New methodological approach for the evaluation of executive function, gait control and cognitive reserve : perspectives for earlier prediction of Alzheimer's and Parkinson's diseases

Maroua Belghali

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Normandie Université

THÈSE

Pour obtenir le diplôme de doctorat

Spécialité RECHERCHE CLINIQUE, INNOVATION TECHNOLOGIQUE, SANTE PUBLIQUE

Préparée au sein de l'Université de Caen Normandie

New methodological approach for the evaluation of executive function, gait control and cognitive reserve: Perspectives for earlier prediction of Alzheimer's and Parkinson's diseases

Nouvelle approche méthodologique pour l'évaluation des fonctions exécutives, du contrôle locomoteur et de la réserve cognitive :
Perspectives dans le dépistage précoce des maladies d'Alzheimer et de Parkinson

Présentée et soutenue par
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To my mother Radhia

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Foreword

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Publications

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National congress

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Abbreviations

AD: Alzheimer's disease

AST: Auditory stroop task

ATS: Auditory switching task

ASTS: Auditory stroop task switching

AUC: Area under the Curve

BR: Brain reserve

CBT: Counting backward task

CSSCT: Computerized version of the stroop switching card test

CR: Cognitive reserve

CRS: Cognitive reserve scale

CRQ: New cognitive reserve questionnaire

CRIq: Cognitive reserve index questionnaire

CV: Coefficient of variation

DTC: Dual-task cost

DSST: The Digit Symbol Test

EF: Executive functions

GRAIL: Gait Real-Time Analysis Interactive Lab

IS: interference score

IES: Inverse efficiency score

IRBD: Idiopathic rapid-eye-movement sleep behavior disorder

MCI: Mild Cognitive Impairment

PD: Parkinson's disease

RT: Response time

ROC: Receiver Operating Curve

PD: Parkinson's disease

SD: Standard deviation

SIS: Switching index score

SSCT: Stroop switching card test

SWT: Stroop switching test

SNT: Standard neuropsychological tests

TMT: Trial-Making Test

WCST: Wisconsin Card Sorting Test

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French summary

La maladie d'Alzheimer (MA) et la maladie de Parkinson (MP), sont considérées aujourd'hui comme un problème majeur de santé publique du fait qu'elles touchent plus de 45 millions de personnes âgées de plus de 50 ans dans le monde (Muangpaisan et al. 2011; Prince et al. 2015). Jusqu'à ce jour, la MA et la MP sont diagnostiquées trop tardivement, alors que plusieurs signes sont déjà présents plusieurs années avant leur expression clinique. Cette période silencieuse peut être divisée en deux phases: la phase dite « préclinique », durant laquelle la maladie a débuté mais les symptômes sont absents (i.e., personnes présentant une prédisposition génétique), et la phase dite «prodromale», durant laquelle certains symptômes apparaissent mais ne sont pas suffisants pour poser un diagnostic, e.g., le trouble cognitif léger (« Mild Cognitive Impairment », MCI) dans la MA ou le trouble du comportement en sommeil paradoxal (« Idiopathic Rapid Eye Movement Sleep Behavior Disorder », IRBD) dans la MP. Dans le contexte de la MA, les patients MCI amnésique (i.e., déficit mnésique isolé) ou amnésique à domaines multiples (i.e., associant un déficit mnésique et d'autres déficits cognitifs, tels que le langage, les fonctions exécutives, ou la sphère visuospatiale) sont les plus à risque de développer la maladie (i.e., 80 % après environ 6 ans ; Petersen et al. 2001). Les plaintes mnésiques (i.e., mémoire épisodique) précèdent l'apparition d'un MCI (Juncos-Rabadán et al. 2014) et se manifestent 9 à 10 ans en moyenne avant le diagnostic clinique de la MA (Amieva et al. 2005). Dans le contexte de la MP, un suivi longitudinal sur 5 ans a montré que 38 % des patients initialement diagnostiqués avec un IRBD ont développé un syndrome parkinsonien (Schenck et al. 1996) ; ce chiffre atteint 65 % après 10 ans (Schenck et al. 2003) et 81 % après 26 ans (Schenck et al. 2013).

Le dépistage tardif de la MA et la MP s'explique par l'absence d'un diagnostic précoce de certitude. Autrement dit, à ce jour, les marqueurs précliniques et prodromales identifiés ne sont pas suffisamment fiables pour affirmer d'une manière certaine la présence d'un trouble neurodégénératif. D'importants efforts doivent donc être mis en œuvre pour identifier des marqueurs précliniques sensibles et spécifiques au risque de développer une maladie neurodégénérative. Le but d'un diagnostic précoce est d'envisager une stratégie neuroprotectrice permettant de ralentir l'évolution de la maladie bien avant le stade où elle est aujourd'hui détectée. En effet, alors qu'un traitement pourrait avoir une utilité mineure s'il est prescrit tardivement, il pourrait retarder l'expression clinique de la maladie s'il est prescrit

suffisamment tôt (avant même que les symptômes cliniques ne débutent). La neuroprotection est donc la principale motivation pour prédire les maladies neurodégénératives.

Dans cette optique, plusieurs auteurs ont récemment montré que les fonctions exécutives notamment l'inhibition et la flexibilité cognitive telles qu'évaluées par le test de STROOP et le Trail Making Test (TMT), et le control locomoteur dans une situation de double tâche dans laquelle les sujets doivent marcher tout en effectuant une tâche cognitive, sont altérés aux stades précliniques et prodromales de la MA et la MP (Balota et al. 2010; Postuma et al. 2012; Beauchet et al. 2014; Montero-Odasso 2016). Cependant, malgré l'importance de ces données, l'utilisation préclinique/prodromale des tests de STROOP et TMT demeure difficile parce qu'ils sont, d'une part non standardisée, et d'autre part impures (i.e., font intervenir plusieurs fonctions cognitives autre que exécutives), ce qui rend l'interprétation des résultats très difficile. De la même manière, si les doubles tâches ont un intérêt clinique indéniable, le type de tâche cognitive à administrer et les paramètres spatio-temporels les plus discriminants en fonction des pathologies neurodégénératives restent mal précisés.

En routine clinique, une importante hétérogénéité dans l'altération des capacités cognitives peut être présente chez les personnes âgées, certaines étant plus à même de conserver des niveaux importants de fonctionnement bien que développant, comme leurs pairs, d'inévitables lésions cérébrales. Pour rendre compte de telles différences interindividuelles, les auteurs ont élaboré le concept de réserve cognitive (RC) qui postule que la manière dont sont traitées les tâches cognitives fournit le substrat des capacités de lutte contre les pathologies cérébrales. Des différences individuelles dans le style de vie, la scolarité ou le type de hobby et des différences d'ordre génétique, comme les capacités intellectuelles, ont été associés à la RC. Ainsi, les études épidémiologiques ont montré que des capacités intellectuelles élevées, un nombre plus important d'années de scolarité formelle ou le fait d'avoir mené un travail intellectuel stimulant, réduisent le risque de déclin cognitif associé au vieillissement ou le risque de démence (Stern, 2009). Les résultats obtenus auprès de populations cliniques indiquent que les personnes atteintes de maladies neurodégénératives dont la RC est élevée maintiendront un degré de fonctionnement cognitif équivalent à celui des personnes dont la RC est faible malgré la présence d'atteintes cérébrales plus importantes. Cet effet paraît se manifester dans les phases précliniques de la MA et la MP. Il est intéressant de souligner que les différences de métabolisme cérébral se manifestent dans les régions typiquement associées au type de maladie neurodégénérative dont souffrent les patients. La RC paraît donc agir de façon précoce dans le développement d'un grand nombre de maladies cérébrales évolutives en retardant l'apparition

des premiers signes et en diminuant leur sévérité (Stern, 2012). L'évaluation clinique ne suffit donc pas pour définir le stade d'avancement de la maladie d'un patient. Il est donc nécessaire d'établir une mesure de la RC utilisable en routine clinique, qui contribuerait non seulement à estimer le stade d'avancement de la maladie, mais aussi à pronostiquer son évolution dans le but d'envisager une prise en charge mieux adaptée. A notre connaissance, il n'existe à l'heure actuelle aucune mesure précise de la RC du fait que toutes les études conduisaient à des conclusions très différentes.

L'originalité de cette thèse réside dans le développement d'un « nouveau test neuropsychologique : Le Stroop Switching Card Test » évaluant l'efficience exécutive globale avec des mesures spécifiques à chaque composante et deux nouvelles mesures de la réserve cognitive dont une qualitative (i.e., un nouveau questionnaire) et l'autre quantitative (la variation du déclin exécutif). En parallèle nous avons développé trois nouveaux paradigmes de doubles tâches fondés sur le profil physiopathologique de la MA et la MP (Belghali et al. 2017a ; Belghali et al. 2017b).

L'ensemble de ces nouveaux tests a été validé sur une population de sujets jeunes, sujets d'âges moyens et sujets âgés en bonne santé. Une telle approche est essentielle pour prouver que notre travail d'innovation méthodologique peut résoudre d'une manière appropriée les différentes limites méthodologiques mentionnées précédemment.

Conception d'un test rapide d'efficience des fonctions exécutives

Le fonctionnement exécutif regroupe un ensemble d'habiletés cognitives de haut niveau nécessaires à la réalisation d'un comportement dirigé vers un but (Luria, 1966 ; Fuster, 1997). Son rôle est de faciliter l'adaptation du sujet aux situations complexes ou nouvelles. Il intervient lorsque les habiletés cognitives « surapprises » ne sont plus suffisantes et que l'usage de processus contrôlés, dits *top-down*, est requis (Seron et al. 1999). Afin de sélectionner les «*cores*» des fonctions exécutives, le modèle de Miyake et al. (2000), propose trois fonctions exécutives qui sont la mise à jour, la flexibilité et l'inhibition. L'inhibition se traduit par la capacité à supprimer, ou à mettre à l'arrière-plan, les informations (externes ou internes) qui ne sont pas pertinentes pour réaliser une tâche. La flexibilité mentale se définit quant à elle comme la capacité à passer alternativement d'une opération cognitive à une autre, à se désengager d'une tâche pour en traiter une autre. Enfin, la mise à jour implique de modifier le contenu de la mémoire de travail en tenant compte de l'information entrante la plus récente. Les données de Miyake et al. (2000) indiquent que, chez les sujets jeunes, ces trois processus exécutifs se distinguent clairement l'un de l'autre mais ne sont toutefois pas complètement indépendants, traduisant ainsi « l'unité et la diversité » des fonctions exécutives. D'après les auteurs, le facteur commun aux trois fonctions pourrait être soit la nécessité de maintenir en mémoire de travail des informations à propos du but et du contexte de la tâche, soit la mise en œuvre de processus inhibiteurs. Le modèle intégratif hiérarchisé proposé par Diamond (2013) synthétise ce modèle et suggère que, la flexibilité serait tributaire des fonctions d'inhibition cognitive et de mémoire de travail. A notre connaissance, il n'existe à l'heure actuelle aucun test neuropsychologique évaluant l'efficience exécutive globale telle que proposée par Miyake et al. (2000).

Il est communément admis qu'un déficit du fonctionnement exécutif constitue un marqueur précoce de la MA et de la MP, car il peut apparaitre plusieurs années avant le diagnostic. Les études neuropsychologiques appuyant ces données ont montré qu'à un stade précoce, voire préclinique, de la maladie, l'inhibition (évaluée par le test de STROOP) serait plus altérée dans la MA (Balota et al. 2010 ; Hutchison et al. 2010), alors que la flexibilité cognitive (évaluée par le Trail Making Test ou par des paradigmes de switching) le serait surtout dans la MP (Lees and Smith, 1983 ; Owen et al. 1992 ; Cools et al. 2001). Du point de vue neuropathologique, dans la MA, le déficit d'inhibition résulterait principalement de l'accumulation du peptide β-amyloïde dans l'isocortex (Harrington et al. 2013), tandis que, dans la MP, le déficit de flexibilité serait expliqué en grande partie par le dysfonctionnement

de la voie préfronto-striatale, démodulée par la déplétion dopaminergique intrastriatale (Cools, 2006 ; Sawada et al. 2012 ; Kehagia et al. 2017). Rappelons ici que la mise à jour en mémoire de travail est sollicitée par la plupart des tâches d'inhibition et de flexibilité, d'une part, en raison de la nécessité de maintenir et, éventuellement, de rafraîchir les consignes (Emerson and Miyake, 2003), et d'autre part, parce que les informations stockées doivent fréquemment être manipulées avant de pouvoir générer une réponse correcte.

Il est important de souligner que, l'inhibition et la flexibilité cognitive telles qu'évaluées par les tests de STROOP et TMT impliquent des régions cérébrales communes dont le cortex préfrontal. De ce fait, certains auteurs ont récemment combiné ces tests dont l'objectif est de proposer un marqueur cognitif robuste apte à prédire d'une manière précoce un trouble neurodégénératif originaire d'un dysfonctionnement exécutif ; « Le Stroop Switching Test (SWT) », élaboré par Fine et al. (2008), et repris plus tard par Hutchison et al. (2010). Dans ce test, des mots de couleur (i.e., rouge, jaune, bleu, vert) écrits avec une encre de couleur différente (e.g., VERT écrit en rouge) sont présentés sur un écran d'ordinateur. Les participants avaient pour instruction de nommer la couleur de l'encre (e.g., « rouge ») ou de lire le mot (e.g., « vert ») selon une consigne donnée au préalable. Le sens du mot et la couleur de l'encre étaient incongruents (ROUGE) dans l'étude de Fine et al. (2008), alors qu'ils étaient tantôt incongruents, tantôt neutres (PAUVRE) dans l'étude de Hutchison et al. (2010). Lors de la passation de ce test, il ressort que les sujets âgés subissent un effet d'interférence supérieur à celui observé chez les jeunes dans le temps de réponse, mais pas dans le nombre d'erreurs, suggérant que leur capacité d'inhiber une réponse dominante est préservée, néanmoins au prix d'un temps de réponse allongé. Comparativement aux sujets âgés, l'effet d'interférence est encore plus prononcé chez des patients MA à un stade précoce (Clinical Dementia Rating Scale entre 0,5 et 1 ; Morris, 1993), et se manifeste non seulement dans le temps de réponse, mais aussi et surtout dans le nombre d'erreurs. Toutefois, les auteurs n'ont pas pu mettre en évidence de différences intergroupes dans l'alternance entre les deux tâches (« task-switching cost »), parce qu'un indice était présenté avant chaque essai rappelant la consigne à appliquer (i.e., « nommer la couleur de l'encre » ou « lire le mot »).

Le premier objectif de cette thèse était de partir de ce travail pour réussir à moduler l'effet d'interférence, par la manipulation de la nature des essais et de leur agencement. Le but était d'évaluer précisément les processus cognitifs à l'origine de la qualité de la régulation dynamique du contrôle exécutif. Cette démarche méthodologique nous a permis d'élaborer un

nouveau test neuropsychologique évaluant l'efficience exécutive telle que proposée par Miyake et al. (2000).

Nous avons recueilli les données auprès de 103 participants, en bonne santé, dont 25 entre 15 et 19 ans (sujets adolescents), 25 entre 20 et 39 ans (sujets jeunes), 27 entre 40 et 59 ans (sujets d'âge moyen), et 26 entre 60 et 79 ans (sujets âgés). Tous ont effectué une version modifiée du SST, baptisée « Stroop Switching Card Test » (SSCT), décrite ci-après, et des tests neuropsychologiques classiques évaluant les processus exécutifs sollicités dans le SSCT, à savoir : l'inhibition (Victoria Stroop Test ou VST ; Bayard et al. 2011), la flexibilité (Trail Making Test ou TMT ; Reitan, 1992), la mise à jour (Digit Span Forward/Backward ou DS-FB ; Wechsler, 1997), et la vitesse de traitement (Digit Symbol Substitution Test ou DSST ; Wechsler, 1981).

Le SSCT se présente sous la forme d'un jeu de carte. Quatre cartes de couleur (i.e., rouge, vert, jaune, bleu) sont placées sur une table à une distance de 20 cm du sujet assis. Le sujet a, dans sa main non dominante, 36 cartes dont le recto (face) est retourné vers la paume. Au centre de chacune de ces cartes, un mot de couleur (i.e., rouge, vert, jaune, bleu) est écrit sur un fond noir ou gris. Le sens du mot et la couleur de l'encre avec laquelle le mot est écrit peuvent être congruents (50 %) ou incongruents (50 %). Le sujet a pour instruction de retourner chacune des 36 cartes, puis de nommer la couleur de l'encre si le fond de la carte est gris ou de lire le mot si le fond de la carte est noir. Selon la réponse donnée, à haute voix, le sujet doit disposer la carte sur l'une des 4 cartes de couleur disposées devant lui sur la table. Le test doit être effectué le plus précisément et le plus rapidement possible.

Le temps d'exécution, le nombre d'erreurs prononcées à haute voix, et l'IES (« Inverse Efficiency Score » ; Townsend and Ashby, 1978, 1983) reflétant l'efficience exécutive globale ont été mesuré. Le nombre d'erreurs de classement (i.e., disposition sur les cartes de couleur ; évaluant la composante de mise à jour), et le type d'erreurs résultant d'un défaut d'inhibition de réponse (i.e., résolution du conflit) seul, ou associé soit à un défaut d'adaptation au conflit soit à un défaut de flexibilité réactive, soit aux deux ont été aussi mesurés.

Les résultats ont montré que le temps d'exécution, le nombre d'erreurs prononcées à haute voix, et l'IES conçus pour évaluer l'efficience exécutive globale, sont plus élevés chez les sujets âgés par rapport aux sujets jeunes. Après ajustement de la vitesse de traitement de l'information, les différences intergroupes restent significatives juste pour L'IES et le temps d'exécution. Tenant compte de ces données, nous suggérons que la vitesse de traitement de

l'information et les théories préfrontal-exécutives expliquent l'effet de l''âge sur la SSCT et qu'aucune d'entre elles ne peut être considérée comme un seul contributeur (Bugle et al. 2006 ; Puccioni and Vallesi 2012).

Concernant le type d'erreurs, les sujets âgés font plus d'erreurs que les jeunes et les adultes d'âge moyen lorsque l'essai en cours nécessite à la fois des capacités d'inhibition (mot) et d'adaptation au conflit (changement de congruence). Cette différence demeure significative même après ajustement de la vitesse de traitement de l'information, ce qui suggère un déficit sélectif d'adaptation au conflit (impliqué dans l'inhibition de mots) lié à l'âge (60-79 ans).

Afin de comparer le SSCT aux tests neuropsychologiques classiques évaluant les processus exécutifs impliqués dans le SSCT, à savoir l'inhibition d'une réponse dominante et la flexibilité réactive, nous avons comparé les scores z de l'IES (STSS, TMTB, STROOPC). Grace à cette analyse nous avons pu mettre à jour que seul le SSCT permet de distinguer les sujets d'âge moyen des sujets âgés. L'IES est donc plus sensible à l'effet de l'âge que les tests neuropsychologiques classiques. Il est important de souligner que la différence intergroupe demeure significative même après ajustement de la vitesse de traitement de l'information, ce qui suggère que l'IES pourrait être une mesure pure de l'efficience exécutive globale.

Pour conclure, les résultats de cette étude suggèrent que le SSCT est un outil robuste pour évaluer les fonctions exécutives. Nous proposons l'IES comme une mesure pure de l'efficience exécutive qui pourrait être bénéfique pour dépister précocement un dysfonctionnement exécutif.

Conception d'une version informatisée du test rapide d'efficience des fonctions exécutives

En parallèle avec le développement du test SSCT, une version informatisée a été conçue, notamment pour analyser précisément le temps de réponse à chaque stimulus (i.e., différents processus cognitifs sous-jacent au SSCT) et aussi faciliter l'utilisation clinique du SSCT. Pour cette validation, les sujets jeunes, les sujets d'âge moyen et les sujets âgés de l'étude précédente ont été testés. La consigne était quasi identique (i.e., nommer la couleur de l'encre du mot écrit si le fond de l'écran est gris, ou lire le mot si le fond de l'écran est noir), excepté le fait que le participant n'avait pas à effectuer la tâche de classement. Sur le plan méthodologique, le design de cette étude a été légèrement amélioré en ajoutant deux séquences sollicitant l'adaptation au conflit qui, dans l'étude précédente était spécifiquement altérée avec le vieillissement. Les stimuli ont été présentés via le logiciel E-Prime® (version 2.0), et le temps de réponse pour chaque stimulus a été enregistré à l'aide du système Chronos® (Psychology Software Tools). Le temps de réponse et le nombre d'erreurs ont été mesurés pour chaque stimulus.

Trois résultats intéressants ressortent de cette étude.

Le premier résultat obtenu montre que quel que soit le groupe d'âge, après un essai congruent, l'effet d'interférence est plus fort à l'essai suivant (incongruent). Cet effet, observé pour la première fois par Gratton et al. (1992), suggère qu'à chaque instant, le niveau de contrôle exécutif est ajusté aux besoins : après un essai incongruent, le niveau de contrôle est élevé, et donc l'interférence est moindre à l'essai suivant (incongruent). Inversement après un essai congruent, un relâchement du contrôle survient si bien que l'effet d'interférence est plus important. L'« effet Gratton » s'explique si l'on considère que la détection du conflit, effectuée par le cortex cingulaire antérieur, est dissociée de l'ajustement comportemental, effectué par le cortex préfrontal latéral, siège du contrôle cognitif. En effet, une fois que le conflit est détecté, le niveau de contrôle est accru, ce qui facilite pour l'essai suivant la sélection de la réponse appropriée en cas d'interférence. La réactivité du cortex cingulaire antérieur est de ce fait amoindrie lorsqu'apparaît une nouvelle interférence alors que la réactivité du cortex préfrontal latéral est toujours aussi importante (Kerns et al. 2004 ; Kerns, 2006 ; Egner, 2007).

L'effet Gratton est plus marqué (i.e., temps de réponse augmenté) chez les sujets âgés comparativement aux adultes d'âge moyen et aux sujets jeunes même après ajustement de la vitesse de traitement de l'information. Ces résultats confirment l'étude précédente, à savoir un déficit sélectif d'adaptation au conflit (impliqué dans l'inhibition) lié à l'âge (60-79 ans).

Le deuxième résultat intéressant est l'augmentation considérable du temps de réponse lorsque le sujet est amené à changer de tâche (i.e., lire le mot incongruent au lieu de dénommer la couleur de l'encre incongruente). Bien que cette augmentation ait été observée dans tous les groupes d'âge, elle est bien plus marquée chez les sujets âgés, et les adultes d'âge moyen, comparativement aux jeunes même après ajustement de la vitesse de traitement de l'information. De plus, contrairement aux jeunes, les sujets âgés et les adultes d'âge moyen font plus d'erreurs. Ainsi, l'alternance entre deux tâches cognitives incongruentes nécessitant une résolution du conflit et de flexibilité cognitive semble être altérée de façon isolée lors de l'avancée en âge (40-59 ans).

Enfin, les sujets âgés comme les adultes d'âge moyen se trouvent en difficulté lorsque l'essai en cours nécessite à la fois des capacités d'inhibition d'une réponse dominante, d'adaptation au conflit (changement de congruence) et de flexibilité réactive (changement de tâche). En effet, les sujets âgés sont plus ralentis et font plus d'erreurs que les jeunes et les adultes d'âge moyen (qui sont eux-mêmes plus lents que les jeunes). Ces difficultés pourraient s'expliquer à la fois par l'augmentation de l'effet d'interférence chez les sujets âgés, et d'autre part l'augmentation du coût d'alternance (i.e., « task-switching cost ») qui est associé au processus de flexibilité réactive (Kray and Lindenberger, 2000). La contribution directe de l'âge à la performance des processus exécutifs reste toutefois significative puisque les déficits d'inhibition d'une réponse dominante, d'adaptation au conflit, et de flexibilité réactive observés avec l'avancée en âge restent significatifs après ajustement de la vitesse de traitement. Cette contribution spécifique de l'âge (i.e., non médiatisée par la vitesse de traitement) sur le fonctionnement exécutif proviendrait de l'altération des structures cérébrales antérieures, sensibles aux effets du vieillissement (Philipps and Henry, 2008). On peut également présumer que les capacités attentionnelles et celles en mémoire de travail sont en mesure d'expliquer une grande partie des difficultés majorées chez les plus âgés (60-79 ans).

Pour conclure, les résultats de cette étude suggèrent que la résolution et l'adaptation des conflits sont altérées de façon marquée lors de l'avancée en âge. Des études futures en neuro-imageries sont indispensables pour valider ces résultats.

Conception des nouvelles mesures de la réserve cognitive

Le concept de « capacité de réserve » a été proposé afin de mieux rendre compte de l'absence de lien direct entre le degré d'atteinte cérébrale et les manifestations cliniques de cette atteinte dans plusieurs pathologies. Selon Stern (2002, 2006, 2009), la « capacité de réserve » prendrait deux formes : la « réserve cérébrale » et la « réserve cognitive ». La réserve cérébrale postule que le cerveau doit être suffisamment endommagé avant que les symptômes cliniques associés à une pathologie émergent. La réserve cérébrale serait dépendante de facteurs de développement du cerveau, tels que l'hérédité, les apports alimentaires et l'accès aux soins qui ont eu lieu au cours de la petite enfance. Ces facteurs joueraient un rôle majeur dans les capacités de résistance aux pathologies du cerveau, notamment en ce qui concerne la substance blanche cérébrale. À l'inverse, le concept de réserve cognitive (RC) postule que la manière dont sont traitées les tâches cognitives fournit le substrat des capacités de lutte contre les pathologies cérébrales. Des différences individuelles dans le style de vie, la scolarité ou le type de hobby et des différences d'ordre génétique, comme les capacités intellectuelles, ont été associées à la RC. Ainsi, les études épidémiologiques ont montré que des capacités intellectuelles élevées, un nombre plus important d'années de scolarité formelle ou le fait d'avoir mené un travail intellectuel stimulant, réduisent le risque de déclin cognitif associé au vieillissement ou le risque de démence (Stern, 2009 ; Villeneuve and Belleville, 2010). Les résultats obtenus auprès de populations cliniques indiquent que les personnes atteintes de maladies neurodégénératives dont la RC est élevée maintiennent un degré de fonctionnement cognitif équivalent à celui des personnes dont la RC est faible malgré la présence d'atteintes cérébrales plus importantes. Cet effet paraît se manifester dans les phases pré-démentielles des affections dégénératives et n'est pas spécifique à la maladie d'Alzheimer, puisqu'il caractérise également d'autres maladies comme la maladie de Parkinson. Cependant, malgré son intérêt heuristique, la RC n'a jamais été directement quantifiée et seules certaines variables qui pourraient la déterminer, telles que l'éducation, l'intelligence ou les niveaux d'implication dans des activités sociales ou de loisir, sont utilisées comme indicateurs de cette RC.

Des études récentes ont cependant montré que la RC module le déclin exécutif. En effet, ceux qui sont à haute RC semblent avoir un niveau de fonctionnement cognitif bien plus élevé par rapport à celui de leurs pairs à basse RC et ce malgré un niveau équivalent d'atteintes cérébrales notamment préfrontal. Étant donné que la RC reflète la capacité d'un individu à faire face au déclin exécutif, nous suggérons que la variation de ce dernier pourrait constituer une

mesure quantitative de la RC. L'objectif principal de la troisième étude de cette thèse est donc d'examiner cette hypothèse en proposant deux mesures de la RC, dont une est qualitative (i.e., indirecte) et l'autre est quantitative (i.e., directe).

La mesure qualitative était représentée par un nouveau questionnaire de RC (cognitive reserve questionnaire ; CRQ) comprenant des proxies spécifiques à chaque étape de vie allant de l'enfance jusqu' au vieillissement. Le score global de ce questionnaire varie de 0 à 564 points. La mesure dynamique a été représentée par la variation du déclin exécutif apparaissant chez les sujets âgés. Le déclin exécutif a été calculé grâce à un score z, permettant de quantifier l'écart des performances des sujets âgés par rapport aux sujets jeunes. Les variables dépendantes d'intérêt sont décrites comme suivant : (i) score z de Wechsler (i.e., le taux de déclin de la mise à jour) ; score z de TMT B_{IES} (i.e., le taux de déclin de la flexibilité), score z de Stroop C_{IES} (le taux de déclin du contrôle inhibiteur), et le score z de $SSCT_{IES}$ (le taux de déclin de l'efficience exécutive). Les mêmes sujets âgés (60 et 79 ans) de l'étude précédente ont été recrutés et testés.

Le résultat intéressant obtenu dans cette étude est que le nouveau questionnaire de réserve cognitive est un outil adéquat pour distinguer les sujets âgés à haute réserve cognitive de ceux à basse réserve. Plus précisément, nous suggérons qu'un score supérieur à 250 points est un indicateur de haute RC, et un score inférieur à 150 points est un indicateur de basse RC. Un cut-off de z-score de $SSCT_{IES,}$ de 8 est aussi un indicateur dynamique robuste de basse réserve cognitive, avec 100% de sensibilité et 55% de spécificité.

Des études futures, comprenant un large échantillon avec différentes expériences de vie, sont nécessaires pour confirmer ces résultats et sélectionner les proxies les plus appropriés qui contribuent à la construction ou à la destruction de la CR. Un autre intérêt est d'améliorer la spécificité de la mesure quantitative de la CR.

Conception des nouveaux paradigmes de double tâche

Des études récentes ont montré que des modifications de la marche précédaient les symptômes cliniques de la MA et de la MP. Cela semble être plus marqué en situation de double tâche, où il est nécessaire de gérer les ressources attentionnelles allouées à chaque tâche. Dans le contexte de la MA, une étude longitudinale a été récemment menée pour déterminer si la modification des paramètres de marche en situation de double tâche pourrait prédire l'évolution vers une MA chez des patients MCI (Gillain et al. 2016). Parmi les 23 patients MCI qui ont été suivis de 2007 à 2008, 15 ont converti vers une MA (MCI+) et 8 sont restés stables (MCI-). Les paramètres de marche ont été enregistrés sur une distance de 30 mètres (soit environ 20 cycles de marche) au moyen d'un capteur accélérométrique placé au niveau lombaire. En situation de double tâche, les MCI+ présentaient une vitesse de marche ralentie ainsi qu'une moindre régularité et symétrie du pas, comparativement aux MCI-. Ces deux derniers paramètres ne différencient pas les deux groupes en situation de simple tâche (i.e., sans charge cognitive additionnelle). Ces résultats sont à mettre en lien avec ceux d'une étude de cohorte prospective (« Gait and Brain Study »), dans laquelle 112 patients MCI ont été suivis pendant 6 ans. Parmi eux, 27 ont converti vers une démence (quel que soit le type). Les résultats ont montré que, chez ces derniers (MCI évolutifs), le ralentissement de la marche en situation de double tâche était associé à la survenue d'une démence (quel que soit le type), et que cette association était largement expliquée par un déclin des fonctions exécutives (Montero-Odasso et al. 2017). Il est important de souligner qu'une vitesse de marche ralentie (< 0.8 $m.s^{-1}$) en situation de simple tâche n'était en revanche pas associée à l'apparition d'une démence. Une autre étude, transversale, a été réalisée chez des patients présentant une plainte cognitive (MacAulay et al. 2017). Après un examen clinique et un bilan neuropsychologique dans le cadre d'une consultation mémoire, 34 de ces patients répondaient aux critères diagnostiques du MCI. En situation de double tâche (uniquement), la vitesse de marche de ces derniers était ralentie, comparativement à ceux ayant une plainte cognitive mais subjective (i.e., non objectivée par le bilan neuropsychologique). D'autres études transversales ont été conduites parmi des patients atteints de différents sous-types de MCI (voir notre récente revue ; Belghali et al. 2017a). Il ressort de ces études que les paramètres de marche sont modifiés de façon plus marquée chez ces patients comparativement aux sujets contrôles. Les paramètres en question concernent quatre « domaines (aspects) de la marche » (précédemment décrits par Hollman et al., 2011) que sont la fréquence (diminution de la vitesse et de la longueur du pas, augmentation de la variabilité de la durée du cycle et du double appui), le rythme (augmentation de la durée du

cycle et de la phase d'oscillation), les phases du cycle de marche (augmentation de la durée du double appui), et la variabilité (augmentation de la variabilité de la longueur du pas).

Dans le contexte de la MP, deux études ont été conduites pour étudier le lien entre la mutation G2019S du gène LRRK2 (i.e., cause génétique la plus connue de la MP) et la marche chez des sujets asymptomatiques. La première étude (Mirelman et al. 2011) a porté sur 52 parents au premier degré de patients MP qui portaient la mutation. Les « non porteurs » (n = 27) et « porteurs » (n = 25) étaient similaires en ce qui concerne l'âge, les caractéristiques anthropométriques, les scores sur l'échelle UPDRS (« Unified Parkinson's Disease Rating Scale », évaluant la sévérité de la symptomatologie de la MP), les performances cognitives, et les signes non moteurs (i.e., troubles dysautonomiques, de l'olfaction, de l'humeur, et du sommeil). Les paramètres de marche ont été enregistrés au moyen d'un capteur accélérométrique placé au niveau lombaire sur une distance de 20 mètres, tantôt à vitesse préférentielle, tantôt à vitesse rapide, puis en situation de double tâche. Outre le calcul des paramètres spatiotemporels de la marche, une analyse spectrale du signal accélérométrique dans la bande de fréquence de la marche (0.5-3 Hz) a été effectuée pour en extraire le pic d'amplitude de la fréquence dominante dans la direction antéropostérieure (un pic réduit reflétant une marche plus variable). Les résultats ont montré que la vitesse de marche, ainsi que la longueur et la durée du pas, étaient comparables entre les deux groupes dans toutes les conditions. En revanche, la durée du pas était plus variable et le pic d'amplitude de la fréquence dominante du signal accélérométrique plus faible dans les deux conditions les plus difficiles (marche rapide et en double tâche) chez les porteurs comparativement aux non porteurs. Ainsi, parmi les aspects de la marche cités précédemment, la fréquence et le rythme sont préservés, alors que la variabilité est sélectivement altérée (augmentée). Une seconde étude, très récente (Mirelman et al. 2016) a porté sur 122 participants qui portaient la mutation. Les paramètres de marche considérés comme susceptibles d'être altérés très précocement dans la MP ont été enregistrés, à savoir : le ballant des bras et la rotation (rigidité) axiale (i.e., l'angle de rotation autour de l'axe vertical lors d'un cycle de marche, quantifié à partir d'un gyroscope). L'amplitude, la symétrie, la variabilité et la fluidité (« smoothness ») de ces paramètres ont été explorées. Aucune différence n'a été observée entre les porteurs et non porteurs en situation de simple tâche. En revanche, en situation de double tâche, les porteurs ont montré une plus grande asymétrie du ballant des bras, ainsi qu'une moindre fluidité du mouvement de rotation axiale que les non porteurs. Un autre résultat intéressant concerne la corrélation observée entre l'asymétrie du ballant des bras et la variabilité de la durée du pas, en situation de double tâche,

chez les porteurs. Une approche longitudinale permettrait de savoir si ces deux aspects de la marche sont altérés simultanément, ou si l'un d'eux est altéré plus précocement au cours de l'évolution de la pathologie.

Les résultats de ces deux études sont importants car ils suggèrent que des déficits locomoteurs sont présents à un stade préclinique (asymptomatique) de la MP. Ils sont non détectables en situation de simple tâche, notamment grâce à des mécanismes compensatoires permettant de retarder l'apparition des symptômes moteurs jusqu'à ce qu'environ 60-70 % des neurones dopaminergiques soient perdus. En effet, la dénervation dopaminergique striatale est à l'origine du dysfonctionnement (en cascade) dans les ganglions de la base qui, par voie de conséquence, retentit sur le cortex frontal.

Pris ensemble, les résultats des études antérieures suggèrent fortement que le recours à des doubles tâches cognitivo-locomotrices permettrait d'épuiser les mécanismes de compensation (i.e., réorganisation) à l'origine des symptômes cliniques, et ainsi de « pronostiquer » l'émergence d'une MA ou d'une MP, chez des sujets encore asymptomatiques (cette proposition est présentée plus en détail dans un article perspectif ; Belghali et al. 2017b). Au préalable, il est nécessaire de parfaire la méthodologie de ces études, bien que très novatrices, présentent des limites.

La première de ces limites est que les performances cognitives en simple et double tâche n'ont pas été évaluées, si bien que le coût attentionnel lié à l'exécution de la double tâche n'est que partiellement mesuré. De la même manière, la stratégie de partage attentionnel (i.e., priorité de réalisation donnée à l'une ou à l'autre des deux tâches) n'a pas été prise en considération.

La seconde de ces limites concerne les tâches cognitives choisies. En effet la majorité de ces études utilisent souvent une tâche de décompte ou une tâche de fluence verbale, or, ces dernières ne ciblent pas spécifiquement les processus exécutifs pertinents par rapport à la nature du processus neuropathologique sous-jacent. De plus, le décompte, qui peut être assimilé à une tâche de mémoire de travail (Beauchet al. 2005), dépend largement du niveau d'expertise en calcul mental, ce qui rend les comparaisons intergroupes difficiles. Il en est de même pour la fluence verbale (sémantique ou phonémique), qui nécessite d'accéder à l'information maintenue en mémoire à long terme et de la manipuler (Troyer et al. 1997), et dont la performance dépend du niveau d'éducation mais aussi du niveau culturel (e.g., Gierski and Ergis, 2004 ; Er-Rafiqi et al. 2017). En outre, dans ce type de tâche (langage spontané), les 30 premières secondes de fluence correspondraient à une recherche quasi automatique et les

suivantes à un processus de recherche stratégique (Crowe, 1998), si bien que l'interférence en double tâche fluctuerait pendant l'essai.

Une troisième limite est que l'influence du ralentissement de la marche en double tâche sur les paramètres de marche étudiés n'a pas été contrôlée, si bien qu'il est difficile de savoir si la modification de ces derniers est un corollaire d'une vitesse de marche ralentie, ou reflète l'interférence *per se* entre les deux tâches. Il a été montré que la vitesse de marche influence les paramètres biomécaniques de la marche (e.g., Chiu et al. 2013 ; Hebenstreit et al. 2015 ; Romkes et al. 2017), et donc la variabilité du pas (Jordan et al. 2007, 2008).

Revisiter les paradigmes de double tâche semble ainsi indispensable pour favoriser leur utilisation en routine clinique. Le fruit de nos réflexions dans ce domaine de recherche a fait l'objet de deux articles scientifiques dont une revue de littérature (Belghali et al. 2017b) et un article perspectif (Belghali et al. 2017a). Brièvement, nous avons suggéré qu'une double tâche associant à la tâche locomotrice une tâche cognitive sollicitant la fonction exécutive la plus altérée au stade préclinique de la MA et la MP (i.e., inhibition dans la MA et flexibilité cognitive dans la MP) permettrait d'identifier des marqueurs cognitivo-locomoteur spécifiques à ces maladies. Concernant les paramètres locomoteurs à explorer, le domaine « rythme » semble sélectivement altéré dans la MA, tandis que fluidité du mouvement de rotation axiale, ainsi que l'asymétrie et la variabilité du ballant des bras apparaissent l'être davantage dans la MP. Certains paramètres, tels que la vitesse de marche et l'augmentation de la variabilité de la durée du pas, se trouvent dégradés dans les deux pathologies, et pourraient signer, de manière aspécifique, un déclin des ressources d'origine centrale.

Avant de vérifier nos hypothèses sur des patients ou des sujets à risque, nous avons conduit une étude pilote sur des sujets jeunes (n=15) afin de comprendre les différentes stratégies cognitivo-locomotrice optimales. A notre connaissance, aucune étude expérimentale n'a été conduite jusqu' à l'heure actuelle pour explorer d'une manière fine l'interférence exécutive avec la marche chez les jeunes. En réponse à ce besoin, quatre paradigmes de double tâches ont été élaborés. Dans ces paradigmes, les participants doivent marcher sur un tapis GRAIL tout en effectuant 4 tâches cognitives, dont 3 nouvelles sollicitant d'une manière isolée ou combinée les fonctions exécutives (décrites ci-après) (AST : Auditory Stroop task sollicitant l'inhibition, ATS : Auditory task switching sollicitant la flexibilité cognitive, et l'ASTS ; Auditory Stroop Task Set Switching sollicitant l'inhibition et la flexibilité) et une standard (la tâche de compte à rebours). La tâche de compte à rebours a été utilisée afin de montrer la valeur ajoutée de nos tâches en comparaison à cette tâche standard fréquemment utilisée dans la

littérature pour étudier la relation entre fonctions exécutives et marche. Chaque essai durait 1 min et 30 sec, et comprenait 30 sec d'accélération (i.e. où il été demandé au participant d'accélérer jusqu'à obtenir sa vitesse préférentielle), puis une minute d'acquisition. Lors des conditions de double tâche le sujet avait pour consigne de marcher le plus naturellement possible, et de ne pas prioriser l'une des deux tâches.

Le temps de réponse et le nombre d'erreurs ont été mesurés pour chaque tâche cognitive en simple et double tâche. Concernant la performance motrice, la vitesse et la longueur du pas, la largeur et la durée du pas, la durée de la phase oscillante, et la durée de la phase d'appui ont été mesurés.

Auditory stroop task set switching : Cette tâche dure 1 minute et sollicite l'ensemble des fonctions exécutives. Deux mots « Bas » ou « Haut » sont présentés aux participants dans deux fréquences différentes « basse » ou « haute ». Chaque mot est présenté soit dans la fréquence congruente (e.g., BAS avec une fréquence basse ou Haut avec une fréquence Haute) soit dans la fréquence incongruente (Bas avec une fréquence haute ou HAUT avec une fréquence basse). Les participants doivent dire le plus rapidement possible tantôt le mot prononcé lorsque la voix est celle d'un homme, tantôt la fréquence lorsque la voix est celle d'une femme.

Auditory task switching : Cette tâche dure 1 minute et sollicite la flexibilité cognitive et la mise à jour. Dans cette tâche, des chiffres sont présentés aux participants qui doivent dire le plus rapidement possible tantôt le chiffre impair lorsque la voix est celle d'un homme, tantôt le chiffre pair lorsque la voix est celle d'une femme.

Auditory Stroop task. Cette tâche dure 1 minute et sollicite l'inhibition (i.e., la composante exécutive la plus altérée au stade préclinique de la MA). Deux mots « Bas » ou « Haut » sont présentés aux participants dans deux fréquences différentes « basse » ou « haute ». Chaque mot est présenté soit dans la fréquence congruente (e.g., BAS avec une fréquence basse ou Haut avec une fréquence Haute) soit dans la fréquence incongruente (Bas avec une fréquence haute ou HAUT avec une fréquence basse). Les participants doivent dire le plus rapidement possible la fréquence du mot prononcé.

Comptage à rebours : Chaque participant doit compter à rebours de 3 en 3 à partir de 300 (i.e., en simple tâche) ou 500 (i.e., en double tâche).

Les premières expériences pilotes ont été menées, pour la première fois, au sein d'environnements virtuels de la Rome Antique, en partenariat avec l'équipe du Centre

Interdisciplinaire de Réalité Virtuelle (CIREVE). Les résultats ont permis de mettre à jour les stratégies d'adaptation utilisées par les jeunes adultes dans des situations écologiques de double tâche. Le premier résultat obtenu montre que les fonctions exécutives sollicitées d'une manière isolée ou combinée sont impliquées dans la régulation de la vitesse de la marche. Ce résultat pourrait être expliquée par le fait que les fonctions exécutives et la vitesse de la marche dépendent du même sous siège cérébral qui est le cortex préfrontal.

Le deuxième résultat montre que la réalisation d'une double tâche associant la marche et une tâche cognitive sollicitant à la fois les processus exécutifs d'inhibition et de flexibilité conduit à une détérioration du contrôle de la marche dans sa composante médiolatérale, via une augmentation de la largeur du pas, et une diminution de la variabilité de la largeur du pas, et ce indépendamment de la vitesse de marche. Plusieurs études ont montré une plus importante instabilité mécanique de la marche dans le plan frontal que dans le plan sagittal. Il s'en est suivi la proposition que la marche serait contrôlée de façon plus exécutive dans le plan frontal pour résoudre ce problème d'instabilité. La présente étude confirme cette hypothèse. La réduction des ressources exécutives allouées au contrôle de la marche s'est traduite par des modifications du contrôle locomoteur davantage dans le plan frontal que dans le plan sagittal, confirmant l'idée que la marche requiert un contrôle plus exécutif dans le premier plan que dans le second.

Si la performance motrice a été détériorée lors de la réalisation d'une seconde tâche exécutive, la performance cognitive quant à elle a été maintenue exceptée pour l'ASTS dans laquelle le nombre total d'erreurs augmentait significativement en double tâche par apport à la simple de tâche. Le maintien de la performance cognitive lors de la réalisation de la double tâche pourrait être expliqué par le fait que les sujets jeunes donnent la priorité à la tâche cognitive et préfèrent dégrader la stabilité de la marche. Cette stratégie inconsciente est nommée stratégie de « seconde posture ». La détérioration de la performance de l'ASTS pourrait être expliquée par un épuisement de ressources attentionnelles.

Pour conclure, cette thèse propose une nouvelle approche méthodologique pour l'évaluation des fonctions exécutives (STSS), du contrôle locomoteur (trois nouveaux paradigmes de double tâche) et de la réserve cognitive [(une nouvelle mesure qualitative : un nouveau questionnaire) et (une nouvelle mesure quantitative : Cut-off du score Z de $SSCT_{IES}$)]. Ces tests ont été validés avec une grande sensibilité au près des sujets sains de tout âge excepté pour les nouveaux paradigmes de double tâche qui ont été testés uniquement sur des sujets jeunes sains. Au vu de l'importance des résultats, la spécificité de ces tests devrait être explorée dans des études futures.

