed independently, measured separately and have distinct goals”. Dual-tasking can lead to changes in gait performance and these changes are considered as the costs of carrying out a second task concurrently. EEG oscillations have been evaluated during dual-tasking. In [83], four tasks were performed: normal walk on a treadmill, two dual tasks involving gait as well as additions and subtractions or video watching, and a visual-cueing task asking the subject to adapt its gait pattern. No clearly different patterns of neural oscillations in classical frequency bands were observed, although support vector machine procedures were able to classify attention tasks by differences in gamma-band activity. In another protocol replicating scenarios in which humans were required to evaluate the environment for accurate stepping (i.e., by using different color marks that forced adaptation of step length and width), Oliveira et al [84] showed changes during mid-stance in the frontal lobe and motor/sensorimotor regions, a phase in the gait cycle in which participants defined the correct foot placement for the next step. These changes consisted mainly in increases in electrocortical activity over the prefrontal cortex in beta and gamma bands when precision stepping was required. This higher neuronal synchronization in the gamma band has been related to increased attention but remains, in our opinion, difficult to isolate in scalp EEG, particularly during movement, even with the use of pre-processing methods such as ICA.

## 7. Conclusion

As gait requires cortical resources, measuring cortical activity in real time is a necessary step to understand motor control during gait. Time-frequency analysis of EEG is adequate to record cortical activity. The main pattern of cortical activation during gait is an activation of the sensorimotor areas that is reflected by mu and beta desynchronizations predominantly during the swing phase of a gait cycle and during preparation of movement for gait initiation. Beta synchronization occurs at foot strike. Distinct roles of mu/beta oscillations are less clear than in simple movements since desynchronizations and synchronizations during gait frequently overlap both bands. Gamma oscillations are also crucial to encode gait speed or initiation, but methodological concerns still exist with scalp recordings. These spectral patterns are directly influenced by the walking context (changing the speed, overground versus ramp walking,...) and, when analysing gait with a more demanding attentional task, other areas (prefrontal, posterior parietal cortex) seem specifically involved, with the occurrence of beta/gamma oscillations. The decoding of this brain activity is a necessary step to build valid brain-computer interfaces (BCIs) able to generate gait artificially [85]. As a perspective, a real-time closed-loop BCI that decodes lower limb joint angles from scalp EEG during treadmill walking in order to control the walking movements of a virtual avatar has already been built [86]. This kind of approach could be useful in rehabilitation programs since healthy subjects are able to adapt an avatar’s gait pattern controlled via a closed-loop EEG-based BCI in eight days of training. It could be beneficial in patients suffering from either deficits in upper or lower structures of gait control such as patients with incomplete medullar injury [87], patients with stroke [88], or with Parkinson’s disease [14,89].

**Funding:** Madli Bayot is working on a project that received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 721577.

**Conflicts of Interest:** The authors declare no conflict of interest.

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