Des retombées dans les domaines scientifique et clinique sont attendues à l'issue de ce travail de recherche. Du point de vue des résultats scientifiques, nous prédisons que la mesure quantitative de la RC (Cut-off du score Z de $SSCT_{IES}$), et l'IES du SSCT évaluant l'efficience exécutive globale pourrait avoir une valeur ajoutée pour distinguer le vieillissement normal du vieillissement pathologique originaire d'un dysfonctionnement exécutif. Les adaptations cognitivo-locomotrices lors de situations de double tâche, sollicitant tantôt l'inhibition, tantôt la flexibilité cognitive, seront spécifiquement alertés aux stades prodromale et clinique de la MA et la MP, respectivement. Du point de vue des implications cliniques, si nos hypothèses se confirment, les cliniciens pourront utiliser le nouveau test neuropsychologique, la nouvelle mesure de la RC et les nouveaux paradigmes de double tâche pour diagnostiquer précocement une MA ou une MP, notamment parmi les individus présentant une plainte subjective mnésique ou une plainte subjective motrice.

Introduction

The world's population is aging rapidly: according to the World Health Organization (WHO, 2007), there are around 900 million people aged 60 and over in the world: It is estimated that this number will increase to two billion by 2050 (WHO, 2007), leading to immense implications, due to the prevalence of subsequent functional dependence typically associated with aging.

Nationwide, there were around 15, 2 million French people aged 60 and over in 2012, which represents approximately 23 percent of the total population of 65, 3 million. It has been estimated that this percentage will increase to 30 percent by 2050 (**Figure 1**). The growth phenomenon of aging in France is the consequence of fertility decline and notably increase in life expectancy. For instance, from 1800 to 1900, the average life expectancy at birth rose from 30 to about 45 years (Pison, 2005, p. 1). Since the year of 2004, the average life expectancy at birth reached 80 years. This average is stabilized after that, and France has never witnessed fall below 80 years. As people live longer, demographic interest has shifted to older generations. In 2014, above age 65, out of the 27 union European countries, France ranks first for both women (24 years) and men (19.7 years).

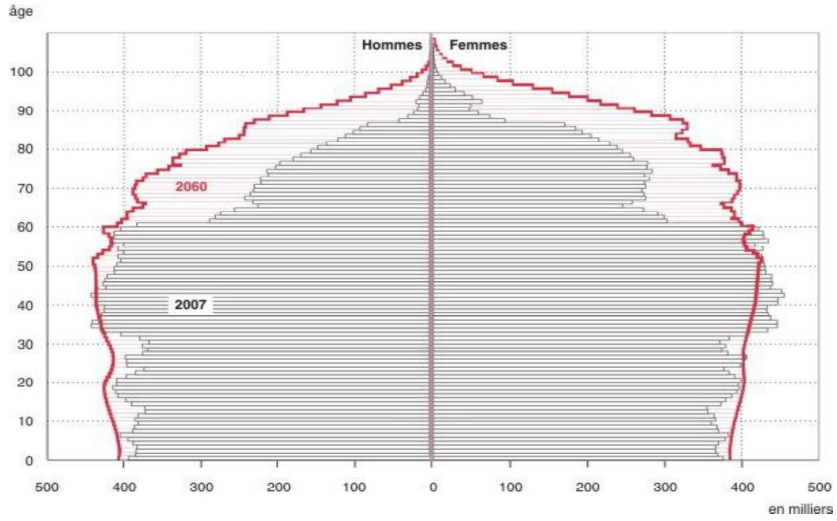

Figure 1. Population Pyramid in France: Adapted from the INSEE, (2007)

The boom of the elderly population in France as the rest of the world is strongly associated with increasing prevalence of people with neurodegenerative diseases, the most common of which are Alzheimer's disease (AD) and Parkinson's disease (PD) that affect today nearly 44 and 10 million people in the world, respectively (Muangpaisan et al. 2011; Prince et al. 2015).

It has been estimated that these numbers will quadruple by 2050 unless a means of prevention or a cure is found. In France, based on the Paquid (Ramaroson et al. 2003) and Eurodam (Lobo et al. 2000) cohorts, the number of people suffering from AD and related diseases has exceeded 850,000 with around 600 new cases occurring every day. For PD and related diseases, more than 100,000 people are affected, with around 8,000 new cases occurring every year (Blin et al. 2015).

Until now, AD and PD are diagnosed in the advanced phase. In the absence of curative therapy, current research is interested in prevention by identifying the first signs of early-phase neurodegeneration. Crucially, early diagnosis would provide a critical opportunity for disease-modulating interventions targeting modifiable risk factors for AD and PD (Barnes and Yaffe 2011), or even neuro-protective therapies, which both would help delay, slow, or even prevent disease progression (i.e., more cases would remain in the mild phase rather than degrade to moderate or severe phases; Petersen 2009). These risk factors are modifiable by making lifestyle changes (e.g., greater participation in physically and intellectually stimulating activities, social engagement, balanced diet with a high proportion of unsaturated fatty acids) and treating long-term health conditions (e.g., excessively high or low blood pressure, insufficient and/or fragmented sleep, diabetes, and midlife obesity (Belghali et al. 2017a).

From these clinical perspectives, increasing evidence supports the idea that the neuropathological process underlying AD and PD begins long before the onset of clinical symptoms as currently defined, thus denoting a "pre-diagnostic phase" of AD and PD. The latter is divided into two phases: "preclinical", in which the disease has started, but symptoms are absent (i.e., the target population is mainly those with genetic markers; Postuma et al. 2012), and "prodromal", in which some clinical symptoms or signs of the disease appear, but the patient does not have clinical symptoms of AD or PD as defined by current diagnostic criteria (Postuma and Berg 2016). The prodromal phase of AD is characterized by depression that appears more than 10 years before the diagnosis (Speck et al. 1995), memory complaints [at least 9–10 years (Amieva et al. 2005) and mild cognitive impairment (MCI) [up to 6 years; (Petersen et al. 2001)]. The prodromal phase of PD is mainly characterized by idiopathic rapid-eye-movement sleep behavior disorder (IRBD) that appears 26 years before diagnosis (Schenck et al. 2013), anxiety (up to 20 years), and reduced gastrointestinal motility and olfaction [up to 12 years, (Gaenslen et al. 2011)]. Nonetheless, these symptoms are non-specific to these diseases, i.e., the presence of any of these symptoms does not necessarily lead to progression to these diseases. However, longitudinal data have confirmed that people with IRBD are at

higher risk of conversion to PD [81% after 26 years (Schenck et al. 2013)] and persons with amnesic MCI and multi-domain MCI are at higher risk of conversion to AD [80% after 6 years (Petersen et al. 2001)].

Despite these findings, clinicians do not have available prodromal markers allowing them to identify MCI and IRBD patients who will develop AD or PD. In these populations, in spite of remarkable developments in neuroimaging, genetics, and molecular biomarkers, there is still an urgent need for disease-specific prodromal markers (referring to "signatures" of an ongoing pathological process that appear before the current clinical diagnosis (Heinzel et al. 2016)]. Recent research in behavioral neurosciences focusing on such markers has already found that executive functions (i.e., notably inhibition and switching) and gait control as assessed by standard neuropsychological tests (e.g., Stroop Test and Trail Making Test) and dual-task walking paradigms, respectively, are already altered at both the preclinical and prodromal phases of AD and PD (Postuma et al. 2012; Montero-Odasso 2016).

Despite the relevance of current results, the preclinical/prodromal use of standard neuropsychological tests and dual-task walking paradigms as accurate diagnostic tools of AD and PD remains limited. The following list outlines these limitations:

For neuropsychological tests assessing executive functions

- Reliable only at a late phase of the disease.
- A problem of task impurity: Very difficult to interpret deficit origin in a particular task.
- No neuropsychological test assessing the overall efficiency of EF.

For dual-task gait testing

- There is no recommendation on the type of cognitive task to use with gait testing.
- Specific recommendations cannot be made about the choice of gait parameters.

Another critical limitation common to these tools is that behavioral measures have been computed without considering the impact of cognitive reserve (i.e., refers to the different experiences accumulated throughout the life span). The latter theory posits that individuals with high cognitive reserve could resist better against brain damages than those with low reserve. From a clinical point of view, such difference help explain why among two individuals with the same amount of brain damages, one develops a disease whereas another one stays healthy. In line with this hypothesis, adding cognitive reserve's evaluation test in behavioral analysis seems crucial to understand inter-individual performance differences. Another interest is to

determine who grows old gracefully and who declines rapidly. Today, and despite the urgency of this need, there is no consensus on how to measure CR, making the choice of tools very difficult.

Innovating cognitive reserve assessment and improving current dual-task walking paradigms and neuropsychological tests leads to the heart of this thesis. Our contribution is twofold: theoretical and methodological.

The theoretical purposes are to: (i) review the nature of EF and gait deficits occurring in AD and PD, from the preclinical to clinical phase of the disease, and pros and cons of existing dual-task studies dedicated to predict early AD and PD (Belghali et al. 2017a), and (ii) propose a new conceptual framework to elaborate relevant dual-task paradigms susceptible to induce disease-specific gait changes at the preclinical phase (Belghali et al. 2017b).

The methodological purposes are to develop: (i) a new neuropsychological test, assessing executive functions, separately and together, (ii) new measures of CR; and (iii) new dual-task walking paradigms based on the neuropathological profiles of AD and PD, by manipulating both the nature of executive processes and cognitive load.

The set of developed tests has been validated across a wide range of ages (15-75 years) except for new dual-task walking paradigms that have been tested only in healthy young adults (18-25 years). This approach was crucial to prove that our revisited methodological work resolves the different limitations previously mentioned, appropriately.

This thesis consists of three parts:

The first part is devoted to the theoretical framework that includes three sub-parts:

1. First, we will address the concept and theories of aging and executive functions. Then, we will review the nature of executive dysfunction occurring in: (i) healthy aging, and (ii) AD and PD from the preclinical to clinical phase of the disease.
2. Secondly, we will review the interaction between gait and executive functions in AD and PD. Specifically; we will (i) address the concept and theories of dual-task walking, (ii) review the pros and cons of existing dual-task walking studies dedicated to predict early AD and PD (Belghali et al. 2017a), and (iii) propose a new conceptual framework to elaborate relevant dual-task paradigms susceptible to induce disease-specific gait changes at the preclinical phase (Belghali et al. 2017b).
3. Lastly, we will review the concept of cognitive reserve, theories, and measurement.

After a summary of the theoretical framework aiming to expose our working objectives, we will present in the second part, the four experimental studies realized during this thesis.

In the first two studies, we will propose a new neuropsychological test (i.e., study 1: card version and study 2 computerized version), assessing EF and related cognitive processes, separately and together. In the third study, we will propose two measures of cognitive reserve, one of which is qualitative and the other is quantitative. Lastly, we will examine the effect of executive task type (i.e., altered explicitly in the preclinical phases of both AD and PD) on gait control among young adults.

The third part of this thesis will be devoted to the general discussion including a summary of main findings of this thesis. Possible directions for future research conclude the discussion.

Part 1. Theoretical framework

1. Executive function changes in healthy aging, Alzheimer's and Parkinson's diseases

1.1 Aging

1.1.1 What age is considered elderly?

The age of retirement (60 - 65 years) is often recognized to be the beginning of old age notably in most developed countries (WHO 2007). Gerontologists contradict such a view by arguing that most individuals in this age are still active and independent. However, after the age of 75, they will become increasingly frail and less efficient. Therefore, rather than considering all people aged 65 years and more as old, some gerontologists defined three sub-groups, which are the: "Young old" (65-74), "Old" (75-84), and "Old-Old" (85 years and more).

1.1.2 What does aging mean?

"*Aging is a complex and multifactorial process characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death*" (Guillaumet-Adkins et al. 2017). This phenomenon is associated with a high degree of inter-individual variability. According to Chauchard, (2006), "*growing old is not a slope that everyone descends at the same speed. It is an irregular flight of stairs that some tumble down faster than others do*". Therefore, it is necessary to understand the different types of aging, their meanings and consequences. Through the literature, we can list three types of aging (Rowe and Kahn 1987, 1997), which are: (i) the "**normal**" aging that is characterized by natural changes at the brain level; (ii) the "**successful**" aging, that is characterized by minimal brain changes, even when compared to young adults, high psychological and physical functions, active engagement with life and low or absence risk of a disease; and (iii) the "**pathological**" aging that is associated to abnormal brain changes that don't occur either in normal or successful aging. This type of aging is associated to a large variety of diseases (e.g., psychiatric disorder, neurodegenerative diseases…) affecting several health domains notably: the cognition, psychology, and motor skills.

Collectively, it is clear that living longer does not systematically means living healthier. Thus, it is essential to ask whether we (on average) are not only living longer and healthy. These questions will challenge our understanding of healthy Human aging and aging-related disease, notably, mechanisms that make people more vulnerable to neurodegenerative diseases.

This thesis focus on changes in executive functions and gait control occurring in healthy aging, AD and PD, from the preclinical to clinical phase of the disease. It starts with a brief

description of structural brain-changes occurring in aging, as well as its cognitive consequences and explanatory theories.

1.1.3 Structural brain-changes and cognitive consequences

Several post-mortem studies have shown negative effects of age on the brain: Generally, older adults are affected by a loss of brain mass at a rate of around 5% per decade after the age of 40 years (Svennerholm et al. 1997; Peters, 2006), atrophy of gray matter that seems to be related to a lower synaptic density, and a white matter hyperintensity marked in the parietal and frontal lobes (Gunning-Dixon and Raz 2000, 2003; Nordahl et al. 2006). In addition to these changes, neuroimaging studies have shown that the amygdala formation, hippocampal, entorhinal cortices, and parahippocampal gyrus experience volume loss (for review see Raz and Rodrigue 2006). The dopaminergic system involved in the regulation of prefrontal functions is also affected by aging.

At a behavioral level, age-related changes in the brain affect several cognitive functions such as the executive functions (EF; the concept of these cognitive functions will be detailed in *page 31*), episodic memory (i.e., refers to the ability to recall individual past events; Tulving, 2002) working memory (i.e., refers to a cognitive system allowing both holding and monitoring information in a brief period time; Baddeley, 2000), attention (i.e., refers to the ability to focus on, or perceive, specific information; Steptoe, 2010), processing speed (i.e., refers to the time that the person take to perform a cognitive task; Balota et al. 2010) and reasoning ability (i.e., refers to the ability to gather information and provide arguments in order to form conclusions and solve problems; Wu, 2003). Growing evidence suggests that EF are the most vulnerable to age because the prefrontal cortex (i.e., the most disrupted region by aging) mediates these cognitive functions. Notably, the prefrontal cortex of older people aged 65 years and more is reduced by 10–17%, while the temporal, parietal, and occipital cortices reduced by approximately 1% compared to young adults (Beurskens and Bock 2012).

1.1.4 Theories of cognitive aging

Although age-related cognitive declines are well understood, the specific mechanisms underlying these changes are still a topic of discussion. Recent investigations have proposed several unitary frameworks attributing age-related changes in cognition to one “core” cognitive deficit. Three of the main theories are described below.

1.1.4.1 Working memory's theory

Two important theoretical theories have associated age-related changes in cognition to working memory. The first model by Craik, (1986) suggests that changes in cognition may result from a reduced capacity of working memory, which is necessary to perform any cognitive task. These limited resources make older adults less able to engage in the self-initiated processes necessary for optimal cognitive performance. The second by (Hasher and Zacks 1988) focuses on how the information is contained within working memory. Notably, the authors suggest that decrease in inhibition efficiency may disrupt working memory leading to suggest that it is not the overall amount of resources that declines, but rather the utilization of these resources. Hasher and Zack´s (1988) identified three main functions of inhibition that decreased with aging, which are: 1) the access function, which keeps recent information activated but keeps irrelevant out from working memory; 2) the deletion function that eliminates information that becomes irrelevant, especially when the task goals change and 3) the restraint function, which prevents things from moving further into cognition.

1.1.4.2 Processing speed's theory

The processing speed theory by (Salthouse 1996), suggests that the reduction in processing speed is the principal factor that could explain all cognitive performance difference between young adults and older adults. Two mechanisms mediating the relationship between speed and cognition were proposed: the "limited time mechanism" and the "simultaneity mechanism". The "limited time mechanism" postulates that with advancing in age, older adults require more time to execute earlier cognitive processes. Besides, when a cognitive task is executed, some processes must be done earlier than others must. As we get older, the time needed to execute those earlier processes became slow. In this case, cognitive performance is degraded when relevant processes cannot be efficaciously executed within the required period. The "simultaneity mechanism" postulates that older adults cannot consider numerous relevant tasks together compared to young adults. This has been explained by the inability to access products of earlier processing, which may no longer be available by the time that later processes are accomplished.

1.1.4.3 Frontal lobe's theory

The frontal lobe hypothesis of cognitive aging (West 1996, 2000) suggests that cognitive functions mediated by the prefrontal cortex are the most sensitive to age, whereas those mostly independent of frontal lobes remain relatively intact. The frontal lobe hypothesis makes the

decline of frontal functions mainly executive functions the main cause of age-related changes in cognition.

1.2 Executive functions

Executive functions (EF) constitute one of the primary interest of this thesis. Both the concept and models of these cognitive functions will be detailed in the following section.

1.2.1 Definition

EF are typically described as an 'umbrella term 'including a set of higher-order of cognitive processes involved notably in a novel situation (Norman and Shallice, 1980). EF are believed to comprise a heterogeneous collection of skills, including the ability to generate strategies and switch between tasks, planning, goal maintenance, inhibition of routine tasks, and detection of errors. Rabbit, (1997) proposed eight situations, in which EF could be required, which are:

- Novelty
- Active search of information in long-term memory
- Supervisory attention, referring to the ability to adapt the Human behavior according to the environmental requirements
- Inhibition of inappropriate responses
- Coordination of two tasks carried out simultaneously
- Detection and correction of errors (which implies a modification of the initial plan)
- Sustained maintenance of attention
- Accessibility to consciousness

EF emerged for the first time with the work of (Luria, 1972), when he found that the behavior of individuals who suffered from frontal lobe damages had major difficulties in problem-solving tasks requiring the inhibition, planning and judgment abilities (Luria, 1972). Since this work, "EF" have been related to the frontal lobe, notably the prefrontal cortex. Recent theories contradict this view, by arguing that subcortical regions could also be critically involved in EF, as the case of PD patients. This has led to the suggestion that EF depend not only on the frontal lobe, but also on the cortical-striatal circuitry. Evidence for such a view comes from neuroimaging studies that have shown that the performance of executive tasks relies on both the frontal lobe and subcortical areas (e.g., Hartley and Speer 2000).

1.2.2 Key models of executive functions

Given that that there is no consensus which functions constitute the basic components of EF, different models have been proposed in the literature to determine the cores of EF. The most common models are reviewed below.

1.2.2.1 Luria's model

Luria, (1966, 1972)'s model link the EF with the prefrontal cortex of the brain. Specifically, he ssuggested that the prefrontal cortex is responsible for four EF which are the: 1) anticipation (setting realistic expectations, understanding consequences), 2) planning (organization), 3) execution (switching, maintaining set), and 4) self-monitoring (emotional control, error recognition). Following such finding, he concluded that the Human brain comprises essentially three basic functional units "whose participation is needed for any cognitive task". The first unit (i.e., referred to the arousal and attention unit) involves the brainstem, including the reticular formation, midbrain, pons, and medulla oblongata and is responsible for regulating tone, waking and mental states. The second unit (i.e., referred to the sensory input and integration unit) involves the temporal, parietal and occipital lobes and -is responsible for receiving, processing, and storing information. The third unit (i.e., referred to the executive planning and organization unit) is composed of association cortex located in the frontal and prefrontal areas of the brain, anterior to the sensory-motor strip and is responsible for programming, regulating, and verifying human behavior.

Although the three units have distinct functions, they always work together. Luria had claimed that the failure in performing a specific cognitive task is not necessarily explained by a deficit in a specific function, but rather by a failure of connections between all of these three units.

1.2.2.2 Norman and Shallice's model

Norman and Shallice, (1986) had extended the precedent model by Luria, and they suggested that Human behavior involves mainly two systems, which are: 1) the contention scheduling, and 2) supervisory attentional system. The first system is responsible for routine tasks without any deliberate attention. The second system corresponds to EF and is responsible for regulating new tasks requiring attention. An attentional situation is involved in the following conditions: (1) tasks involving planning, error correction, or decision-

making; (2) tasks containing new sequences of actions; (4) tasks including a danger that should be anticipated; and (5) tasks requiring the ability to resist against habitual response.

1.2.2.3 Baddeley's model

In the Baddeley's model (1986, 2000, 2007), EF correspond to the central executive of working memory. The latter includes two components: i) the central executive (EF) hat is responsible for both the control and regulation of several cognitive processes such as the planning and organization of information, and ii) three slave systems, which are the phonological loop, visual-spatial sketchpad, and episodic buffer (**Figure 2**).

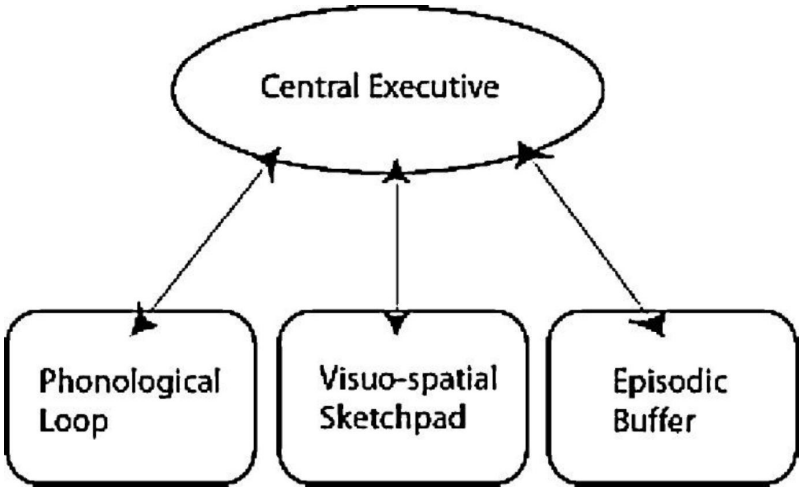

Figure 2. Schematic representation of Baddeley's model: Adapted from Baddeley, (2000)

1.2.2.4 Miyake's model

Miyake's model (Miyake et al. 2000) suggests that there are three components of EF, which are the: (1) **updating,** referring to *the "ability to both hold and monitor different information modalities"*; (2) **inhibition**, referring to *the "ability to inhibit in a controlled way the production of prepotent, automatic, or impulsive responses when necessary*," and (3) **switching** referring to *the "ability to flexibly change forward and backward in relation to different tasks, mental processes, or schemas"* (Miyake et al. 2000), which can work either together or separately according to both the nature and cognitive demand of the situation (**Figure 3**). For Miyake, the origin of the unity of EF could lie in the fact that the latter share common requirements when performing a task, notably the ability to both hold and monitor

the information in working memory. Another possibility is that all components of EF require inhibition processes to work properly. The recent model by Diamond, (2013) confirmed this view by suggesting that "*switching requires and builds on both the inhibition and updating"*.

The diversity and unity character of EF was also obtained in other studies including different samples of young adults (Friedman et al. 2006), older adults (Fisk and Sharp 2004; Hedden and Yoon 2006) and children (van der Sluis et al. 2007).

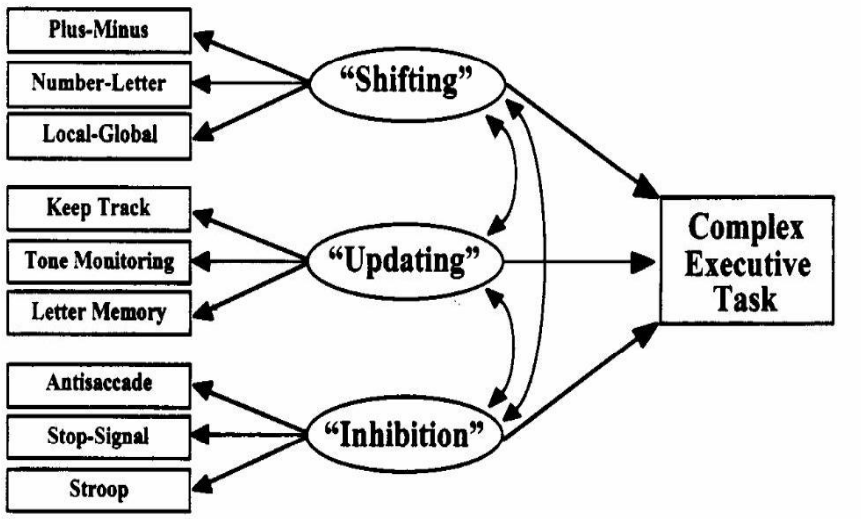

Figure 3. Schematic representation of Miyake's model: Adapted from Miyake et al. (2000). Ellipses represent the three executive functions (latent variables), and the rectangles represent the tasks that have been selected to study executive functions, as indicated by the straight, single headed arrow. The curved double-headed arrows represent correlations between latent variables.

Miyake's model is the most cited in the literature since it offers a well-specified description of EF components and has been the basis of a range of cognitive and clinical studies. Following Miyake's model, this thesis will focus on three executive functions, namely, updating, inhibition and switching.

To summarize, EF can be described as an ‘umbrella term ‘including a set of higher-order of cognitive processes involved notably in a new situation. EF allow to manage self-control behavior, as well as to represent multiple aspects of a problem, detect errors, plan a future course of action and act on it. Despite this wide range of cognitive and behavioral abilities, there is broad agreement that there are three components of EF, which are: the inhibition, switching, and updating of working memory representations (Miyake et al. 2000, Miyake and Friedman 2012) that can work either together or separately according to the cognitive demand of the situation. It is widely admitted that the updating has a continuous monitor over inhibition and switching. The switching for its part "*requires and builds on both the inhibition and updating*" (Diamond, 2013).

In the following section, the effect of normal aging on inhibition, updating and switching (i.e., Miyake's model) will be reviewed.

1.3 Executive functions in healthy aging

1.3.1 Age-related changes in inhibition

The effect of age on inhibition has been investigated in numerous studies through a wide variety of executive tests; the most common of which is the Stroop test (Stroop, 1935). The latter (i.e., the test of interest for this thesis) includes two basic conditions of color naming and word reading and, a third condition requiring individuals to name the ink color that does not correspond to the meaning of the written word (i.e., incongruent trials: e.g., blue written in red; BLUE). Several transversal studies using the Stroop test have shown that older adults increased their response time and/or errors in the third condition (incongruent trials ; BLUE) compared to young adults (Dulaney and Rogers 1994; West 1996; Kieley and Hartley 1997; West and Alain 2000; Davidson et al. 2003; Belleville et al. 2006; Andrés et al. 2008; Ludwig et al. 2010). While these findings have sometimes been attributed to general slowing effects (Salthouse and Meinz 1995; Jennings et al. 2007; Gamboz et al. 2010), others have shown important contributions of age to the Stroop performance even after controlling for processing speed (Williams et al. 1999; Wecker et al. 2000; Andrés and Van der Linden 2000; Bugg et al. 2008). Mechanistically, the slowness of performance in older adults was mainly explained by a greater sensitivity to interference (i.e., the inability to resolve the competition between the two responses evoked by each of the stimulus dimensions; Dyer 1973). Recent neuroimaging studies (Milham et al. 2002; Davidson et al. 2003) supported this finding and have shown that the patterns of neural activity associated with Stroop performance were different between young adults and older adults. Specifically, the dorsolateral prefrontal cortex in the older group was less activated than the younger ones (Milham et al. 2002; Davidson et al. 2003).

1.3.2 Age-related changes in switching

The Wisconsin Card Sorting Test and Trail Making Test (TMT) have provided the main tests used in the literature to examine age-related change in switching. The TMT test (i.e., the test of interest for this thesis) includes two conditions: Part A, requiring the serial connection of the numbers 1 through 25 (1–2–3, etc.), and Part B, requiring the serial alternation between number and letter sequences (1– A–2–B-3-C, etc.). Several studies using the TMT test have shown that older adults increased their response times and/or errors in Part B compared to young adults (Giovagnoli et al. 1996; Wecker et al. 2000; Hester et al. 2005; Hashimoto et al.

2006; Seo et al. 2006; MacPherson et al. 2017). While these findings have sometimes been attributed to non-executive components (visual speed, motor speed; Salthouse et al. 2000; MacPherson et al. 2017), others have found important contributions of age even after controlling for external factors engaged by this task such as the visual scanning and both the motor and perceptual speed (Wecker et al. 2005).

In the Wisconsin Card Sorting Test, each individual must sort series of cards into different piles by the number, shape, or color of geometric objects that are printed on the cards. Following 10 correct sorts, the administrator changes the correct rule for categorization and the participant must discover the new sorting rule based on administrator feedback. Individuals are measured by how fast they learn rules and how fast they switch to new rules (Berg 1948). Regarding the effect of age on this test, conflicting results have been reported in the literature. The study by (Mejia et al. 1998) does not show any significant performance difference between the young-old (55-70) and old-old groups (71-85), whereas the study by (Haaland et al. 1987) has shown a negative effects of age, only after the age of 80 years. The studies by Crawford et al. (2000) and Plumet et al. (2005) have shown a significant performance difference between young adults and older adults (i.e., increase in the total number errors) from the age of 60 years.

1.3.3 Age-related changes in updating

Numerous studies have been conducted in the literature to explore the effect of age on updating. Overall, despite the diversity of tasks, updating seems to be sensitive to age (Van der Linden et al. 1994; Chen and Li 2007; Verhaeghen and Basak 2005; Sorel and Pennequin 2008). The study by Van der Linden et al. (1994) is one of the first studies showing such finding, notably by using the dynamic memory-updating task of Morris and Jones (1990). Age-related changes in updating have been also shown by using the Forward and Backward Digit Span test (i.e., the test of interest for this thesis), (Babcock and Salthouse 1990; GrÉGoire and Linden 1997). A first meta-analysis of 14 studies by Babcock and Salthouse, (1990) has shown that age-related changes in the backward sequence were greater than in the forward sequence (14% to 8%). To explain such performance, the authors have suggested that the backward sequence requires the central executive component of working memory whereas the forward sequence is more related to the capacity of the phonological loop (Baddeley, 2000). Recent studies (GrÉGoire and Linden, 1997; De Beni et al. 2004; Kumar and Priyadarshi, 2013) contradicted above findings and showed the same rate of decline for both sequences.

To conclude the relationship between age and EF (inhibition, updating and switching) is not fully understood. Some investigators have noted age-related changes in EF whereas others have not. These contradictive results could result from the large variety of methods used by authors to assess these cognitive functions. Taking into account these contradictive results, we suggest that age-related changes in EF are not an inevitable **deficit** that should occur systematically with aging but rather a **decline** that may occur progressively in light or accentuated manner, depending on the brain profile of the person that is largely influenced by different life-experiences. Longitudinal data are needed to confirm such a view as well as to better understand age-related changes in EF.

1.4 Executive functions in the clinical and preclinical phases of Alzheimer's disease

In the following section, the nature of executive dysfunction occurring in AD from the preclinical to clinical phase of the disease will be reviewed.

1.4.1 Executive functions in the clinical phase of Alzheimer's disease

AD is characterized by the presence of both amyloid beta plaques and neurofibrillary tangles [i.e., the two hallmark pathologies (Ballard et al. 2011; Ittner and Götz 2011)] in the medial temporal lobe structures (particularly the hippocampus) and neocortex, together with neuronal loss and volume reductions (Braak and Braak 1991; Terry et al. 1991). At a behavioral level, AD is characterized by a marked impairment in several cognitive domains including the episodic, working, and semantic memories, EF, visuospatial abilities and language (Nordahl et al. 2006; Mayda et al. 2011). As for EF changes, it is widely documented that AD patients are affected progressively in all components of EF. The study by Grady et al. (1988) was among the first to find such results. Specifically, the authors have shown that AD patients were altered in executive tests assessing switching (Form B of the Trail-Making Test; Reitan, 1958), inhibition (Stroop interference test; Stroop, 1935), and updating. These findings were latter supported by numerous studies (e.g., Perry and Hodges 1999; Allain et al. 2013; Luedke et al. 2016).

It is well admitted that executive dysfunction (deficit) appears in the very early clinical phase of AD and precedes impairments of other cognitive domains such as the language, sustained attention, and constructional praxis (Binetti et al. 1996; Bondi et al. 2002; Luedke et al. 2016) leading to suggest that executive dysfunction in AD, is the trigger of many cognitive disorders occurring at the clinical phase of this disease.

1.4.2 Executive functions in the preclinical phase of Alzheimer's disease

Converging evidence from both genetic at-risk cohorts and clinically normal older individuals suggests that the neuropathological process of AD begins at least 20 years before its clinical diagnosis (Sperling et al. 2011). To understand the neuropathological process of this disease, an autopsy study on brains from non-demented and demented individuals (Braak and Braak 1991) has shown that extracellular amyloid deposition usually appears before any intra-neuronal neurofibrillary changes, first in the entorhinal cortex before spreading in a hierarchical manner into the hippocampus and cortex (Braak et al. 1991). At a behavioral level, a

longitudinal neuropsychological study (12 years) of the transition from healthy aging to AD (Balota et al. 2010) revealed that impairment in inhibition as assessed by the computerized version of the Stroop test precedes impairment in the episodic memory in the disease course and, importantly, predicts AD. Notably, older adults that converted to AD had **incongruent error rates** that were 2.2 times higher than non-converters. Mechanistically, this finding could be explained by the fact that abnormal extracellular amyloid accumulation in the basal isocortex impairs first inhibition [as assessed by the Stroop task (Stroop, 1935)] in asymptomatic individuals with abnormal beta-amyloid 42/tau ratios (i.e., preclinical phase of AD, Harrington et al. 2013). It is worth mentioning that the underlying pathways of the Stroop test include the bilateral dorsolateral prefrontal cortex, inferior frontal gyrus, anterior cingulate cortex, and posterior parietal cortex (Nee et al. 2007), leading to suggest that prefrontal dysfunction is present during the early phase (preclinical) of AD (Harrington et al. 2013, Belghali et al. 2017a).

As for the Stroop test, the task-switching paradigms (e.g., TMT) also involve regions of the prefrontal cortex (Braver et al. 2002; Brass and Heyes 2005; Brass et al. 2009). For this reason, some authors have combined these tests to identify a more sensitive cognitive marker predicting the early onset of AD**;** 'the **Stroop switching test** (SWT)', in which the principal instruction is to switch between naming the incongruent ink of colors and reading the conflicting words in a random order. Growing evidence suggests that the SWT is more sensitive than standard neuropsychological tests in predicting executive dysfunction. The longitudinal study of one year by (Fine et al. 2008) confirmed this view and has shown that older adults who reduced their cognitive performance over the year had larger Stroop switch discrepancy scores (i.e., the difference between Stroop switch performance and average performance on classical Stroop) compared to those whose cognitive performance remained stable. Similarly, the recent study by Hutchison et al. (2010) comparing healthy older adults to individuals diagnosed with mild dementia has shown that the SWT performance exceeded current psychometric tests in discriminating healthy aging from the early phase of AD. Notably, patients with an early AD produced larger Stroop interference and made more error rates than healthy older adults. This finding replicates past studies that propose the percentage of errors in incongruent trials as a signature of an early phase of AD (Balota et al. 2010).

It is worth mentioning that the SWT designed by Hutchison differs than the one proposed by Fine et al. (2008). In fact, Hutchison et al. (2010) used not only a single condition including incongruent color words stimuli (i.e., Fine et al. 2008), but also neutral words (e.g., the word "bad" presented in green, blue, or yellow). These stimuli were presented in two

conditions (control versus experimental) in an alternating runs (e.g., AABBAABB) fashion (Rogers and Monsell 1995) such that every two trials, the participant would switch their responding from one dimension (color or word) to the next. The SWT is the test of interest for this thesis, which will be criticized and improved in the first experimental study in order to be used in clinical practice as a powerful tool predicting early executive dysfunction.

At the onset of MCI (i.e., the prodromal phase of AD), the neuropathological mechanisms underlying progression to AD become more complex. Nevertheless, several studies have demonstrated reduced hippocampal and entorhinal cortex volume, as well as a reduced cortical thickness in the medial and lateral temporal cortex, parietal lobe, and frontal lobes in MCI patients who have converted to AD (MCI-converters), up to 2 years prior to clinical conversion, as compared to MCI patients who remained stable (MCI-stable) (deToledo-Morrell et al. 2004; Risacher et al. 2010). At a behavioral level, longitudinal studies have found that MCI-converters performed worse than controls on measurements of episodic and working memories (Cloutier et al. 2015), and EF notably inhibition (Belleville et al. 2007). These results support the suggestion that executive dysfunction (deficit), specifically in inhibition can be used as a potential predictor of AD, given that it is markedly affected at all clinical phases of AD (i.e., preclinical, prodromal and clinical).

1.5 Executive functions in the clinical and preclinical phases of Parkinson disease

In the following section, the nature of executive dysfunction occurring in PD from the preclinical to clinical phase of the disease will be reviewed.

1.5.1 Executive functions in the clinical phase of Parkinson's disease

PD is a chronic neurodegenerative disease caused by a progressive and profound loss of nigrostriatal dopaminergic neurons projecting to the striatum, which includes the caudate nucleus and the putamen (Kish et al. 1988), and the presence of Lewy Bodies in the central, peripheral, and autonomic nervous systems (Jellinger 2012). Clinically, PD is characterized by the emergence of at least two cardinal motor features, including bradykinesia (i.e., slowness of movement) and either rigidity, tremor, gait disorders or postural instability (Tolosa et al. 2006; Massano and Bhatia 2012). In addition to classical cardinal motor deficits, neuropsychological studies have revealed deficits in a wide range of cognitive functions even at the early clinical phase of the disease (Taylor et al. 1986; Taylor and Saint-Cyr 1995; Dubois and Pillon 1997; Hanganu et al. 2015). The major deficit lies in EF (García et al. 2017), notably, switching (i.e., as assessed by both the Wisconsin Card Sorting and TMTtests: Taylor et al. 1986; Gotham et al. 1988; Muslimovic et al. 2007), inhibition (i.e., as assessed by the Stroop test; Taylor et al. 1986; Gotham et al. 1988; Uekermann et al. 2003; Bouquet et al. 2003), updating (see Kudlicka et al. 2011 for meta-analysis) and planning (i.e., as assessed by the Tower of Toronto task; Saint-Cyr et al. 1988; Dujardin et al. 2001; Cools et al. 2001). Notably, some authors suggest that the deficit in switching arising mainly from a disruption of meso-prefrontal and prefrontal striatal circuits (Cools 2006; Kehagia et al. 2010) and dysfunction in the dorsolateral prefrontal cortex (Sawada et al. 2012), is the primary neuropsychological feature of PD (Kehagia et al. 2010). The recent meta-analysis by (Kudlicka et al. 2011) combining data from 33 studies on EF in early-phase (HoehnandYahr I–III) of PD, confirmed previous findings, and further suggests that the effect size of both switching (i.e., as assessed by the alternating fluency) and inhibition (i.e., as assessed by the Stroop) was slightly more affected than the other measures, at the early clinical phase of the disease (**Figure 4**).

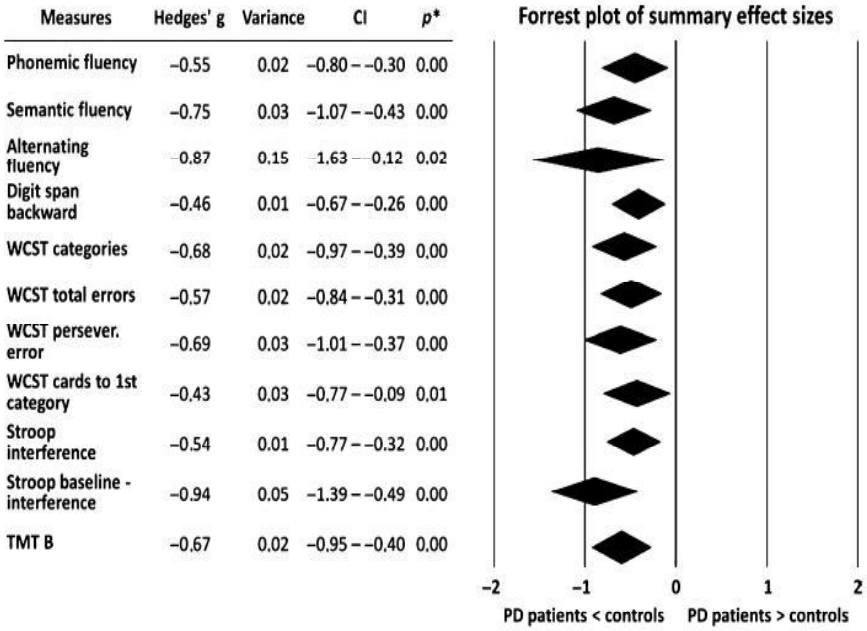

Figure 4. Results of the meta-analysis by Kudlickaet et al. (2011). Hedges' g = corrected mean weighted effect size; CI = 95% confidence interval; WCST = Wisconsin Card Sorting Test; TMT B = Trail Making Test, part B. *Two-tailed test.

1.5.2 Executive functions in the preclinical phase of Parkinson's disease

The onset of PD appears after depletion of 70–80% of striatal dopamine, corresponding to 30–50% of dead cells of dopaminergic neurons (Postuma et al. 2012; Postuma and Berg 2016). The time span between the onset of cell loss in the substantia nigra pars and the manifestation of typical motor symptoms is referred to as the preclinical phase of PD (Hawkes 2008). The duration of this phase is still in debate (Gaenslen et al. 2011), and has been estimated to last many years, with an average of 5 years (Morrish et al. 1998; Postuma et al. 2012), or even decades (Marek and Jennings 2009). To date, several motor and non-motor symptoms characterize this preclinical phase, but unfortunately, they are insufficient to make an accurate preclinical diagnosis. According to the model by Braak et al. (2003), the neuropathological process of non-motor symptoms could not start in the substantia nigra pars compacta. In fact, the Lewy Body pathology associated with PD can first be found in the medulla oblongata/pontine tegmentum and anterior olfactory structures (Braak's phases 1 and 2), and then in the dopaminergic neurons of the substantia nigra (phase 3 and 4). At a behavioral level, phases 1 and 2 manifest through reduced gastrointestinal motility (i.e., constipation) and olfaction (up to 12 years before the diagnosis of PD), mood disorders such as anxiety (up to 20

years) or depression (up to 10 years), and sleep disorders such as idiopathic rapid-eye-movement sleep behavior disorder (IRBD, up to 10-12 years). In phases 3 and 4, the clinical signs of Parkinsonism appear, and it becomes possible to diagnose PD by current criteria (Gaenslen et al. 2011). Until now, among all the non-motor symptoms found in the literature, IRBD (i.e., prodromal phase of PD), which is characterized by "*vivid, often fearful dreams and loss of normal muscle atonia during rapid eye movement sleep"* (Olson et al. 2000), is the highest risk factor for PD and affects up to half of patients over the course of disease.

Very few studies have explored the cognitive profile of IRBD patients (n=2), and have shown a large variety of cognitive deficits, including the visuospatial functions (e.g., visuoconstructive abilities and visuospatial learning), EF (i.e., switching, inhibition and updating), and verbal memory (Chahine et al. 2016; Li et al. 2016). The PARS cohort by (Chahine et al. 2016) confirmed the previous finding in other individuals who also are considered at higher risk of developing PD, notably, those with olfactory loss and dopamine transporter deficit. These findings highlight that PD is a complex disease affecting not only the movement but also the cognition in which executive dysfunction (deficit) is present from the prodromal phase of the disease.

Recent longitudinal studies suggest that executive dysfunction (deficit) is also present at the preclinical phase of PD (Ross et al. 2012; Darweesh et al. 2017). During a follow-up over 40 years, the Honolulu-Asia Aging Study of the transition from healthy aging to PD, has shown that a deficit in cognitive switching as assessed by the verbal fluency test (i.e., number of animals named in 30 seconds) is a powerful candidate of pre-motor features of PD. Notably, those with a lower score in verbal fluency test had an incidence of PD of 26.1/10,000 person/ years, compared with 10.9 for those with a good switching performance (Ross et al. 2012). Results from the Rotterdam study (Darweesh et al. 2017) adds further evidence that individuals who developed PD had significantly worse scores in both inhibition (6.2 years) and switching (3.3 years).

To conclude, PD is also an executive disorder in which both switching and inhibition are deteriorated at all clinical phases of the disease (i.e., preclinical, prodromal and clinical).

To conclude, deficits in inhibition and switching are remarkably present at all clinical phases (i.e., preclinical, prodromal and clinical) of AD and PD. Despite this similarity, the executive profile of these diseases is never compared at the preclinical phase. Nonetheless, given that inhibition is more related to the isocortex (i.e., one of the first structure altered in the preclinical AD), and switching to the frontal-striatal circuit and dopamine efficiency, we suggest that inhibition and switching could be more specific to AD and PD, respectively (Belghali et al. 2017a). This view will be discussed further later in the two articles published during this thesis (Belghali et al. 2017a; Belghali et al. 2017b).

1.6 Critical view on the standard neuropsychological tests

Until now, any test sensitive to frontal lobe damage is deemed to assess EF (i.e., such as the WCST, Stroop, TMT and verbal fluency). A major problem of these tests is that they are no specific to the executive component that they evaluate, 'task impurity' (Packwood et al. 2011). This means that standard neuropsychological tests may assess different executive components and even other cognitive domains, making thus the interpretation of results very difficult (Packwood et al. 2011). For example, verbal fluency is used not only to measure switching (Rosen and Engle 1997), but also fluency capacities (Baldo et al. 2001), memory retrieval (Troyer et al. 1997) and even inhibition (Brosnan et al. 2002). Similarly, the Stroop test is used to measure a large variety of cognitive domains such as the inhibition (Miyake et al. 2000), switching (Zalonis et al. 2009), working memory (Kane and Engle 2003), selective attention (Melcher and Gruber 2006), impulse control (Peterson et al. 1999), and concentration (Van Diest et al. 2000). The impurity of executive tests is a problem for clinical diagnosis such that a clear executive profile specific to healthy aging, AD, and PD cannot be proposed. Taking into account all of these limits, there is an urgent need to elaborate new executive tests that should specify the executive component tapped by each.

In the context of early prediction of AD and PD, growing body of evidence suggests that both inhibition (as assessed by the Stroop test) and switching (as assessed by switching paradigms: TMT test or Verbal fluency) are deteriorated at all stages of both diseases (Belghali et al. 2017a, 2017b). The question arises as to whether we can detect early executive dysfunction. Some authors already addressed this issue and recommended the use of the Stroop Switching Test, notably because it increases the sensitivity of the Stroop test in predicting executive dysfunction (Delis et al. 2001; Fine et al. 2008; Hutchison et al. 2010). Despite the relevance of these findings, some limitations prevent a complete understanding of SWT's benefit. For studies by Delis et al. (2001) and Fine et al. (2008), only the overall time to complete the entire block of trials was assessed; however, without taking into consideration the total number of errors and trial-specific switching effects. Hutchison et al. (2010) worked on these dependent variables but without taking into consideration the general processing speed effect in data analysis. Adjustment of such covariate is crucial to understand different factors contributing to task performance. Another limit that should be mentioned in the study by Hutchison et al. (2010) is that the authors used neutral words instead of congruent stimuli and a cue indicating how to perform each trial. From our view, this methodological choice prevents researchers from examining the updating component and the conflict monitoring, which are

systematically involved when combining switching and inhibition. The concept of the conflict monitoring will be detailed in the experimental part of the first study.

2 Interaction between executive functions and gait control: Dual-task walking paradigm in healthy aging, Alzheimer's and Parkinson's diseases

In addition to neuropsychological assessment, it is widely admitted that gait analysis under dual-task condition provide a reliable brain screening. The next section describes in details this relationship. Before, both the concept and measurement of gait control will be reviewed.

2.1 Gait control

2.1.1 Definition

Walking is one of the necessities of life. According to Perry, (1992), it can be defined as " *a repetitious sequence of limb motions that move the body forward while simultaneously maintaining stance stability* ", (Perry 1992, p 3, Kong and Tomizuka 2008). Biomechanically, the term "gait" is used to describe the way of walking and consists of a consecutive gait cycle. The latter refers to the successive contact of the same limb during forwarding progression.

Gait cycle has two phases: a stance phase and a swing phase. Stance phase corresponds to the entire period during which the foot is on the ground. It represents 60% of gait cycle while swing phase represents the others 40%. During stance phase, there is an initial phase of double support (15%), following by a single support phase (30%) and ends with a double support phase (15%), again (Viel, 2000). The swing phase applies to the time the foot is in the air for limb advancement. It can be split into the initial swing (60-73%), mid-swing (73-87%), and terminal swing (87-100%). The gait cycle is illustrated in **Figure 5**.

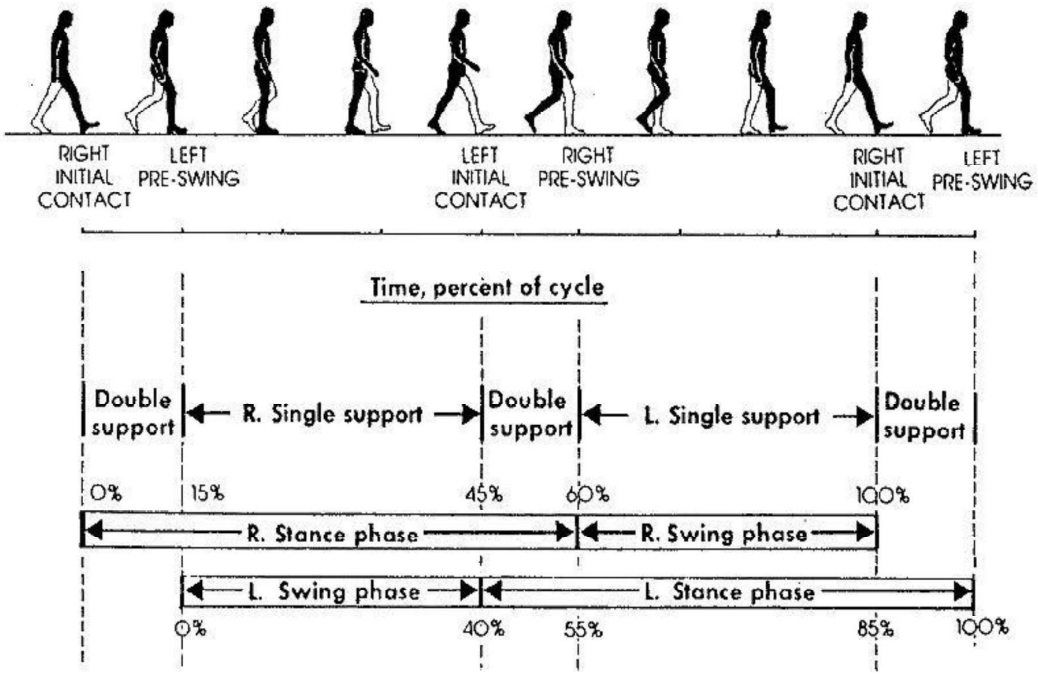

Figure 5. Illustration of one stride in the gait cycle. Adapted from Viel, (2000)

2.1.2 Quantitative assessment

2.1.2.1 Spatiotemporal gait parameters

Some temporal and spatial parameters of the gait cycle can be objectively measured to evaluate gait (**Table 1**).

Table 1. Spatiotemporal gait parameters

	Parameters	**Descriptions**
SPATIAL	Stride length	*"Distance covered from one heel strike to the next heel strike of the same foot"*
	Step length	*"Distance from one heel strike to the heel strike of the contralateral foot"*
	Step width	*"Distance between the outer most borders of two consecutive footprints"*
	Cadence	*"The number of steps taken in a given time, there are two steps in a single gait cycle"*
TEMPORAL	Stride time	*"Time from initial contact of one foot to initial contact of the same foot"*
	Step time	*"Time from initial contact of one foot to initial contact of the contralateral foot"*
	Stance time	*"Time initiated by heel strike and ends with toe off of the same foot"*
	Swing time	*"Time initiated with toe off and ends with heel strike of the same foot"*
	Double-support time	*"Period of time when both feet are in contact with the ground"*

2.1.2.2 Gait variability

Like most physiologic signals, "*gait parameters reveal complex fluctuations between and within strides even under constant environmental conditions"* (Hausdorff 2005). In the past, fluctuations in gait measures were considered as an experimental artifact that should be ignored and filtered out of any analysis to reveal average behavior (Newell and Corcos, 1993; Hausdorff 2007). However, recent literature from various disciplines and medical fields has shown that apparently "noisy" phenomena are the result of nonlinear interactions and have deterministic origins. As such, the noisy component may provide important information (i.e., rhythmicity, irregularity, or complexity) about the system that produced it (Stergiou and Decker 2011).

Contrary to standard measures of gait, there is to date no gold standard quantifying gait variability. Some authors used the standard deviation, whereas others used the coefficient of

variation of spatiotemporal gait parameters. It is maintained that the standard deviation is an "*absolute measure of variability"*, while the coefficient of variation is a measure of "*relative variability"* (Newell and Corcos, 1993; Socie and Sosnoff 2013). Methodologically, some authors stress that just the CV allows for the comparison of gait variables measured in different units (Hausdorff, 2005).

It is widely admitted that low gait variability reflects efficient gait control whereas high variability reflects abnormal regulation of gait performance (Beauchet et al. 2008; Montero-Odasso et al. 2012). In line with this view, the recent meta-analysis by Beauchet et al. (2014) has shown that a CV value lower than 3% in the parameters of stride time and stride length, is an indicator of a normative variability (Hausdorff et al. 1997; Montero-Odasso et al. 2011). However, when this threshold value is exceeded, gait control is considered as abnormal as in the case of several neurodegenerative diseases such as AD and PD.

The loss of gait control has been associated to deficits in a large variety of physiological systems, including the nervous system, muscle function, postural control, as well as cardiovascular and cognitive domains, notably EF (Hausdorff 2005; Allali et al. 2007). The loss of gait control is commonly evaluated by a dual-task walking paradigm. From a clinical point of view, this approach is very advantageous compared to others because it reveals subtle age- and disease-related abnormalities in both the gait control and cognition which are masked by internal factors such as cognitive reserve and compensation mechanisms, and thus difficult to detect using either traditional neuropsychological tests or single-task walking (Muir et al. 2012; Perrochon et al. 2013; Perrochon and Kemoun 2014; Perrochon et al. 2015).

In the following chapter, we will describe in more details the concept of dual-task walking paradigm as well as its theories and measurements.

2.2 Dual-task walking paradigm

2.2.1 Definition

Dual-task walking paradigm refers to a situation in which a secondary cognitive task (attention demanding) is performed while walking. Behavioral performance in dual tasking is measured by the dual-task cost that measures performance difference between dual-task (DT) and single-task (ST) conditions, in each task (Woollacott and Shumway-Cook 2002; McIsaac et al. 2015). The percentage of dual-task cost (DTC) is determined according to the following formula proposed by Kelly et al. (2010):

$$\mathbf{DTC}\ (\%) = \frac{\mathbf{DT} - \mathbf{ST}}{\mathbf{ST}} \times \mathbf{100}$$

A high dual-task cost value indicates decreased performance under dual-task conditions compared to the single-task condition, through attentional resource competition (Li and Lindenberger 2002; Beauchet et al. 2009; Schaefer 2014). Inversely, low dual-task cost often indicates that the process of both tasks is proceeding with little cognitive control (Newell and Corcos 1993; Hausdorff 2005; Decker et al. 2016).

2.2.2 Theories of dual-task cost

Decreased performance under dual tasking has been explained by three general theories, which are, the serial bottleneck theory, the capacity sharing theory, and the prioritization task theory. The serial bottleneck theory proposes that if two tasks are processed by the same neural processor or networks, dual-task interference arises. Thus, only one information can be proceeding at one time (Pashler 1984, 1994a, 1994b). In contrast to this view, the capacity sharing theory argues that multiple tasks can be processed in parallel, but attentional resources are limited in capacity (Tombu and Jolicoeur 2003). Thus, the simultaneous performance of two tasks will cause deterioration of at least one of them (Tombu and Jolicoeur, 2003, 2005). This suggests that when there is competition for attentional resources, the person must prioritize a specific task (the theory of task prioritization; Tombu and Jolicoeur, 2003; Yogev-Seligmann et al. 2012). Consequently, this decision-making process, which depends on several factors (such as postural reserve, hazard estimation, self-perception of the postural reserve, executive function, levels of anxiety and depression, and expertise), influences the magnitude and direction of dual-task interference in each task (Plummer and Eskes 2015).

2.2.3 Dual-task related gait changes as early predictor of Alzheimer's and Parkinson's diseases

Dual-task walking paradigm is widely used to show the strong interaction between gait and cognition, mainly, the involvement of EF (Camicioli et al. 1997; Sheridan et al. 2003; Allali et al. 2007). Such interaction (i.e., interference or cost) can be seen when the overall efficiency of EF is either reduced (i.e., healthy older adults) or abnormally damaged (older adults at risk to develop or already developed a neurodegenerative disease, as in AD or PD). According to Beauchet et al. (2014), the fact that changes in EF can be measured through dual-task assessment has opened up a new line of research devoted to identify a "gait phenotype" of abnormal cognitive decline due to underlying AD or PD. Beyond this interest, other studies suggest that dual-task is a mean to exhaust compensation strategies aimed at preserving the motor function when the basal ganglia system is altered, as in PD (Lerche et al. 2014; Chen et al. 2014). From this perspective, it is understandable that dual-task walking may be a good tool to reveal deficits unseen during single-task walking, and therefore be an especially sensitive predictor of AD and PD. Despite this interest, the use of dual-task paradigm in clinical practice requires further clarifications on some methodological aspects. First, the type of cognitive task to be used as a concurrent secondary task has to be selected among the plurality of tasks proposed in the literature. Second, the key aspects of gait control that represent sensitive and specific "gait signatures" for prodromal AD or PD need to be determined. Third, inter-individual differences in factors known to play a strong role in shaping expression and timing of onset of disease should be taken into account when analyzing dual-task performance.

A proposal for solutions constitutes one of the major aims of this thesis. Our innovative ideas in this area of research have lead to two publications in which we: (i) reported results supporting the view suggesting that changes in gait control may constitute early, non-invasive, and sensitive prodromal markers of underlying neurodegeneration in PD and AD, (ii) identified patterns of dual-task-related gait changes that are specific to AD and PD, (iii) reviewed pros and cons of existing dual-task studies (Belghali et al. 2017b), and (iv) proposed two dual-task models that could help specifically detect these two diseases (Belghali et al. 2017a).

Below the two articles

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REVIEW ARTICLE

Loss of gait control assessed by cognitive-motor dual-tasks: pros and cons in detecting people at risk of developing Alzheimer's and Parkinson's diseases

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Abstract Alzheimer's and Parkinson's diseases are age-related progressive neurodegenerative diseases of increasing prevalence worldwide. In the absence of curative therapy, current research is interested in prevention, by identifying subtle signs of early-stage neurodegeneration. Today, the field of behavioral neuroscience has emerged as one of the most promising areas of research on this topic. Recently, it has been shown that the exacerbation of gait disorders under dual-task conditions (i.e., simultaneous performance of cognitive and motor tasks) could be a characteristic feature of Alzheimer's and Parkinson's diseases. The cognitive-motor dual-task paradigm during walking allows to assess whether (i) executive attention is abnormally impaired in prodromal Alzheimer's disease or (ii) compensation strategies are used in order to preserve gait function when the basal ganglia system is altered in prodromal Parkinson's disease. This review aims at (i) identifying patterns of dual-task-related gait changes that are specific to Alzheimer's and Parkinson's diseases, respectively, (ii) demonstrating that these changes could potentially be used as prediagnostic markers for disease onset, (iii) reviewing pros and cons of existing dual-task studies, and (iv) proposing future direc- tions for clinical research.

Keywords Dual-task · Gait control · Attention · Executive function · Alzheimer's disease · Parkinson's disease · Prediagnostic phase · Prodromal phase · Clinical phase

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are a major public health concern as the world's population ages. Unfortunately, AD and PD are up-to-date diagnosed in the advanced stage. In the absence of curative therapy, current research is interested in prevention by identifying subtle signs of early-stage neurodegeneration. Crucially, early diagnosis would provide a critical opportunity for disease-modulating interventions targeting modifiable risk factors for AD or PD (Barnes and Yaffe 2011), or even neuroprotective therapies, which both would help delay, slow, or even prevent disease progression (i.e., more cases would remain in the mild stage rather than degrade to moderate or severe stages; Petersen 2009).

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These risk factors are modifiable by making lifestyle changes (e.g., greater participation in physically and intellectually stimulating activities, social engagement, balanced diet with a high proportion of unsaturated fatty acids) and treating long-term health conditions (e.g., excessively high or low blood pressure, insufficient and/or fragmented sleep, diabetes, and midlife obesity).

From these clinical perspectives, increasing evidence supports the idea that the neuropathological process underlying AD and PD begin long before the onset of clinical symptoms as currently defined. This prodromal phase has opened new lines of research to identify the earliest markers that confirm the beginning of the disease. Behavioral neuroscience has emerged as one of the most promising areas of research on this topic. Recently, it has been shown that gait control is already affected in the prodromal phases of AD and PD (Postuma et al. 2012; Montero-Odasso et al. 2014), and thus may have the potential to serve as a new prodromal marker of these diseases. Prodromal markers represent Bsignatures^ of an ongoing pathological process before the presence of typical symptoms allowing the clinical diagnosis (Heinzel et al. 2016). The loss of gait control is commonly evaluated by dual-task walking paradigms, during which the subject performs a cognitive (attention-demanding) task while walking, to assess any modifications compared to the reference (i.e., single-task condition), in either the cognitive or the walking subtasks (Bdual-task cost^; Woollacott and Shumway-Cook 2002; McIsaac et al. 2015). At the onset of mild cognitive impairment (MCI, which may in some cases represent the prodromal phase of AD), this method has been widely used to assess whether or not executive attention functions (i.e., refers to higher cognitive processes used to allocate attention among different tasks performed simultaneously) are abnormally impaired. Such cognitive dysfunctions (i.e., predominantly inhibitory control) are considered today as a predictor of AD (Balota et al. 2010; Harrington et al. 2013; Seo et al. 2016). In the prodromal phase of PD, the dual-task paradigm is used to exhaust compensation strategies aimed at preserving the motor function when the basal ganglia system is altered (Chen et al. 2013; Lerche et al. 2014). Collectively, previous evidence that dual-task conditions significantly affect patients in the prodromal phases of AD and PD with respect to healthy controls might offer a rationale for the use of this paradigm as a screening tool for the risk of developing AD and PD. This background leads to the heart of this review. Thus, our purposes were fourfold (i) to identify patterns of dual-task-related gait changes that are specific to AD and PD, respectively, (ii) to demonstrate that these changes could potentially be used as prodromal markers for clinical disease onset, (iii) to review pros and cons of existing dual-task studies, and (iv) to propose future directions for clinical research.

Changes in gait control under single-task condition in Alzheimer's disease

Clinical phase of Alzheimer's disease

AD, the primary cause of irreversible dementia among elderly people, is a progressive neurodegenerative disease characterized by the presence of amyloid beta plaques and neurofibrillary tangles (Ballard et al. 2011; Ittner and Götz 2011) together with synaptic reduction, neuronal death, and atrophy (Braak and Braak 1991; Terry et al. 1991). In addition to these classical neuropathological markers, some studies have shown a disease burden in the motor cortex equivalent to the entorhinal cortex, hippocampus, and the association areas of the frontal and parietal lobes (Suvà et al. 1999). Behaviorally, patients with early AD have mainly severe episodic and working memories impairments, deficits in language, and semantic knowledge. Also, they fail tasks requiring relatively complex brain communication, such as under dual-task conditions; these tasks depending substantially on executive attention control (Nordahl et al. 2006; Mayda et al. 2011). Interestingly, cognitive impairment in AD, specifically executive attention control deficits, and the hyperexcitability of the motor cortex affect gait (van Iersel et al. 2004; Sheridan and Hausdorff 2007; Beauchet et al. 2008; Coelho et al. 2012). Overall, AD patients present a lower gait speed (Verghese et al. 2007; Rucco et al. 2017), shorter stride length (Coelho et al. 2012; Rucco et al. 2017) and cadence (Sheridan and Hausdorff 2007), and greater stride time variability (Beauchet et al. 2008, 2014). Stride length variability has rarely been studied but appear to be increased compared to healthy older adults (van Iersel et al. 2004; Coelho et al. 2012). According to Beauchet et al. (2008), stride time variability is a fine marker of gait control, thus, highlighting that gait in AD should not be considered as a simple automatic motor behavior, but one requiring Bhigh-level cognitive

functions,^ particularly executive attention control (Allali et al. 2007).

Prodromal phase of Alzheimer's disease

Converging evidence suggests that executive attention control, predominantly inhibitory control, changes before episodic memory impairment, which is the clinical hallmark of early AD (Harrington et al. 2013). Importantly, such changes could predict AD (Balota et al. 2010). Neuropathological findings suggest that extracellular amyloid could appear first in the basal isocortex including the entorhinal cortex and only later in the hippocampus (Harrington et al. 2013). As mentioned earlier, deficits in executive attention control may be responsible for gait disorders. Interestingly, this association also exists in the prodromal phase of AD and may predict older adults at risk of developing dementia. In fact, longitudinal studies that examined baseline gait disorders and the risk of dementia have shown that gait slowing appears 12 years before the onset of MCI and precedes a decline in cognitive function (Buracchio et al. 2010; Mielke et al. 2013). The Oregon Brain Aging study supports this view and found that a longer time to complete a 30-ft (15-m) walk at baseline was an independent predictor of cognitive impairment over a 6-year period of follow-up (Marquis et al. 2002). In addition to these findings, the 5-year longitudinal study conducted by Verghese et al. (2007) showed that changes in both rhythm (i.e., cadence, swing time, stance time, and double support time) and variability (i.e., stride length variability and swing time variability) domains of gait predicted decline in both executive attention control and episodic memory. The latter two were in turn shown to be associated with an increased risk for cognitive decline and dementia (Marquis et al. 2002; Verghese et al. 2007). Recently, during a median follow-up of 2.7 years, Taniguchi et al. (2012) found that shorter stride length was an independent predictor of cognitive decline in a general population of older adults and could be a better predictor than gait slowing.

Collectively, the abovementioned findings are consistent with the view that the loss of cognitive and motor functions observed in the prodromal phase of AD may share common underlying neuropathological mechanisms, namely, an executive attention control deficit. According to Buchman and Bennett (2011), the fact that several non-cognitive symptoms, such as gait disorders, predict the subsequent development of AD, suggests that non-cognitive behaviors may serve as phenotypic markers of prodromal AD. Likewise, Beauchet et al. (2014) suggested that there might be a motor phenotype of cognitive performance decline, which could be used to improve the prediction of dementia, particularly in AD. Currently, such a view is mainly explored using dual-task-walking paradigms. This approach is very advantageous compared to others, because it reveals subtle age- and disease-related abnormalities in gait control, which are masked by internal factors such as compensation mechanisms underlying cognitive reserve, and thus difficult to detect using either conventional neuropsychological tests or single-task walking assessment (Muir et al. 2012; Perrochon and Kemoun 2014; Perrochon et al. 2013, 2015).

Changes in gait control under single-task condition in Parkinson's disease

Clinical phase of Parkinson's disease

PD is a chronic neurodegenerative disease caused by progressive and profound loss of nigrostriatal dopaminergic neurons projecting to the striatum and the presence of Lewy bodies in the central, peripheral, and autonomic nervous systems (Jellinger 2012). Clinically, PD is characterized by the emergence of at least two cardinal motor features, including bradykinesia (i.e., slowness of movement) and either rigidity, tremor, gait disorders, or postural instability (Tolosa et al. 2006; Massano and Bhatia 2012). Overall, gait disorders appear in early in PD. They are characterized by (i) decreases in gait speed, stride length, and arm swing amplitude (Lewek et al. 2010; Volpe et al. 2017) and (ii) increases in cadence, double support time, arm swing amplitude, swing time asymmetry (Yogev et al. 2007), and variability in stride time and swing time (Baltadjieva et al. 2006; Mirek et al. 2007; Svehlík et al. 2009; Lewek et al. 2010; Volpe et al. 2017). From a behavioral point of view, the gait showing results from the inability of PD patients to generate sufficient stride length and arm swing amplitude (i.e., gait hypokinesia) even though cadence control remains intact (Morris et al. 1994; Hausdorff 2009), whereas the increased variability in temporal parameters from an alteration of the internal cueing mechanism needed to walk in a rhythmic fashion (Sheridan and Flowers 1990; Morris et al. 1994; Ebersbach et al. 1999; Schaafsma

et al. 2003). From a neuropathological point of view, the causes of these gait disorders may result from (i) dopaminergic striatal deficit (Wu et al. 2015), (ii) excessive inhibition of the mesopontine locomotion center by the basal ganglia (Sterling et al. 2015), and (iii) cortical cholinergic denervation (Bohnen et al. 2013; Müller et al. 2015).

Prodromal phase of Parkinson's disease

Positron emission tomography data revealed that clinical symptoms of Parkinsonism could develop after 70–80% of striatal dopamine is depleted, corresponding to 30–50% cell death of dopaminergic neurons (Fearnley and Lees 1991; Stoessl 2007; Postuma et al. 2012). The duration of this phase prior to diagnosis of PD is still in debate (Gaenslen et al. 2011) and has been estimated to last many years, with an average of 5 years (Morrish et al. 1998; Postuma et al. 2012), or even decades (Marek and Jennings 2009). To date, several motor and non-motor symptoms characterize this prodromal phase. While prodromal non-motor symptoms (e.g., mood disorders and olfaction) are largely explored, motor symptoms, on the other hand, remain poorly studied. However, because PD is currently diagnosed by its motor features, it is reasonable to speculate that subtle changes in the motor function will be present before the appearance of the cardinal motor signs required for diagnosis (Mirelman et al. 2016). In line with this view, Postuma et al. (2012) suggested that the stage when idiopathic rapid eye movement (REM) sleep behavior disorder (i.e., characterized by vivid, often-fearful dreams, and loss of normal muscle atonia during rapid eye movement sleep) (Olson et al. 2000) is diagnosed may provide a window to better understand prodromal motor symptoms. Accordingly, motor skills of 78 patients with idiopathic REM sleep behavior disorder, as assessed by the Unified Parkinson Disease Rating Scale, the Purdue Pegboard Test, the Alternate Tap Test, and the Timed Up and Go Test, became abnormal ~4.5 years before the diagnosis of PD (Postuma et al. 2012). Specifically, voice and face akinesia seem to be the first signs to appear (estimated prodromal interval: 9.8 years), followed by rigidity (4.4 years), gait abnormalities (4.4 years), and limb bradykinesia (4.2 years). As regards gait changes, these findings suggest that patients with early PD should present subtle gait disorders (Panyakaew and Bhidayasiri 2013; Mirelman et al. 2016). Yet, they are not detectable under undisturbed walking conditions (i.e., self-selected comfortable speed under single-task condition) in the prodromal phase. This is perhaps due to satisfactory motor system mechanisms compensating the slowly progressive nigrostriatal dopamine depletion within and outside the basal ganglia (Buhmann et al. 2005; Maetzler and Hausdorff 2012; Bezard and Fernagut 2014). Unfortunately, the exact compensatory mechanisms underlying gait disorders in the prodromal phase of PD remain unclear. Previous studies examining manual motor performance proposed the following mechanisms: (i) an increased activity in lateral premotor and parietal areas as well as in the anterior cingulate cortex to counterbalance defective striatofrontal motor circuits (Samuel et al. 1997; Sabatini et al. 2000; Buhmann et al. 2005), (ii) an increase in corticostriatal excitatory input to the basal ganglia (Wu et al. 2015), and (iii) the use of extrastriatal areas, such as executive attention control and more B‘voluntary^ brain activity efforts to execute movements usually performed automatically in healthy people (Wu et al. 2015).

Although the above studies did not examine gait, the findings are consistent with the possibility of changes in the neural networks underlying control of gross motor skills such as gait, and perhaps also in the recruitment of compensatory processes (or cognitive strategy use), which might themselves depend on the individual's cognitive reserve (Stern 2009). The challenge remains about how to capture these gait disorders despite compensatory capabilities? An intriguing possibility, which has recently been envisioned by very few studies (Lerche et al. 2014; Mirelman et al. 2011, 2016), is that dual-task walking may serve as a new, sensitive prodromal marker of PD.

Changes in gait control under dual-task condition in Alzheimer's disease

Clinical phase of Alzheimer's disease

In the clinical phase of AD, all studies showed that dual-task-related gait changes are larger in AD patients than in healthy controls. Such disorders include decreases in gait speed (Camicioli et al. 1997; Sheridan et al. 2003; Cocchini et al. 2004; Pettersson et al. 2007; Maquet et al. 2010; Coelho et al. 2012; Muir et al. 2012; Rucco et al. 2017), cadence (Coelho et al. 2012; Rucco et al. 2017), stride length, and increases in stride

width (Rucco et al. 2017), double support time (Muir et al. 2012; Rucco et al. 2017), swing time, stance time (Rucco et al. 2017), stride time (Muir et al. 2012), stride length asymmetry (Maquet et al. 2010), stride length variability (Rucco et al. 2017), stride time variability (Sheridan et al. 2003; Muir et al. 2012), stance time variability, swing time variability, and stride width variability (Rucco et al. 2017). In most studies, the authors analyzed dual-task-related changes in gait but not in cognitive performance. The few studies that also did the latter showed a decline in the two domains (Cocchini et al. 2004; Coelho et al. 2012; Ijmker and Lamoth 2012). From a neuropathological point of view, dual-task-related gait changes in AD could reflect metabolic changes in cells of the associative cortices and hippocampal complex (Rolls and Grabenhorst 2008). The study of Marshall et al. (2007) suggests that the reduction in glucose consumption and perfusion in the cingulate gyrus and orbitofrontal cortex may also explain the difficulty of patients with AD to perform dual-task walking.

Prodromal phase of Alzheimer's disease

In the prodromal phase of AD, dual-task-related gait changes are larger in MCI patients than in healthy controls, and greater dual-task complexity further worsens gait performance. The gait disorders reported in MCI patients include (i) decreases in gait speed (Pettersson et al. 2007; Maquet et al. 2010; Montero-Odasso et al. 2009a; Montero-Odasso et al. 2012; Muir et al. 2012; Doi et al. 2014; Tseng et al. 2014; Tarnanas et al. 2015) and stride length (Montero-Odasso et al. 2009b; Maquet et al. 2010) and (ii) increases in stride time (Muir et al. 2012), swing time (Boripuntakul et al. 2014), stride length variability (Boripuntakul et al. 2014), double support time variability (Montero-Odasso et al. 2009b), and stride time variability (Camicioli et al. 2006; Allali et al. 2007; Montero-Odasso et al. 2009b; Muir et al. 2012; Ijmker and Lamoth 2012; Montero-Odasso et al. 2014). From a neuropathological point of view, dual-task-related gait changes were interpreted as resulting from impairments in working memory and executive attention control (Maquet et al. 2010), both altering the ability of patients to execute more than one task at a time. Another interpretation proposed by Montero-Odasso et al. (2009a) is the limitation of attentional resources (the Bcentral capacity-sharing model of dual-task performance^; Tombu and Jolicoeur 2003), which could account for dual-task interference in gait among people with MCI. Hence, it is likely that both explanations of dual-task interference during gait are relevant.

In contradiction with the above results, two studies (Pettersson et al. 2005; Nascimbeni et al. 2015) have reported no dual-task walking effect. This counterintuitive finding is likely due to either the gait assessment method (i.e., use of clinical performance-based measures, such as Timed Up and Go Test, Tinetti Gait Test, instead of instrumental gait analysis), the choice of the secondary cognitive task (i.e., type and complexity), the selection criteria for the control group (e.g., in Pettersson et al. 2005: people complaining of subjective cognitive impairment), the large heterogeneity of the MCI group, and/or the low sample size. Furthermore, it is reasonable to assume that part of these MCI patients will not evolve to dementia, but rather remain cognitively stable or even revert to normal during follow-up. It is hypothesized that dual-task walking could have the potential to improve the power of discrimination between MCI converters and non-converters. In a longitudinal study, comparing MCI patients who developed AD to those who remained stable, Gillain et al. (2016) provided first evidence supporting this view. Specifically, the authors showed that MCI converters deteriorated their gait speed and gait variability under dual-task conditions more than non-converters. Other longitudinal studies recruiting both healthy older adults and MCI patients are needed to confirm these findings. Besides, such studies are important to determine the threshold of change under dual-task walking that would differentiate healthy compensation mechanisms from pathological ones.

Table 1 summarizes the findings of dual-task-related gait changes in AD and MCI patients.

Changes in gait control under dual-task condition in Parkinson's disease

Clinical phase of Parkinson's disease

In the clinical phase of PD, dual-task-related gait changes are larger in PD patients than in healthy controls. Such disorders include (i) decreases in gait speed (Fuller et al. 2013; Wild et al. 2013; Stegemöller et al. 2014; Strouwen et al. 2016), stride length (O'Shea et al. 2002; Rochester et al. 2004; Plotnik et al. 2011; Tseng et al.

Table 1 Summary of dual-task testing protocols in the prodromal and clinical phases of Alzheimer's disease

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parameters	Dual-task cost analysis	Dual-task findings
Camicioli et al. 1997	EAD (n = 15) HOA (n = 43)	Verbal fluency task	Walking 30 ft at usual pace	Not indicated	Not measured	Time to walk 30 ft Cadence	Repeated measures ANOVA	↓ time to walk 30 ft in EAD compared to HOA
Sheridan et al. 2003	EAD (n = 28)	Forward digit span task	Walking 50 ft at usual pace	Foot switches placed inside the shoe (i.e., at the ankle)	Not measured	Gait speed, Stride time variability	Wilcoxon signed-rank test	↑ stride time variability, ↓ gait speed
Cocchini et al. 2004	EAD (n = 15) HOA (n = 15)	Verbal fluency task Digit span task	Walking 11 m at usual pace	Not indicated	Number of words verbally enumerated Percentage of digits correctly recalled	The distance covered by each participant in 30 s	Not indicated	- When task difficulty was not titrated, EAD walked a shorter distance than HOA - When task difficulty was titrated, group difference disappeared - Decreased cognitive performance in EAD compared to HOA
Pettersson et al. 2005	NCI (n = 33) MCI (n = 59) EAD (n = 22) HOA (n = 26)	Verbal fluency task	Walking 10 m at usual pace	Not indicated	Not measured	Time to walk 10 m	Two-way factorial ANCOVA	↓ time to walk 10 m in EAD compared to HOA
Camicioli et al. 2006	EAD (n = 42)	Forward digit span task	Walking 15 m at usual and fast paces	GAITRite® system	Not measured	Gait speed Cadence Stride time Stride length Swing time Double support time	Repeated measures ANOVA	↑ stride time, ↑ swing time, ↑ swing time variability, ↓ cadence
Pettersson et al. 2007	AD (n = 6) MCI (n = 6) HOA (n = 25)	Verbal fluency task	Walking 10 m at usual pace	Stopwatch	Not measured	Gait speed	Difference in mean between single- and dual-task walking	↓ gait speed in EAD compared to MCI and HOA
Allali et al. 2007	AD, VaD, mixed AD/VaD	Forward and backward counting	Walking 10 m at usual pace	GAITRite® system	Number of figures	Stride time Stride time variability	Dual-task cost[a] for each parameter	↑ stride time variability

Table 1 (continued)

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parameters	Dual-task cost analysis	Dual-task findings
	(*n* = 16)				verbally enumerated			- No difference in cognitive performance
Montero-Odasso et al. 2009a	MCI (*n* = 55)	Serial substraction task Verbal fluency task	Walking 10 m at usual pace	Stopwatch	Not measured	Gait speed	Difference in time between single and dual-task walking	↓ gait speed
Montero-Odasso et al. 2009b	MCI (*n* = 11)	Serial substraction task (from 100)	Walking 6 m at usual pace	GAITRite® system	Not measured	Gait speed Stride length Stride time Double support time Gait variability for all parameters	Paired *t* test	↓ gait speed, ↑ stride time variability, ↑ stride time, ↑ double support time
Maquet et al. 2010	MCI (*n* = 14) MAD (*n* = 6) HOA (*n* = 14)	Serial substraction task	Walking 45 m at usual pace	Locometrix® Electrical photocells	Not measured	Gait speed Stride frequency Stride length Stride symmetry Number of stops	Difference in mean between single- and dual-task walking	↓ gait speed in MAD and MCI compared to HOA
Ijmker and Lamoth 2012	AD and FTD (*n* = 15) YOA (*n* = 12) HOA (*n* = 14)	Phonemic fluency task (letters: BR,^ BG,^ and BP^)	Walking for 3 min at a self-selected pace up and down a 10 m long course	Ambulant accelerometer	Number of words verbally enumerated	Gait speed Stride time Stride time variability	Wilcoxon signed-rank test	↑ stride time variability and - Decreased cognitive performance in FTD and AD compared to YOA and HOA
Muir et al. 2012	AD (*n* = 23) MCI (*n* = 29) HOA (*n* = 22)	Verbal fluency task Serial substraction task (by ones and sevens)	Walking 6 m at usual pace	GAITRite® system	Not measured	Gait speed Stride time variability	Dual-task cost[b] for each parameter	↑ stride time, ↑ stride time variability, ↓ gait speed in AD and MCI compared to HOA
	MAD (*n* = 23)			Digital camera		Cadence		↓ cadence,

Table 1 (continued)

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parameters	Dual-task cost analysis	Dual-task findings
Coelho et al. 2012		Serial substraction task (from 20)	Walking 8 m at usual pace	Passive marker to the fifth right metatarsus	Number of errors	Stride length Gait speed	Repeated measures ANOVA	↓ gait speed, ↓ stride length - MAD made more errors
Montero-Odasso et al. 2012	MCI (n = 43) HOA (n = 25)	Serial substraction task (from 100) Semantic fluency task	Walking 6 m at usual pace	GAITRite® system	Not measured	Gait speed Stride time Stride time variability	Repeated measures ANOVA	↑ stride time variability, ↓ gait speed in MCI compared to HOA (all the more with increasing task complexity)
Boripuntakul et al. 2014	MCI (n = 30) HOA (n = 30)	Serial substraction task (by threes from 20 or 50)	Gait initiation (first and second stride) Walking at usual pace	GAITRite® system	Not measured	Swingtime Stride time Stride length Stride width Gait variability for all parameters	Repeated measures ANOVA	↑ swing time, ↑ stride length variability for the first and second stride gait initiation in MCI compared to HOA
Tseng et al. 2014	a-MCI (n = 16) HOA (n = 10)	Phonemic fluency task (letter BC^) 5-digit backward span task Serial substraction task (by sevens) 3-item delayed recall task	Walking 10 m at usual pace	Not indicated	1 point for each word correctly recited 1 point for each digit in the right order 1 point for each correct subtraction	Gait speed	Repeated measures ANOVA	↓ gait speed in a-MCI compared to HOA - Decreased cognitive performance in a-MCI compared to HOA
Montero-Odasso et al., 2014	a-MCI (n = 42) na-MCI (n = 22) HOA (n = 35)	- Serial substraction task (by ones from 100) - Verbal fluency task	- Walking at usual pace	- GAITRite® system	- Not measured	- Stride time variability - Gait speed	- Dual-task cost[2] for each parameter	↑ stride time variability, ↓ gait speed in a-MCI compared to HOA and na-MCI
Doi et al. 2014	a-MCI (n = 191)	Serial substraction	Walking 11 m at usual pace	Horizontal walkway	Not measured	Gait speed	Repeated measures ANOVA	↓ gait speed in both a-MCI and na-MCI compared to HOA

Table 1 (continued)

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parameters	Dual-task cost analysis	Dual-task findings
	na-MCI (n = 198) HOA (n = 35)	task (from 100)						
Nascimbeni et al. 2015	MCI (n = 13) HOA (n = 10)	Serial substraction task (by ones from 378 or 283) Verbal fluency task Short story recall task	Walking at usual pace back and forth over a distance of 12 m	Footswitches based on force sensitive resistors placed on the first and fifth metatarsal heads and the posterior part of heel Stopwatch	Number of correctly produced digits Number of correctly produced items Number of correctly recalled items	Stride time Stride time variability Double support time Gait speed	Repeated measures ANOVA	↓ gait speed, ↑ stride time, ↑ stride time variability, ↑ double support time in both groups - Performance decreased on serial substraction and improved on short story recall in both groups
Tarnanas et al. 2015	EAD (n = 86) Na-MCI (n = 65) HOA (n = 76)	Serial substraction task (by ones from 100) Verbal fluency task	Walking at usual pace over a distance of 10 m	GAITRite® system	Not measured	Gait speed Stride time variability	Difference in mean between single-and dual-task walking	↓ gait speed, ↑stride time variability in EAD and na-MCI compared to HOA
Gillain et al. 2016	MCI (n = 13)	Serial substraction task (from 50)	Walking at usual pace	Locometrix®	Not measured	Gait speed Stride time variability Stride length Cadence	Difference in mean between single-and dual-task walking	↓ gait speed, ↑ stride time variability in MCI who developed AD
Rucco et al. 2017	AD (n = 22) FTD (n = 23) HOA (n = 20)	Serial substraction task (by sevens from 100)	Walking at usual pace over a distance of 10 m	Stereo-photogram-metric system	Not measured	Gait speed Cadence Stride length Stride time Stride width Stance time Swing time Double support time	Difference in mean between single-and dual-task walking	↓ gait speed, ↓ cadence, ↑ double support time, ↑ stance time variability, ↑ swing time variability, ↑ stride length variability, ↑ stride width variability in AD and FTD compared to HOA

Table 1 (continued)

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parame	Dual-task cost analysis	Dual-task findings
						Gait variability all parameter:		

NCI subjects with no cognitive impairment, *EAD* early Alzheimer's disease, *AD* Alzheimer's disease, *MAD* mild Alzheimer's disease, *FTD* frontal temporal dementia, *MCI* mild cognitive impairment, *a-MCI* amnesic mild cognitive impairment, *na-MCI* non-amnesic mild cognitive impairment, *HOA* healthy older adults, *YOA* younger older adults, *VaD* vascular dementia, ↑ increased, ↓ decreased

[a] Gait DTC = [(dual-task gait performance − single-task gait performance)/(dual-task gait performance + single-task gait performance)/2] × 100

[b] DTC = [(single-task value − dual-task value)/single-task value] × 100

2012; Panyakaew and Bhidayasiri 2013; Kelly and Shumway-Cook 2014; Stegemöller et al. 2014), bilateral gait coordination (i.e., the generation of left-right antiphase stepping), and swing time (Plotnik et al. 2009; 2011; Tseng et al. 2012; Vervoort et al. 2016) and (ii) increases in stride time (Panyakaew and Bhidayasiri 2013; Stegemöller et al. 2014), cadence (Rochester et al. 2014), stance time (Wild et al. 2013), stride width (Stegemöller et al. 2014), stride length asymmetry (Rochester et al. 2014; Vervoort et al. 2016), swing time variability (Stegemöller et al. 2014), stride time variability, and stride length variability (Hausdorff et al. 2003; Yogev et al. 2007; Plotnik et al. 2009, 2011; Yogev-Seligmann et al. 2012; Rochester et al. 2014; Stegemöller et al. 2014). Decreases in arm swing amplitude and increases in both arm swing asymmetry and arm swing variability have also been documented (Mirelman et al. 2016). The few studies that have examined dual-task-related changes in both gait and cognitive performance showed a decline in the two domains (O'Shea et al. 2002; Yogev et al. 2005).

In contradiction with these findings, two studies (Kelly and Shumway-Cook 2014; Rochester et al. 2014) found that certain aspects of gait, namely gait speed, stride length, stride length variability, and stride time variability, were unexpectedly unaffected under dual-task conditions. This may be due to the use of an auditory Stroop task (Kelly and Shumway-Cook 2014) and an auditory Wechsler Forward Digit Span task (Rochester et al. 2014) as secondary tasks. Indeed, the auditory modality may provide beneficial cueing effects on gait rhythm through compensatory cerebellar-parieto-premotor pathways or by facilitating task prioritization and/or executive attention control (Rochester et al. 2008). Overall, PD patients were less able than healthy controls to use a Bposture first^ strategy (i.e., prioritizing walking over other concurrent tasks). In fact, some patients may give inappropriate prioritization to the concurrent attention-demanding task, thus, sacrificing attention resources needed for gait by using a Bposture second^ strategy (Bloem et al. 2006). Evidence for this strategy use was observed in several studies in which explicit instructions regarding task prioritization were not given (Yogev-Seligmann et al. 2010). Hence, one could posit that the auditory cueing provided by the cognitive task improve walking automaticity, and thus reduce the attentional demands of gait control.

From a neuropathological point of view, theoretical mechanisms that could explain dual-task-related gait changes in clinical PD are (i) a reduced movement

automaticity (i.e., the ability to perform a skilled movement without conscious or executive control or attention directed toward the movement) and the need for increased reliance on cognitive resources to control gait because of basal ganglia dysfunction (Wu et al. 2004; Poldrack et al. 2005), (ii) dopamine-mediated dysfunction of the basal ganglia (Middleton and Strick 2000), and (iii) presence of non-dopaminergic pathology, such as serotonin, norepinephrine (noradrenaline), or acetylcholine (Leverenz et al. 2009). Recently, Nieuwhof et al. (2016) suggest that altered functioning of the prefrontal cortex may also contribute to difficulties in dual-task walking. These mechanisms are not mutually exclusive but might overlap with one another.

Prodromal phase of Parkinson's disease

There exist three studies that have examined dual-task-related gait changes in the prodromal phase of PD (Lerche et al. 2014; Mirelman et al. 2011, 2016). All of them have reported dual-task interference during gait. Specifically, two cross-sectional studies conducted by Mirelman et al. (2011, 2016) have shown decreases in arm swing amplitude and axial rotation smoothens and increases in arm swing variability, arm swing asymmetry (Mirelman et al. 2016), and stride time variability (Mirelman et al. 2011) in LRRK2 G2019S mutation carriers without a clinical diagnosis of PD. The third study by Lerche et al. (2014) has demonstrated dual-task decrement in gait speed in patients with mild parkinsonian signs to the same extent as non-demented patients with PD. From a neuropathological point of view, the authors suggested that impairment of movement automaticity because of early basal ganglia dysfunction and cognitive inflexibility might explain these changes in gait under dual-task conditions.

Table 2 summarizes the findings of dual-task-related gait changes in patients with PD, mild parkinsonian signs, and LRRK2-G2019S mutation carriers without a clinical diagnosis of PD.

Summary of methodological issues of dual-task studies

Currently, a comparison between dual-task studies in the clinical and prodromal phases of both AD and PD is made difficult because of the variety of all aspects of the protocols. Cognitive tasks used include the following: auditory Stroop task; serial subtraction by ones, threes, and sevens from a given number (e.g., 100 and 283); working memory task (i.e., listening to strings of digits while walking and repeating them back and letter 2-back task); short story recall memory task; 3-item delayed recall episodic memory task; and semantic fluency (i.e., naming animals and reciting male or female names) or phonemic fluency (i.e., letters F, A, S, R, G, P, and C) tasks. Gait tasks used include walking at a comfortable, self-selected pace or at a maximum pace over varying distances (6, 8, 9, 10, 11, 15, 12, 25, and 45 m), walking backward, or walking 3 min). Instruments that have been used to assess both gait parameters (gait speed, stride time, stride length, stride height, stride width, double support time, stride frequency, symmetry, regularity, and gait variability) and cognitive performance (number of correct responses, reaction time, error rate, and accuracy) include treadmill, GAITRite®, stopwatch, Locometrix®, and motion capture system. Other sources of variability are the choice of the clinical population (MCI subtypes, different stages of AD: from moderate to severe), sample size, medication, and statistical approach (i.e., repeated ANOVA, paired Student *t* test, specific dual-task cost formulas). Tables 1 and 2 summarize the different dual-task testing protocols and findings in both the clinical and prodromal phases of AD and PD.

Discussion

To our knowledge, this is the first review that provides a comprehensive overview of dual-task-related gait changes that are specific to AD and PD (Table 3).

Dual-task-related gait changes in AD at the clinical stage The pace (i.e., gait speed, stride length, stride time variability, swing time variability, stance time variability, and double support time), rhythm (i.e., stride time, stance time, swing time, and cadence), variability (stride length variability and stride width variability), and postural control (i.e., stride width and stride length asymmetry) domains of gait showed to be consistently sensitive to dual-task interference in AD. Unfortunately, the exact neuropathological mechanisms underlying changes in each domain of gait are still unknown. Yet, based on neuropsychological studies, changes in the pace domain could be related to impairments in either executive attention control (Sheridan et al. 2003; Maquet et al.

Table 2 Summary of dual-task testing protocols in the prodromal and clinical phases of Parkinson's disease

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parameters	Dual-task cost analysis	Dual-task findings
O'Shea et al. 2002	PD ($n = 15$) HOA ($n = 15$)	Coin transference Serial substraction task (by threes from 125 or 250)	Walking 10 m at usual pace	Footswitches based on force sensitive resistors placed on the hallux and the first, second, and fourth metatarsal heads	Not measured	Gait speed Stride length Cadence Double support time	Paired *t* test	↑ double support time, ↓ stride length, ↓ gait speed, ↓ cadence in PD (with either a motor or cognitive secondary task)
Hausdorff et al. 2003	PD ($n = 10$)	Serial substraction task (by threes from 200, 193, and 186)	Walking 20 m at usual pace	Footswitches based on force sensitive resistors	Not measured	Stride time Stride time variability	Wilcoxon signed-rank test	↑ stride time variability
Yogev et al. 2005	PD ($n = 30$) HOA ($n = 28$)	Serial substraction task (by sevens from 500) Listening through ear phones to a text	Walking 20 m at usual pace	Footswitches based on force sensitive resistors	Not measured	Stride time Swing time Stride time variability	Repeated measures ANOVA	↑ stride time variability in PD compared to HOA
Plotnik et al. 2009	PD ($n = 21$) HOA ($n = 13$)	Serial substraction task (by sevens)	Walking at usual pace for 2 min	Footswitches based on force sensitive resistors	Not measured	Gait speed Stride time variability Swing time variability Stride time asymmetry Left-right stepping coordination	Repeated measures ANOVA	↓ left-right stepping coordination, ↑ swing time variability, ↑ stride time variability in PD compared to HOA
Plotnik et al. 2011	PD ($n = 30$)	Serial substraction task (by threes and sevens)	Walking 80 m at usual pace	Footswitches based on force sensitive resistors	Not measured	Gait speed Stride length Stride time variability Swing time variability Swing time asymmetry Left-right stepping	Paired *t* test	↓ left-right stepping coordination, ↓ stride length, ↓ gait speed, ↑ swing time asymmetry, ↑ swing time variability - Gait changes are more pronounced with concomitant serial subtraction task by sevens

Table 2 (continued)

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parameters	Dual-task cost analysis	Dual-task findings
						coordination		
Mirelman et al. 2011	LRRK2 ($n = 25$) HOA ($n = 27$)	Serial substraction task (by sevens)	Walking 20 m at usual and maximal pace	Accelerometer	Not measured	Gait speed Stride time Stride length Stride time variability	Paired *t* test	↑ stride time variability in LRRK2 compared to HOA at both paces
Tseng et al. 2012	PD ($n = 30$) HOA ($n = 28$)	Serial substraction task (from 100)	Walking forward and backward 6 m at usual pace	GAITRite® system	Not measured	Gait speed Stride length - Stride time Double support time Gait variability for each	Paired *t* test	↓ gait speed, ↓ swing time, ↓ stride length, in both walking directions in PD compared to HOA
Yogev-Seligmann et al. 2012	PD ($n = 18$) HOA ($n = 15$)	Verbal fluency task	Walking 30 m at usual pace	Ambulatory recorder Footswitches based on force sensitive resistors	Not measured	Stride time Swing time Stride time variability Gait speed Swing time variability	Repeated measures ANOVA	↓ gait speed, ↑ stride variability, ↑ swing time variability, in both groups
Fuller et al. 2013	PD ($n = 154$)	Phonemic fluency (letters: BF^, BA^, and BS^)	Walking 15 m at usual pace	Not indicated	Number of words verbally enumerated	Gait speed	Hierarchical regression	↓ gait speed - Decreased cognitive performance
Panyakaew and Bhidayasiri 2013	PD ($n = 21$) HOA ($n = 21$)	Serial substraction task (by threes from 200)	Walking 7.82 m at usual pace	GAITRite® system	Not measured	Gait speed Cadence Stride length Stride time Swing time Double support time Stride width Gait variability for each parameter	Paired *t* test	↑ cadence, ↑ stride width, ↓ swing time, ↑ stride time in PD compared to HOA
	PD ($n = 18$)					Stride length		↑cadence,

Table 2 (continued)

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parameters	Dual-task cost analysis	Dual-task findings
Wild et al. 2013	HOA (n = 18)	Serial substraction task (by sevens from 500) Text comprehension task Phoneme counting task	Walking 9 m at usual pace	Kinemetric with a fixed camera	Total correct serial subtractions Percent of correct responses (text comprehen-sion) Percent of total phonemes	Cadence Swing time Stance time	Gait DTC formula[a]	↓ swing time, ↓ stance time in PD compared to HOA - Decreased cognitive performance in PD in all conditions compared to HOA
Yogev-Seligmann et al. 2012	PD (n =18) YA(n =21) HOA (n = 15)	Verbal fluency task	Walking 30 m at usualpace	Ambulatory recorder Footswitches based on force sensitive resistors Accelerometer located on posterior distal part of theshin above the malleoli	Number of words verbally enumerated	Gait speed Stride time Stride time variability	Repeated measures ANOVA	↓ gait speed, ↑ stride time, ↑ stride time variability in PD compared to YA and HOA
Rochester et al. 2014	PD (n =44) HOA (n = 55)	Working memory task (participants listened to strings of digits and repeated them back)	alking for 2 min at usualpace	GAITRite® system	Error rate	Gait speed Stride length Stride time Stride width variability Stride time variability Stride width variability Stance time asymmetry	Gait DTC formula[b]	↓ gait speed, ↑ stride length, ↑ stride time, ↑ stride width Variability, ↑ stride time variability, ↑ stride width variability, ↑ stance time asymmetry in both HOA and PD
Kelly and Shumway-Cook 2014	PD (n =11) HOA (n = 12)	Auditory Stroop task	Usual-base and narrow-base walk-ing over a distance of 8.8 m	Motion capture system (Qualisys)	Response latency Response accuracy	Stride length Stride width Cadence Stride width variability Stride time variability	Repeated measures ANOVA	↓ gait speed in PD compared to HOA - Decreased cognitive performance in PD compared to HOA

Table 2 (continued)

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parameters	Dual-task cost analysis	Dual-task findings
						Center of mass		
Lerche et al. 2014	PD (n = 27) MPS (n = 73) HOA (n = 892)	Box-checking task Serial substraction task (by sevens)	Walking 20 m at usual and maximal paces	Accelerometer	Not measured	Gait speed	Gait DTC formula[c]	↓ gait speed in both conditions
Stegemöller et al. 2014	PD (n = 35)	Serial substraction task (by threes)	Walking 12 m at usual pace	Motion capture system	Not measured	Gait speed Stride time Stride length Stride width Swing time Variability for each parameter	Repeated measures ANOVA	↓ gait speed, ↑ stride length, ↑ stride time, ↑ stride width, ↑ variability for each parameter
Strouwen et al. 2016	PD (n = 121)	Serial substraction task Auditory Stroop task Mobile phone task	Walking 10 m at usual pace	GAITRite® system	Reaction time Number of errors	Gait speed	Regression models	↓ gait speed - A strong correlation between gait speed and cognitive flexibility
Vervoort et al. 2016	PD (n = 73) HOA (n = 20)	Auditory Stroop task	Walking 6 m at usual pace	Motion capture system (Vicon)	Reaction time (average and variability)	Gait speed Stride length Stride width Stride time Stance time Swing time Double support time Gait variability for each gait parameter	MANOVA	↑ stance time, ↑ stride length asymmetry, ↓ swing time in PD compared to HOA - Decreased cognitive performance in PD compared to HOA - A strong correlation between gait speed and cognitive flexibility
Mirelman et al. 2016	PD (n = 194) LRRK2 (n = 122) HOA (n = 64)	Serial substraction task (by threes)	Walking 15 m at usual pace	Lightweight body-fixed sensor Velcro straps		Arm swing amplitude Arm swing variability Arm swing asymmetry	Paired t test	↑ stride time variability, ↑ arm swing variability, ↑ arm swing asymmetry, ↓ axial rotation smoothness in LRRK2 compared to HOA

Table 2 (continued)

Studies	Populations	Cognitive tasks	Gait tasks	Instruments	Cognitive parameters	Gait parameters	Dual-task cost analysis	Dual-task findings
						Stride time variability Axial rotation smooth- ness		

HOA healthy older adults, *YA* younger adults, *PD* Parkinson's disease, *LRRK2* carriers of the LRRK2-G2019S mutation, *MPS* mild Parkinsonian signs in older adults, *IRBD* patients with REM idiopathic behavioral disorder, ↑ increased, ↓ decreased

[a] Gait DTC = [(single-task gait performance − dual-task gait performance)/single-task gait performance × 100

[b] Gait DTC = dual-task gait performance − single-task gait performance

[c] Gait DTC = (1 − dual-task speed/single-task speed) × 100

2010; Coelho et al. 2012) or global cognitive functions (Coelho et al. 2012). Based on the study of Nakamura et al. (1996), decreased regional cerebral blood flow in the frontal lobe may also contribute to changes in the pace domain (particularly, stride time variability). Other studies suggested that atrophy in the hippocampus and entorhinal cortex, which are two key regions responsible for the sequential ordering of movement (Smith and Milner 1981) may explain changes in both the variability and rhythm domains of gait under dual-task conditions (Morris et al. 2016). From a clinical point of view, dual-task paradigms have been used to distinguish fallers from non-fallers among AD patients. For example, Reelick et al. (2011) showed that only stride length variability discriminate significantly between the faller groups in the dual-task, and not the single-task, condition. Furthermore, if clinicians are seeking further information on attention and executive functions of their patients, dual-task gait paradigms might be of value to explore the attentional requirement of balance during locomotion (Amboni et al. 2013; Menant et al. 2014).

Dual-task-related gait changes in PD at the clinical stage The rhythm (i.e., cadence, stride time, and stance time), asymmetry (i.e., stride time asymmetry), postural control (i.e., stride width and stride length asymmetry), pace (i.e., gait speed, stride length, stride time variability, swing time variability, and double support time variability), and variability (i.e., stride length variability and stride width variability) domains of gait, but also arm swing parameters (i.e., arm swing amplitude, arm swing variability, and arm swing asymmetry) showed to be consistently sensitive to dual-task interference in PD. Biomechanically, gait slowing is mainly due to reduced stride length. The reason for reduced stride length has not yet been fully elucidated, although it has been suggested that gait hypokinesia could reflect a difficulty in activating the locomotor control system (i.e., inadequate contribution to cortical motor set by the basal ganglia (Hausdorff 2009). PD patients typically increased their cadence to compensate for reduced stride length (Morris et al. 1994). Concerning the other pace parameters, some studies showed that increases in stride time variability and swing time variability are likely due to the inability to generate Binternal cues^ in the supplementary motor areas, a necessary step in the creation of a normal sequenced movement (Yogev et al. 2005) According to Blin et al. (1990), deficits in muscle strength, of which the exact neuropathological

Table 3 Dual-task-related gait changes in the prodromal and clinical phases of Alzheimer's and Parkinson's diseases, including six domains of spatiotemporal gait parameters inspired from Hollman et al. 2011 and Lord et al. 2013 (pace, rhythm, phases, asymmetry, variability, and postural control), and arm swing parameters inspired from Mirelman et al. 2016 (amplitude, variability, and asymmetry)

Gait domains	Clinical phase		Prodromal phase	
	AD	PD	AD	PD
Pace	↓ gait speed ↓ stride length ↑ stride time variability ↑ swing time variability ↑ stance time variability	↓ gait speed ↓ stride length ↑ stride time variability ↑ swing time variability	↓ gait speed ↓ stride length ↑ stride time variability ↑ double support time variability	↓ gait speed ↑ stride time variability
Rhythm	↓ cadence ↑ swing time ↑ stance time ↑ stride time	↑ cadence ↓ swing time ↑ stance time ↑ stride time	↑ swing time ↑ stride time	–
Phases	↑ double support time	↑ double support time	↑ double support time	–
Asymmetry	–	↑ stride time asymmetry	–	–
Variability	↑ stride length variability ↑ stride width variability	↑ stride length variability ↑ stride width variability	↑ stride length variability	
Postural control	↑ stride width ↑ stride length asymmetry	↑ stride width ↑ stride length asymmetry	–	–
Arm swing parameters	–	↓ arm swing amplitude	–	↓ arm swing amplitude
		↑ arm swing asymmetry ↑ arm swing variability		↑ arm swing asymmetry ↑ arm swing variability

AD Alzheimer's disease, *PD* Parkinson's disease, ↑ increased, ↓ decreased

mechanisms may come from central activation impairments (Stevens-Lapsley et al. 2012), may also explain changes in the pace domain. Beyond motor explanation, Yogev et al. (2005) suggest that deficits in executive attention control may also contribute to these changes among PD patients.

Decreased arm swing amplitude of the more affected body side is frequently reported in the literature. Such parameter seems to be related to both rigidity (Kwon et al. 2014) and dopamine-mediated dysfunction of the basal ganglia (Wu et al. 2015). Also, it mechanically induces a reduction in both bilateral arm coordination and arm swing symmetry (Lewek et al. 2010; Huang et al. 2012) as well as greater arm swing variability (Mirelman et al. 2016). From a neuropathological point of view, these changes in arm swing parameters appear to be linked to the asymmetric process of nigrostriatal dopaminergic denervation (Lewek et al. 2010; Huang et al. 2012). In an effort to clarify the origin of dual-task-related gait changes in PD, Lord et al. (2010) have suggested that some gait domains are levodopa-sensitive and others are levodopa-resistant. In support of this view, Hausdorff (2009) showed that temporal gait variability is independent of dopaminergic pathways, and that both spatial gait variability and arm swing parameters are dependent of dopaminergic pathways (Lord et al. 2010). Hence, such findings suggest that the latter have potential utility to predict gait dysfunction related to PD (Lord et al. 2010). As for AD, dual-task-related gait changes in the clinical phase of PD is clinically relevant to detect patients at risk of falls. Also, some studies have shown that dual-task walking performance was associated with gait quality (Kelly et al. 2012), freezing (Spildooren et al. 2010), disease severity, and disability (Fuller et al. 2013).

Dual-task-related gait changes: comparison between AD and PD at the clinical stage Even though the neuropathological origin of dual-task-related gait changes is different between the two diseases, the corresponding gait patterns display some similarities, particularly in the pace, rhythm, postural control, and variability domains of gait. Mechanistically, similar dual-task-related gait changes between AD and PD are likely due to a limited attentional capacity (serial bottleneck theory; Pashler 1984, 1994) resulting from more brain damage that prevents patients to share their attentional resources and perform both tasks simultaneously (capacity sharing theory; Tombu and Jolicoeur 2003). In addition, dysfunction in executive attention, anxiety, and depression, which are known to have negative effects on cognition and motor performance, may also be another common factor (Hausdorff et al. 2003; Beurskens and Bock 2012). Despite this commonality, gait parameters between the two patient groups have never been directly compared. Thus, the question arises as to whether the dual-task walking paradigm is sensitive enough to characterize specific spatiotemporal gait profiles of AD and PD, respectively. Such a question has not yet been addressed in the literature. Nonetheless, our review suggests that the rhythm (i.e., cadence), pace (i.e., stride length and stride time variability), and variability (i.e., stride length variability) domains of gait as well as arm swing parameters (i.e., arm swing amplitude, arm swing asymmetry, and arm swing variability) could differentiate these two diseases. Specifically, we suggest that cadence and arm swing parameters would be more altered in PD, whereas stride length, stride time variability, and stride length variability would be more altered in AD (Table 3). Further studies comparing patients with AD, PD, and healthy controls are needed to confirm this proposal.

The second result that clearly emerges from this review is that dual-task-related gait changes could potentially be used as prodromal markers for clinical disease onset.

Added value of the dual-task paradigm in the prediction of AD and PD Both PD and AD share a long prediagnostic phase in which gait control under dual-task conditions is already altered. The dual-task walking paradigm showed benefit either (i) to explore the involvement of cortical level in gait control (Beauchet et al. 2014), thus, allowing to assess whether or not executive attention control is abnormally impaired, as in prodromal AD or (ii) to exhaust compensation strategies aimed at preserving motor function when the basal ganglia system is altered, as in prodromal PD. Taking together, it is understandable that dual-task walking may be a useful tool to reveal deficits unseen during single-task walking, and therefore be a particularly sensitive predictor of AD and PD. Given that the neuropathological profile of PD differs from AD, the question arises as to whether the dual-task walking paradigm is sensitive enough to identify disease-specific gait patterns during the prediagnostic phase. To our knowledge, this question has not been addressed in the literature. Currently, decreased gait speed is one of the most reported gait parameters in the literature for both diseases. Despite the relevance of such a finding, gait slowing could not be considered as a specific parameter for either disease, as it also occurs in healthy aging. From a neuropathological point of view, gait slowing may be primarily due to neuropathological mechanisms that are common to normal aging and neurodegenerative diseases, especially increased prion-inflammatory makers and vascular burden (Valkanova and Ebmeier 2017). In the next sections, we identified dual-task-related changes in other parameters than gait speed that could be specific to AD and PD at the prodromal stage.

Dual-task-related gait changes in AD at the prodromal stage Patients with various subtypes of MCI decrease their speed under dual-task conditions (Pettersson et al. 2007; Maquet et al. 2010; Montero-Odasso et al. 2009a, 2012; Muir et al. 2012; Doi et al. 2014; Tseng et al. 2014; Tarnanas et al. 2015). This gait slowing may result from reduced stride length and increased double support time (Bahureksa et al. 2017) and is mostly due to cerebrovascular disease (Annweiler et al. 2013). Besides, the rhythm (i.e., stride time, stance time, and cadence), pace (i.e., stride length, stride time variability, and double support time variability), and variability (i.e., stride length variability) domains of gait showed to be consistently sensitive to dual-task interference. Notably, in a recent meta-analysis including 14 studies, Bahureksa et al. (2017) found that dual-task walking highlights the sensitivity of the latter gait parameters for discriminating between MCI subtypes and healthy controls. Furthermore, it has been shown that dual-task-related gait changes could differentiate between non-amnestic and amnestic MCI (Montero-Odasso et al. 2014; Valkanova and Ebmeier 2017). Specifically, the pace domain (i.e., gait speed and stride length) was more affected in non-amnestic MCI, whereas the rhythm (i.e.,

cadence, swing time, stance time, and double support time) and variability (i.e., stride length variability and swing time variability) domains were worse in amnestic MCI (Verghese et al. 2008). Of note, Verghese et al. (2008) used another model to study the gait domains compared to the one used in our review (inspired from Hollman et al. 2011 and Lord et al. 2013).

From a neuropathological point of view, imaging studies using magnetic resonance spectroscopy in MCI patients showed that dual-task-related gait changes are associated with altered neurochemistry (i.e., lower N-acetyl aspartate/creatine) and lower volume of both the hippocampal and primary motor cortex (Annweiler et al. 2013). Specifically, stride length variability was correlated negatively with the hippocampal neurochemistry, whereas stride time variability was correlated negatively with the volume and neurochemistry of the primary motor cortex (Annweiler et al. 2013). Mechanistically, such findings suggest that dual-task-related gait changes in MCI patients likely result from impaired frontal-hippocampal circuits that are important in spatial orientation and navigation (Montero-Odasso et al. 2014). Furthermore, these results highlight the possible involvement of primary motor cortex changes in the onset of high-level gait disorders during the prodromal stage of AD (Annweiler et al. 2013). In addition to imaging data, neuropsychological studies suggest that reduced performance in episodic memory (Montero-Odasso et al. 2014), working memory, and executive attention control (Maquet et al. 2010) may alter the ability of MCI patients to execute more than one task at a time. Particularly, reduced performances in both episodic memory and executive attention control are strongly associated with stride time variability (Maquet et al. 2010; Beauchet et al. 2014; Montero-Odasso et al. 2014). Furthermore, the meta-analysis of Beauchet et al. (2014) showed that higher stride time variability was related to both MCI and dementia. Therefore, dual-task-related changes in stride time variability could be a motor signature of MCI, and thus be potentially used as a marker of cognitive decline before and during dementia, including AD (Beauchet et al. 2014). From a neuropathological point of view, such results suggest that dual-task-related gait changes in MCI do not only result from impaired frontal-hippocampal circuits but also from fronto-striatal circuits that are important in executive attention control (Montero-Odasso et al. 2014). Hence, it is likely that both explanations are relevant to explain dual-task interference in prodromal AD. Concerning the other gait domains found in the literature, the specific underlying mechanisms are unknown. Yet, other neuropsychological studies suggest that the pace domain of gait (i.e., stride length) is mainly associated with decreased performance in both visuospatial abilities and executive attention control (Maquet et al. 2010). The recent meta-analysis of Morris et al. (2016) further suggested that the variability (i.e., stride length variability) and rhythm (i.e., stride time, stance time, and cadence) domains of gait could be associated with global cognition.

Dual-task-related gait changes in PD at the prodromal stage LRRK2 G2019S mutation carriers without a clinical diagnosis of PD (i.e., likely representing a prodromal stage of PD) decrease their speed under dual-task conditions (Mirelman et al. 2011, 2016). This gait slowing results from reduced stride length, which itself is mainly due to co-contraction of proximal muscles. Besides, stride time variability and arm swing parameters (i.e., arm swing amplitude, arm swing variability, and arm swing asymmetry) are both impaired. According to Mirelman et al. (2016), the poorer performance of the mutation carriers may be consistent with initial abnormalities in the central gait network. Notably, only arm swing parameters under dual-task conditions discriminate between LRRK2 G2019S mutation carriers and healthy controls. Such findings confirm the sensitivity of dual-task walking to unmasked compensation strategies aimed at preserving the motor (gait) function when the basal ganglia system is altered. Overall, these mechanisms depend on brain regions relatively unaffected by dopamine depletion, such as the anterior striatum (Brück et al. 2006; Mounayar et al. 2007). Using fMRI in early-stage PD, Helmich et al. (2010) showed a shift in cortico-striatal connectivity from severely affected striatal regions (posterior putamen) to less affected striatal regions (anterior putamen). If these changes reflect compensation, they should also occur in the prodromal phase of PD, when a functional reorganization of cerebral circuits prevents overt clinical symptoms (Palop et al. 2006). Accordingly, asymptomatic LRRK2 G2019S mutation carriers show a reorganization of cortico-striatal circuits that mirrors findings in idiopathic PD (Helmich et al. 2015).

Future directions for clinical research

The findings of this review suggest that dual-task-related gait changes can be detected in early stages of

AD and PD and can, therefore, be a marker of these diseases. However, before its use in clinical practice, some methodological concerns need clarification. First, the majority of findings reported in this review come from transversal studies. Therefore, longitudinal studies characterizing the continuum of gait profile of AD and PD from complaints to the clinical expression of the disease are needed not only to confirm findings from transversal studies but also to identify a critical threshold for dual-task-related gait changes which would allow discriminating healthy populations from pathological ones. To our knowledge, this threshold is unknown in the literature. Methodologically, in order to propose a reliable threshold, it is imperative to take into account factors modulating the capacity to cope with a concurrent cognitive load while walking, among which, the most important are age, gender, stress, processing speed (Sleimen-Malkoun et al. 2013), and cognitive reserve (i.e., the background cognitive capacity that a subject brings to a given task; Stern 2009). Applying these methodological recommendations for the conduct of future research would likely enhance the reliability of dual-task gait assessment and its large-scale application in clinical practice.

Another matter that requires further refinement and clarification is the choice of the secondary cognitive task. Although the serial subtraction task (substracting by sevens) has been reported with the highest sensitivity to challenge dual-task walking performance (Bahureksa et al. 2017), it remains non-specific to neurodegenerative process underlying AD and PD. Furthermore, this cognitive task depends on arithmetic skills, which are very heterogeneous between individuals. In our view, a way to make better use of dual-task walking paradigms is to select a secondary cognitive task that both interferes with gait control and challenges the underlying neuropathological processes (in favor of the bottleneck model) of each disease. As such, a possible solution comes from neuropsychological findings that have recently demonstrated that patients with prodromal AD are particularly deficient in tasks requiring inhibition (i.e., Stroop task; Balota et al. 2010) and patients in prodromal PD in tasks involving cognitive flexibility (i.e., task set switching; Cools et al. 2001; Lerche et al. 2014). Importantly, these executive function components are known to interfere with gait (Maquet et al. 2010; Morris et al. 2016) and begin to decrease early in the disease course. Moreover, cognitive flexibility and inhibition depend on dopamine function in the basal ganglia (Berry et al. 2016) and entorhinal cortex (Velayudhan et al. 2013), respectively. Thus, our proposition, requiring more investigation, could open new avenues to use gait as a robust marker for prediagnostic AD and PD.

In conclusion, a growing body of evidence shows that dual-task-related gait changes may be a potential marker that could increase the likelihood of early detection of AD and PD. Longitudinal studies and new dual-task walking paradigms based on the neuropathological profile of each disease are needed to better understand the dual-task interference origins and the interaction between brain damage and gait control, notably by comparing patients from complaints to disease expression (preclinical, prodromal, and clinical) from those who will remain stable.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Improving Dual-task Walking Paradigms to Detect Prodromal Parkinson's and Alzheimer's Diseases

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Gait control is a complex movement, relying on spinal, subcortical, and cortical struc- tures. The presence of deficits in one or more of these structures will result in changes in gait automaticity and control, as is the case in several neurodegenerative diseases, such as Alzheimer'sdisease(AD)andParkinson'sdisease(PD).Byreviewingrecentfind- ings in this field of research, current studies have shown that gait performance assess- ment under dual-task conditions could contribute to predict both of these diseases. Such suggestions are relevant mainly for people at putatively high risk of developing AD (i.e., older adults with mild cognitive impairment subtypes) or PD (i.e., older adults with either Mild Parkinsonian signs or LRRK2 G2019S mutation). Despite the major impor- tance of these results, the type of cognitive task that should be used as a concurrent secondary task has to be selected among the plurality of tasks proposed in the literature. Furthermore, the key aspects of gait control that represent sensitive and specific "gait signatures" for prodromal AD or PD need to be determined. In the present perspective article, we suggest the use of a Stroop interference task requiring inhibitory attentional control and a set-shifting task requiring reactive flexibility as being particularly relevant secondary tasks for challenging gait in prodromal AD and PD, respectively. Investigating how inhibition and cognitive flexibility interfere with gait control is a promising avenue for future research aimed at enhancing early detection of AD and PD, respectively.

Keywords: gait, dual-task, attention, executive function, Alzheimer's disease, Parkinson's disease, prodromal phase

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Gait control is a complex movement involving a large class of processes, from sensory integration to movement execution and internal models of action. These processes rely on spinal, subcortical, and cortical structures (1). The presence of deficits in one or more of these structures will result in changes in gait automaticity and control, as is the case in several neurodegenerative diseases such as Alzheimer's disease (AD) (2) and Parkinson's disease (PD) (3).

To date, AD and PD are diagnosed in the advanced stage of degenerative brain processes, when clinical symptoms occur. In the absence of curative therapy, current research is focused on prevention by identifying subtle signs of early stage neurodegeneration. Crucially, early diagnosis would provide a critical opportunity for disease-modulating interventions targeting modifiable risk factors for AD or PD (4), or even neuro-protective therapies, both of which would help delay, slow, or even prevent disease progression [i.e., more cases would remain in the mild stage rather than degrading to moderate or severe stages (5)]. These risk factors are modifiable by making lifestyle changes (e.g., greater participation in physically and intellectually stimulating activities,

social engagement, balanced diet with a high proportion of unsaturated fatty acids) and/or treating long-term health condi- tions (e.g., excessively high or low blood pressure, insufficient and/or fragmented sleep, diabetes, midlife obesity).

In the light of these clinical perspectives, increasing evidence supports the idea that the neuropathological process underlying PD and AD begins long before the onset of clinical symptoms as currently defined. In PD, longitudinal studies have shown that idiopathic rapid-eye-movement sleep behavior disorder (IRBD) appears 26 years before diagnosis (6), followed by anxiety (up to 20 years), and reduced gastrointestinal motility and olfac- tion [up to 12 years (7)]. In AD, other longitudinal studies have shown that depression appears more than 10 years before the onset of AD (8), followed by memory complaints [at least 9–10 years (9)] and mild cognitive impairment (MCI) [up to 6 years (10)]. Nonetheless, these symptoms are non-specific to these diseases, i.e., the presence of any of these symptoms does not necessar- ily lead to progression to these diseases. However, longitudinal data have confirmed that people with IRBD are at higher risk of conversion to PD [81% after 26 years (6)] and persons with amne- sic MCI and multi-domain MCI are at higher risk of conversion to AD [80% after 6 years (10)]. Despite these findings, clinicians do not have available prodromal markers allowing them to iden- tify MCI and IRBD patients who will develop AD or PD. In these populations, in spite of remarkable developments in neuroimag- ing, genetics, and molecular biomarkers, there is still an urgent need for disease-specific prodromal markers [referring to "signa- tures" of an ongoing pathological process prior to the presence of typical symptoms, thus allowing clinical diagnosis (11)]. Recent research focusing on such markers has already found that gait control under dual-task conditions [i.e., referring to a situation in which a secondary cognitive task is performed concurrently with a primary task while walking (12)] could contribute to predicting AD and PD in their prodromal phases (3, 13).

To summarize, both PD and AD share a long prodromal phase in which gait control under dual-task conditions is already altered. Given that the neuropathological profile of PD differs from AD, the question arises as to whether the dual-task walking paradigm is sensitive enough to identify disease-specific gait pat- terns. To our knowledge, this question has not been addressed in the literature. In this perspective article, we first report results supporting the idea that changes in gait control may constitute early, non-invasive, and sensitive prodromal markers of underly- ing neurodegeneration in PD and AD (**Figure 1A**). Second, we propose two dual-task models that could help specifically detect these two diseases (**Figure 1B**).

DUAL TASK RELATED GAIT CHANGES IN PRODROMAL PD

Parkinson's disease is manifested by loss of dopamine-secreting neurons in the substantia nigra (14), leading to a lack of dopamine in the striatum and causing disruption of the basal ganglia circuit (15). At the behavioral level, it is widely accepted that gait deficits are among the most important motor problems associated with PD. The latter are characterized by deficits in all spatio-temporal gait parameters (16), rhythmic limb movements (17), arm swing amplitude and symmetry (18), bilateral arm coordination (19), and adjustment of postural muscle tone (20). Mechanistically, gait deficits may result from a mixture of several factors includ- ing: (i) a loss of motor automaticity mediated by impaired internal cueing mechanisms and less effective connectivity between motor areas (21), (ii) use of attentional control strategies in order to bypass impaired automatic motor processes (21), (iii) impaired motor planning mediated by decreased activity in the caudal cingulate motor area (22), (iv) axial rigidity mediated by exagger- ation of long-latency reflexes (23), (v) cognitive inflexibility medi- ated by changes in frontal-striatal circuits (24, 25), and (vi) the inability to use a "posture-first" strategy (i.e., prioritizing gait over other concurrent tasks). The presence of non-dopaminergic path- ology, such as serotonin, norepinephrine or acetylcholine, and muscle weakness may also explain gait deficits in PD (16).

In contradiction with these findings, some studies (26, 27) found that certain aspects of gait such as gait speed and step length were unexpectedly unaffected under dual-task conditions. According to the review by Bloem et al. (28), PD patients improved their gait performance by using external cues allowing the frontal cortex to compensate for the defective basal ganglia circuitry (28–30). Another possible explanation is that PD patients were able to prioritize gait to the detriment of cognitive tasks ["posture-first" strategy (28, 31)]. Recently, the study by Rochester et al. (31) sug- gests that the use of an auditory cognitive task may also improve the gait performance of PD patients. Such a modality may also provide beneficial cueing effects on gait rhythm through com- pensatory mechanisms or by facilitating task prioritization (31).

At present, the onset of PD appears after depletion of 70–80% of striatal dopamine, corresponding to 30–50% of dead cells of dopaminergic neurons (3). Clinically, gait deficits that should appear because of basal ganglia dysfunction and loss of dopamine are not detectable under undisturbed walking conditions (i.e., self- selected comfortable speed under single-task condition) in pro- dromal PD (32). This might be due to satisfactory compensatory mechanisms in the motor system which compensate for the slowly progressing nigrostriatal dopamine depletion, both within and outside the basal ganglia (33). It has been suggested that dual- task walking might be a valuable tool for unmasking the use of compensatory strategies (32, 34, 35). Currently, all studies ($n = 3$) conducted in the prodromal stage of PD support this view. The first study by Lerche et al. (35) showed that individuals with mild parkinsonian signs slowed down to the same extent as non- demented patients with PD when performing dual-task walking. The two other studies (34, 36) showed increasing in-stride time variability, arm swing asymmetry, and arm swing variability under dual-task walking conditions in LRRK2 G2019S mutation carriers without a clinical diagnosis of PD. To our knowledge, no study has been conducted in IRBD.

Given the limited number of studies focusing on gait in the prodromal phase of PD, the exact mechanisms underlying dual-task-related gait changes remain unclear. Nonetheless, it is likely that these changes reflect early impairment of motor automaticity due to an early dysfunction in basal ganglia–brain- stem pathways (34, 35) and cognitive inflexibility (35). Thus, we suggest that frontal–striatal network deficits involved in both

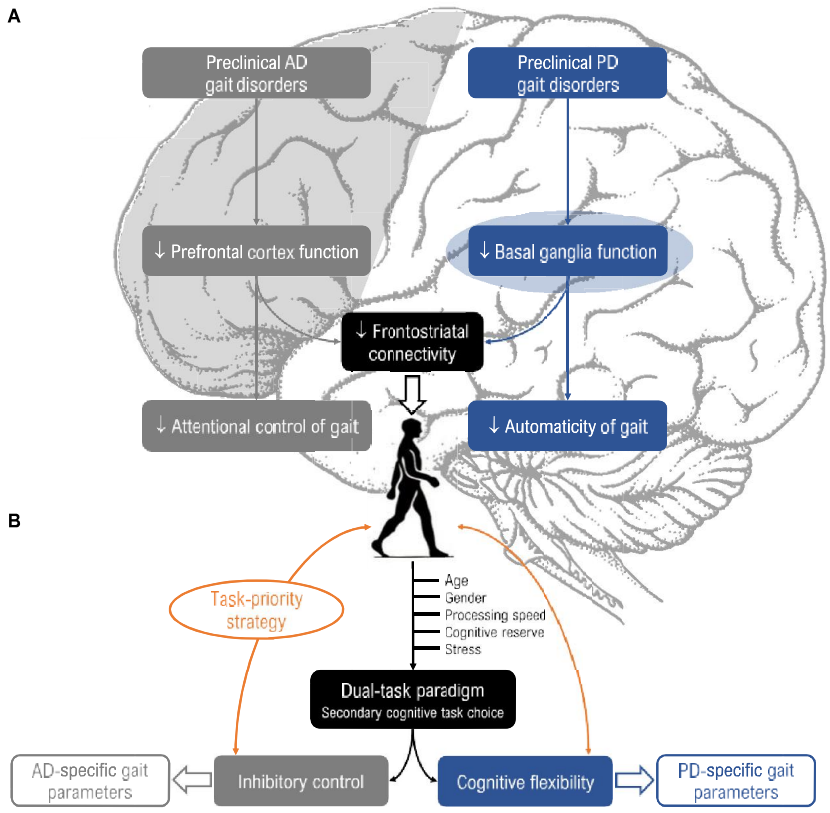

FiGUre 1 | **(A)** Relevance of dual-task paradigms in detecting gait disorders in preclinical Alzheimer's disease (AD) and Parkinson's disease (PD). Gait disorders are characteristic features of AD (gray, left side) and PD (blue, right side) and can be unmasked under dual-task conditions. These disorders could arise from different neuropathological mechanisms in the preclinical stage, as impaired prefrontal cortex function in AD and impaired basal ganglia function in PD, and alter attentional control of gait in AD (i.e., "cortical gait disorders") and automaticity of gait in PD (i.e., "cortical-subcortical gait disorders"). **(B)** Suggestions for choice of cognitive tasks and gait parameters. Dual-task gait assessment using targeted cognitive tasks (i.e., inhibitory control for AD, and cognitive flexibility for PD), taking into account task prioritization (trade-off effects) and factors known to modulate susceptibility to dual-task interference (age, gender, processing speed, stress, and cognitive reserve) would be valuable for enhancing detection of prodromal AD and PD.

cognitive flexibility and gait automaticity could be considered as possible mechanisms contributing to dual-task-related gait changes in prodromal PD. Besides, we suggest that limited attentional capacities could also prevent patients from sharing attention (i.e., central capacity sharing model) and/or correctly processing the attentional demands of each task (i.e., central bottleneck model). Indeed, the central bottleneck model postu- lates that central processing acts on only one task at a time, and therefore, constitutes a bottleneck that processes tasks serially (37, 38), whereas the central capacity sharing model claims that the central stage is a limited-capacity parallel processor that divides resources among to-be-performed tasks (39, 40).

DUAL TASK RELATED GAIT CHANGES IN PRODROMAL AD

Alzheimer's disease is characterized by the presence of both amy- loid beta plaques and neurofibrillary tangles [i.e., the two hallmark pathologies (41, 42)] in the medial temporal lobe structures (particularly the hippocampus) and neocortex, together with neuronal loss and volume reductions (43, 44). At behavioral level, AD is characterized by marked impairment in several cognitive domains including the episodic, working and semantic memories, visuo-spatial abilities, language, and executive attention control (45, 46). Interestingly, these cognitive impairments affect gait control (1, 47–50). From the literature, the picture emerges that deficits in cognition are manifested through subtle gait control deficits in pace (i.e., step velocity, step length, step time variability, swing time variability, stance time variability) and variability (i.e., step velocity variability, step length variability, step width variability) domains of gait (50). In addition, other studies suggest that the hyperexcitability of the motor cortex may also contribute to gait deficits in clinical AD.

An autopsy study on brains from non-demented and demented individuals (43) has shown that extracellular amyloid deposition usually appears before any intraneuronal neurofibril- lary changes, first in the entorhinal cortex before spreading in a

hierarchical manner into the hippocampus proper and cortex (43). A longitudinal neuropsychological study of the transition from healthy aging to AD (51) revealed that impairment in *executive attention control*, particularly *inhibition* [i.e., ability to deliber- ately inhibit dominant, automatic, or prepotent responses when required and/or requested (52)], precedes impairment in episodic memory in the course of the disease and, importantly, predicts AD. The recent neuroimaging study by Harrington et al. (53) has shown that abnormal extracellular amyloid accumulation in the basal isocortex impairs inhibition [as assessed by the Stroop task (54)] in asymptomatic individuals with abnormal beta- amyloid 42/tau ratios. It is worth mentioning that the underlying pathways of inhibition include the bilateral dorsolateral pre- frontal cortex, inferior frontal gyrus, anterior cingulate cortex, and posterior parietal cortex (55). Collectively, these findings suggest that prefrontal dysfunction is present during the early stages (preclinical) of AD (53).

At the onset of MCI (i.e., prodromal phase of AD), the neuropathological mechanisms underlying progression to AD become more complex. Nevertheless, several studies have demonstrated reduced hippocampal and entorhinal cortex volume, as well as reduced cortical thickness in the medial and lateral temporal cortex, parietal lobe, and frontal lobes in MCI patients who have converted to AD (MCI-converters), up to 2 years prior to clinical conversion, as compared to MCI patients who remained stable (MCI-stable) (56–59). At the behavioral level, longitudinal stud- ies found that MCI-converters performed worse than controls on measurements of episodic and working memory (60) and of executive attention control, particularly inhibition (61). Hence, it is likely that executive inhibitory control could also represent a hallmark of early AD.

Anatomically, the prefrontal cortex plays a major role not only in executive attention control but also in gait control through its connection with the striatum (62). Thus, one could hypo- thesize that changes in executive attention control should be reflected in gait, notably when having to devote attentional resources to a simultaneously performed secondary task. Several studies using dual-task walking paradigms support this view. Clinically, the fact that changes in executive attention control can be measured through dual-task assessment has opened up a new line of research devoted to identify a "gait phenotype" of abnormal cognitive decline due to underlying AD or other types of dementia (2). Unfortunately, to date, no studies using the dual-task walking paradigm have been conducted at the preclinical stage of AD. However, several cross-sectional studies have been performed at the prodromal stage among various MCI patient subtypes. Findings revealed that walking under dual-task conditions induced differential changes in gait velocity and variability of various spatio-temporal parameters (13, 63–67). Such changes, named "cortical gait disorders," have been interpreted to reveal impairments in both working memory and executive attention control (67). Studies using magnetic resonance spec- troscopy in MCI patients showed that dual-task-related gait changes are associated with changed neurochemistry (i.e., lower *N*-acetyl aspartate/creatine) and lower hippocampal and primary motor cortex volumes (68). Other interpretations are the central bottleneck and central capacity sharing models (37–40).

Collectively, these findings suggest that the neuropathological mechanisms underlying dual-task-related gait changes in MCI patients may result from a combination of several factors. How- ever, recent studies support the idea that impairments in both frontal–hippocampal circuits [involved in spatial orientation and navigation (64)] and prefrontal–striatal circuits [involved in executive attention control (2)] may potentially contribute to gait deficits.

Importantly, in contrast to the above findings, two studies found a pattern of dual-task interference in MCI patients that was not significantly different from healthy older adults (69, 70) since both groups became slower and more variable during dual- task walking. Although not reported by the authors, one can speculate that not all of the MCI patients would have converted to dementia. Therefore, it remains highly plausible that the use of dual-task gait assessment could allow improved discrimination between converters and non-converters. A longitudinal study has provided evidence supporting this hypothesis (71), by show- ing that MCI-converters reduced gait speed and increased gait variability under dual-task conditions more than non-converters. However, additional longitudinal studies are needed to confirm these findings.

HOW COULD DUAL-TASK GAIT ASSESSMENT BE IMPROVED TO Be USED POTENTIALLY AS A ROBUST AND CLINICALLY RELEVANT MARKER OF PRODROMAL AD OR PD?

As discussed above, dual-task-related gait decrements may provide a powerful prodromal marker of neurodegenerative diseases, such as AD and PD. However, the use of dual-task paradigm in clinical practice requires further clarifications on some methodological aspects. First, the type of cognitive task to be used as a concurrent secondary task has to be selected among the plurality of tasks proposed in the literature. Second, the key aspects of gait control that represent sensitive and specific "gait signatures" for pro- dromal AD or PD need to be determined. Third, interindividual differences in factors known to play a strong role in shaping expression and timing of onset of disease should be taken into account when analyzing dual-task performance.

Suggestions for Future research Directions

Dual-task-related gait changes may vary depending on the type of secondary cognitive task. Previous literature suggests that cognitive tasks involving internal interfering factors seem to disturb gait performance more than those involving external interfering factors (72). The modality of the secondary cogni- tive task may also influence gait performance, particularly in PD patients who are less sensitive to dual-task interference under the auditory modality. In our view, a way to make better use of dual-task walking paradigms is to select a secondary cogni- tive task that both interferes with gait control and challenges the underlying neuropathological processes (in favor of the

bottleneck model). Since specific impairments are found in inhibition for AD (51, 53) and cognitive flexibility for PD (35), we suggest the use of a visual Stroop interference task requir- ing executive inhibitory control (73) and a visual set-shifting task requiring reactive flexibility (74) as particularly relevant secondary tasks for challenging gait in prodromal AD and PD, respectively. Such tasks are known to interfere with gait control (50, 75) and importantly, begin to deteriorate years prior to the onset of the first clinical symptoms. Moreover, cognitive flexibility and inhibition depend on dopamine function in the basal ganglia (76) and entorhinal cortex (77), respectively (**Figure 1B**). In order to reduce patient stress induced by dual- task gait assessment, virtual environments using embedded secondary cognitive tasks appear to offer a good solution due to their ecological character (78).

Regarding the choice of gait parameters, lower-limb gait para- meters have been widely studied and characterized, whereas less is known about upper-limb gait parameters in both AD and PD. However, previous studies have highlighted that deficits in the latter parameters (e.g., arm swing amplitude and symmetry, bilateral arm coordination) are characteristic features of PD. Surprisingly, these upper-limb gait parameters, known to be linked to dysfunction of basal ganglia (18, 19, 79, 80), were explored in only one study in the prodromal stage of PD (36). Therefore, investigating how gait parameters related to basal ganglia dysfunction change in prodromal PD is a useful approach that should be considered in future studies.

In response to the need for theoretical development in measur- ing dual-task performance, Plummer et al. (81, 82) have proposed an elegant conceptual model for pattern classification of dual- task interference by assessing the interactions between two simul- taneously performed tasks (i.e., trade-off strategy). In addition, we would argue that it is also imperative to take into account factors modulating the capacity to cope with a concurrent cogni- tive load while walking, among which the most important are age, gender, processing speed (83), stress, and cognitive reserve [i.e., the background cognitive capacity that a subject brings to a given task (84)]. Applying these methodological recommenda- tions for the conduct of future research would likely enhance the reliability of dual-task gait assessment and its large-scale applica- tion in clinical practice.

More broadly, the only study design approach allowing iden- tification of robust, clinically relevant gait markers for preclinical AD or PD consists in longitudinal studies aimed at comparing patients from complaints to disease expression (preclinical, pro- dromal, and clinical) from those who will remain stable. To date, no such studies have been conducted on patients with cognitive complaints and/or IRBD, and only one has been carried out on MCI, although without a control group.

In conclusion, we can consider dual-task-related changes in gait control, taking into account task prioritization (trade-off effects) and factors known to modulate susceptibility to dual-task interference, as potential markers for prodromal neurodegenera- tion. Investigating how inhibition and cognitive flexibility inter- fere with gait control is a promising avenue for future research aimed at enhancing early detection of AD and PD, respectively. Longitudinal studies and standardized protocols would certainly ensure consistency and aid interpretation.

AUTHOR CONTRIBUTIONS

MB and LMD wrote the manuscript. NC and DD revised it criti- cally for important intellectual content. All authors approved its final version and contributed to the conceptual figure.

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3 Cognitive reserve

The cognitive and motor performances of two persons are rarely similar even at the young age. When we get old, this difference became more apparent, mainly because our life experiences 'build our brains differently'. Thus, the ***slope*** that everyone descends with aging is mediating by these experiences, which together form a kind of reserve

3.1. Concept of reserve

The concept of 'reserve' has been proposed in the literature to explain the mismatch between brain damages and their clinical expression (Stern 2002, 2009). Katzman et al. (1988) were among the first authors to confirm the existence of this theory by discovering that 10 elderly women in good cognitive health throughout their lives have an advanced AD in their brains at death (Katzman et al. 1988). To explain such finding, Stern, (2009) proposed two kinds of "reserve" that may contribute for preserving cognitive functions against brain damages, which are the brain reserve (passive model) and cognitive reserve (active model).

3.1.1 Brain reserve

The Brain Reserve is the passive model of the reserve. It refers mainly to the anatomical measures of the brain such as the brain size or neuronal count. Schematically, those with more brain reserve tend to have better clinical outcomes for any given level of pathology, mainly because of greater synaptic density or larger number of healthy neurons. It is widely accepted that there is a threshold of pathological resistance, at which clinical deficits will occur, and individuals with high brain reserve can tolerate more pathology to reach such threshold than those with low reserve (Satz 1993, Jones et al. 2011). For example, if two patients with the same brain damages but different levels of brain reserve, the clinical deficit will first appear in the patient with low brain reserve, and later in the patient with high reserve, (Stern, 2012, **Figure 6**).

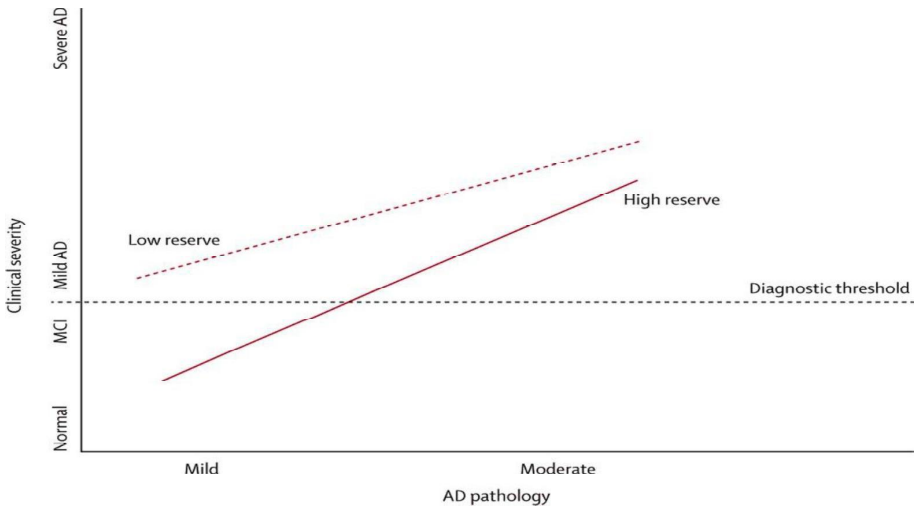


Figure 6. Schematic representations of the relationships between neuropathology burden and diagnosis of AD, according to the threshold model: Adapted from Stern, (2012)

3.1.2 Cognitive reserve

Cognitive reserve (CR) is the active model of the reserve (i.e., the model of interest of this thesis). It refers to "*how flexibly and efficiently the person makes use of available brain reserve"* (Stern, 2002). Dynamically, CR allows two mechanisms, which are: The neural reserve and neural compensation (**Figure 7**): The "neural reserve" refers to the inter-individual variability in the use of brain networks underlying the performance of any task (Stern, 2002). Two kinds of the neural reserve could make the processing of information different between individuals, which are, (i) the efficiency of brain networks and (ii) capacity of brain networks. The efficiency of brain networks suggests that the cognitive cost of people with high CR is much lower than those with low reserve. A lower cognitive cost is mainly expressed by a less activation in task-related brain networks to produce the same/or better level of performance. Conversely, the capacity of brain networks refers to the ability to activate a network to a greater degree at a high level of cognitive demand. The "**neural compensation**" refers to the process by which individuals suffering from brain connectivity disruptions, use brain structures or networks not usually used by those with an intact brain.

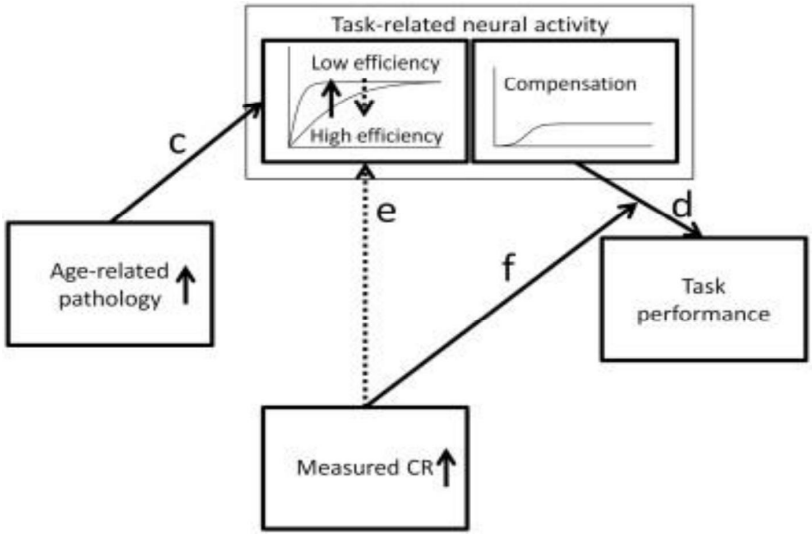


Figure 7. Mechanistic roles of cognitive reserve: Adapted from Steffener and Stern 2012)

Although treated independently, it is widely admitted that both brain reserve and CR increase reserve. Indeed, a large number of neurons and synapses coupled with cognitive

strategies and flexible neural circuits tend to moderate age-related changes in cognitive functions (Kalpouzos et al. 2008). Taking into account such a view, the question that arises is how the reserve is built.

In the next part, we will report different factors (proxies) that contribute to the construction of this theoretical concept.

3.2 How the reserve is built?

The reserve theory is thought to reflect life experiences, notably, the education attainment, leisure activities and social network, occupation, and bilingualism.

3.2.1 Educational attainment

Educational attainment is considered as the most crucial reserve's proxy, notably because it can act as a modulator between the brain pathology and dementia, such that highly educated individuals resist more against brain pathology than less educated ones. Mortimer, (1988) was one of the first authors who proposed such a view. Specifically, he suggested that education could be protective against dementia by raising the level of "intellectual reserve". Since this early work, many researchers have confirmed that low education is a risk factor for developing dementia, notably AD (Katzman et al. 1989; Zhang et al. 1990; Stern et al. 1994, 1999; Anttila et al. 2002; Mortimer et al. 2003; Karp et al. 2004). Specifically, individuals with less than 8 years of education had 2.2 times higher risk of developing dementia than those with more years of education (Stern et al. 1994; Ott et al. 1999; Letenneur et al. 2000). Similarly, the study by Roe et al. (2007) has shown that for each additional year of education, there was 13-18% less risk of developing AD and death, by at least one year. Evidence of these findings comes from the autopsy study made by (EClipSE Collaborative Members et al. 2010) that has shown that highly educated people have greater brain weight compared to the less educated ones. Notably, for each educational year, there was a 10% increase in brain weight tertile at death. It is worth mentioning that the protective effect of education against dementia remains even after adjusting for socioeconomic indicators, health problems, intelligence, and other life experience such as occupation and leisure activities (McDowell et al. 2007; Ngandu et al. 2007).

The above findings were contrary to the recent meta-analysis by Sharp and Gatz, (2012), that has shown that 58% of studies have reported a protective effect whereas 42% have not. This could be explained by the diversity of methods used in the literature to assess education.

Indeed, some authors used the number of years of formal education, including university or apprenticeship whereas other used educational level.

3.2.2 Leisure activities and social network

Leisure activities could be defined as ''*activities that individuals engage in for enjoyment or well-being that are independent of work or activities of daily living*'' (Verghese et al. 2006). Growing evidence through a wide range of epidemiological studies suggests that an active engagement in cognitive, social, and physical activities protects individuals against cognitive impairments (Wilson et al. 2002; Barnes et al. 2004; Newson and Kemps 2005; Wang et al. 2012) and dementia (Scarmeas et al. 2001, 2011; Wilson et al. 2002; Wang et al. 2006). For example, a Swedish study following 1449 persons (age 65–79 years) for 21 years has shown that practicing physical-activity for at least twice a week, notably at midlife was associated to 60 % reduced risk of developing dementia and neurodegenerative diseases (Rovio et al. 2005). The study by (Fratiglioni et al. 2000), following 1203 individuals for an average period of 3 years has shown that an extensive social network was a protective factor against dementia. The same group added that those living alone, and/ or without any close social ties increased the risk of dementia by 60%. The recent prospective study by Sundström et al. (2016) following 288 489 (age 50-74 years) for 10 years, confirmed previous findings and added that unmarried people and/ or divorced people had an increased risk of incidence of dementia as compared with married individuals. The benefit of marriage was stronger for men.

Other studies conducted in various countries around the word such as France, Chine and United states of America confirmed previous findings and have shown that the participation in either intellectual (eg, reading magazines, newspapers, or books; playing cards, games, or bingo; going to classes) or social (eg, travelling, knitting, visiting or being visited by friends or relatives) activities, were associated to a lower risk of dementia (Fabrigoule et al. 1995; Scarmeas et al. 2001, 2003; Verghese et al. 2003). Interestingly, in term of frequency, each additional leisure activity reduced the risk of developing dementia by approximately 12%.

In contradiction to above findings, other longitudinal studies found no association between leisure activities (i.e., cognitive, social, and physical) and dementia (Anttila et al. 2002). According to the review by Wang et al. (2012), the discrepancies of findings could be due to: 1) demographic characteristic of the participants, notably the age and gender; 2) assessment of activities: type, frequency, intensity of activities; 3) duration of follow-up; and 4) tests assessing cognitive functions.

3.2.3 Occupation

Numerous studies have explored the possible effects of the occupation exerted during the lifespan on the risk of developing dementia. The picture that emerges is that those who exerted an intellectual profession had a lower risk of developing dementia than those who exerted manual profession. The large prospective study by Stern et al. (1994) following 593 individuals (mean age 74 years) for 10 years confirmed such a view and has shown that higher lifetime occupational attainment (manager business/government, professional/technical), as opposed to lower attainment (unskilled/semiskilled, skilled trade or craft, clerical/office worker) was associated to decreased risk of developing dementia, particularly AD. The study by Schooler et al. (1999) further suggested that complex intellectual work increased the cognitive functions of older workers.

3.2.4 Bilingualism

It is widely admitted that lifelong bilingualism (i.e., refers to the ability to speak two languages) could protect individuals against dementia (Bialystok et al. 2007; Gold et al. 2013). In line with this view, the study by Bialystok et al. (2007) has shown that bilingualism was associated with 47 % reduced risk of developing dementia. This finding is recently supported by Alladi et al. (2013), who has shown that bilinguals delayed the onset of several types of dementia, by at least 4.5 years.

In contradiction to these findings, some studies have suggested that there is no beneficial effect of speaking two languages. According to Atkinson, (2016), the discrepancies of findings could be explained by the large difference in studies design and definitions of bilingualism used between studies (e.g., the age of acquisition of the second language and frequency of practice). Atkinson et al. (2016) conclude that lifelong bilingualism, where both languages are frequently used from the young age, could be protective against dementia; however, such effect could disappear if the individual becomes bilingual during adulthood or occasionally use their second language.

To summarize, although still in discussion, several studies have shown that more education, greater cognitive demands of work, involvement in leisure activities and social engagement, and speaking at least two languages at an early age could increase the reserve by making individuals more resilient to brain damages.

3.3 Mechanisms by which the cognitive reserve protects individuals against dementia

Education, bilingualism, occupation, leisure time activities and social network are the most studied proxies in the literature. One of the possibilities to understand how the reserve is built, is to understand mechanisms through which these life-experiences could protect the brain against dementia (Amieva et al. 2014). Unfortunately, these mechanisms are still unclear. Nonetheless, animal research that studied the relationship between neuronal plasticity and enriched environment suggested the following hypothesis: i) "*changes in the thickness of cerebral cortices"* (Markham and Greenough 2004), "*amyloid load"* (Lazarov et al. 2005), "*cortical capillary formation"* (Black et al. 1987), "*neurogenesis"* (Kempermann et al. 1997), "*dendritic and synaptic growth"* (Kozorovitskiy et al. 2005), and ii) "*increases in neural processing and synaptic organization"*. Taking into account such mechanisms we can suggest that life-experiences have either a protector role against the onset of neurodegenerative diseases through increasing brain reserve or mediator role regulating the association between brain pathology and cognition after the occurrence of a disease or even aging.

3.4 Assessment of reserve

Anatomical measures of the brain such as the brain size or neuronal count represent the principal measures of brain reserve. For CR, there is today no consensus proposing an exact method to measure it. However, recent studies suggest the use of two questionnaires, which are: i) the cognitive reserve index, and ii) the cognitive reserve Scale, and specific proxies such as the level of education, and occupation status (see **Table 3**).

3.4.1 Cognitive Reserve Index questionnaire (CRIq)

The CRIq was developed by (Nucci et al. 2012) to quantify CR proxies accumulated over the lifespan. This questionnaire contains 20 items grouped into three sections: (CRI-Education, CRI-Working Activity, and CRI-Leisure Time). The CRI-Education was assessed by the number of years of schooling, combined with the number of training courses; CRI-Working Activity was represented by the number of working years multiplied by the cognitive level of the work. Professions carried out during adulthood were classified into five different levels of working activities according to the degree of intellectual involvement and personal responsibility: unskilled, manual work (e.g., farmer, car driver, call center operator); skilled manual work (e.g., craftsman, clerk, hairdresser); skilled non-manual or technical work (e.g.,

trader, kindergarten teacher, real estate agent); professional occupation (e.g., lawyer, psychologist, physician), and highly intellectual occupation (e.g., university professor, judge, top manager). CRI-Leisure Time was quantified by the number of years and frequency (i.e., often/always) of the practice of 16 activities, from the age of 18 years. These three subscores were then averaged to obtain an overall score of CR. The latter was classified into five ordered levels: Low (less than 70), Medium-low (70-84), Medium (85-114), Medium-high (115-130) and High (more than 130).

3.4.2 Cognitive Reserve Scale (CRS)

The CRS (Leon et al. 2011) is a new questionnaire assessing different brain-stimulating activities exerted across the lifespan (**Table 2**). The CRS contains 24 items divided into four categories: (i) activities of daily living, (ii) training–information, (iii) hobbies, and (iv) social life. The CRS was quantified by the frequency of practice of these activities in which different periods of life were considered: young adulthood (18–35 years), adulthood (36–64 years) and late adulthood (over the age of 65 years). The total score ranges from 0 to 96 points, with higher CRS scores indicating greater CR.

Table 2. Cognitive Reserve Scale Questionnaire

Category	Example items
Activities of daily living	Controlling my own life (e.g. what to wear each day, hotel bookings, doctor's appointments
	Controlling financial matters at home (e.g. bills, mortgage)
Training/ information	Taking a course (e.g. language, internet use)
	Speaking a non-native language or dialect
Hobbies	Reading (e.g. newspapers, magazines, books)
	Playing games (e.g. crosswords, Sudoku, cards, draughts, chess)
	Writing for pleasure (e.g. letters, personal diary)
	Listening to music or watching television
	Playing a musical instrument (e.g. guitar, flute)
	Collecting things (e.g. stamps, coins)
Social life	Visiting relatives, friends, neighbors, etc.
	Volunteering, going to church, etc.

3.5 Critical view on cognitive reserve assessment

According to the recent review by Opdebeeck et al. (2015), 159 studies used one proxy to assess CR (i.e., education: 109 studies; occupational status: 19 studies; engagement in cognitively stimulating activities: 31 studies), whereas only six combined proxy measures (**Table 3**). Critically, using only one proxy seems not recommended, as it may reduce the accuracy of associated results (Jones et al. 2011), notably because each proxy independently contributes to the development of CR (Foubert-Samier et al. 2012). In line with this view, we can admit that a reliable measure of CR is possible only by assessing its different proxies. While few studies have attempted to measure CR through a combination of some of these proxies (Nucci et al. 2012; Leon et al. 2011; León et al. 2014), none of them has proposed an accurate methodology allowing the assessment of CR. In fact, even if the same proxies (or combination) are used, the procedures and measurement scale are extremely heterogeneous making thus the choice of assessment methods of proxies very difficult.

It should be noted that CR is often estimated from young adulthood (18–35 years), until late adulthood (over the age of 65 years). To our knowledge, the childhood period is often ignored in the majority of study. However, this period of life is crucial for the building of Human reserve as it plays a central protective role against the development of neurodegenerative diseases. Evidence of this view comes from the studies by Whalley et al. (2000), and Dekhtyar et al. (2015) showing that childhood mental ability scores and childhood school grades are strong predictors of poor cognitive function and dementia in late life. Therefore, it is crucial to elaborate proxies specific to the childhood period.

We would like to highlight that both questionnaires and proxies are just qualitative measurements (i.e., or qualitative indicators) of CR, and none of them could reflect its dynamic aspect. At a behavioral level, one of the possibility to assess CR, dynamically, is to quantify the mismatch between cognitive functions and the extent of brain disease or damage (Mitchell et al. 2012). In line with this view, some authors suggest that the assessment of EF has special importance, given that the prefrontal cortex is the most sensitive part of the brain to the adverse effects of aging (Lamar et al. 2004). Therefore, the assessment of EF in older adults is particularly relevant to study the possible protective effects of CR. The next part of this thesis will expose in more details this relationship.

Table 3. An example of methods assessing the proxies of cognitive reserve

Studies	Education	Occupation	Leisure activities	Social network	Bilingualism	Socioeconomic status
Alexander et al. 1997	number of years of education	no	no	no	no	no
Bialystok et al. 2007	number of years of education	5-point scale (human resources and skills development, canada, 2001)	no	no	no	no
Christensen et al. 2007	3-point scale (less than 10, 10-12, over 12 years of education)	no	self-directed search test	no	no	no
Daffner et al. 2005	number of years of education	no	no	no	no	no
Garibotto et al. 2008	number of years of education	6-point scale (nest-dd project protocol)	no	no	no	no
Garrett et al. 2010	number of years of education	no	no	no	no	no
Le Carret et al. 2005	4-point scale (less than 5, 6-9, 10-12, over 12 years of education)	no	no	no	no	no
Martino et al. 2008	number of years of education	no	no	no	no	no
McDowell et al. 2007	4-point scale (qualification)	6-point scale (statistics canada's standard occupational codes, 1981)	no	no	no	no
Ngandu et al. 2007	3-point scale (less than 5, 6-8, over 8 years of education)	no	no	no	no	no
Perneczky et al. 2006	number of years of education	no	no	no	no	no
Ropacki and Elias 2003	no	7-point scale (us census categories, 1994)	no	no	no	no

Roselli et al. 2009	dichotomous scale (less or more than 8 years of education)	no	no	no	no	no
Scarmeas et al. 2003	number of years of education	no	customized questionnaire	no	no	no
Solé-Padullés et al. 2009	4-point scale (qualification)	customized 4-point scale	customized questionnaire	no	no	no
Schweizer et al. 2012	number of years of education	4-point scale (human resources and skills development canada, 2009).	no	no	simple question: are you bilingual? y/n	no
Staff et al. 2012	number of years of education	9-point scale (gb: office of population censuses and surveys, 1990)	no	no	no	no
Stern et al. 1994	number of years of education	no	no	no	no	no
Tucker-Drob et al. 2009	dichotomous scale (less or more than 12 years of education)	no	no	no	no	no
Craik et al. 2010	number of years of education	4-point scale (human resources and skills development canada, 2009).	no	no	criterion of bialystok : bilingual "… had spent the majority of their lives, at least from early adulthood, regularly using at least two languages,"	no
Valenzuela and Sachdev, 2006	number of years of education plus courses	9-point ordinal scale (australian standard classification of occupations, 1997)	customized questionnaire	no	no	no
Foubert-Samier et al. 2012	Level of education	4-categories (the international standard classification of occupations, 1988)	customized questionnaire	no	no	no

Reed et al. 2010	number of years of education	occupation in middle life	customized questionnaire	no	no	a composite scale consisting of both individual-level and community-level early in life and at midlife
Brayne et al. 2010	number of years of education	no	no	no	no	no
Fratiglioni et al. 2000	dichotomous scale (less or more than 8 years of education)	no	no	personal interview: marital status: married, single, divorced, widowed	no	no
Sundström et al. 2016	number of years of education	no	no	marital status: married, single, divorced, widowed	no	no
Kowoll et al. 2016	number of years of education	no	no	no	Criterion of bialystok	no
Qiu et al. 2003	dichotomous scale (less or more than 8 years of education)	nordic occupational classification	no	no	no	swedish socioeconomic classi-fication system
Leon et al. 2011	dichotomous scale (less or more than 8 years of education)	spanish national classification of occupations stratified into high, medium and low levels	the cognitive reserve scale	the cognitive reserve scale	the cognitive reserve scale	no
Grotz et al. 2017	-number of years of education and courses (> 6 months) - educational diplomas	4-categories (the international standard classification of occupations, 2008) total number of working years	customized questionnaire	no	no	no
Wang et al. 2006	educational diplomas	questionnaire (lifespan work activities of all jobs lasting at least 6 months)	customized questionnaire	no	no	number of siblings

Bialystok et al. 2007	number of years of education	historical working	no	no	language history: languages spoken, english fluency, place of birth, date of birth, and year of immigration to Canada	no
Amieva et al. 2014	level of education	no	no	no	no	no
Daly and Bass 2006	no	no	historical leisure activity questionnaire	no	no	no
Dekhtyar et al. 2015	level of education	historical working	no	no	no	father's occupation family status

3.6 Cognitive reserve, age, and executive function

Growing evidence suggests that EF are strongly influenced by CR (Le Carret et al., 2003). Specifically, it has been theorized that CR may enhance the performance of several executive tests (TMT B, verbal fluency test, Digits Forward and Backward subtests, Stroop Test, WCST) in healthy older adults (Hashimoto et al. 2006; Moradzadeh et al. 2015), moderating thus the adverse effects of aging on EF (Galioto et al. 2013). For example, the study by Schneeweis et al. (2014) has shown that a higher level of education reduced significantly the rate of decline in switching as assessed by the verbal fluency test. Studies by Hashimoto et al. (2006) and Fine et al. (2012) further suggested that the level of education moderated the the rate of decline in updating as assessed by the digit span backward test. The recent study by Roldán-Tapia et al. (2012) conducted in 160 healthy participants aged from 20 to 65 years confirmed previous findings and has shown that higher CR score was associated to a better performance in cognitive tasks assessing inhibition, updating and switching.

Theoretical framework's key points

AD and PD are considered today as a major public health concern. In the absence of curative therapy, recent research is interested in prevention by trying to early detect the first signs of early-phase of the neurodegeneration. In this vein, growing evidence through longitudinal data suggests that deficits in EF and gait control (i.e., under dual-task conditions) are one among the first symptoms occurring at the preclinical phase of these diseases (Beauchet et al. 2014; Li et al. 2016; Belghali et al. 2017a, 2017b).

It was suggested that deficit in inhibition may be specific to AD, whereas deficit in switching may be specific to PD (Belghali et al. 2017a, 2017b). Given that inhibition (as assessed by the Stroop test) and switching (as assessed by task-switching paradigms; e.g., TMT test) share brain networks, notably the prefrontal one, some neuropsychological studies (n=3) suggest the use of the Stroop Switching Test (SWT), notably because it increases the sensitivity of the Stroop Test in predicting early executive dysfunction (Delis et al. 2001; Fine et al. 2008; Hutchison et al. 2010). Despite the relevance of this test, some improvements are required in order to be used in clinical practice. In particular, there are needs for specific measures assessing inhibition, switching, and updating, separately and together. The first two studies of this thesis addressed this issue by developing a new design of the SWT (Card and computerized versions) assessing the overall efficiency of EF with specific measures related to each component. The different cognitive processes underling this test will also be explored, notably in study 2. The new neuropsychological test was validated across a wide range of ages (15-75 years).

It is widely admitted that CR strongly influences executive performance. Until now, there is no consensus explaining the best method to measure it. The third study of this thesis will address this issue and proposes two measures of CR, one of which is qualitative and the other is quantitative (dynamic). Both measures were tested in older adults (60-79 years).

Gait control under dual-task conditions is also a powerful tool to early diagnose AD and PD. In our perspective article (Belghali et al. 2017b), we suggest the use of the Stroop test requiring executive inhibitory control and a set-shifting task requiring switching as particularly relevant secondary tasks for challenging gait in prodromal AD and PD, respectively. To our knowledge, the effect of these cognitive tasks on gait interference remains unclear. The aims of the last study of this thesis will address this issue by examining the effect of executive task type (i.e., new cognitive tasks assessing inhibition and switching, separately and together) on gait control. New dual-task walking paradigms will be tested in young adults (18-25 years).

Part 2. Experimental studies

Methodological innovation in executive functions assessment

The first two studies of this thesis propose a new neuropsychological test (i.e., study 1: card version and study 2 computerized version), assessing executive function and related cognitive processes, separately and together.

Stroop Switching Card Test: Brief screening for executive function across the lifespan

1. Introduction

According to Miyake et al. (2000), there are three components of EF, which are the: (1) **inhibition** (i.e., *"ability to inhibit in a controlled way the production of prepotent, automatic, or impulsive responses when necessary"*); (2) **updating** (i.e., *"ability to both hold and monitor different information modalities"*), and (3) **switching** (i.e., *"ability to flexibly change forward and backward in relation to various tasks, mental processes, or schemas"*), which can work either, together or separately depending on both the nature and cognitive demand of the situation (Miyake et al. 2000).

To date, the majority of studies explored age-related changes in EF by using standard cognitive tests widely known in the literature to involve inhibition (e.g., Stroop Test), updating (e.g., Digit Span Forward and Backward Test), and switching (e.g., Trail Making Test), providing insight into how the diversified nature of EF evolves or deteriorates with aging. As mentioned previously, EF may also work together notably in a novel situation (Miyake et al. 2000). In line with this view, there is today no neuropsychological test assessing EF, with specific measures related to each component (inhibition, switching and updating). Thus, changes in efficiency of EF due to either normal or pathological aging remains poorly explored.

How should we modify the Stroop Switching Test to assess the overall efficiency of EF?

Some authors have tried to elaborate new executive tests combining two components of EF, which are the inhibition and switching; *The Stroop Switching Test* (i.e., SWT, developed by Delis et al. 2001, Fine et al. 2008, and Hutchison et al. 2010), in which the main instruction was to switch between naming the incongruent ink of color and reading the word that was either neutral (Hutchison et al. 2010) or incongruent (Delis et al. 2001; Fine et al. 2008), presented in a random order. From a clinical point of view, recent studies (n=3) have shown that the SWT is more relevant than standard neuropsychological tests, because it allows for early detection of executive dysfunction in both healthy and pathological aging (i.e., notably AD). Despite the relevance of these findings, some limitations prevent a complete understanding of the added value of the SWT. In the studies by Delis et al. (2001) and Fine et al. (2008), only the overall time to complete the entire block of trials was assessed; however, without taking into

consideration the total number of errors and trial-specific switching effect (Hutchison et al. 2010). Hutchison et al. (2010) worked on these dependent variables but without taking into consideration interindividual differences in processing speed. Adjustment for such covariate is crucial since efficiency of EF depends on the ability and speed of the brain to process information. Another limit that should be mentioned in the study by Hutchison et al. (2010) is that the authors used neutral words instead of congruent stimuli, and a cue indicating how to perform each trial. From our view, these methodological choices do not allow to examine specifically the updating component of EF and the conflict monitoring.

The conflict-monitoring refers to a flexible cognitive process allowing to continuously monitor and adjust human behavior in order to maintain a goal-directed performance (Aschenbrenner and Balota 2015). In the Stroop test, the conflict monitoring is involved in incongruent trials and it is typically measured using the "Gratton effect" (Gratton et al. 1992). The latter is a theory suggesting that the characteristics of a stimulus on the trial N-1 influence the dynamic response on the trial N. Specifically, responses are faster and accurate when incongruent trials occurred immediately after an incongruent trial (II) than occurred after a congruent trial (CI) (Gratton et al. 1992; Aschenbrenner and Balota, 2015; Kim et al. 2016). It is worth mentioning that the "proportion of congruence" is one of the prominent factors that influences the conflict-monitoring adopted for a given task. It is admitted that 50/50 condition (50% congruent stimuli and 50% incongruent stimuli) produces the highest possible interference (Levin and Tzelgov 2014).

Taking all the above into consideration, the main aims of this study are twofold: i) to propose a new design of the SWT (i.e., Stroop Switching Card Test; SSCT) assessing efficiency of EF and its components, separately and together, and 2) to examine the utility of the SSCT in the assessment of EF from adolescence to old age, by comparing it to standard neuropsychological tests widely used in the literature to assess inhibition (Stroop test), switching (Trail Making Test), and updating (Digit Span Forward and Backward test). Our central hypothesis is that the new neuropsychological test will be more sensitive to age than standard neuropsychological tests.

2. Methods

2.1. Participants

A sample of 103 participants, aging from 15 to 75 years, participated voluntarily to this experiment. The study sample was divided into 4 groups: adolescents (n = 25; 15-19 years), young adults (n = 25; 20-39 years), midlife adults (n = 27; 40-59 years) and older adults (n = 26; 60-79 years). Demographic characteristics of participants are summarized in **Table 4**. The inclusion criteria were: (i) literate, (ii) a score of Mini-Mental State Examination (MMSE; **Appendix 1**) greater or equal to 27, and (iii) absence of visual and auditory impairments. The exclusion criterion was the presence of any medical, psychiatric, or neurologic impairment that could significantly affect cognitive functions. All participants gave their written informed consent before participation.

Table 4. Mean (standard deviation) of demographic characteristics of participants

	Adolescents	**Young adults**	**Midlife adults**	**Older adults**
Gender				
Female	52 %	52 %	48,1 %	42,3 %
Male	48 %	48 %	51,9 %	57,7 %
Age (years)	17.40 (1.29)	26.40 (4.30)	50.25 (5.15)	67 (4.55)
Education (years)	12.45 (1.21)	15.70 (2.87)	9.25 (5)	8.16 (5.39)

2.2. Protocol overview

This experiment took place in the participant's residence in the quietest workspace. Each participant completed in randomized order, a battery of widely used tests designed to assess: (i) inhibition (i.e., the STROOP test; **Appendix 2**), (ii) switching (i.e., Trail Making Test; **Appendix 3**), (iii) updating (i.e., Digit Span Forward and Backward test; **Appendix 4**), and (iv) processing speed (i.e., Digit Symbol Substitution Test; **Appendix 5**), and the new neuropsychological test assessing the overall efficiency of EF (i.e., Stroop Switching Card Test, SSCT). Each participant was tested individually in a single session lasting about one hour.

2.1.1. Standard neuropsychological test

Stroop test

The Stroop test (Stroop, 1935) assesses inhibition and includes two basic conditions of color naming (STROOP A) and word reading (STROOP B) and, a third condition in which individuals must name the ink color that does not correspond to the meaning of the written word (STROOP C: e.g., YELLOW written in green; YELLOW). Completion times of STROOP A, STROOP B, and STROOP C and the total number of errors of STROOP C were considered. Two interference scores (IS) assessing inhibition are calculated:

IS-1 = STROOP C − [(STROOP A + STROOP B)/2]
IS-2 = STROOP C− STROOP A

IS-1 and IS-2 are the dependant variables of interest.

Trail Making Test

The Trail Making Test (TMT; Reitan and Wolfson, 1985; Spreen and Strauss, 1998) assesses switching and includes two conditions: Part A, requiring the serial connection of the numbers 1 through 25 (1–2–3…), and Part B, requiring serial alternation between number and letter sequences (1– A–2–B–3…). Completion times of Parts A and B, and total number of response errors of TMT-B were considered.
Two switch scores (SIS) assessing switching are calculated:

SIS-1 = TMT B – TMT A
SIS-2 = TMT B/ TMTA

SIS-1 and SIS-2 are the dependant variables of interest.

Beyond standard measures, we used the 'Inverse efficiency score' (IES), which combines speed and error to assess inhibition and switching. According to Bruyer and Brysbaert (2015) the IES is an objective measure that could reflect the average energy consumed by the system over time (i.e., the "*power of the system"*). The IES was determined according to the following formula proposed by (Bruyer and Brysbaert 2011):

$$\mathbf{IES} = \frac{\text{Response time}}{1 - \text{Total number of errors}}$$

Digit Span Forward and Backward Test

The Digit Span Forward and Backward Test assesses updating and includes two sequences (i.e., Forward and Backward). During the Forward sequence, the participant must repeat in direct order digits given by the experimenter. In the Backward sequence, digits must be repeated in an inverse order. Two trials are given for each list length. Each trial starts with two digits until reaching nine digits for the Forward sequence, and eight digits for the Backward sequence. Testing stops when the subject fails successively two trials at one list length or when the maximal list length is reached. The total number of lists reported correctly in both sequences (i.e., referring to the Wechsler total score) is the dependent variable of interest.

Digit Symbol Substitution Test

This Digit Symbol Substitution Test (Wechsler, 1981), assesses the processing speed. It consists of a key grid of nine numbers and matching symbols, and a test section with symbols and empty boxes. Under each digit the subject must write down the corresponding symbols as fast as possible. The total number of correct symbols within the allowed time (i.e., 90 sec) was the dependent variable of interest.

2.1.2. Stroop Switching Card Test

2.1.2.1. Description

Four cards that differ only in color (i.e., red, blue, green, or yellow) were placed in front of the participant. The latter had 36 colored cards in either black or grey background. The instruction was to say aloud and as quickly as possible either the color ink of the written word when the background of the card is gray or the written word when the background of the card is black. Depending on the response, each card must be classified on the corresponding color (**Figure 8**).

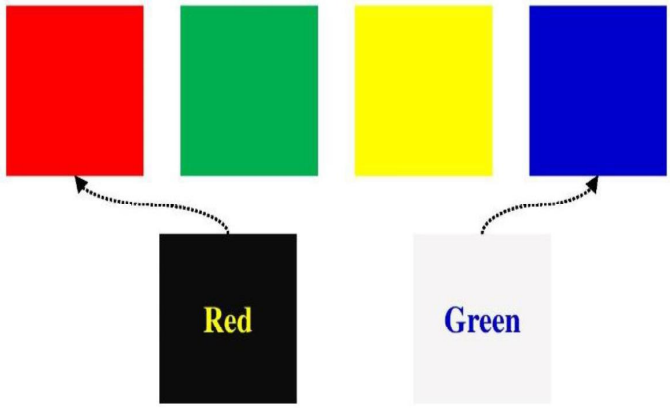


Figure 8. Stroop Switching Card Test

Specific instruction: "I will give you a deck of cards. You have to say, as quickly as possible and without making errors either the color of the ink of the written word when the background of the card is gray or the written word when the background of the card is black. Depending on your answer, you have to place your card on the corresponding color. If you make a mistake, don't stop the test, don't stress, don't talk to me and keep doing your best. Do you have any questions? Are you ready? "

2.1.2.2. Stimuli sequence

The stimuli consisted of four-color words (red, blue, yellow and green) presented either in the color corresponding to the colored word for four stimuli (congruent) or each of the three incongruent colors (e.g., the word "red" presented in green, blue, or yellow). The sequence contains 36 stimuli, half of them were congruent (e.g., RED), and the other half were incongruent (e.g., RED). The combination of congruence designed such that the information processing is continuously monitoring allowed creating: (i) six sequences assessing EF and related cognitive processes, separately and together, and (ii) six sequences dedicated to relieve cognitive control.

The first six sequences assessing EF are:

➢ **Inhibition without a change in congruence**

1. An incongruent word stimulus followed by an incongruent word stimulus (II_WW)
2. An incongruent color stimulus followed by an incongruent color stimulus (II_CC)

Figure 9. Example of Cards (II-WW) assessing inhibition without a change in congruence

➢ **Inhibition with a change in congruence**

3. A congruent word stimulus followed by an incongruent word stimulus (CI_WW)
4. A congruent color stimulus followed by an incongruent color stimulus (CI_CC)

Figure 10. Example of Cards (CI-WW) assessing inhibition with a change in congruence

➢ **Inhibition and switching without a change in congruence**

5. An incongruent color stimulus followed by an incongruent word stimulus (II_CW)
6. An incongruent word stimulus followed by an incongruent color stimulus (II_WC)

Figure 11. Example of Cards (II-CW) assessing inhibition and switching without a change in congruence

➢ **Updating**

- Card classification after each trial assessing inhibition and switching with inhibition.

<u>The sequences dedicated to relieve attentional control are:</u>

1. A congruent word stimulus followed by a **congruent word stimulus** (CC_WW)
2. A congruent color stimulus followed by a **congruent color stimulus** (CC_CC)
3. A congruent color stimulus followed by a **congruent word stimulus** (CC_CW)
4. A congruent word stimulus followed by a **congruent color stimulus** (CC_WC)
5. An incongruent word stimulus followed by a **congruent color stimulus** (IC_WC)
6. An incongruent color stimulus followed by a **congruent word stimulus** (IC_CW)

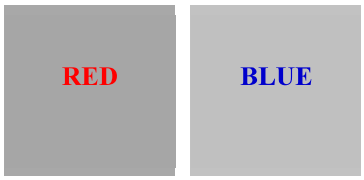


Figure 12. Example of Cards (CC-CC) dedicated to relieve attentional control

2.1.2.3. Description of possible cognitive processes underlying the SSCT

Two possible types of cognitive processes may underlie the SSCT: (i) the conflict resolution (first sub-type of the conflict monitoring) and (ii) the conflict adaptation (second sub-type of the conflict monitoring).

The **conflict resolution** refers to the ability to select the relevant information while suppressing the distracting information that is not relevant to the current goal of the task. A measure of the conflict resolution could be given by response error difference (i.e., the accuracy in the performance) between incongruent and congruent trials (Puccioni and Vallesi, 2012). In the context of EF, we suggest that the **conflict resolution** could be applied in a cognitive sequence involving either **inhibition without a change in congruence** (e.g., naming an incongruent ink color preceded by an incongruent ink color), or **inhibition and switching without a change in congruence** (i.e., switching between naming the incongruent ink of colors and reading the words or vice-versa; **Figure 13**: The left side of part A, and part C).

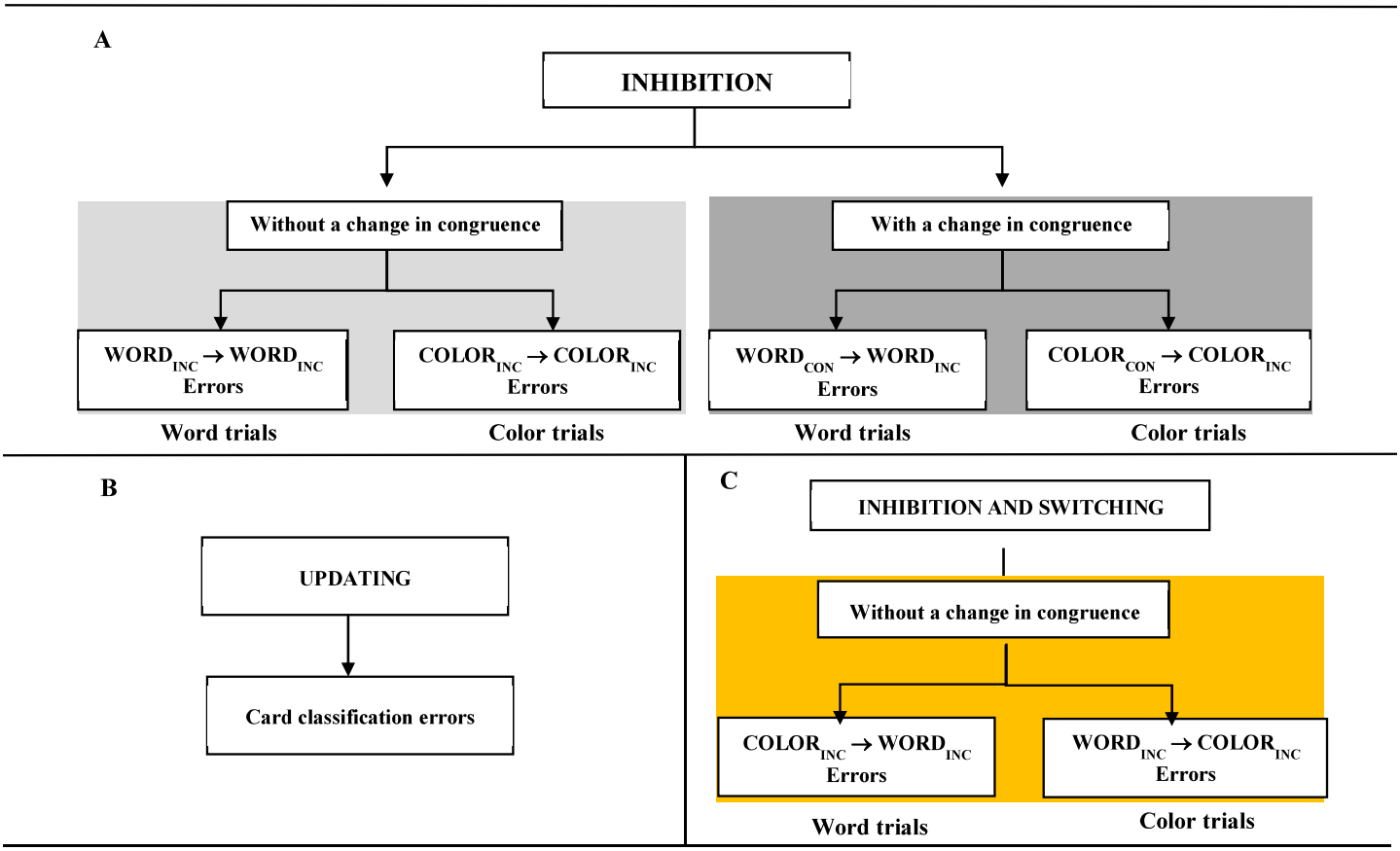
The **conflict adaptation** refers to the ability to adjust the response in accordance to the congruence of both current and precedent trials. A measure of the conflict adaptation could be given by response error difference between congruent following incongruent trials and incongruent following incongruent trials (CI minus II). In the context of EF, we suggest that the **conflict adaptation** could be applied in the cognitive sequence involving **inhibition with a change in congruence** (e.g., naming an incongruent ink color preceded by a congruent ink color; **Figure 13;** the right side of part A).

2.1.2.4.Dependent variables of the Stroop Switching Card Test

We have created two types of dependent variables: The global and specific variables. As its name suggests, the 'global variable' was created for assessing the overall efficiency of EF, while the 'specific variable' was created to assess each component of EF.

The **global dependent variable** was represented by the global response time to complete the SSCT, total number of response errors, and IES.

The type of errors made while performing each sequence assessing inhibition, updating, and inhibition and switching, represented the specific dependent variables of interest (**Figure 13**).



A: Specific dependent variables related to inhibition; **B**: Specific dependent variables related to updating; **C**: Specific dependent variables related to inhibition and switching; **CON**: congruent; **ING**: incongruent
Color trials: name the color of the ink in which the word is written. **Word trials**: read the word.

Inhibition (conflict resolution); Inhibition (conflict adaptation)
Inhibition (conflict resolution) and switching

Figure 13. Specific dependent variables of the Stroop Switching Card Test and related cognitive processes

3. Statistical analysis

The dependent variables were not normally distributed as assessed by the Shapiro-Wilk test. Therefore, non-parametric tests were used for statistical analysis. Three set of analysis have been performed. The first set of analyses examined the possible effects of age on the standard neuropsychological tests (IS 1, IS 2, STROOP C_{IES}, SIS 1, SIS 2, TMT B_{IES}, total number of the solved symbol and the Wechsler total correct score), and SSCT (global and specific variables) (Kruskall-Wallis test). Post-hoc comparisons were performed with Bonferroni corrections for multiple comparisons. The second set of analyses examined the possible contributions of processing speed to age-related changes in EF (ANCOVA test). The last set of analyses explored the benefit of the SSCT in assessing EF compared to standard neuropsychological tests (Student's test). Specifically, we compared the Z score of $SSCT_{IES}$ to the Z scores of $TMTB_{IES}$ and STROOP C_{IES}, in midlife adults compared to older adults.

The Z-score was used to quantify the performance deviation of midlife adults and older adults ($\mathbf{x_i}$), compared to young adults ($\overline{\mathbf{X}}$; 20-29 years). These were considered as the target population who have the best performance.

$$\text{Z-Score} = \frac{\mathbf{x_i} - \overline{\mathbf{X}}_{\text{young adults}}}{\text{Standard deviation}_{\text{young adults}}}$$

All statistical analyses were performed using SPSS software version 22 (IBM, SPSS, statistics). The level of significance for all tests was set at $p < 0.05$.

4. Results

4.1. Effect of age on standards neuropsychological tests and SSCT: Before adjustment for processing speed

4.1.1. Standards neuropsychological tests

4.1.1.1. Processing speed

The processing speed decreased significantly, and to the same extent in midlife adults and older adults compared to young adults ($p = 0.001$). No significant difference was observed between adolescents and young adults ($p = 1$) (**Figure 14)**.

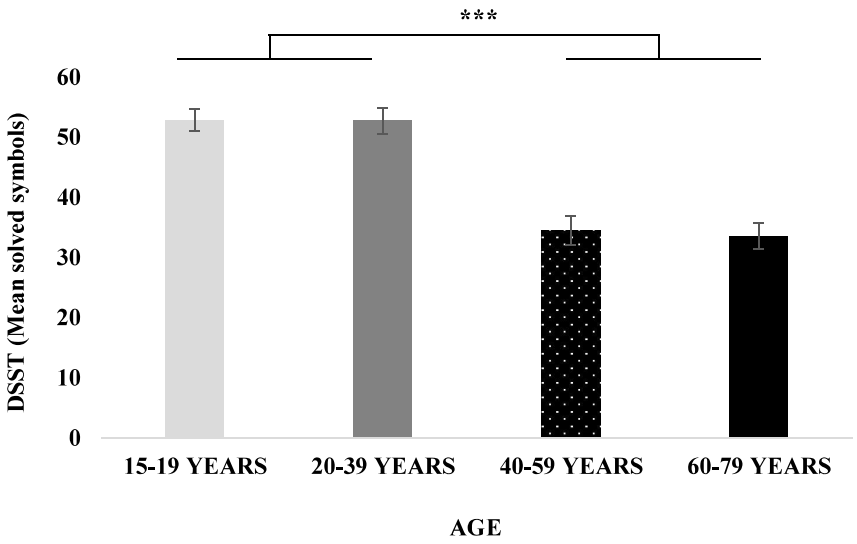


Figure 14. Mean (± SEM) performance of the Digit Symbol Substitution Test (DSST) in adolescents (15-19 years), young adults (20-39 years), midlife adults (40-59 years) and older adults (60-79 years). Mean solved symbols are displayed at the top and the age (years) at the bottom. (Older adults *versus* young adults and adolescents; p-value: *** < 0.001), (Midlife adults *versus* young adults and adolescents; P-value: *** < 0.001).

4.1.1.2. Switching and inhibition

- **Standard measures**

Mean scores of (i) SIS 1 (TMT B-TMT A), (ii) IS1 (STROOP C- STROOP A) and IS 2 [STROOP C- (STROOP A+ STROOP B/2)] increased significantly in older adults by

comparison with young adults, but not with midlife adults. No significant differences were observed between (i) adolescents and young adults, and (ii) young adults and midlife adults. The SIS 2 (TMTB/TMTA) was not significantly different between groups (**Table 5**).

- **Inverse efficiency score**

STROOP C_{IES} and TMT B_{IES} increased significantly, and to the same extent in midlife adults and older adults compared to young adults. No significant difference was observed between adolescents and young adults (**Table 5**).

4.1.1.3. Updating

The Wechsler score decreased significantly, and to the same extent in midlife and older adults compared to young adults. No significant difference was observed between adolescents and young adults (**Table 5**).

4.1.2. Effect of age on the SSCT: Before adjustment for processing speed

4.1.2.1. Global dependent variables

Mean scores of RT and IES increased significantly, and to the same extent in midlife adults and older adults compared to young adults. No significant difference was observed between adolescents and young adults. The total number of response errors increased significantly only in older adults compared to both young and midlife adults (**Table 6**).

4.1.2.2. Specific dependent variables

The total number of response errors of (i) classification, (ii) Inhibition (Color) without a change in congruence (II_CC), (iii) Inhibition (Color) with a change in congruence (CI_CC), and (iv) inhibition and switching (II_WC; II_CW), increased significantly in older adults by comparison with young adults, but not with midlife adults. Interestingly, the total number of response errors of inhibition (Word) with a change in congruence requiring a conflict adaptation (CI_WW) increased significantly only in older adults compared to both young and midlife adults (**Table 7**).

4.2. Effect of the processing speed on the relationship between age and cognitive performance

The processing speed has a significant effect on all dependent variables of both standard neuropsychological tests and SSCT ($p = 0.001$). After adjustment for this covariate, the effect

of age remains significant only for the following SNT's dependent variables: (i) TMT SIS1, (ii) TMT B_{IES}, (iii) STROOP IS 1 and (iv) STROOP C_{IES}. For the SSCT, the effect of age remains significant only for the following dependent variables: (i) global RT, (ii) IES and (iii) total number of response errors in inhibition (Word) with a change in congruence (**Tables 5 and 6**).

Table 5. Mean (standard deviation) performance of standard neuropsychological tests (TMT, STROOP, and Digit Span Forward and Backward test) in adolescents (15-19 years), young adults (20-39 years), midlife adults (40-59 years) and older adults (60-79 years) before and after adjustment for processing speed

		AD	YA	MA	OA	F value	AD > YA	YA > MA	YA > OA	MA > OA
Switching SM	TMT SIS 1	45.24 (16.70)	40.76 (16.63)	61.56 (37.11)	77.04 (38.10)	3.661	P = 1	P = 1	P = 0.019	P = 0.89
	TMT SIS 2	2.66 (0.88)	2.48 (0.70)	2.22 (0.77)	2.32 (0.84)	0.217	P = 1	P = 1	P = 0.270	P = 1
Switching NM	TMT B IES	0.76 (0.17)	0.70 (0.18)	1.28 (0.51)	1.44 (0.38)	14.248	P = 1	P = 0.030	P = 0.001	P = 1
Inhibition SM	STROOP IS 1	24.32 (18.18)	34.88 (19.82)	51.30 (23.12)	59.65 (24.27)	5.907	P = 1	P = 0.310	P = 0.003	P = 1
	STROOP IS 2	29.30 (16.41)	30.42 (29.31)	53.48 (21.93)	62.48 (19.93)	5.386	P = 1	P = 0.691	P = 0.005	P = 1
Inhibition NM	STROOP C IES	0.91 (0.19)	0.94 (0.18)	1.27 (0.24)	1.41 (0.26)	12.195	P = 1	P = 0.019	P = 0.001	P = 1
Updating	DSB + DSF	18.64 (3.05)	20.80 (4.41)	16.19 (3.14)	16.54 (3.56)	0.288	P = 1	P = 0.010	P = 0.006	P = 1

Red: Significant after adjustment for processing speed
Blue: Significant without adjustment for processing speed
Black: No significant
F value: After adjustment for processing speed
SIS 1: (TMTB-TMTA): SIS 2 (TMTB/TMTA); IES (inverse efficiency score); IS 1: [STROOP C-(STROOPA + STROOP B)/2]; IS 2: (STROOP C-STROOP A); TNE: total number of errors
DSB: digit span backward; DSF: Digit span forward; SM: standard measures; NM: new measures; AD: adolescents; YA: young adults; MA: midlife adults; OD: older adults

Table 6. Mean (standard deviation) performance of the Stroop Switching Card Test in adolescents (15-19 years), young adults (20-39 years), midlife adults (40-59 years) and older adults (60-79 years) before and after adjustment for processing speed

		AD	YA	MA	OA	F value	AD > YA	YA > MA	YA > OA	MA > OA
Global executive functioning efficiency	RT	84.24 (22,86)	82.2 (22.44)	177.925 (65.53)	221.423 (99.94)	11.413	P = 1	P = 0.001	P = 0.001	P = 1
	TNE	1.32 (1.51)	1.88 (2.61)	3.92 (3.31)	6.8 (4.31)	2.862	P = 1	P = 0.178	P = 0.001	P = 0.323
	IES	0.88 (0.24)	0.87 (0.25)	2.06 (0.93)	2.90 (1.63)	8.030	P = 1	P = 0.005	P = 0.001	P = 1
Inhibition without a change in congruence	TNE (Word)	0.32 (0.63)	0.68 (1.25)	0.89 (1.28)	1.62 (1.50)	1.293	P = 1	P = 1	P = 0.105	P = 0.641
	TNE (Color)	0.20 (0.50)	0.28 (0.84)	0.85 (1.17)	1.50 (1.30)	1.848	P = 1	P = 0.187	P = 0.001	P = 0.441
Inhibition with a change in congruence	TNE (Word)	0.12 (0.33)	0.12 (0.33)	0.37 (0.49)	0.81 (0.40)	3.852	P = 1	P = 0.356	P = 0.001	P = 0.010
	TNE (Color)	0.24 (0.44)	0.08 (0.28)	0.30 (0.47)	0.58 (0.50)	1.024	P = 1	P = 0.519	P = 0.002	P = 0.326
Inhibition and switching	TNE (Color)	0.16 (0.37)	0.08 (0.28)	0.41 (0.69)	0.50 (0.51)	0.583	P = 1	P = 0.310	P = 0.007	P = 1
	TNE (Word)	0.24 (0.60)	0.44 (0.65)	0.56 (0.75)	1.15 (0.88)	1.099	P = 1	P = 1	P = 0.047	P = 0.148
Updating	TNE classification	0.04 (0.20)	0.12 (0.33)	0.41 (0.75)	0.65 (0.94)	0.959	P = 1	P = 0.977	P = 0.050	P = 1

RT: Response time; TNE: total number of errors; IES: inverse efficiency score; AD: adolescents; YA: young adults; MA: midlife adults; OD: older adults
Red: Significant after adjustment of processing speed; Blue: Significant without adjustment for processing speed; Black: No significant; F value: After adjustment for processing speed

4.3. Stroop Switching Card Test *versus* Standard neuropsychological tests (Z-score of $SSCT_{IES}$ *versus* Z-scores of TMT B_{IES} and STROOP C_{IES})

$SSCT_{IES}$ was significantly greater in older adults than in midlife adults (t = -2.30, p = 0.021). Z scores of both $TMTB_{IES}$ (t = -1.29, p = 0.201) and STROOP C_{IES} (t = -1.83, p = 0.072) were not significantly differents between groups (**Figure 15**).

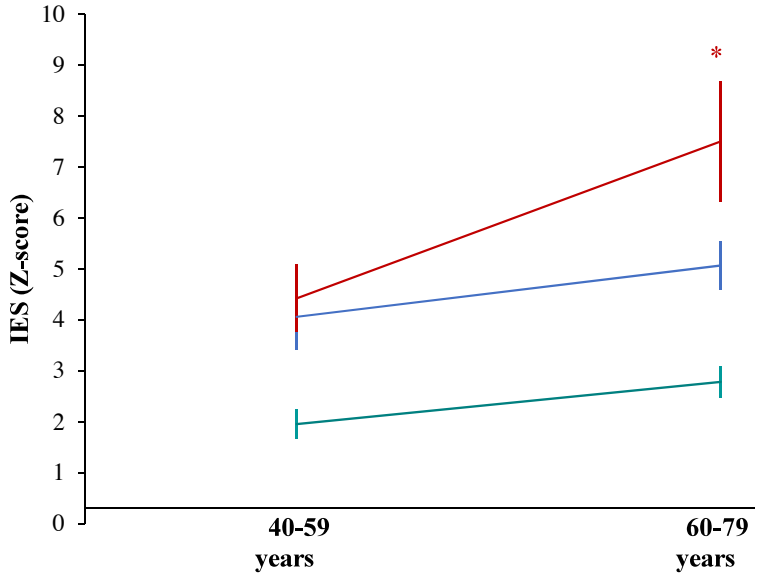


Figure 15. Mean (± SEM) performance of Z- scores of STROOP C_{IES}, TMT B_{IES} and $SSCT_{IES}$ in midlife adults (40-59 years) and older adults (60-79 years). The Z-score of the IES is displayed at the top and the age (years) at the bottom. **Red line: $SSCT_{IES}$; Green line: STROOP C_{IES} ; Blue line: TMT B_{IES};** P-value: * < 0.05

5. Discussion

It is widely admitted that there is no neuropsychological test assessing EF and its components. This study sought to address this issue by designing a new neuropsychological test, the "**Stroop Switching Card Test**" (SSCT) assessing EF-components, separately and together. The main objective was to examine the utility of the SSCT in the assessment of EF from adolescence to old age, by comparing it to standard neuropsychological tests, assessing inhibition (STROOP), switching (TMT), and updating (Digit Span Forward and Backward).

5.1. Effect of age on processing speed and executive function as assessed by standard neuropsychological tests

Aging affects both the processing speed and all components of EF. A differential effect of age was also found such that the processing speed and updating were affected earlier (40-59 years) than other EF components (i.e., inhibition and switching: 60-79 years). A decrease in processing speed has been previously shown in earlier studies (see Hoyer et al. 2004, for a meta-analysis) and it was thought to result from a diffuse or global deterioration of white matter integrity throughout the brain (Albinet et al. 2012; Kerchner et al. 2012). Early decline in updating also supports previous studies (e.g., Kumar and Priyadarshi 2013) and was thought to result from changes in the prefrontal cortex (frontal lobe hypothesis; West, 1996) and a decrease in processing speed (Salthouse, 1996). Results of our study are in favor of an age-related slowing in processing speed (Salthouse, 1996). Even if attentional and working memory capacities (Li et al. 2001) were not assessed in this study, we suggest that these general cognitive resources are likely to have contributed to updating decline. In fact, working memory is heavily loaded in the SSCT since cognitive processes underlying this test are multiple and complex (Emerson and Miyake, 2003). As for attentional capacities, various studies have shown that older adults had major difficulties in tasks assessing different aspects of attention (e.g., Adam et al. 2002). Thus, it is clear that declines in such general resources could also contribute of the updating component.

By contrast with the updating component, we can admit that declines in both switching (i.e., as assessed by the SIS 1) and inhibition (i.e., as assessed by the IS 1 and IS 2) are beginning only at older age (60-79 years) and this, independently of age-related slowing in processing speed. Thus, the frontal lobe hypothesis (West, 1996) is the safest assumption explaining age-related declines in inhibition and switching. Nonetheless, a contribution of the decline in general cognitive resources (working memory and attention) cannot be excluded. Age-related

declines in inhibition and switching closely replicate and extend previous studies comparing efficiency in inhibition and switching between young adults and older adults (Mutter et al. 2005; Hashimoto et al. 2006).

Notably, some midlife adults had performance closer to the young adults while others close to the oldest ones. Such finding leads to suggest that the midlife period (40-59 years) is the transition period of EF changes, in which some people success, better than others, their cognitive aging. For this reason, some midlife adults are already cognitively old at midlife whereas others were indistinguishable from young adults. Our view is in line with the moderating role of cognitive reserve (Stern, 2009). The latter posits that those with high cognitive reserve display better executive performance than those with low cognitive reserve, despite an equivalent level of frontal brain damages. The **study 3** of this thesis will provide more insight into the relationship between cognitive reserve and executive function.

It is worth mentioning that not all standard measures assessing EF are sensitive to age (SIS2). In fact, it seems more appropriate to use the SIS 1 measure to assess switching than the SIS 2. To our knowledge, the IES is not conventionally applied to assess performance in the Stroop interference task (inhibition) or the TMT B (switching). However, this measure could be of interest in particular when there are individual differences in speed-accuracy trade-offs, in which both RT and accuracy data could show different patterns of results (Davidson et al. 2006; Khng and Lee 2014). Surprisingly, no longitudinal studies were conducted today to explore the effect of age on this new measure. For the first time, we found that the efficiency in inhibition and switching as assessed by the IES of TMT B and STROOP C, respectively, starts to decline at middle age (40-59 years), and this independently from the effect of the processing speed. Hence, the IES appears to be more relevant than standard measures (SIS 1, SIS 2, IS 1, and IS 2) to reveal early age-related changes in switching and inhibition (40-59 years).

5.2. Effect of age on executive function as assessed by the Stroop Switching Card Test

For the first time, this study suggests adverse effects of age on the overall efficiency of EF (i.e., response time, total number of errors, and IES), and more specifically on updating, inhibition (Color) without a change in congruence, inhibition with a change in congruence (Color and Word), and inhibition plus switching (Color and Word). After controlling for processing speed, the adverse effect of age remains significant only on the (i) $SSCT_{RT}$, (ii) $SSCT_{IES}$ and (iii) inhibition (Word) with a change in congruence (CI_WW). Taking together,

we suggest that both processing speed and prefrontal-executive theories explain parts of the age effect on SSCT and that none of them can be considered as the sole contributor (Schretlen et al. 2000; Bugg et al. 2006; Albinet et al. 2012). Thereafter, only results that are independent of the effect of processing speed will be discussed.

The overall efficiency of EF as represented by either the RT or IES starts to decline at middle age (40-59 years). A decline was also observed in the STROOP C_{IES} and TMT B_{IES}, and the Digit Span Forward and Backward Test, thus confirming that the STSS taps into the three components of EF, simultaneously. More interestingly, our results suggest that the rate of the decline in EF from 50 to 79 years is not identical for all cognitive processes underlying EF. In fact, it seems to be more critical for inhibition (Word trials) component requiring a conflict adaptation (CI_WW), than other components or combination (60-79 years). It is likely that, this measure could be particularly relevant for future studies to distinguish healthy EF aging from the pathological one. Mechanistically, the fact that the total number of errors in CI_WW trials increased independently from processing speed constitutes a strong and consistent support for an age-related decline in conflict-adaptation. Neuroimaging studies have associated the conflict adaptation to (i) the anterior cingulate cortex that assures the detection of the congruence conflict, and (ii) the lateral prefrontal cortex that regulates the conflict (Gratton et al. 1992; Botvinick et al. 2001; Aschenbrenner and Balota, 2015; Kim et al. 2016). Considering the frontal lobe-damage hypothesis, it is not surprising that older adults had the worsted performance in CI conditions.

5.3. Stroop Switching Card Test *versus* standard neuropsychological tests

To understand the benefit of the SSCT for EF assessment, we computed a Z-score quantifying the performance deviation of midlife adults and older adults, compared to young adults. In the present study, we have chosen to compare Z-scores of $SSCT_{IES}$, STROOP C_{IES} and TMT B_{IES}, because all of these dependant variables are sensitive to age (40-59 years) and independently of processing speed. The principal result that emerged is that only the Z-score of $SSCT_{IES}$ differentiates the performance of older adults from that of midlife adults. This result provides evidence that the SSCT is more sensitive to age than standard neuropsychological tests, probably because it requires more cognitive control in older adults than the STROOP or TMT tests. Given that the Z-score of $SSCT_{IES}$ is independent from processing speed, we propose this measure as a pure measure of global EF efficiency and may provide a tool for an

early detection of executive dysfunction. To confirm this hypothesis, we need to accumulate more data.

5.4. Strengths and limitations

To our knowledge, this is the first study proposing a new neuropsychological test assessing the overall efficiency of EF, including specific measures related to inhibition, switching and inhibition, and updating. The main strengths are the task design, choice of dependent variables and the use of a statistical procedure allowing adjustment for processing speed. This study has essentially two limitations. The first limitation is that attentional capacities of participants were not considered. However, such kind of cognitive resource is crucial to perform the SSCT. The second limit is the small sample size of each group. Furthermore, the groups of midlife adults and older adults were lowly educated, thus limiting the generalization of our results. Including a large representative samples might benefit to propose a threshold of EF changes related to the different types of aging.

Methodologically, beyond processing speed effect, motor speed could also influence SSCT performance. To control this external factor, it will be interesting to use the Finger-Tapping Test (Strauss et al. 2006). Another crucial limitation that should be mentioned is that the specific dependent variables were only limited to the type of errors, restricting thus the possibility to understand healthy cognitive speed-accuracy trade-off strategies. These strategies could be explored by combining both response time and accuracy for each stimulus of the SSCT sequence. Thus, a computerized version could be of interest in this regard (Part 2. Study 2). Another important point to emphasis is that color stimuli seam impact differently individual performance than word stimuli. For this reason, neuroimaging studies are needed to explore the origin of this mechanism difference.

In conclusion, findings of this study suggest that the SSCT was appropriate to assess EF. We propose the Z-score of $SSCT_{IES}$ as a pure measure of the overall efficiency of EF that could have benefit for the early detection of executive deficit. Future studies including a large sample size with a broad diversity of life experiences are needed to propose a threshold of EF changes associated to different types of aging.

Computerized Stroop Switching Test: How people adjust their behavior in response to this conflict

1. Introduction

In the previous study, we have shown that the SSCT was relevant to assess age-related changes in EF. Given the importance of this finding, we were interested in elaborating a computerized version of the SSCT to facilitate its use in clinical practice as well as to assess changes in response time related to each stimuli, accurately. Together, the aims of this study are twofold: (i) to elaborate a computerized version of the SSCT, and (ii) to explore the possible effects of age on cognitive processes underlying inhibition (conflict resolution and adaptation) and switching, separately and together.

2. Participant, material and design

2.1 Participants

Young adults, midlife adults, and older adults of the previous study participated voluntary and free to this experiment. The latter was performed one week later than the first study. It lasted 15 minutes and took place in the participant's residence in the quietest workspace.

2.2 Material

The computerized version of the SSCT was run on a TOSHIBA computer, with a standard 17-inch monitor, and was implemented using E-Prime 2.0 presentation software (Psychology Software Tools, Pittsburg, PA, USA). Participants viewed the display from an approximate distance of 80 cm and were asked to respond to each experimental trial as quickly and as accurately, aloud into a microphone (Line 6 XD-V55HS-B, 2.4 GHz). The microphone was attached to E-prime's Chronos® box to both record and measure with millisecond accuracy reaction times (RT) for verbal responses. The computerized version of SSCT included one practice trial to ensure that the participants fully understood the instructions.

2.3 Design

In the previous study, we have shown that the inhibition (Word trials) with a change in congruence requiring a conflict adaptation (CI_WW) is deteriorated in older adults, selectively. To more challenge this kind of cognitive process, the stimuli sequence of the current study has

been improved comparing to the previous one (**Figure 16**). Specifically, we added two sequences (**sequences 13 and 14**) requiring inhibition and switching with a change in congruence:

13. A congruent word stimulus followed by an incongruent color stimulus (CI_WC)
14. A congruent color stimulus followed by an incongruent word stimulus (CI_CW)

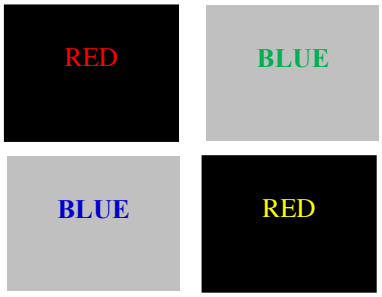
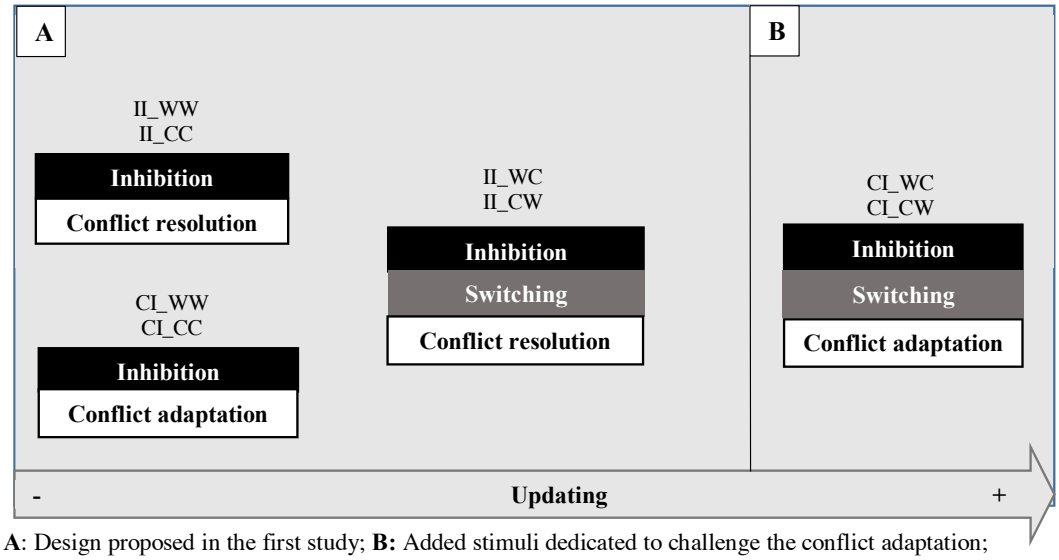


Figure 16. Example of Cards assessing inhibition and switching with a change in congruence

Collectively, four different types of cognitive processes are examined in this study, which are the: 1) conflict resolution related to inhibition: *inhibition (conflict resolution)*; 2) conflict resolution related to inhibition and switching: *inhibition (conflict resolution) and switching*; 3) conflict adaptation related to inhibition; *inhibition (conflict adaptation)*; and 4) conflict adaptation related to inhibition and switching: *inhibition (conflict adaptation) and switching* (sequences 13 and 14). The **Figure 17** summarizes these cognitive processes and related stimulus.



A: Design proposed in the first study; **B:** Added stimuli dedicated to challenge the conflict adaptation; **A+B**: Design proposed in the current study

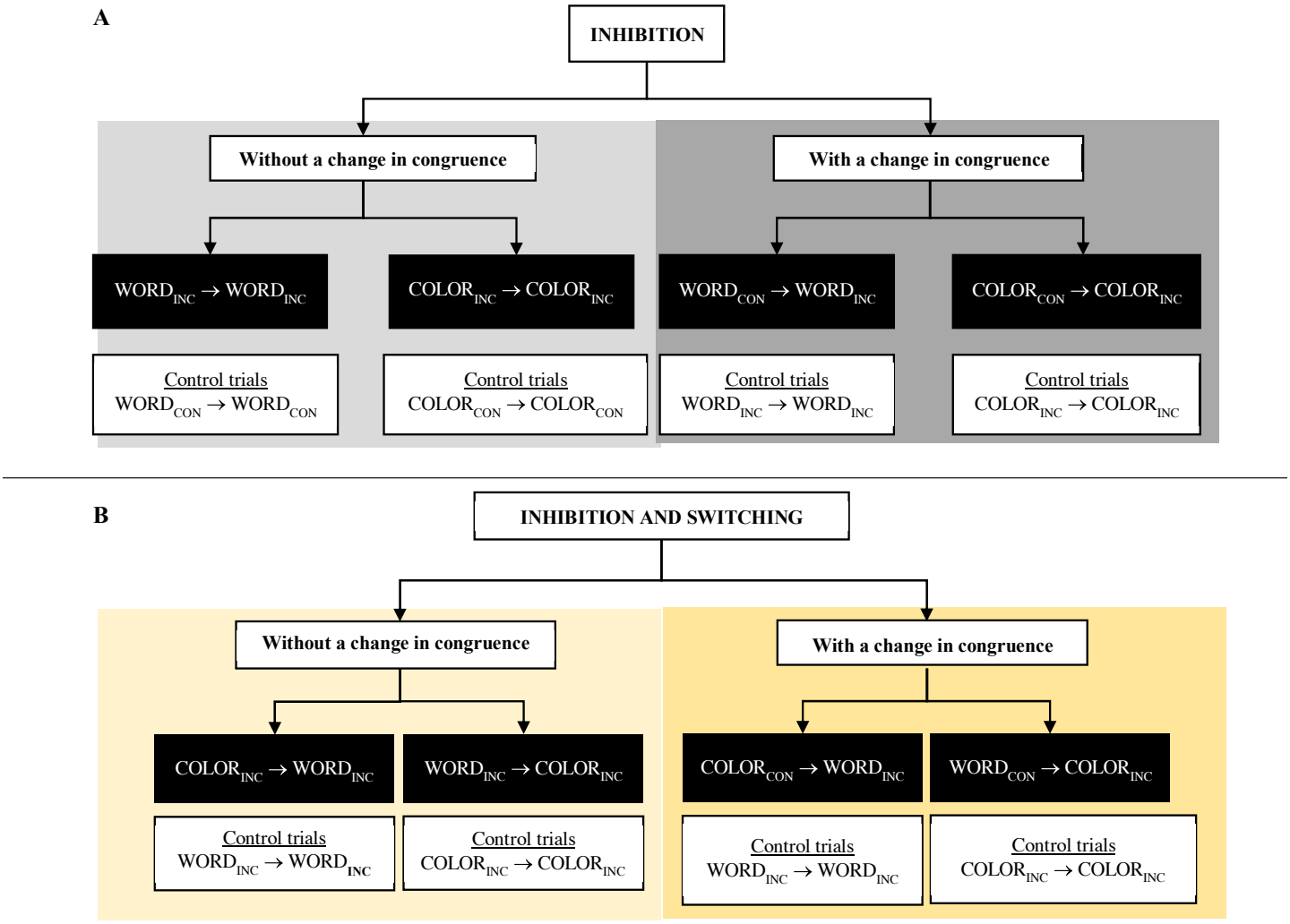
Figure 17. Cognitive processes underlying the computerized version of the Stroop Switching Card Test and related stimuli

2.4 Instruction and procedure

The principal instruction of the computerized version of SSCT was to say, as quickly and as accurately without making errors either, the font color in which the words are written when the color of the screen is gray, or the written word when the color of the screen is white. If the participant responded correctly on the sample trials, he received 48 experimental trials. Each experimental trial started with a 700 ms fixation cross (+) followed by the target that remained on the white screen for 2300 ms followed immediately by the fixation cross for the next trial. An experimenter coded each response as (i) correct response or (ii) response error. Response errors consisted of either responding with the wrong word (e.g., responding "green" to the word "green" written in blue) or responding with a blended word (e.g., "blu-red"), Hutchison et al. (2010).

2.5 Dependent variables

The set of 48 stimuli was classified into control and experimental trials. Response time (RT) and response error difference between experimental and control trials represented the dependent variables of interest. **Figure 18** summarizes control and experimental trials, and related cognitive processes. **Table 7** summarizes the dependent variables of interest (i.e., the calculation method).



Black rectangle: Experimental trials; **CONG**: congruent; **INC**: incongruent; **A**: Specific dependent variables related to inhibition **B**: Specific dependent variables related to switching; **C**: Specific dependent variables related to inhibition and switching

Inhibition (conflict resolution)
Inhibition (conflict adaptation)
Inhibition (conflict resolution) and switching
Inhibition (conflict adaptation) and switching

Figure 18. Control and experimental trials of the computerized version of the SSCT

Table 7. Dependent variables of the computerized version of the SSCT and related cognitive processes

	Cognitive processes	Types of trials	Dependent variables
Inhibition without a change in congruence	Conflict resolution	Color	RT_II_CC minus RT_CC_CC
			Response errors II_CC
		Word	RT_II_WW minus RT_CC_WW
			Response errors II_WW
Inhibition with a change in congruence	Conflict adaptation	Color	RT_CI_CC minus RT_II_CC
			Response errors CI_CC
		Word	RT_CI_WW minus RT_II_WW
			Response errors CI_WW
Inhibition and switching without a change in congruence	Conflict resolution Switching	Color	RT_II_WC minus RT_II_CC
			Response errors II_WC
		Word	RT_II_CW minus RT_II_WW
			Response errors II_ CW
Inhibition and switching with a change in congruence	Conflict adaptation Switching	Color	RT_CI_WC minus RT_II_CC
			Response errors CI_WC
		Word	RT_CI_CW minus RT_II_WW
			Response errors CI_CW

Type of trials. **Color**: name the color of the ink in which the word is written. **Word**: read the word; **RT**: response time.

3. Statistical analysis

Cognitive variables were normally distributed as assessed by the Shapiro-Wilk test. Therefore, parametric tests were used for statistical analysis. In each group, a paired student test was used to compare RT difference between experimental and control trials. After that, a one-way ANOVA was used to examine the possible effects of age on cognitive processes underlying the inhibition, switching and inhibition. Post-hoc comparisons were performed with Sidak correction for multiple comparisons. In the aim to control for interindividual differences in processing speed on the relationship between age and cognitive performance, we used the ANCOVA test. All statistical analyses were performed using SPSS software version 22 (IBM, SPSS, statistics). The level of significance for all tests was set at $p < 0.05$.

4. Results

In order to avoid the analyses being influenced by extreme scores, RTs above or below 3 standard deviations of each participant's mean were removed from the analysis (Huff, 2015). We considered response time for the correct responses only.

4.1 Response time

4.1.1 Inhibition (conflict resolution)

For both kinds of stimuli (word and color), all participants reacted faster in congruent trials (CC) than in incongruent trials (II), ($p < 0.001$). The one-way ANOVA revealed significant effects of age on RT difference between incongruent and congruent trials [i.e., Color ($F (2, 76) = 7.385$, $p < 0.001$); Word ($F (2, 76) = 39{,}556$, $p < 0.001$)]. For Color trials, Sidak post hoc analysis showed that older adults were significantly slower by comparison with young adults but not with midlife adults. For word trials, older adults were slower than both young adults and midlife adults. No significant difference was observed between young adults and midlife adults (**Table 8**).

4.1.2 Inhibition (conflict resolution) and switching

For color trials, all participants reacted faster in incongruent color trials when the previous trial was incongruent color (II_CC) than when it was incongruent word (II_WC) ($p < 0.001$). There was a significant effect of age on RT difference between II_WC and II_CC trials ($F (2, 76) = 9.394$, $p < 0.001$), due to slower responding of both midlife and older adults compared to young adults (**Table 8**).

For word trials, all participants reacted faster in incongruent word trials when the previous trial was incongruent word (II_WW) than when it was incongruent color (II_CW). There was a significant effect of age on RT difference between II_CW and II_WW trials ($F (2, 76) = 8.065$, $p < 0.001$), due to slower responding of older adults compared to young adults ($p < 0.001$) but not when compared to midlife adults (**Table 8**).

4.1.3 Inhibition (conflict adaptation)

For color trials, only older adults were faster in incongruent following incongruent trials (II) than in congruent following incongruent trials (CI) ($t = -3.05$, $p < 0.005$).

For word trials, all participants were faster in incongruent following incongruent trials (II) than in congruent following incongruent trials (CI), ($p < 0.001$). There was a significant

effect of age on RT difference between CI and II trials ($F (2, 76) = 30.467$, $p < 0.001$), due to slower responding of older adults compared to both young adults and midlife adults. No significant performance difference was observed between young adults and midlife adults (**Table 8**).

4.1.4 Inhibition (conflict adaptation) and switching

For color trials, all participants reacted slower in CI_WC trials than in II_CC trials ($p < 0.001$). No significant effect of age was observed on RT difference between CI_WC and II_CC trials ($F (2, 76) = 1.061$, $p = 0.351$) (**Table 8**).

For word trials, all participants reacted slower in CI_CW than in II_WW trials ($p = 0.0001$). A significant effect of age was observed in RT difference between CI_CW trials and II_WW trials ($F (2, 76) = 16{,}270$, $p < 0.001$) due to slower responding of both midlife and older adults compared to young adults. A significant difference was also observed between midlife adults and older adults (**Table 8**).

4.2 Number of response errors

4.2.1 Inhibition (conflict resolution)

There was a significant effect of age on the total number of response errors in word trials (II_WW; $F (2, 76) = 3{,}996$, $p = 0.022$). Older adults made more errors compared to young adults. There was no significant effect of age in color trials (II_CC; $F (2, 76) = 1.121$, $p = 0.331$) (**Table 8**).

4.2.2 Inhibition (conflict resolution) and switching

There was a significant effect of age on the total number of response errors in word trials (II_CW; $F (2, 76) = 9{,}515$, $p < 0.001$). Older adults made more errors compared to young adults. There were no significant effects of age on color trials (II_WC; $F (2, 76) = 2.9581$, $p = 0.057$) (**Table 8**).

4.2.3 Inhibition (conflict adaptation)

There was a significant effect of age on the total number of response errors in all trials assessing the inhibition (conflict adaptation): CI _WW ($F (2, 76) = 21.621$, $p < 0.001$), CI_ CC ($F (2, 76) = 8.188$, $p < 0.001$). The total number of response errors in CI_CC trials increased significantly in older adults compared to young adults but not when compared to midlife adults.

The total number of response errors in CI_WW increased significantly only in older adults compared to both young adults and midlife adults (**Table 8**).

4.2.4 Inhibition (conflict adaptation) and switching

There was a significant effect of the age on the total number of response errors in all trials assessing the inhibition (conflict adaptation) and switching: CI_WC ($F(2, 76) = 8.261$, $p < 0.001$), and CI_CW ($F(2, 76) = 6.816$, $p < 0.001$). Sidak post hoc analysis revealed that the response errors in CI_ CW trials increased significantly in older adults compared to young adults but not when compared to midlife adults. Response errors in CI_ WC trials increased significantly only in older adults compared to both young adults and midlife adults (**Table 8**).

4.3 Effect of processing speed on the computerized version of STSS

The processing speed had a significant effect on all dependent variables ($p < 0.001$). However, the effect of age remains significant even after adjusting this covariate excepting for: the inhibition (conflict adaptation; Word trials), and inhibition (conflict adaptation) plus switching (i.e., Word trials: young adults versus midlife adults), (Wilks lambda = 0.082; $F(3, 96) = 1.190$; $p = 0.318$) (**Table 8**).

Table 8. Mean (standard deviation) performance of cognitive processes underlying the computerized version of the Stroop Switching Card Test

Inhibition without a change in congruence	Conflict resolution (color)	RT_II_CC minus RT_CC_CC	129.16 (62.53)	160.92 (98.53)	210.11 (80.42)	P = 0.927	P = 0.012	P = 0.081	η^2 = 0.162
		TNE_II_CC	0,04 (0,20)	0,17 (0,39)	0,18 (0,48)	P = 0.736	P = 0.701	P = 1	-
	Conflict resolution (word)	RT_II_WW minus RT_CC_WW	133.25 (49.46)	150.82 (42.16)	228.55 (31.23)	P = 0.765	P = 0.001	P = 0.001	η^2 = 0.510
		TNE_ II_WW	0,03 (0,19)	0,10 (0,31)	0,08 (0,27)	P = 0.986	P = 0.025	P = 0.222	η^2 = 0.095
Inhibition with a change in congruence	Conflict adaptation (color)	RT_CI_CC minus RT_II_CC	172.62 (59.82)	345.85 (116.98)	367.66 (105.13)	P = 0.001	P = 0.001	P = 0.556	η^2 = 0,436
		TNE_ CI_CC	0,04 (0,20)	0,28 (0,46)	0,51 (0,50)	P = 0.133	P = 0.006	P = 0.295	η^2 = 0,177
	Conflict adaptation (word)	RT_CI_WW minus RT_II_WW	136.04 (60.01)	161.32 (60.85)	255.03 (53.21)	P = 0.982	P = 0.001	P = 0.001	η^2 = 0.444
		TNE_ CI_WW	0.08 (0,28)	0,14 (0,35)	0,70 (0,46)	P = 1	P = 0.001	P = 0.001	η^2 = 0,362
Inhibition and switching without a change in congruence	Conflict resolution and switching (Word-Color)	RT_II_WC minus RT_II_CC	124.58 49.63	91.82 (86.98)	45.77 (67.26)	P = 0.615	P = 0.006	P = 0.163	η^2 = 0.175
		TNE_ II_WC	0,04 (0,20)	0,25 (0,44)	0,29 (0,46)	P = 0.212	P = 0.074	P = 0.996	-
	Conflict resolution and switching (Color-Word)	RT_II_CW minus RT_II_WW	78.54 (130.67)	208.17 (142.99)	205.33 (80.18)	P = 0.020	P = 0.006	P = 0.981	η^2 = 0,269
		TNE_ II_CW	0,04 (0.20)	0,39 (0.62)	0,74 (0.71)	P = 0.024	P = 0.001	P = 0.069	η^2 = 0.268
Inhibition and switching with a change in congruence	Conflict adaptation and switching (Word color)	RT_CI_WC minus RT_II_CC	302.708 (139.69)	288.89 (107.83)	330.90 (72.41)	P = 0.777	P = 0.998	P = 0.422	-
		TNE_ CI_WC	0.16 (0,38)	0,25 (0,44)	0,70 (0,66)	P = 1	P = 0.171	P = 0.149	-
	Conflict adaptation and switching (Color-Word)	RT_CI_CW minus RT_II_WW	170.79 (51.01)	245.28 (66.77)	320.85 (136.68)	P = 0.024	P = 0.001	P = 0.001	η^2 = 0.269
		TNE_ CI_CW	0,08 (0.28)	0,25 (0.44)	0,51 (0.50)	P = 0.709	P = 0.001	P = 0.050	η^2 = 0.269

Black: No significant; Blue: Significant without adjustment for processing speed; Red: Significant even after adjustment for processing speed; Blue: Key findings that will be discussed in this study; η^2: Partial Eta Squared after adjustment for processing speed; YA: young adults; MA: midlife adults; OD: older adult

5. Discussion

The current study examined the effect of aging on the different cognitive processes underlying the computerized version of the SSCT, in a paradigm aimed to assess inhibition (conflict resolution and conflict adaptation) associated, or not, with switching.

Given the multitude of findings reported in this study, we aimed in this discussion to select the most relevant ones (Key findings; **Tables 8 and 9**), notably results showing that: (i) older adults were slower and less accurate than both young adults and midlife adults, and (ii) both midlife and older adults were slower and less accurate than young adults, even after adjustment for processing speed. From our point of view, this selection of findings might help to provide an adequate response to when decline begins in cognitive processes underlying EF. Following this choice of data, the key findings that emerged are that the inhibition (conflict resolution) and switching begin to decline at middle age (40-59 years), whereas the inhibition (conflict adaptation) in an association, or not, with switching, begins to decline only at older age (60-79 years).

Table 9. Key findings

	Before 60 years	**After 60 years**
Inhibition (conflict adaptation)	NO	**YES**
Inhibition (conflict adaptation) and switching	NO	**YES**
Inhibition (conflict resolution) and switching	**YES**	NO

5.1 Inhibition (conflict adaptation)

All participants produced faster responses in incongruent trials when the previous trial was incongruent (II_WW) than when it was congruent (CI_WW). Previous studies have suggested that resolving prior incongruent trial enhances attentional focus and amplifies representations of relevant features of the stimulus, leading to reduced influence of the distractor (irrelevant information) on response execution, thus faster RT for II_WW trials than CI_WW trials (Egner and Hirsch, 2005; Egner, 2007; Lorist and Jolij 2012). These adjustments in RTs are referred to as "conflict adaptation" or "Gratton" effect (Gratton et al. 1992). Neuroimaging studies have associated the conflict adaptation to (i) the anterior cingulate cortex that assures the detection of the congruence conflict, and (ii) the lateral prefrontal cortex that

regulates the conflict (Gratton et al. 1992; Botvinick et al. 2001; Aschenbrenner and Balota, 2015; Kim et al. 2016). As for age effect, older adults were slower and less accurate than both young adults and midlife adults. This finding supports the frontal lobe damage hypothesis and are in line with previous studies showing a decline in inhibition requiring a conflict adaptation (Mutter et al. 2005; Larson et al. 2016).

5.2 Inhibition (conflict adaptation) and switching

To our knowledge, this study is the first to propose trials assessing inhibition (conflict adaptation) and switching, which may provide a better understanding of age-related changes in adjustment of cognitive control. Our results suggest that older adults were slower and less accurate in CI_CW trials compared to both young and midlife adults. The present finding suggests that when a cognitive task involves both inhibition (conflict adaptation) and switching, a decline in cognitive control become evident at older age (60-79 years). In terms of performance, we suggest that older adults need more top-down control to switch from a congruent trial requiring to name the ink color to an incongruent trial requiring to say the meaning of the word. This additional cost in switching may be related to the change in instruction that may disturb their ability to maintain properly the goal of the current task. Therefore, older adults were unable to make important performance adjustments. It should be noted that the goal maintenance is related to the working memory capacity (Emerson and Miyake, 2003) whereas top-down control requires attentional resources (Adam et al. 2002). Thus, decline in general resources (working memory, attention) could also contribute to the decline in performance of older adults in CI_CW trials.

Taking into account the findings of the section 5.1, decline in inhibition (conflict adaptation) associated or not with switching, becomes evident at older age (60-79 years), leading to suggest that WW_CI and CW_CI trials are associated with equivalent conflict demand.

5.3 Inhibition (conflict resolution) and switching

All participants reacted faster in II_WW trials compared to II_CW trials. It is likely that RT difference between these trials appears from task-set inertia and higher top-down control (Allport et al. 1994; Wu et al. 2015). The task inertia suggests that after a switch trial, the color naming task set is still active on a word reading trial. The top-down control is required to establish a new task set while resolving interference from previous task set.

As for age effect, both midlife adults and older adults were slower and less accurate in II_CW trials compared to young adults, suggesting that the inhibition (conflict resolution) and switching begin to decline at middle age (40-59 years). This finding confirms the findings of our previous study showing declines in both inhibition (as assessed by the STROOP C_{IES}) and switching (TMT B_{IES}) from the age of 40. The decreased performance in both midlife and older adults arises probably because they were more sensitive to interference and less able to switch between tasks (Hutchison et al. 2010). It should be recalled that the prefrontal cortex plays an important role in inhibition (conflict resolution; Botvinick et al. 2001; Mansouri et al. 2007; Floden et al. 2011) and switching (Killiany et al. 2000; Mintun et al. 2007; van derFlier et al. 2002; Yanaguchi et al. 2001). Given that, both the Stroop and task-switching paradigms involve regions of the prefrontal cortex (Harrington et al. 2013, Belghali et al. 2017a), it is not surprising that the CI_CW trial, which combines both paradigms, is specifically altered with aging.

To our knowledge, only one study is conducted today to assess inhibition (conflict resolution) and switching together (Hutchison et al. 2010). The authors have shown that young adults and older adults decreased to the same extent their cognitive performance (switch cost based on response time) in II_CW trials. A possible explanation of this contradictive finding is that the authors used a cue indicating how to perform each trial, while in our study no cue was used. We suggest that adding a cue may decrease the cognitive load of the task, thereby minimizing the possibility to capture changes in cognitive control associated with aging.

5.4 Conclusion and perspective

To the best of our knowledge, we are the first to propose a computerized test assessing the different cognitive processes underlying inhibition, and inhibition with switching, simultaneously. Findings of this study suggest that the cognitive processes underlying EF are deteriorated differently and gradually over time. The inhibition (conflict resolution) and switching begin to decline at middle age (40-59 years), whereas the inhibition (conflict adaptation) in an association, or not, with switching, begin to decline only at older age (60-79 years). The main limitation of this study is that older adults are low educated (8 years), thus limiting the generalizability of our results. Future studies including a large sample size are needed to confirm these results. As a result of this work, our perspectives are to:

1) develop a more sophisticated computerized version of the SSCT allowing the assessment of updating. This development is undergoing in collaboration with Nicolas LEFEVRE (an engineer with experience in computer science).

2) perform analysis to understand why word stimuli affect more individual performance than color stimuli.

Methodological innovation in cognitive reserve assessment

The third study of this thesis proposes two measures of CR, one of which is qualitative and the other is quantitative.

Qualitative and quantitative measures of cognitive reserve

1. Introduction

The concept of CR was proposed to explain the mismatch between brain damages and their clinical manifestations. Behaviorally, it is well admitted that individuals with high CR display better cognitive performances than those with low CR despite an equivalent level of pathology or damages.

CR is often estimated using a specific proxy such as the level of education, language status, occupational status, and engagement in cognitively stimulating activities (Nucci et al. 2012; Leon et al. 2011; León et al. 2014). As previously mentioned, the majority of studies used only one proxy to estimate CR (**Table 3**). Critically, using just one proxy seems not recommended as it may reduce the accuracy of associated results (Jones et al. 2011). This is probably because each proxy independently contributes to the development of CR (Foubert-Samier et al. 2012). Therefore, we can admit that a reliable measure of CR is possible only by assessing its different proxies. While few studies have attempted to measure CR through a combination of some of these proxies (Nucci et al. 2012; Leon et al. 2011; León et al. 2014), none of them has proposed an exact methodology assessing CR. In fact, even if the same proxies (or combination) are used, the procedures and measurement scale are extremely heterogeneous making thus the choice of assessment methods of proxies very difficult.

It should be noted that CR is often estimated from young adulthood (18–35 years), until late adulthood (over the age of 65 years). To our knowledge, the childhood period is often ignored in the majority of study. However, this period of life is crucial for the building of reserve as it plays a central protective role against the development of neurodegenerative diseases. Evidence of this view comes from the studies by Whalley et al. (2000), and Dekhtyar et al. (2015) that have shown that childhood mental ability scores and childhood school grades are strong predictors of poor cognitive function and dementia in late life. Therefore, it is crucial to elaborate proxies specific to the childhood period.

Another important critical point to emphasize is that the age of stopping elementary school, and both health and professional status after retirement were not considered in all studies, whereas such kind of proxies may also affect the cognitive health of older adults (Murphy and O'Leary 2010; Ihle et al. 2016; Clare et al. 2017). Following this finding, it is

necessary to develop a new questionnaire of CR that take into account all periods of life (with specific proxies for each), and a new scoring helping to estimate CR, accurately.

We would like to highlight that the different proxies of CR allow just a qualitative estimation of this hypothetical construct. At a behavioral level, one of the possibility to assess CR, dynamically, is to quantify the mismatch between cognitive performance and the extent of brain disease or damage (Mitchell et al. 2012). In the context of normal aging, some authors suggest that the assessment of EF has special importance given that the prefrontal cortex is the most sensitive part of the brain to the adverse effects of aging (Lamar et al. 2004). Therefore, the assessment of EF in older adults is particularly relevant to study the possible protective effect of CR. Following this suggestion, recent studies have shown that older adults with high CR display better executive performance than those with low CR. The maintenance of executive performance in older adult with high CR is probably due to the better use of brain reserve and flexible strategy usage (Tuker and Stern, 2011). Despite the relevance of these findings, there is today no threshold for an executive decline indicating either high or low CR. Such threshold is crucial to determine who grows old gracefully and who declines rapidly. Taking into account the dynamic aspect of CR, we suggest that an executive test requiring strategy usage would allow a quantitative measure of CR in older adults; therefore determine threshold for an executive decline.

Statistically, one of the possibilities to determine a threshold for an executive decline specific to either high or low CR is the technique of Receiver Operating Characteristic, or "ROC analysis". The latter is often used in clinical biology to determine threshold values (Delacour et al. 2005) to distinguish patients from healthy individuals. To our knowledge, this technique has never been used to establish the links between cognitive reserve and EF.

Taking all the above into consideration, the main aim of this study is to propose new qualitative (questionnaire-based) and quantitative (threshold for the executive decline specific to low CR) approaches to the measurement of CR.

2. Protocol overview

Older adults of the previous study voluntarily participated to this experiment and gave their written informed consent. They completed in a single session of approximately 45 minutes the CRQ (**Appendix 6**). The latter was developed to quantify through a large diversity of questions the amount of CR accumulated over the lifespan (i.e., childhood, adolescence, youth, middle age and old age). Each life phase includes specific proxies described and scored in **Tables 10-18**. The total score of the CRQ ranges from 0 to 564 points.

Childhood (6-12 years): This life period includes specific proxies related to both parents (i.e., including the profession, education, salary ranges and leisure activities), and child (i.e., including the language status, leisure activities, quality of life, social network size and education).

Table 10. Specific proxies related to parents

	Parents	**Total score specific to each proxy**	**Total score**
Education	Participants were asked to report the educational level of their parents. We categorized education using a nine-level variables computed as below: 0 point = Illiterate 0,5 point = Primary school without diploma (equivalent to 0–4 years of schooling) 1 points = Primary school validated with a diploma (equivalent to 6 years of schooling) 1,5 points = Secondary school without diploma (equivalent to 7–8 years of schooling) 2 points = Secondary school with diploma (equivalent to 9 years of schooling) 2,5 points = High school without diploma (equivalent to 10–12 years of schooling) 3 points = High school with diploma (equivalent to 13 years of schooling) 4 points = University level without diploma (equivalent to 14–15 years of schooling) 5 points = University level with one diploma (equivalent to 16 years of schooling) 7 points = University level with two diplomas (equivalent to 18 years of schooling) 9 points = University level with three diplomas and more (over 20 years of schooling)	A Likert-type scale of 0–9 points	A Likert-type scale of 0–24 points
Profession	Participants were asked to report the profession of their parents. We categorized profession using five-level variables computed as below: 1 point = Unskilled manual work; 2 points = Skilled manual work; 3 points = Technical work; 4 points = Professional work; 5 points = Intellectual work	A Likert-type scale of 1–5 points	
Salary ranges	Participants were asked to report the salary ranges of their parents. We categorized salary ranges using a four-level variables computed as below: 0 point = Very low; 1 point = Low; 2 points = Middle; 3 points = High; 4 points = Very high	A Likert-type scale of 0–4 points	
Leisure activities	Participants were asked to report the leisure activities of their parents. We proposed 6 groups for leisure activities: Intellectuals (eg, reading books/ newspapers, jigsaw puzzles), physical activities (eg, walking	A Likert-type scale of 0–6 points	

	or sports), and social activities (eg, playing cards/ board games, visiting friends or relatives), artistic activities (eg, painting, playing an instrument), Travelling and volunteering (eg, counselling, gardening,). One point was attributed for each activity. Thus, activities were scored from 0 to 6 points
	Mother or Father's score: level of education+ profession+ salary ranges+ leisure activities **Parent' score: (score of mother + score of father) / 2**

Table 11. Specific proxies related to childhood

	Normal childhood	Total score specific to each proxy	Total score
Education	Participants were asked to report their educational training path at childhood (i.e., primary school performance, diplomas) Primary school performance: We categorized school performance using four-level variables, which were computed as below: 0 point = Very week (school performance less than 5/20) 1 points = Weak (school performance between 5 and 9/20) 2 points = Medium (school performance between 10 and 12/20) 3 points = Good (school performance between 13 and 15/20) 4 points = Very good (school performance between 16 and more/20) Diplomas: We categorized diplomas using two-level variables computed as below: 0,5 point = Primary school without diploma; 1 point = Primary school validated with a diploma	A Likert-type scale of 0–5 points	A Likert-type scale of 0–75 points
Quality of life	We categorized the quality of life using a three-level variables, computed as below: 0 point = Dissatisfied; 1 point = Little satisfied; 2 points = Satisfied; 3 points = Very satisfied	A Likert-type scale of 0–3 points	
Social network size	Participants were asked to report their place of residence and their social network. We categorized the place of residence using a four-level variables computed as below:	A Likert-type scale of 1–7 points	

	1 point = Lived in an orphanage and Child Care Centre; 2 points = Lived with a family member 3 points = Lived with one of your parents (mother or father); 4 points = Lived with both mother and father	
	We categorized the social network using a three-level variables, computed as below: 0 point = Unsociable; 1 point = Little sociable 2 points = Sociable; 3 points = Very sociable	
Leisure activities	Participants were asked to report their leisure activities. We proposed 5 groups for leisure activities: Artistic, sports, intellectuals, social, and travel. Each activity belonging to a different category was computed as below: (DURATION*FREQUENCY) + MANNER OF PRACTICE	
	Duration 1 point= 1-2 hours; 2 points = 2-3 hours, 3 points = 3 - 4 hours, Frequency 1 point = monthly; 2 points = 1 time a week; 3 points = 3 times a week; 4 points = daily Manner of practice 1 point= individually; 2 points = collectively.	A Likert-type scale of 2–14 points for each activity belonging to a different category
	For each additional activity belonging to the same category (e.g., Handball and swimming), we attributed a half of score of an activity belonging to a different category Duration 0,5 point= 1-2 hours; 1 points = 2-3 hours, 1,5 points = 3 - 4 hours Frequency 0, 5 point = monthly; 1 points = 1 time a week; 1, 5 points = 3 times a week; 2 points = daily Manner of practice 0, 5 point= individually; 1 points = collectively.	A Likert-type scale of 0,75–4 points for each additional activity belonging to the same category
Language status	Participants were asked to report their language status at childhood (e.g. language performance, language practice outside the school, language learning in primary school). Language learning in primary school was computed as below: AGE OF INDUCING LEARNING + (DURATION*FREQUENCY)	A Likert-type scale of 1,5–15
	Age of inducing learning: 1 point= 10-12 years; 2 points = 8-10 years; 3 points = 6-8 years Duration: 0,5 point= 6 months-1 year; 1 point= 1-2 years; 2 points = 2-4 years; 3 points = more than 4 years Frequency: 1 point = seasonal; 2 points= weakly; 3 points= daily Language training outside the school was computed as below DURATION*FREQUENCY	

	Duration: 0,5 point = less than 6 months; 1 point= 6 months-1 year; 2 point= 1-2 years; 3 points = 2-4 years; 4 points = more than 4 years Frequency: 1 point = seasonal; 2 points= weakly; 3 points= daily Language performance: We categorized language performance using 5-level variables, computed as below:	A Likert-type scale of 1,5–15
	Oral language comprehension: 0 point = Low; 1 point= Medium; 2 points = Good; 3 points = Excellent Written language comprehension: 0 point = Low; 1 point= Medium; 2 points = Good; 3 points = Excellent Oral expression: 0 point = Low; 1 point= Medium; 2 points = Good; 3 points = Excellent) Written expression: 0 point = Low; 1 point= Medium; 2 points = Good; 3 points = Excellent) Bilingual or trilingual: 12 points were attributed for either bilingual or trilingual	A Likert-type scale of 0–12
	Childhood's score = Parent' score + Normal childhood score	

Table 12. Specific proxies related to children who stopped their education at early age

It is widely admitted that stopping school at early age could an adverse effect in CR building. This new proxy was computed as below.

	Exception for children who stopped their education at early age	Total score specific to each proxy	Total score
Working activities at childhood	Participants who stopped their education at early age were asked to report their working activities at childhood, which are computed as below.		
	AGE+ WORKING ACTIVITIES	A Likert-type scale of -1 to –3 points	
	Working age: We categorized the working age using 3-level variables, computed as below:		
	-1 point = 10-12 years; -2 point = 8-10 years; - 3 point = 6-8 years		
	Each manual activity was computed as below		A Likert-type scale of -1 to -12 points
	DURATION * FREQUENCY		
	Duration: -1 point = less than 6 months; -2 points = 1-2 years; -3 points = 2-4 years Frequency: 1 point = seasonally; 2 points = monthly; 3 points = weakly; 4 points = daily	A Likert-type scale of -1 to –12 points	
	Other working activities were computed as below		
	DURATION * FREQUENCY		
	Duration: -0,5 point = less than 6 months; -1 point = 1-2 years; -1,5 = 2-4 years Frequency: 0, 5= seasonally; 1 points = monthly; 1, 5 = weakly; 2 = daily	A Likert-type scale of -0,25 to –3 points	

Adolescence (13-19 years): Proxies selected for adolescents are: College and high school performances, training, language status, leisure activities, quality of life, social network size and financial well-being. These proxies were computed as below:

Table 13. Specific proxies related to adolescence

	Adolescence	Total score specific to each proxy	Total score
Education	Participants were asked to report their educational training path at adolescence (i.e., college and high school performance, diplomas, training outside the school) College and high school performances College and high school performances were computed as the primary school performance.	A Likert-type scale of 0–5-2 points	A Likert-type scale of 0–95 points
	We categorized diplomas using four-level variables computed as below Diplomas: 0,5 points = Secondary school without diploma; 1 point = Secondary school with diploma; 1,5 points = High school without diploma; 2 points = High school with diploma	A Likert-type scale of 0,5–5 points	
	Training outside the school Participants were asked to report the different training performed outside the school. We proposed 2 groups for training: cognitive and manual Cognitive stimulating training was computed as below DURATION*FREQUENCY Duration: 0, 5 point = 1-3 months; 1 point = 3-6 months; 2 points = 6 months - 1 year; 3 points = 1- 2 years; 4 points: 2 years and more Frequency: 1 point = seasonal; 2 points= weakly; 3 points= daily	A Likert-type scale of 0,5– 12 points	
	Manual training was computed as below DURATION*FREQUENCY Duration: 0, 5 point = 1-3 months; 1 point = 3-6 months; 1, 5 points = 6 months - 1 year; 2 points = 1- 2 years; 2, 5 points-2 years and more Frequency: 0,5 point = seasonal; 1 points= weakly; 2 points= daily	A Likert-type scale of 0,25–5 points	

***Leisure activities** *** Quality of life** ***Social network size**	Leisure activities, quality of life and social network size were computed as the childhood period.	A Likert-type scale of 0–18 points A Likert-type scale of 0–10
Language status	Participants were asked to report their language status at adolescence (e.g. language performance, language practice outside the school, language learning at college and high school). Language learning at college and high school was computed as below. AGE OF INDUCING LEARNING + (DURATION *FREQUENCY) Age of inducing learning: 1 point= 17-19 years; 2 points = 15-17 years; 3 points = 13-15 years Duration: 0,5 point= 6 months-1 year; 1 point= 1-2 years; 2 points = 2-4 years; 3 points = more than 4 years Frequency: 1 point = seasonal; 2 points= weakly; 3 points= daily Language practice outside the school and language performance were computed as the childhood period.	A Likert-type scale of 1,5–12 A Likert-type scale of 0–27
Financial well-being	Participants were asked to report their financial well-being. We categorized financial well-being using a four-level variables computed as below: 0 point = Very low; 1 point = Low; 2 points = Middle; 3 points = High; 4 points = Very high	A Likert-type scale of 0–4

Table 14. Specific proxies related to adolescents who stopped their education at early age

	Adolescents who stopped their education at early age	Total score specific to each proxy	Total score
Professional training	Participants who stopped their education at early age were asked to report their training at adolescence. We categorized training using two-level variables (i.e., cognitive stimulating training and unskilled and skilled manual training), which are computed as below: Cognitive stimulating training = DURATION*FREQUENCY Duration: 0, 5 point = less than 6 months; 1 point = 6 months - 1 year; 2 points = 1- 2 years; 3 points =2 years and more Frequency: 1 point = seasonal; 2 points= weakly; 3 points= daily	A Likert-type scale of 0,5–9	A Likert-type scale of 0,25–18
	Unskilled and skilled manual training = DURATION*FREQUENCY Duration: 0, 5 point = less than 6 months; 1 point = 6 months - 1 year; 1,5 points = 1- 2 years; 2 points =2 years and more Frequency: 1 point = seasonal; 2 points= weakly; 3 points= daily	A Likert-type scale of 0,25–6	
Working activities	Participants who stopped their education at early age were asked to report their working activities at adolescence. We categorized working activities using three-level variables (Unskilled Manual work, Skilled Manual work, Technical work). Each activity was computed as below. WORKING ACTIVITIES= AGE OF WORKING STARTING + DURATION*FREQUENCY **Age of working starting**: We categorized age of working using three-level variables -1 point = 17-19 years; -2 point = 15-17 years; - 3 point = 13-15 years	A Likert-type scale of -1 to -3	
	Unskilled Manual work Duration: 0, 5 point = less than 6 months; 1 point = 6 months - 1 year; 1,5 points = 1- 2 years; 2 points =2 years and more Frequency: 0,5 point = seasonal; 1 points= weakly; 1,5 points= 2 points= daily	A Likert-type scale of 0,25–4	
	Skilled Manual work Duration: 0, 5 point = less than 6 months; 1 point = 6 months - 1 year; 1,5 points = 1- 2 years; 2 points =2 years and more Frequency: 0,5 point = seasonal; 1 points= weakly; 2 points= 2,5 points= daily	A Likert-type scale of 0,25–5	
	Technical work Duration: 0, 5 point = less than 6 months; 1 point = 6 months - 1 year; 2 points = 1- 2 years; 3 points =2 years and more Frequency: 0,5 point = seasonal; 1 points= weakly; 2,5 points= 3 points= daily	A Likert-type scale of 0,25–9	

Youth (20-40 years): Proxies selected for young adults are: profession, training, language status, leisure activities, quality of life, social network, financial wellbeing (student's period) and salary ranges. These proxies were computed as below:

Table 15. Specific proxies related to young adults

	Youth	Total score specific to each proxy	Total score
Education	Participants were asked to report their educational training path at the period of youth (i.e., university performance, diplomas) University performance University performance was computed as the college and high school performances. Diplomas We categorized diplomas using four-level variables computed as below: 1 point = University level without diploma; 2 points = University level with one diploma; 4 points = University level with two diplomas; 6 points = University level with three diplomas and more	A Likert-type scale of 0–5 points A Likert-type scale of 1–6	A Likert-type scale of 0–102,5 points
Profession	Participants were asked to report their profession at the period of youth. Five categories were created and were computed as below. **Unskilled Manual work** = DURATION*FREQUENCY Duration:1 point =1-5 years;2 points = 2 - 10 years; 3 points = 10 -15 years; 4 points = 15- 20 years and more Frequency: 0,5 point = seasonal; 1 point = weakly; 1,5 points= daily **Skilled Manual work** = DURATION*FREQUENCY Duration: 2 points =1-5 years; 3 points = 2-10 years; 4 points = 10-15 years; 5 points = 15- 20 years Frequency: 0,5 point = seasonal; 1 point= weakly; 1,5 points= daily **Technical work** = DURATION*FREQUENCY Duration: 3 points =1-5 years; 4 points= 2-10 years; 5 points = 10-15 years; 6 points = 15-20 years Frequency: 0,5 point = seasonal; 1 point= weakly; 1,5 points= daily **Professional occupation** = DURATION*FREQUENCY Duration: 4 points =1-5 years; 5 points = 2-10 years; 6 points = 10-15 years; 7 points = 15 - 20 years Frequency: 1 point = seasonal; 1,5 points= weakly; 2 points= daily **Intellectual occupation** = DURATION*FREQUENCY Duration: 5 points =1-5 years; 6 points = 2- 10 years; 7 points = 10-15 years; 8 points = 15- 20 years Frequency: 1 point = seasonal; 2 points= weakly; 2,5 points= daily	A Likert-type scale of 0,5–6 points A Likert-type scale of 1–7,5 points A Likert-type scale of 1,5–9 points A Likert-type scale of 4–14 points A Likert-type scale of 5–20 points	

Professional training	Participants were asked to report their professional training at the youth period. We categorized training using two-level variables (i.e., cognitive stimulating training and unskilled and skilled manual training), which are computed as below: Cognitive stimulating training = DURATION*FREQUENCY Duration: 0, 5 point = less than 6 months; 1 point = 6 months - 1 year; 2 points = 1- 2 years; 3 points =2 years and more Frequency: 1 point = seasonal; 2 points= weakly; 3 points= daily Unskilled and skilled manual training = DURATION*FREQUENCY Duration: 0, 5 point = less than 6 months; 1 point = 6 months - 1 year; 1,5 points = 1- 2 years; 2 points =2 years and more Frequency: 0,5 point = seasonal; 1 points= weakly; 3 points= daily	A Likert-type scale of 0,5–9 points A Likert-type scale of 0,25–6 points
Leisure activities	Leisure activities were computed as the previous periods	A Likert-type scale of 0–18 points
Language status	Participants were asked to report their language status at the period of youth (language performance, language practice outside the university, language learning at the university). Language learning at the university was computed as below. AGE OF INDUCING LEARNING + (DURATION *FREQUENCY) Age of inducing learning: 0,5 points = 24 years and more 1 point= 22-24 years; 1,5 points = 20-22 years Duration: 0,5 point= 6 months-1 year; 1 point= 1-2 years; 1,5 points = 2-4 years; 2 points = more than 4 years Frequency: 0.5 point = seasonal; 1 point = weakly; 1.5 points= daily Language training and language competence were computed as the previous periods of life.	A Likert-type scale of 0,75-4,5 points A Likert-type scale of 0–27 points
Financial well-being (student's period) or salary ranges	Participants were asked to report either their salary ranges or their financial well-being at the youth period. We categorized salary ranges and financial well-being using a four-level variables computed as below: 0 point = Very low; 1 point = Low; 2 points = Middle; 3 points = High; 4 points = Very high	A Likert-type scale of 0–4 points
Quality of life	The quality of life at the youth period was computed as the previous periods.	A Likert-type scale of 0–3 points
Social network size	Participants were asked to report their place of residence and their social network at the youth period. We categorized the place of residence using a three-level variables computed as below: 1 point = alone; 2 points = living with a family member; 3 points = spouse/wife/husband or friends The social network was computed as the previous periods.	A Likert-type scale of 1–6 points

Adulthood and old age (41-59 years): The specific proxies for both midlife and older adults (60 years until retirement) are: Profession, training, language status, leisure activities, quality of life, social network and salary ranges. These proxies were computed as below:

Table 16. Specific proxies related to midlife adults and older adults (until retirement)

	Midlife and old age until retirement	Total score specific to each proxy	Total score
Profession	Participants were asked to report their profession at adulthood and old age (until retirement). Five categories were created and were computed as below. **Unskilled Manual work** = DURATION*FREQUENCY Duration:1 point =1-5 years;2 points = 2 - 10 years; 3 points = 10 -15 years; 4 points = 15- 20 years and more Frequency: 0,5 point = seasonal; 1 point = weakly; 1,5 points= daily **Skilled Manual work** = DURATION*FREQUENCY Duration: 2 points =1-5 years; 3 points = 2-10 years; 4 points = 10-15 years; 5 points = 15- 20 years Frequency: 0,5 point = seasonal; 1 point= weakly; 1,5 points= daily **Technical work** = DURATION*FREQUENCY Duration: 3 points =1-5 years; 4 points= 2-10 years; 5 points = 10-15 years; 6 points = 15-20 years Frequency: 0,5 point = seasonal; 1 point= weakly; 1,5 points= daily **Professional occupation** = DURATION*FREQUENCY Duration: 4 points =1-5 years; 5 points = 2-10 years; 6 points = 10-15 years; 7 points = 15 - 20 years Frequency: 1 point = seasonal; 1,5 points= weakly; 2 points= daily **Intellectual occupation** = DURATION*FREQUENCY Duration: 5 points =1-5 years; 6 points = 2- 10 years; 7 points = 10-15 years; 8 points = 15- 20 years Frequency: 1 point = seasonal; 2 points= weakly; 2,5 points= daily	A Likert-type scale of 0,5–6 points A Likert-type scale of 1–7,5 points A Likert-type scale of 1,5–9 points A Likert-type scale of 4–14 points A Likert-type scale of 5–20 points	A Likert-type scale of 0,5–98,5
	Participants were asked to report their professional training at adulthood and old age (until retirement). We categorized training using two-level variables (i.e., cognitive stimulating training and unskilled and skilled manual training), which are computed as below: **Cognitive stimulating training** = DURATION*FREQUENCY Duration: 0, 5 point = less than 6 months; 1 point = 6 months - 1 year; 2 points = 1- 2 years; 3 points =2 years and more Frequency: 1 point = seasonal; 2 points= weakly; 3 points= daily	A Likert-type scale of 0,5–9 points	

	Unskilled and skilled manual training = DURATION*FREQUENCY Duration: 0, 5 point = less than 6 months; 1 point = 6 months - 1 year; 1,5 points = 1- 2 years; 2 points =2 years and more Frequency: 0,5 point = seasonal; 1 points= weakly; 3 points= daily	A Likert-type scale of 0,25–6 points
Leisure activities	Participants were asked to report their leisure activities. We proposed 5 groups for leisure activities: Artistic, sports, intellectuals, social, and travel. Each activity belonging to a different category was computed as below: (DURATION*FREQUENCY) + MANNER OF PRACTICE Duration: 0,5 point= 30 min; 1 point = 1 hour and more Frequency: 1 point = monthly; 2 points = 1 time a week; 3 points = 3 times a week; 4 points = daily Manner of practice: 1 point= individually; 2 points = collectively.	A Likert-type scale of 1,5–6 points
	For each additional activity belonging to the same category (e.g., Handball and swimming), we attributed a half of score of an activity belonging to a different category: Duration: 0,5 point= 30 min; 1 point = 1 hour and more Frequency: 0, 5 point = monthly; 1 points = 1 time a week; 1, 5 points = 3 times a week; 2 points = daily Manner of practice: 0, 5 point= individually; 1 points = collectively.	A Likert-type scale of 0,75–3 points
Language status	Participants were asked to report their language status at adulthood and old age until retirement (language training, language practice). Language practice was computed as below. (DURATION *FREQUENCY) Duration: 0,5 point= 6 months-1 year; 1 point= 1-2 years; 1,5 points = 2-4 years; 2 points = more than 4 years Frequency: 0,5 point = seasonal; 1 points= weakly; 1,5 points= daily	A Likert-type scale of 0,25–3 points
	Language training was computed as below. (DURATION *FREQUENCY) Duration: 0,5 point= 6 months-1 year; 1 point= 1-2 years; 1,5 points = 2-4 years; 2 points = more than 4 years Frequency: 0,5 point = seasonal; 1 points= weakly; 1,5 points= daily	A Likert-type scale of 0,25–3 points

Salary ranges	Participants were asked to report their salary ranges at adulthood and old age (until retirement). We categorized salary ranges using a four-level variables computed as below: 0 point = Very low; 1 point = Low; 2 points = Middle; 3 points = High; 4 points = Very high	A Likert-type scale of 0–4 points
Quality of life	We categorized the quality of life using a three-level variables, computed as below: 0 point = Dissatisfied; 1 point = Little satisfied; 2 points = Satisfied; 3 points = Very satisfied	A Likert-type scale of 0–3 points
Social network size	Participants were asked to report their place of residence and their social network at adulthood and old age (until retirement). We categorized the place of residence using a three-level variables computed as below: 0 point= alone; 1 point = living with a family member, 2 points = spouse/wife/husband or friends We categorized the social network using a three-level variables, computed as below: 0 point = Unsociable; 1 point = Little sociable; 2 points = Sociable; 3 points = Very sociable	A Likert-type scale of 0–5 points

Old age (After retirement): Proxies selected for older adults (after retirement) are: Professional status, training, language status, leisure activities, quality of life, social network and salary ranges. These proxies were computed as below:

Table 17. Specific proxies related to older adults after retirement

	Old age after retirement	Total score specific to each proxy	Total score
Professional status	Participants were asked to report their professional status after retirement. The latter was computed as below. - 1 point = inactive for 0 to 4 years; - 2 points = inactive for 5 to 9 years; -3 points = inactive for 10 to 14 years; -4 points = inactive for 15 years and more; 1 point = active for 0 to 4 years; 2 points = active for 5 to 9 years; 3 points = active for 10 to 14 years; 4 points = active for 15 years and more.	A Likert-type scale of –4 to 4 points	A Likert-type scale of - 4 to 35 points
Leisure activities	Participants were asked to report their leisure activities at old age after retirement. We proposed 5 groups for leisure activities: Artistic, sports, intellectuals, social, and travel. Each activity belonging to a different category was computed as below: (DURATION*FREQUENCY) + MANNER OF PRACTICE Duration: 1 point= 30 min; 2 point = 1 hour and more Frequency: 1 point = monthly; 2 points = 1 time a week; 3 points = 3 times a week; 4 points = daily Manner of practice: 1 point= individually; 2 points = collectively.	A Likert-type scale of 2–9 points	
	For each additional activity belonging to the same category (e.g., Handball and swimming), we attributed a half of score of an activity belonging to a different category: Duration: 0,5 point= 30 min; 1 point = 1 hour and more Frequency: 0, 5 point = monthly; 1 points = 1 time a week; 1, 5 points = 3 times a week; 2 points = daily Manner of practice: 0, 5 point= individually; 1 point = collectively.	A Likert-type scale of 0,75–3points	
Language status	Participants were asked to report their language status at old age after retirement (language training, language practice).		

	Language practice was computed as below. (DURATION *FREQUENCY) Duration: 0,5 point= 6 months-1 year; 1 point= 1-2 years; 1,5 points = 2-4 years; 2 points = more than 4 years Frequency: 0,5 point = seasonal; 1 points= weakly;1,5 points= daily Language training was computed as below. (DURATION *FREQUENCY) Duration: 0,5 point= 6 months-1 year; 1 point= 1-2 years; 1,5 points = 2-4 years; 2 points = more than 4 years Frequency: 0,5 point = seasonal; 1 points= weakly; 1,5 points= daily	A Likert-type scale of 0,25–3 points A Likert-type scale of 0,25–3 points
Retirement salary ranges	Participants were asked to report either their salary ranges after their retirement. We categorized salary ranges using a four-level variables computed as below: 0 point = Very low; 1 point = Low; 2 points = Middle; 3 points = High; 4 points = Very high	A Likert-type scale of 0–4 points
Quality of life	We categorized the quality of life using a three-level variables, computed as below: 0 point = Dissatisfied; 1 point = Little satisfied; 2 points = Satisfied; 3 points = Very satisfied	A Likert-type scale of 0–3 points
Social network size	Participants were asked to report their place of residence and their social network at old age (after retirement). We categorized the place of residence using a three-level variables computed as below: 0 point= alone; 1 point = retirement home, 2 points = living with a family member, 3 points = spouse/wife/husband or friends. We categorized the social network using a three-level variables, computed as below: 0 point = Unsociable; 1 point = Little sociable; 2 points = Sociable; 3 points = Very sociable	A Likert-type scale of 0–6 points

Table 18. Specific proxies related to the health status

	Health status	Total score specific to each proxy	Total score
Questions	Participants were asked to report their health status at all the periods of their life. We categorized he health using two-level variables (physical health and psychological health) computed as below: <u>Physical health</u> 0 point = Very low; 1 point = Low; 2 points = Middle; 3 points = High; 4 points = Very high - 1point = Bad; 1 point = Middle; 2 points = Good; 3 points = Very good <u>Psychological health</u> - 1point = Bad; 1 point = Middle; 2 points = Good; 3 points = Very good	A Likert-type scale of -6 to 18 points A Likert-type scale of -6 to 18 points	A Likert-type scale of -12 to 36 points

3. Neuropsychological assessment

For EF assessment, we used the following data from the previous study:

- Stroop Switching Card Test assessing the overall efficiency of EF
- Stroop Test assessing inhibition
- Trail Making Test assessing switching
- Digit Span Forward and Backward Test assessing updating

4. Dependent variables

4.1 Cognitive reserve

The total score of the CRQ was the dependent variable of interest.

4.2 Executive function components

The following dependent variables were of interest:

- Z-score of the Wechsler total correct score (i.e., the rate of decline in updating)
- Z-score of STROOP C_{IES} (i.e., the rate of decline in inhibition)
- Z-score of TMT B_{IES} (i.e., the rate of decline in switching)
- Z-score of $SSCT_{IES}$ (i.e., the rate of decline in the overall efficiency of EF)

5. Statistical analysis

Four set of analysis were performed. First, we used the quartile method to create groups with different levels of CR (low, intermediate, high; qualitative measure of CR). The second set of analysis (Pearson's correlation) examined the strength of the association between CR and EF. The third set of analysis (Kruskall-Wallis) examined the effect of CR on the rate of decline in EF. Post-hoc comparisons were performed with Bonferroni correction for multiple comparisons. The last analysis (Receiver Operating Curve; ROC analysis) was used to determine a threshold for the executive decline specific to low CR (quantitative measure of CR). Roc analysis is a graphical representation of the specificity and sensitivity of all possible threshold values. **Figure 19** describes in more details this analysis (Delacours et al. 2005).

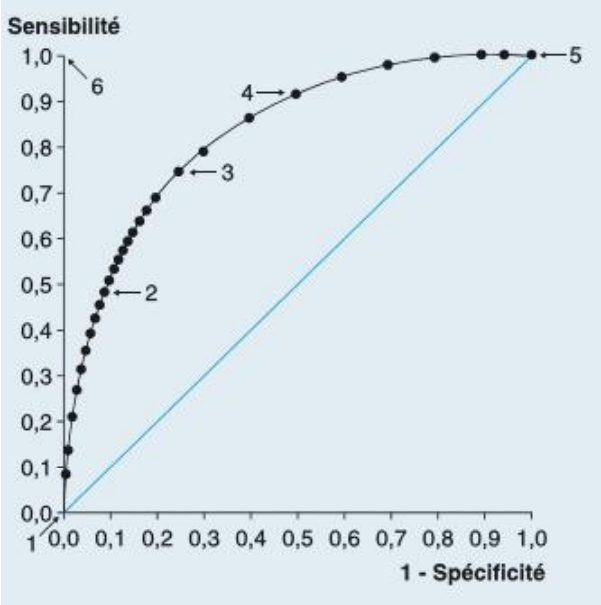


Figure 19. Roc curve; Adapted from Delacours et al. (2005)

The point (1) corresponds to the specificity and sensitivity for the minimum threshold. The sensitivity is maximum (all participants are above the threshold) and the specificity is zero (cannot separate participants). Any decrease in the threshold will lead to an increase in sensitivity and a decrease in specificity (i.e., points 4.3.2). An accurate threshold is represented by both high sensitivity and specificity. Point (6) would be the best threshold.

The area under the ROC curve will represent the predictive power of the best threshold value. A large area will be associated with a high sensitivity and specificity. The blue line represents a flat curve, where none of the possible threshold values would be more predictive than another.

All statistical analyses were performed using SPSS software version 22 (IBM, SPSS, statistics). The level of significance for all tests was set at $p < 0.05$.

6. Results

6.1 Qualitative measure of CR

The quartile method realized for the global score of the CRQ allowed creating the following groups: (i) older adults with high CR (upper quartile > 251 points; n = 6), (ii) older adults with low CR (lower quartile <150 points; n = 13), and (iii) older adults with intermediate CR (values between the lower and upper quartiles (151-250 points) **Table 19**.

Table 19. Mean (±SD) of demographic characteristics of participants with different levels of CR (low, intermediate, high)

	Frequency	**Age**
High (> 251)	6	65,16 (3,18)
Intermediate (151-250)	7	65 (4,60)
Low (<150)	13	68,57 (4,78)
Total	26	

6.2 Correlation between cognitive reserve and the rate of decline in EF

Person's correlation analysis showed a strong correlation between CR and the Z-score of $SSCT_{IES}$, only. As the coefficient of correlation is negative, we can admit that the higher the score of CR, the lower the rate of decline in EF (**Table 20**).

Table 20. Correlational analysis between cognitive reserve (total score) and the Stroop Switching Card test (Z-score of IES), STROOP C (Z-score of IES), Trail Making B (Z-score of IES) and Digit Span Forward and Backward Test (Z-score of Wechsler total correct score).

		SSCT (Z-IES)	**TMTB (Z-IES)**	**STROOP C (Z-IES)**	**WTS (Z-score)**
CR	Pearson's correlation	-.729***	-.315	.362	-.072
	Sig. (bilateral)	.001	.117	.069	.728

CR: Cognitive reserve; **Z-IES**: Z-score of inverse efficiency score; **SSCT**: Stroop Switching Card Test; **TMT B**: Trail Making Test part B, **WTS**: Wechsler total correct score.

6.2. The rate of decline in EF as a function of CR

CR modulated the rate of decline in EF ($F(2) = 6.861$, $p = 0.005$), significantly. Notably, older adults with high CR showed lower rate of decline in EF than those with low reserve (Z-IES, $p = 0.002$). No significant difference was observed between older adults with intermediate CR and those with either low ($p = 1$) or high ($p = 0.248$) CR (**Figure 20**).

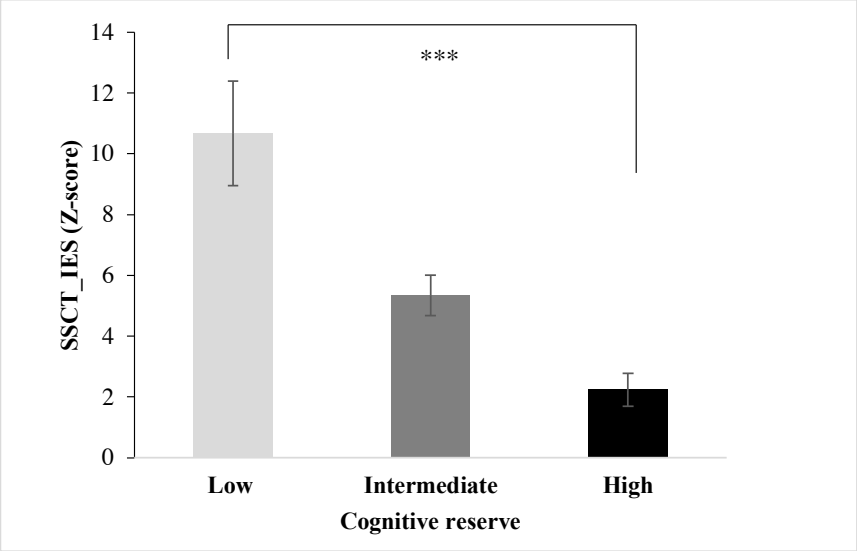


Figure 20. Mean (standard error of the mean) performance of the Z-score of $SSCT_{IES}$ as a function of CR (low, intermediate and high). Mean Z-score of $SSCT_{IES}$ is displayed at the top and the level of CR at the bottom. (Older adults with low CR *versus* older adults with high CR; p-value: *** < 0.005)

6.3. Threshold for the executive decline specific to low CR

Given that the Z-score of $SSCT_{IES}$ differentiated older adults with high CR from those with low CR, we were interested in conducting ROC analysis to determine a threshold for the executive decline specific to low CR.

- **ROC analysis**

ROC analysis of the Z-score of $SSCT_{IES}$ performed for older adults with low CR, as differentiated from those with intermediate and high CR, had an AUC (Area under the Curve) of 0.942. A cut-off score (Z-score of $SSCT_{IES}$) of 8 emphasized a sensitivity of 100 % and a specificity of 55 %. Therefore, cut-off score (Z-score of $SSCT_{IES}$) of 8 is an indicator of low CR (**Figure 21)**.

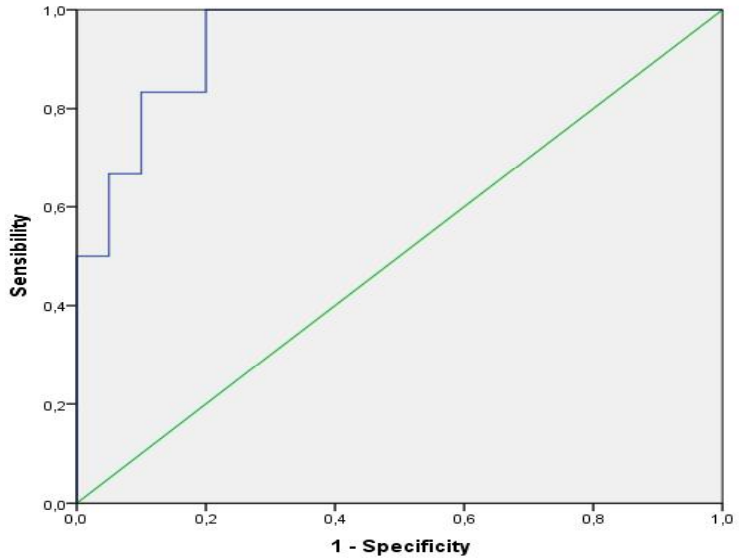


Figure 21. ROC analysis graph for the inverse efficiency score. The sensibility is displayed at the top and the specificity at the bottom.

Table 21. An example of real data showing sensitivity and specificity at various cut- off points of the Z-score of $SSCT_{IES}$ for quantifying cognitive reserve

SSCT (IES) cutoff	Sensitivity	Specificity	Sensitivity + Specificity
3,92	0,833	0,200	1,033
4,32	1,000	0,200	1,200
6,60	1,000	0,500	1,500
8,02	1,000	0,550	1,550

7. Discussion

The main objective of this study was to propose two measures assessing CR; one of which is qualitative and the other is quantitative. The qualitative measure was represented by a questionnaire including a large variety of experiences accumulated over the lifespan, while the quantitative measure was represented by optimal cut-off value of the Z-score of $SSCT_{IES}$ (derived from a ROC curve analysis).

The key findings of this study were:

- A score greater than 251 was an indicator of high CR, whereas a score less than 150 was an indicator of low CR in our sample of 26 older adults.
- CR modulated the rate of decline in the overall efficiency of EF (Z-score of $SSCT_{IES}$).
- Cut-off value of the Z-score of $SSCT_{IES}$ of 8 indicated low CR with a sensitivity of 100 % and a specificity of 55 %.

7.1. Qualitative measure of cognitive reserve

The CRQ was constructed for qualitatively estimating CR accumulated over the lifespan (childhood, adolescence, youth, middle age and old age). Methodologically, the main advantage of the CRQ is that it includes specific proxies related to each period of life, which have been validated in the literature as either contributor to CR (e.g., primary school performance) or protector (e.g., intellectual working in adulthood and active professional status in older age) against the development of neurodegenerative diseases such as AD. Interestingly, each life period includes a specific global score giving thus the possibility for future studies to understand which period of life impact more the building of CR. Another advantage of the CRQ is that it includes new proxies of CR such as the medical health status, age of stopping elementary school and, professional status after retirement, which are widely known in the literature to have a strong impact on the cognitive health of older adults (Clare et al. 2017).

The CRQ has also the advantage to include a large variety of questions allowing an accurate assessment of proxies relative to each period of life. Such an approach is crucial because the same value on a proxy (e.g., 12 years of education) does not necessary reflects the same experience in all people. To clarify this idea in more details, we will focus on the example of education of two older adults who completed 8 years of education. The school performance of the first older adult was modest from the primary school to college. He has obtained a primary school diploma and he never participated in training outside the school. The second older adult

always got excellent grade and during two years, he participated weakly in cognitive stimulating training (training for nurses). As for the first older adult, he has obtained a primary school diploma.

Based on the standard estimation of education (number of years of education or level of education), these older adults are equivalent, however that is not the case. Based on the new scoring of CRQ (**Table 22**) our method to estimate education (diploma, school performance, and the nature of training outside of the school) clearly distinguish experience of these older adults, at the adolescence period.

Table 22. An example of education scoring

	School performance	**Diplomas**	**Training outside the school**	**Global score**
Older adult 1	**4 points** (2 points: medium performance at primary school), (2 points: medium performance at college)	**1 point:** primary school validated with a diploma	**0**	**5**
Older adult 2	**8 points** (4 points: very good performance at primary school), (4 points: very good performance at college)	**1 point:** primary school validated with a diploma	**8 points** (cognitive stimulating activities) Weakly* 2 years	**17**

The total score of the CRQ ranges from 0 to 564 points. To create groups with different levels of CR (low, intermediate, high), we used the quartile method. The latter allowed creating two separable groups: older adults with high CR (upper quartile > 251 points; n=6), and those with low CR (lower quartile <150 points; n=13). It should be mentioned that these scores are only true for this pilot study, notably because of the small sample size.

To understand the association between CRQ score and EF, we conducted a 'Pearson's correlation analysis.' This test allowed concluding that the total score of CRQ was strongly correlated to the Z-score of $SSCT_{IES}$, suggesting that the CRQ score is an adequate tool for estimating CR. In contradiction with the Z-score of $SSCT_{IES}$, the inhibition (i.e., assessed by the Z-score of STROOP C_{IES}), updating (i.e., assessed by the Z-score of the Digit Span Forward and Backward test) and switching (i.e., assessed by the Z-score of TMT B_{IES}) were not

correlated with CR. Our results are in contradiction with several studies (Hashimoto et al. 2006; Fine et al. 2012; Roldán-Tapia et al. 2017) showing a positive correlation between CR and EF by using the same neuropsychological than those used in our study. These contradictive results are probably due to the fact that we used the Z-score of IES whereas authors of other studies used standard measures such as the response time, thus not taking into consideration the speed-accuracy trade-off. The fact that CRQ score was only correlated with the Z-score of $SSCT_{IES}$ suggests that the SSCT requires more cognitive demand than standard neuropsychological tests (STROOP, TMT and Digit Span). This result confirms that the CR influences only tasks that require high cognitive demand (Le Carret et al. 2003).

7.2. Quantitative measure of cognitive reserve

CR significantly modulated the rate of decline in EF as assessed by the Z-score of $SSCT_{IES}$. In fact, older adults with high CR had a lower executive decline than those with low CR. This finding provides further support for the moderating role of CR in executive decline. Our results are in line with several studies, which have explored the link between CR and EF (León et al. 2014; Lavrencic et al. 2017; Roldán-Tapia et al. 2017) . For example, the study by Schneeweis et al. (2014) has shown that a higher level of education reduced significantly the rate of decline in switching as assessed by the verbal fluency test. Studies by Hashimoto et al. (2006) and Fine et al. (2012) further suggested that the level of education moderated the rate of decline in updating as assessed by the Digit Span Backward Test. The recent study by Roldán-Tapia et al. (2012) conducted in 160 healthy participants aged between 20 and 65 years confirmed previous findings and has shown that higher CR score was associated to a better performance in cognitive tasks assessing inhibition, updating and switching. The neurocognitive processes involved in the maintenance of executive performance in older adults with high CR are not fully understood. However, there is broad agreement that the moderating role of CR is probably due to better use of brain reserve and flexible strategy usage (Stern, 2012; Roldán-Tapia et al. 2012).

Given that CR modulated the rate of decline in EF (as assessed by the Z-score of $SSCT_{IES}$), we sought to explore a threshold for an executive decline specific to low CR. Such threshold is crucial to determine who grows old gracefully and who declines rapidly. To achieve this goal, we conducted ROC analysis. Accordingly, a cut-off score (Z-score of $SSCT_{IES}$) of 8 indicated low CR with a sensitivity of 100 % and a specificity of 55 %. Of course, this result is very preliminary, given the extremely small sample size and low specificity. The low specificity

is mainly due to the small sample size (n=13). Typically, a ROC curve analysis is applied on a large sample size (n ≥100). However, this is a pilot study in which we aimed to explore the different methods allowing assessment of CR. Future studies including a large sample size will certainly enhance the specificity.

7.3. Strengths and limitations

To our knowledge, this is the first study proposing two measures of CR, one of which is qualitative and the other is quantitative. This is also the first study proposing a cut-off value to classify individuals as having high or low CR. The limits of this study are: (i) the small sample size, and (ii) the similarity of life experiences within each sub-group. For instance, the majority of older adults with low CR (n= 13) were farmers from childhood until old age. All of them stopped their education at the age of 9-11 years (i.e., for historical and social reasons), and their leisure activities are often chatting with friends in a cafe. Such similarity prevents understanding which period of life impacts more the building of CR, and which proxy could influence the most CR. Another limit that should be noted is that the new questionnaire is lengthy preventing thus its clinical use. However, it has the advantage that it is very comprehensive with a large variety of proxies that could contribute differently and complementarily to CR building. Future studies including a large sample size of children, adolescents, young adults, middle adults and older adults are necessary to select the most appropriate CR proxies that contribute to the building of CR in order to reduce CRQ's size. This will allow the facilitation of the clinical use of this tool.

In conclusion, this study showed that the CRQ is a powerful tool for assessing CR. Notably, in our sample, a score greater than 251 is an indicator of high CR, whereas a score less than 150 is an indicator of low CR. A cut-off score (Z-score of $SSCT_{IES}$) of 8 is potentially a dynamic indicator of CR. Confirmation of this conclusion will require accumulation of more data.

Effects of executive task type on Dual-Task Gait. Does the executive task matter?

1. Introduction

For a long time, gait control was considered as an automatic and 'unconscious' activity, requiring few or no cognitive resources. Numerous recent studies using dual-task walking paradigm contradicted this assumption and showed the involvement of cognition, notably, EF even in young adults (Beauchet et al. 2005; Allali et al. 2007; Dubost et al. 2008; Decker et al. 2016). As mentioned previously, there are three components of EF including the inhibition, updating, and switching that can operate either together or separately according to the cognitive demand of the task (Miyake et al. 2000). Given both the unity and diversity of executive functions, the question arises whether different cognitive tasks tapping into different components of executive function would affect differently on gait control (Belghali et al. 2017a).

Some studies using dual-task walking paradigms suggested that cognitive tasks though to involve specific executive control processes, such as the verbal fluency task (cognitive flexibility and search strategy), the N-back task (working memory), the auditory Stroop task (inhibition), and the serial (thress or sevens) substraction task (most likely involving all components of executive function), interfere with the pace and variability domains of gait (Belghali et al. 2017a, for a review). Such changes were shown in older adults, and were thought to indicate competition between shared resources involved in both cognitive and gait tasks (Yogev et al. 2007; Yogev-Seligmann et al. 2008; Al-Yahya et al. 2011). Despite the relevance of these findings, the effect of executive task type on gait control remains unclear. Indeed, a few studies have examined whether the type of the walking-associated cognitive task matters for the gait performance under a dual-task condition. In a recent review, Bloem et al. (2003) suggested that, regardless of the type of the walking-associated cognitive task, the gait in dual-task condition was affected at same extent. However, Beauchet et al. (2005) found that, among transitionally frail older adults, two different cognitive tasks could have a different impact on lateral gait stability. Precisely, the frequency of lateral stepping-over was higher while counting backward compared to enumerating animal names. In the same vein, Beauchet et al. (2005) found that stride time variability (coefficient of variation of stride time) increased only when they walked and performed the arithmetic task but not the verbal fluency task.

Less is known about the relationships between EF and gait in young adults, since the majority of studies have been conducted in older adults. Exploring young adults' gait control under different types of cognitive challenge is essential to understand optimal cognitive-motor strategies. In line with this regard, two studies by Grabiner and Troy (2005a) and Dubost et al. (2008) have shown that young adults increased their mean stride width while performing a verbal fluency task. The study by Beauchet et al. (2005) has shown a decrease in stride velocity and an increase in stride time variability, while counting backwards; however, the stride length variability remains intact. The recent study by Kelly et al. (2012) also revealed a decrease in stride velocity. As for older adults, the majority of studies conducted on young adults used only one cognitive task tapping into one or multiple executive function components; thus, little is known whether the type of cognitive challenges matters for gait interference.

Besides, all above-mentioned dual-task studies in both young adults and old adults were performed on a treadmill or overground. Conducting gait analysis using overground offers the possibility to assess spatiotemporal gait parameters in ecological conditions; however, it is difficult to get sufficient number of step. Indeed, in order to accurately measure gait variability, subjects must undergo a gait trial composed of a minimum number of steps in order to: i) avoid spurious statistical findings and ii) allow sufficient time for gait rhythm to become established (steady). Short overground walking distances, such as those shorter than 10 m, may not allow for a reliable assessment of spatio-temporal gait parameters. Use of other alternatives to assess walking, such as having subjects walk on a treadmill, has been explored as a solution to this experimental limitation (Owings and Grabiner 2003). However, it has been found that trials of at least 400 steps are necessary in order to accurately assess spatio-temporal gait parameters using a treadmill, which is problematic when exploring individuals with mobility issues. Additionally, walking on a treadmill imposes speed constraints and the associated dynamics do not mimic real-life conditions (i.e., preventing the subject from using his natural coping strategies). To resolve the different limitations of both overground and treadmill approaches, the Gait Real-Time Analysis Interactive Lab (GRAIL) system has recently used as an alternative. The GRAIL is a fully instrumented dual-belt treadmill. The treadmill's self-paced mode enables the subject to initiate gait and walk at a self-selected pace, while the treadmill and the VR environnement run in synchronization to create a natural optical flow. Because of these unique features, subjects walking on the GRAIL can use their natural strategies for coping with dual-task interference, as observed when walking overground (Krogt et al. 2014; Gates et al. 2012; Salinas et al. 2017). It allows detailed real-time gait analysis in both virtual realities

(induces a real-life sensation) and continuous manner. To our knowledge, there is today no study using GRAIL technology to assess gait parameters under a dual-task condition.

Taking into account all of above elements, the main objective of this study was to describe the effects of different types of executive tasks on selected spatial and temporal gait parameters in young adults and to establish whether the type of the walking-associated executive task matters for the gait performance under a dual-task condition. Based on the postulate that two concurrently performed tasks cause greater interference if they compete for the same cognitive processing resources, we hypothesized that the tasks requiring greater reliance on executive functioning will interfere more with gait control. Our tasks differ in terms of their nature and their cognitive load, which is the amount of attention required to be successfully carried out (the task at hand tapping mainly into either inhibition or flexibility or both). Of note is that cognitive load refers to the amount of information to be kept and worked with within the working memory system.

2. Methods

2.1. Participants

Fifteen young adults aged between 18 and 25 years participated voluntarily to this experiment. Demographic characteristics of participants are summarized in **Table 23**. The inclusion criteria were: (i) native French speakers, (ii) absence of visual and auditory impairments and (iii) being right handed. The exclusion criteria were: (i) presence of any medical, psychiatric, or neurologic impairment that could significantly affect gait control or cognitive functions, and (ii) presence of obesity or overweight (body mass index = 18.5–24.9). The study was granted ethical clearance for the entire program of research by the ethical committee Cerstaps 2016-26-04-13 (Comité d'Ethique pour la Recherche en Sciences et Techniques des Activités Physiques et Sportives; (**Appendix 7**). All participants gave their written informed consent before the beginning of the study.

Table 23. Mean (standard deviation) of demographic characteristics of participants

Young adults (n = 15)	
Gender (M/F)	8/7
Age (years)	21.91 (2.12)
Height (m)	1.69 (5.50)
Weight (Kg)	61.30 (8.15)
Education (years)	5.60 (1.35)

2.2. Instrumentation

2.2.1. GRAIL system

The GRAIL system is one of the most recent technologies for gait analysis. It includes: (i) a dual-belt treadmill (length: 2 m, width: 0.5 m), (ii) two integrated force plates and (iii) a motion capture system (VICON, Oxford Metrics Ltd, Oxford UK) for kinematic data acquisition. The D-Flow software, which synchronizes real-time data coming from different types of integrated hardware, controls the whole system.

2.2.2. Chronos box

Cognitive tasks were implemented using the E-Prime 2.0 software (Psychology Software Tools, Pittsburg, PA, USA). Participants were asked to respond to each stimulus as quickly and as accurately as possible, aloud into a microphone (Line 6 XD-V55HS-B, 2.4 GHz). The microphone was connected to the Chronos box to record response time (RT) in milliseconds (ms) after each stimulus presentation.

2.3. Experimental procedure

This experiment took place in the CIREVE (Interdisciplinary Center of Virtual Reality; https://www.unicaen.fr/cireve/). It consisted of a cognitive session and a walking session, counterbalanced between participants. Each session lasted 30 min, with a rest of 15 minutes between sessions.

2.3.1. Cognitive session

The cognitive session consisted in performing four cognitive tasks requiring EF, while sitting in a chair (presented below). All of them lasted 1 minute. Each subject completed one

experimental trial for each task. Prior to testing, one practice trial was provided to ensure that the participants fully understood the instructions. The order of cognitive tasks was counterbalanced between participants.

2.3.1.1. Auditory Stroop Task (AST)

The stimulus sequence was specified to carry out a task requiring inhibition. The stimuli consisted of two words ("LOW" or "HIGH") presented in two different frequencies: congruent (e.g., "LOW" with a low frequency) or incongruent (e.g., "LOW" with a high frequency). Half of the stimuli was congruent and the other half was incongruent. Participants were instructed to say as quickly as possible and without making errors the pitch of the voice. Stimuli were 500 ms in duration with a random inter-stimulus interval between 1500 and 2000 ms. 26 stimuli were created for this task.

2.3.1.2. Auditory Task Switching (ATS)

The stimulus sequence was specified to carry out a task requiring switching. The stimuli consisted of digit pairs (e.g., 23) presented with either a man or female voice. Half of the stimuli was odd (eg., 89) and the other half was even (e.g., 72). Each participant was asked to say as quickly as possible and without making errors either the odd number when hearing a man voice or the even number when hearing a woman voice. Stimuli were 700 ms in duration with a random inter-stimulus interval between 1700 and 2200 ms. 22 stimuli were created for this task.

2.3.1.3. Auditory Stroop Task Switching (ASTS)

The stimulus sequence was specified to carry out a cognitive task requiring both inhibition and switching. The stimuli consisted of two words ("LOW" or "HIGH") presented in two different frequencies: congruent (e.g., "LOW" with a low frequency) or incongruent (e.g., "LOW" with a high frequency), with either a man or female voice. Participants were asked to say as quickly as possible and without making errors the spoken word when hearing a female voice or the pitch of the voice when hearing a man voice. Stimuli were 500 ms in duration with a random interval inter-stimulus values between 1500 and 2000 ms. 26 stimuli were created for this task.

2.3.1.4. Counting Backward Task (CBT)

Each participant counted backwards by threes from either 500 (dual-task condition) or 300 (i.e., single-task condition). The CBT has been used notably to show the added value of the new cognitive tasks (i.e., AST, ATS, and ASTS) to induce greater dual-task interference.

2.3.2. Walking session

Walking was assessed in both single-task (walking alone) and dual-task (walking while performing the four cognitive tasks) conditions. All conditions were counterbalanced across participants. In the virtual environment, a corridor of the theatre of ancient Rome was projected in the front of the treadmill. The speed of the moving corridor was synchronized to the speed of the treadmill, creating an illusion that participants walked through the corridor (**Figure 22**). The position of the subject was computed as the average position of four pelvic markers (RICR, LICR, RASI, LASI) filtered at 2 Hz, "*to reduce the influence of marker occlusion and within-stride pelvic fluctuations"* (Sloot et al. 2014). This method allows each subject to walk at a self-selected speed in the different experimental conditions (Sloot et al. 2014).

Figure 22. Virtual corridor used for the experiment. Theatre of ancient Rome.

Prior to testing, participants were given at least 10 minutes to familiarize themselves with walking on the GRAIL. Before, they were equipped with 43 reflective markers (attached to a tight-fitting suit) according to the Vicon Plug-in-Gait marker system (Full Body, Nexus, Vicon, Oxford; **Figure 23**), a microphone, and 3DVirtual Reality Glasses.

In the walking condition, participants walked at a self-selected speed while viewing the theatre of ancient Rome using 3DVirtual Reality Glasses. In the dual-task conditions, participants walked at a self-selected speed while performing four cognitive tasks (AST, ATS, ASTS, CBT). No specific instructions were given about task prioritization under dual-task conditions. Participants were told not to slow down their gait speed and perform the cognitive task at their best. For each condition, participants walked for 1 min and ample rest was provided between conditions. The order of the walking conditions was counterbalanced between participants.

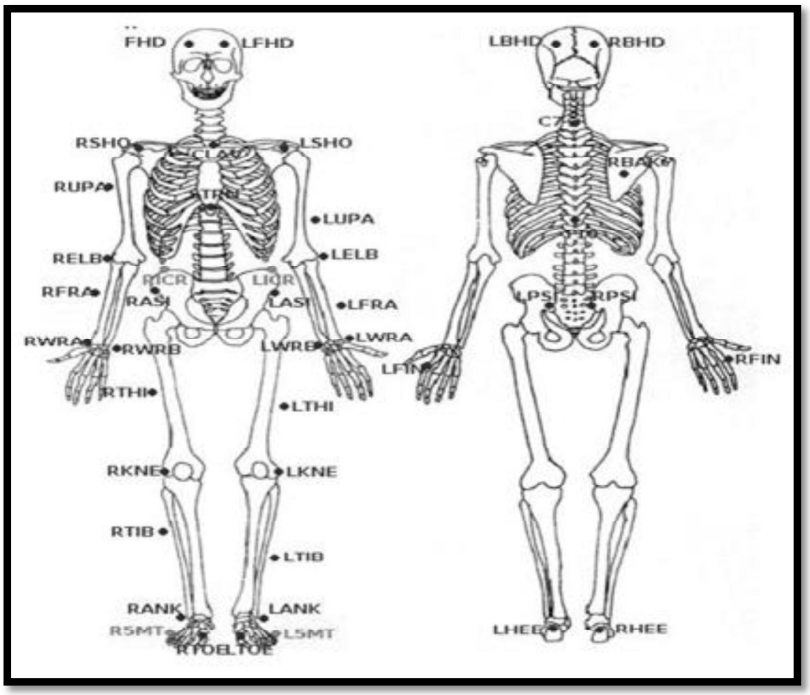


Figure 23. Plug-in-Gait Full-Body model

3. Dependent variables

3.1. Cognitive performance

Both RT and percentage of correct responses were the dependent variables of interest for each auditory executive task. For the counting backwards task, the dependent variable was the total number of generated digits.

3.2. Gait performance

Spatiotemporal gait parameters including step length, step width, step velocity, step time, stance time, and swing time were computed. The variability of each spatiotemporal gait parameters was also computed and was indexed by the CV.

$$\text{CV} = \frac{\textbf{Standard deviation}}{\textbf{Mean}} \times \textbf{100}$$

4. Statistical analysis

The cognitive and motor dependent variables were normally distributed as assessed by the Shapiro-Wilk test. Therefore, parametric tests were used for statistical analysis. The ANOVA with repeated measures was used to: (i) compare cognitive performance across single-task and dual-task conditions, and (ii) changes in spatio-temporal gait parameters (mean and CV) across single-task and dual-task conditions. Post-hoc comparisons were performed with Sidak correction for multiple comparisons. For only significant results, an ANCOVA was used to control step velocity effect.

For each cognitive task, a paired t-student was used to compare the dependent variables of interest (response time; percentage of correct response; total number of generated digits) between single-task and dual-task conditions. All statistical analyses were performed using SPSS software version 22 (IBM, SPSS, statistics). The level of significance for all tests was set at $p < 0.05$.

5. Results

5.1. Cognitive performance

5.1.1. Auditory cognitive tasks

- **Response time**

No effect of condition (sitting versus walking) was observed ($F(5, 24) = 0.555$, $p = 0.733$). On the other hand, RT was longer in TS than in both ASTS ($p = 0.002$) and AST ($p = 0.001$), in both single and dual task conditions (**Figure 24**).

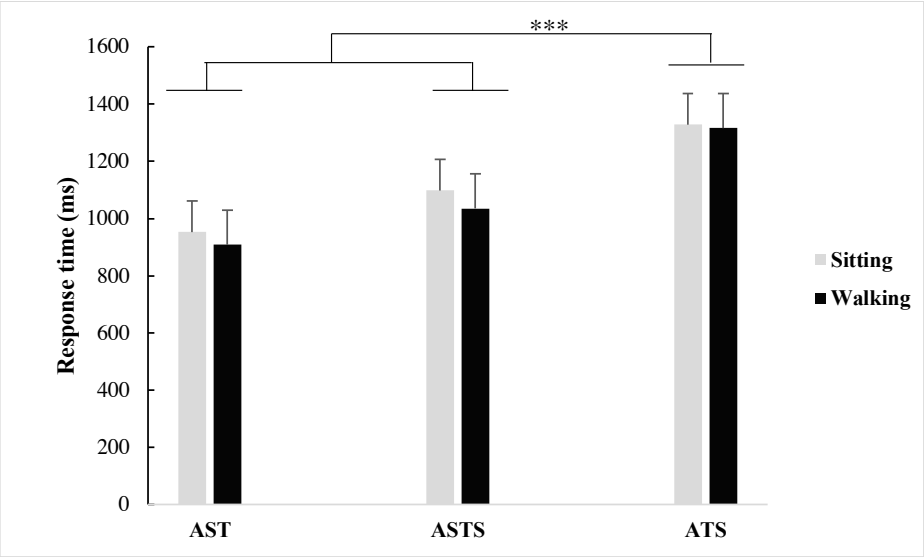


Figure 24. Mean (standard deviation) of response time under sitting and dual task conditions. Mean score of response time (ms) is displayed at the top and the cognitive tasks (AST: Auditory Stroop task; ASTS: Auditory Stroop task switching; ATS: Auditory task switching) at the bottom. ATS *versus* AST and ASTS under sitting and walking; p-value: *** < 0.005.

- **Percentage of correct responses**

Participants made errors only in ATS and ASTS in both single and dual-task conditions. Only the percentage of correct responses of the ASTS decreased significantly under dual-task conditions compared to the single-task condition ($t = 3.37$, $p = 0.002$) (**Figure 25**).

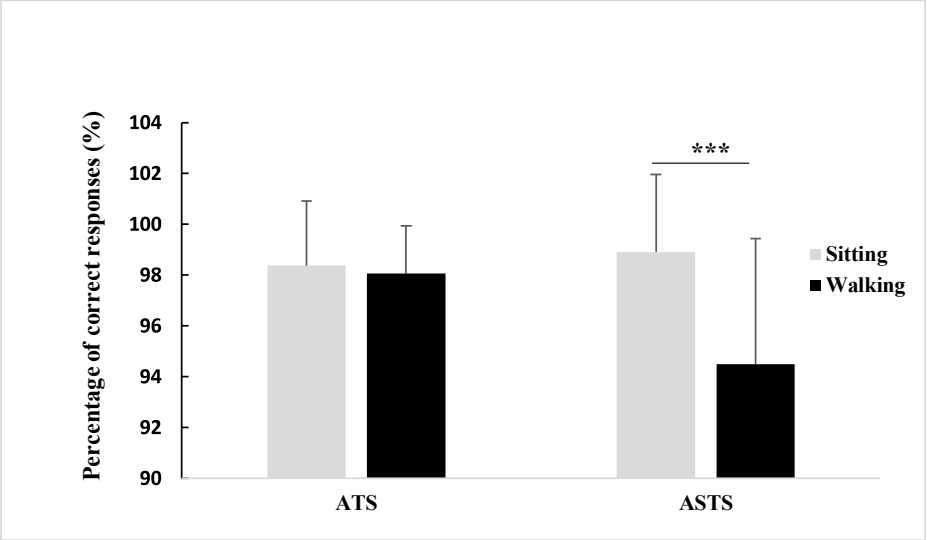


Figure 25. Mean (standard deviation) of the percentage of correct responses in ATS and ASTS under single (sitting) and dual-task conditions. The percentage of correct responses is displayed at the top and the cognitive tasks (AST: Auditory Stroop task; ASTS: Auditory Stroop task switching) at the bottom. P-value: *** < 0.005.

5.1.2. Total number of generated digits

The total number of generated digits was not significantly different between sitting and walking conditions (t = 1.010, p = 0. 33) (**Figure 26**).

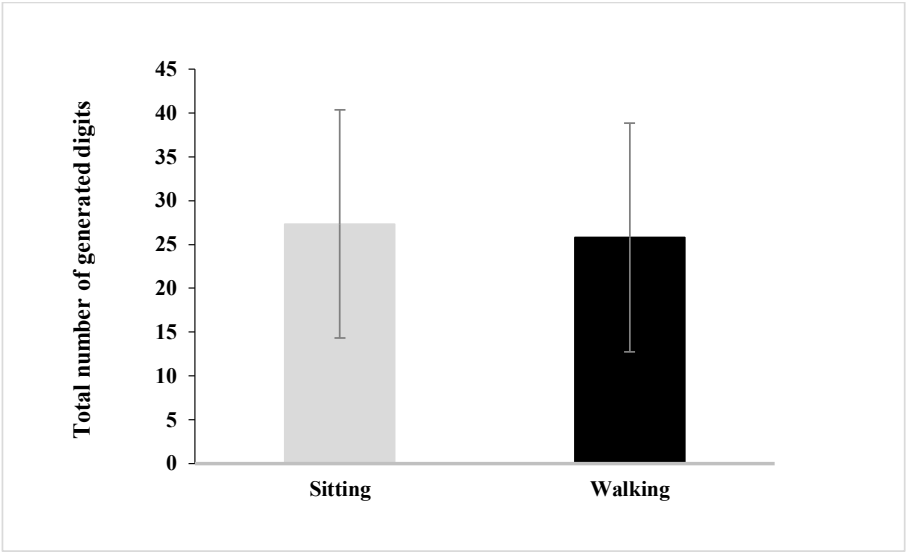


Figure 26. Mean (standard deviation) of the total number of generated digits under single (sitting) and dual-task conditions (walking). The number of generated digits is displayed at the top and the conditions (sitting and walking) at the bottom.

5.2. Effect of executive task type on gait performance: before adjustment of step velocity

The mean step velocity decreased significantly and to the same extent in all dual-task conditions compared to the single-task condition (F (15, 174, 32) = 42.517; p = 0.001). The mean step width increased significantly only while performing the ASTS (F (10, 128) = 5.679; p = 0.022). The step width variability decreased significantly while performing both the ATS (F (10, 128) = 5.679; p = 0.010) and ASTS (F (10, 128) = 5.679; p = 0.019). The step length variability increased significantly while performing the ASTS (F (10, 128) = 81.680; p = 0.018). No significant changes were observed in the other spatiotemporal gait parameters (step length, step velocity variability, swing time, swing time variability, stance time, stance time variability, step time, and step time variability; p =1) (**Tables 24 and 25**).

Table 24. Mean (standard deviation) of spatio-temporal gait parameters.

Conditions	Step velocity ($cm.s^{-1}$)	Step length (cm)	Step width (cm)	Swing time (s)	Stance time (s)	Step time (s)
Single task	128.35 (17.546)	67.86 (6.558)	8.13 (2.379)	0.65 (.058)	0.44 (.007)	0.53 (.014)
AST + Walking	**74.05 *** (8.203)**	65.81 (5.506)	10.30 (3.956)	0.64 (.051)	0.44 (.010)	0.53 (.012)
ATS + Walking	**74.56 *** (8.402)**	66.71 (5.748)	11.37 (2.840)	0.64 (.051)	0.45 (.008)	0.55 (.014)
ASTS + Walking	**72.85 *** (9.180)**	65.35 (6.443)	**12.001* (2.084)**	0.65 (.054)	0.44 (.007)	0.54 (.013)
CBT + Walking	**71.99 *** (9.96)**	64.99 (7.80)	11.07 (2.83)	0.66 (.072)	0.45 (.013)	0.54 (.012)

Single-task: walking alone, **AST + walking**: walking while performing the auditory stroop task, **ATS + walking**: walking while performing the auditory task switching, **ASTS + walking**: walking while performing the auditory stroop task switching, **CBT + walking**: walking while performing the counting backward task. P value: *** < 0.001 (Step velocity: single task *versus* walking while performing the AST, ATS, ASTS, and CB); P value: * < 0.05 (Step width: single task *versus* walking while performing the ASTS).

Table 25. Mean of the coefficient of variation (standard deviation) of gait variability

Conditions	Step velocity Variability ($cm.s^{-1}$)	Step length Variability (cm)	Step width Variability (cm)	Swing time Variability (s)	Stance time Variability (s)	Step time Variability (s)
Single task	0.52 (0.38)	0.22 (0.05)	3.16 (1.35)	0.46 (0.36)	0.22 (0.02)	0.22 (0.06)
AST + Walking	0.43 (0.1)	0.33 (0.08)	2.49 (1.53)	0.67 (0.11)	0.25 (0.01)	0.23 (0.07)
ATS + Walking	0.63 (0.72)	0.32 (0.1)	**1.64 (0.36)** *	0.81 (0.14)	0.27 (0.01)	0.22 (0.05)
ASTS + Walking	0.41 (0.16)	**0.35 (0.12)***	**1.75 (0.66)** *	0.35 (0.17)	0.29 (0.01)	0.23 (0.06)
CBT + Walking	0.42 (0.17)	0.33 (0.11)	2.22 (0.95)	0.39 (0.21)	0.27 (0.01)	0.22 (0.05)

Single-task: walking alone, **AST + walking**: walking while performing the auditory stroop task, **ATS + walking**: walking while performing the auditory task switching, **ASTS + walking**: walking while performing the auditory stroop task switching, **CBT + walking**: walking while performing the counting backward task. P value: * < 0.05 (Step length variability: single task *versus* walking + ASTS); (Step width variability: single task *versus* walking + ATS); (Step width variability: single task *versus* walking + ASTS).

5.3. Effect of executive task type on gait performance: after adjustment for step velocity

ANCOVAs run (with mean step velocity as the covariate) on dependent variables of interest (i.e., step length variability, mean step width, step width variability) only partially confirmed the above results. There remained a significant increase in mean step width ($F[2] = 3.363$, $p = 0.07$) from the control walking condition to the walking+ASTS condition and a significant decrease in step width variability ($F[2] = 0.380$, $p = 0.54$) from the control walking condition to both the walking+ATS and walking+ASTS conditions, while the condition main effect for step length variability was no longer significant. Therefore, increased step length variability resulted from decreased step velocity under the walking+ASTS condition."

6. Discussion

Previous studies have shown that, even in young adults, performing an attention-demanding task while walking interferes with gait performance (Beauchet et al. 2005; Decker et al. 2012; Decker et al. 2013; Decker et al. 2016). Little is known whether the type of concurrent executive task matters for gait interference. The findings among our sample of young adults show that different walking-associated executive tasks have common and differential effects on gait control depending on their nature and cognitive load. Step velocity decreased regardless the type of the simultaneously performed executive task. Step width variability also decreased in tasks requiring either switching (ATS), or both inhibition and switching (ASTS). Both step length variability and mean step width increased in the task requiring the greatest executive interference (i.e., ASTS). In addition to the previously mentioned gait changes, cognitive performance (percentage of correct responses) in ASTS decreased significantly during dual-task compared to single-task conditions. ANCOVAs run (with step velocity as the covariate) on the studied gait dependent variables confirmed the above results, except for step length variability, of which the increase under the walking + ASTS was no longer significant.

6.1. Cognitive performance

Young adults maintained their cognitive performance under dual-task conditions, except in the most challenging cognitive task, i.e., ASTS (reduced percentage of correct responses). The most likely explanation is that the ASTS requires more attentional demand than the ATS. It appears that concurrently performing ASTS with walking cause greater interference likely because both tasks at hand compete for the same executive control resources (Pashler, 1994). A competitive demand for executive functions could thus explain reduced percentage of ASTS' correct responses. Our findings support previous studies indicating that young adults tend to prioritize the cognitive task over the gait task ('a posture second strategy'; Bloem et al. 2006; Yogev-Seligmann et al. 2010). The use of such a strategy could be due to a high postural reserve that enables the young adults to focus on the secondary cognitive task (Bloem et al. 2006; Yogev-Seligmann et al. 2010; Holtzer et al. 2014; Decker et al. 2016).

6.1. Gait performance

Regardless the type of the secondary cognitive task, step velocity decreased significantly, and to the same extent, in all dual-task conditions compared to single-task condition (walking alone), lending support to the bottleneck theory. This assumption is

supported by recent studies showing that the competition between shared resources involved in both cognitive and gait tasks (i.e., the prefrontal cortex; Suzuki et al. 2004; Harada et al. 2009; Al-Yahya et al. 2011), is a major contributor to slower gait speed under dual-task conditions. Beyond competition between shared resources, other studies suggest that the prioritization strategy employed by young adults may also contribute to decrease in step velocity (McLeod, 1977; Patel et al. 2014). The fact that the cognitive performance remained equivalent under both single- and dual-task conditions (except for the ASTS) is important with respect to the task prioritization strategy used by the young adults, for whom the cognitive task, and thus the attentional resources allocated to it, is prioritized over the gait task (McLeod, 1977; Yogev-Seligmann et al. 2012a, b; Patel et al. 2014). Thus, the decrease in step velocity may be the first motor strategy used by young adults to to allocate attentional resources to the cognitive task (McLeod, 1977; Patel et al. 2014). Our results are in line with previous studies showing that young adults decreased their gait speed while performing either an auditory switch task (involving switching; Tomporowski and Audiffren 2014) or an auditory Stroop task (involving inhibition; Kelly et al. 2010; Patel et al. 2014).

The decrease in step velocity is often associated with changes in a large variety of spatio-temporal gait parameters. Based on the ANCOVA analysis, increased step length variability resulted from the dual-task-related decrease in step velocity. Our results are in line with previous research showing a U-shaped relationship between gait variability and gait speed (Sekiya et al. 1997; Owings and Grabiner, 2004; Jordan et al. 2007). However, they are in contradiction with the study by Beauchet et al. (2005) who has not shown any significant change in step length variability. A possible explanation is the difference in the choice of the secondary cognitive task (counting backwards from 50) and instrument assessing gait control (Physilog®-system).

Step width variability also decreased in tasks requiring switching (ATS), and switching plus inhibition (ASTS), likely because the former tasks recruit brain areas that overlap more with those associated with gait control. In addition, mean step width increased in the task inducing the greatest cognitive load (i.e., ASTS). Gabell and Nayak (1984) suggest that step width is related to balance control and that an increase in step width will allows greater stability in the mediolateral direction (Grabiner and Troy 2005). Interestingly, cognitive performance (percentage of correct responses) also decreased under the walking+ASTS condition. Mutual interference (i.e., dual-task decline in both tasks at hand) suggests that there are inadequate attentional resources (i.e., attentional demands exceed total capacity) to maintain single-task

level performance in each task when performed together, and therefore both deteriorate. Taking into account such a view, we can suggest that only an executive task with higher attentional demand could produce changes in step width parameters. This result suggests that secondary tasks involving both inhibition and switching might produce more gait interference than those involving only inhibition (i.e., inhibiting a prepotent reaction in favor of a less automated response), likely because the former tasks recruit brain areas that overlap more with those associated with gait control. Hence, young adults responded to additional cognitive loading by taking wider steps to enhance frontal plane dynamic stability, which is the most attentional component of walking (Gabell and Nayak, 1984).

6.3. Strengths and limitations

To our knowledge, this is the first study using the CRAIL treadmill (self-paced mode) to examine changes in gait control under dual-task conditions. This is also the first study exploring through new cognitive tasks whether the type of executive task (i.e., executive) matters on gait interference among young adults. However, this study has essentially two limitations. First, the size of our sample was small. Second, gait analysis were only limited to lower-limb gait parameters. Additional analysis will be of interest to examine dual-task effect on trunk and upper limb kinematics.

In conclusion, the findings among our sample of young adults studied show that different walking-associated executive tasks have common and differential effects on gait control depending on their nature (executive function requirements) and cognitive load. Step velocity decreased regardless the type of the simultaneously performed executive task. Step width variability also decreased in tasks requiring either switching (ATS), or switching plus inhibition (ASTS). Additionally, cognitive performance decreased and mean step width increased (and this, independently of dual-task-related gait slowing) in the task inducing the greatest cognitive load (ASTS). Collectively, these findings suggest that the choice of the walking-associated task in dual-task gait assessment matters for gait interference, and thus must be made carefully. The different mechanisims underlying dual-task related gait changes in young adults are summarized in **Table 26**.

Table 26. Significant dual-task changes and related mechanisms

				AST	ATS	ASTS	CBT	Mechanisms
Cognition				NO	NO	YES	NO	Attentional resources overloading: Capacity sharing model
Gait	Mediolateral direction	↑	Step width	NO	NO	YES	NO	Balance control
		↓	Step width variability	NO	YES	YES	NO	Attentional resources overloading: Capacity sharing model
	Anteroposterior direction	↓	Step velocity	YES	YES	YES	YES	Bottleneck model
		↑	Step length variability	NO	NO	YES	NO	Decrease in step velocity

Part 3. General discussion and perspectives for future research

The aim of this thesis was to revisit the dual-task paradigm as a promising screening tool to enhance the detection of underlying neurodegeneration in PD and AD. When a patient becomes symptomatic leading to a diagnosis of AD or PD, the neuropathological process is already well-entrenched. Potential neuroprotective and disease-modifying therapies in the prediagnostic phase may slow or halt progressive neurodegeneration, and could delay or prevent the clinical symptoms. Consequently, efforts are needed to identify appropriate early behavioral markers for AD and PD.

In order to achieve this goal, four main contributions have been made through this thesis:

1) the conduct of an extensive literature review supporting evidence that subtle dual-task-related gait changes could potentially be used as prediagnostic markers (Belghali et al. 2017b); and the building of a new conceptual framework dedicated to elaborate relevant dual-task paradigms susceptible, to induce disease-specific gait changes at the preclinical phase of AD and PD (Belghali et al. 2017a) (Part 1),

2) the development and first validation of a new neuropsychological task assessing the overall efficiency of executive function and its components (switching, inhibition, and updating), developed in both a card version (Part 2. Study 1) and a computerized version (Part 2. Study 2),

3) the development of a new approach to qualitatively and quantitatively estimate the cognitive reserve accumulated by individuals through their lifespan (Part 2. Study 3),

4) the determination of whether the type of the walking-associated secondary executive task matters for gait interference in a sample of young adults (Part 2. Study 4).

3.1. A theoretical framework to improve detection of subtle dual-task-related gait changes at the preclinical phases of AD and PD

Gait performance is affected by neurodegeneration in aging and has the potential to be used as a clinical marker for underlying neurodegeneration. A dual-task gait testing (assessing gait while performing a challenging cognitive task) may provide a reliable screening of age-related decline in brain function, notably in efficiency of executive function. However, the application of the dual-task paradigm in clinical practice for early detection of AD and PD requires further clarification on key methodological aspects. First, the type of the walking-associated secondary executive task has to be selected among the plurality of tasks proposed in the literature. Second, the key aspects of gait control that represent sensitive and

specific gait signatures for either preclinical/prodromal AD or PD need to be determined. A theoretical framework has been proposed to overcome these challenges based upon a comprehensive review of the literature on dual-task studies conducted at both the prediagnosis and clinical stages of AD and PD (Belghali et al. 2017a; Belghali et al. 2017b). This framework is based on the postulate that a way to make better use of dual-task walking paradigms is to select a secondary cognitive task that both interferes with gait control and challenges the underlying neuropathological processes of the disease (in favor of the bottleneck model). Since specific impairments are found in inhibition for AD (Balota et al. 2010) and switching for PD (Lerche et al. 2014), we suggest the use of a Stroop interference task requiring inhibitory control (Seo et al. 2016) and a set-shifting task requiring switching (Cools et al. 2001) as particularly relevant secondary tasks for challenging gait control in the pre-diagnosis phase of AD and PD, respectively. Such tasks are known to interfere with gait control (Morris et al. 2016; Strouwen et al. 2016), and importantly, begin to deteriorate years prior to the onset of the first clinical symptoms (Balota et al. 2010; Lerche et al. 2014; Mirelman et al. 2016). As for gait parameters, the literature review revealed that, in the prediagnosis phase, arm swing asymmetry and variability and axial rotation smoothness would be specifically altered in PD (Mirelman et al. 2011; Mirelman et al. 2016), whereas the « rhythm » (e.g., stride time, stance time, swing time) would be specifically altered in AD. On the other hand, the « pace » (e.g., gait speed, stride length) and « variability » (e.g., stride length variability, stride time variability) domains appear to be altered in both diseases (Belghali et al. 2017b).

3.2. A new neuropsychological task challenging efficiency of executive function and its components

Inhibition and switching are specifically deteriorated across all stages (prediagnosis and clinical) of AD and PD. Methodologically, based on the postulate that the Stroop Color-Word interference (inhibition, as assessed by the « STROOP C ») and task switching (cognitive flexibility, as assessed by the « TMT B ») share brain networks, involving notably the prefrontal cortex, some authors have proposed the use of the « Stroop Switching Test » in order to increase the sensitivity of the classical Stroop interference task for early prediction of executive dysfunction in both healthy and pathological aging (Delis et al. 2001; Fine et al. 2008; Hutchison et al. 2010). Despite its relevance, some improvements to this test can be made in order to further increase its sensitivity and propose specific measures of underlying deficient cognitive processes. The first study of this thesis conducted on healthy participants aged from 15 to 75 years addressed this issue, and proposed a new neuropsychological test, the

« Stroop Switching Card Test » to challenge the overall efficiency of executive function with specific measures assessing inhibition, switching, and updating, separately and together. The main finding that emerged is that the Z-score of $SSCT_{IES}$ (i.e., relative decline in the overall efficiency of EF by comparison to the group of young adults) is more sensitive to age than the Z-scores of STROOP C_{IES} and TMT B_{IES}. Specifically, we have shown that only the Z-score of $SSCT_{IES}$ allowed differentiating the performance of older adults from that of midlife adults. Given the good sensitivity of the Z-score of $SSCT_{IES}$ to age-related change in executive function, we suggest that this score could have an added value for early diagnosis of executive dysfunction due to AD and PD. Future longitudinal studies (i.e., from complaint to the clinical expression of the disease) are needed to confirm this view.

A computerized version of the SSCT (Study 2) has also been elaborated in order to facilitate its use on a larger scale, as well as to assess the speed-accuracy trade-off related to each cognitive process involved for performing this test: conflict resolution (the ability to suppress prepotent and distracting, irrelevant information) and conflict adaptation (the adjustment of conflict resolution based on previously experienced conflict level), each being combined, or not, with task switching). We found that a complex cognitive process involving both conflict resolution and task switching begins to decline at middle age (40-59 years), whereas a complex cognitive process involving conflict adaptation (with or without task switching) also deteriorates but at older age (60-79 years). To our knowledge, this is the first study to investigate age-related decline in cognitive control by dissociating conflict resolution and conflict adaptation, with or without the additional requirement of task switching. Further studies are needed to investigate whether cognitive reserve plays a compensatory role against age-related deficits in those cognitive processes. Future neuroimaging studies will also be of interest to explore the cerebral correlates of the two versions of the SSCT.

3.3. A new approach for qualitative and quantitative estimation of cognitive reserve

The cognitive performance of two persons are rarely similar even at a young age. When we get old, this difference becomes more apparent, mainly because of our life experiences (e.g., education, leisure activities) ‘build our brains differently’. Thus, the slope that everyone descends with aging is mediating by these experiences, which together form a kind of cognitive reserve (CR). Thus, taking into account CR is crucial to understand inter-individual differences in performance of any task. To date, CR is often estimated using a specific proxy, such as the educational level, language status, and occupational status. Even when the same proxies are

used, the procedures and measurement scales are extremely heterogeneous making thus the choice of assessment methods very difficult.

Therefore, the third study first aimed to elaborate a new cognitive reserve questionnaire (CRQ) including a large variety of experiences accumulated over the lifespan (from childhood to old age after retirement). The indice of CRQ was calculated using a combination of 8 most common proxies of CR in the literature (profession, education, salary ranges, leisure activities, language status, quality of life, health status, and social network size) and a variety of indicators for each proxy (e.g., for education: level of education combined with school performance, number of training courses, and diplomas). Data on CR proxies were obtained in a sample of 26 older adults (60-75 years). Our results demonstrated that older adults with high CR (CRQ score > 251) display more efficient executive functioning (i.e., lower Z-score of $SSCT_{IES}$) compared to those with low CR (CRQ score < 150). In other words, a higher level of CR was associated with a greater minimization of the effect of age on efficiency of executive function. Furthermore, a ROC curve (a purely exploratory analysis) was performed to attempt to determine an optimal cut-off value of the Z-score of $SSCT_{IES}$. A cut-off of 8 indicated low CR, with a sensitivity of 100 % but a specificity of only 55 %. Of course, this result is very preliminary, given the extremely small sample size and low specificity. Nonetheless, in this pilot study, we ensured that our methodological innovation in CR assessment is both valid and exciting to conduct broader studies. Therefore, further studies applying this approach on a large sample size with different life experiences will allow identifying a reliable cut-off value of the Z-score of $SSCT_{IES}$ to quantitatively estimate CR.

3.4. Dual-task-related gait changes in young adults: does the walking-associated secondary executive task matter?

Little is known whether the type of the secondary executive task performed while walking matters for dual-task-related gait changes in healthy young adults. Comparing different executive tasks may provide insight into the nature of the executive processes required for gait control; however, this comparison has not yet been investigated experimentally. The findings among our sample of young adults studied show that different walking-associated executive tasks have common and differential effects on gait control depending on their nature (executive function requirements) and cognitive load. Step velocity decreased regardless the type of the simultaneously performed executive task. Step width variability also decreased in tasks requiring either switching (ATS) or switching with inhibition (ASTS). Additionally, cognitive

performance decreased and mean step width increased (and this, independently of dual-task-related gait slowing) in the task inducing the greatest interference (ASTS). Investigating how the new dual-task walking paradigms change in healthy aging and both prodromal AD and PD is a promising avenue for future research aimed at enhancing the early detection of AD and PD. We may presume that performing the SSCT during walking will induce specific changes in gait control depending on the underlying brain pathology (AD versus PD).

4. Conclusion

In the context of early prediction of AD and PD, this thesis proposed through two theoretical articles (literature review and perspective article) and four experimental studies, a new methodological approach for the evaluation of EF, CR, and gait control.

The literature review was conducted to support evidence that subtle dual-task-related gait changes could potentially be used as prediagnostic markers (Belghali et al. 2017b) of AD and PD. The perspective article proposed a new conceptual framework dedicated to elaborate relevant dual-task paradigms susceptible, to induce disease-specific gait changes at the preclinical phase of AD and PD. The first two experimental studies proposed a new neuropsychological test (i.e., study 1: card version and study 2 computerized version), assessing executive function and related cognitive processes, separately and together. The third study proposed two measures of CR, one of which is qualitative and the other is quantitative. The last study proposed three new dual-task walking paradigms. These tools were validated in healthy young adults and older adults with a high sensitivity. However, the specificity of these markers needs to be approved in future studies. The diagnostic specificity could be obtained by comparing healthy aging to pathological aging (AD and PD). On the other hand, the pathological specificity could be achieved by comparing AD and PD at both prodromal and clinical phases of the disease (**Figure 27**).

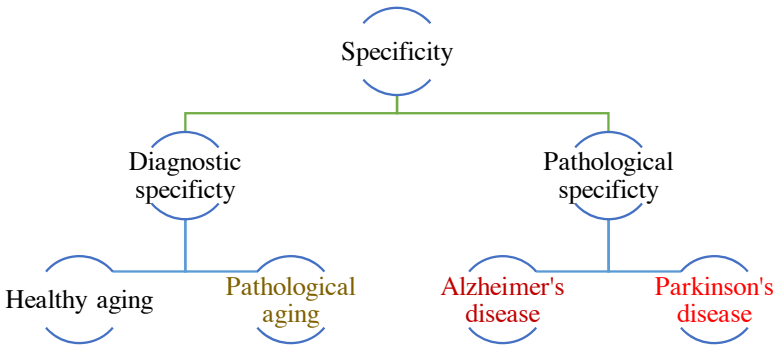


Figure 27. Specificity for an accurate diagnosis

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Appendix 1

Mini Mental State Examination (MMSE) (Version consensuelle du GRECO)

Orientation **/ 10**

Je vais vous poser quelques questions pour apprécier comment fonctionne votre mémoire.
Les unes sont très simples, les autres un peu moins. Vous devez répondre du mieux que vous pouvez.
Quelle est la date complète d'aujourd'hui ? _____

Si la réponse est incorrecte ou incomplète, posées les questions restées sans réponse, dans l'ordre suivant :

1. En quelle année sommes-nous ? ☐
2. En quelle saison ? ☐
3. En quel mois ? ☐
4. Quel jour du mois ? ☐
5. Quel jour de la semaine ? ☐

Je vais vous poser maintenant quelques questions sur l'endroit où nous trouvons.

6. Quel est le nom de l'hôpital où nous sommes ?* ☐
7. Dans quelle ville se trouve-t-il ? ☐
8. Quel est le nom du département dans lequel est située cette ville ?** ☐
9. Dans quelle province ou région est située ce département ? ☐
10. A quel étage sommes-nous ? ☐

Apprentissage **/ 3**

Je vais vous dire trois mots ; je vous voudrais que vous me les répétiez et que vous essayiez de les retenir car je vous les redemanderai tout à l'heure.

11. Cigare		Citron		Fauteuil	☐
12. Fleur	ou	Clé	ou	Tulipe	☐
13. Porte		Ballon		Canard	☐

Répéter les 3 mots.

Attention et calcul **/ 5**

Voulez-vous compter à partir de 100 en retirant 7 à chaque fois ?*

14.	93	☐
15.	86	☐
16.	79	☐
17.	72	☐
18.	65	☐

Pour tous les sujets, même pour ceux qui ont obtenu le maximum de points, demander :
Voulez-vous épeler le mot MONDE à l'envers ?**

Rappel **/ 3**

Pouvez-vous me dire quels étaient les 3 mots que je vous ai demandés de répéter et de retenir tout à l'heure ?

11. Cigare		Citron		Fauteuil	☐
12. Fleur	ou	Clé	ou	Tulipe	☐
13. Porte		Ballon		Canard	☐

Langage **/ 8**

Montrer un crayon.	22. Quel est le nom de cet objet ?*	☐
Montrer votre montre.	23. Quel est le nom de cet objet ?**	☐
24. Ecoutez bien et répétez après moi : « PAS DE MAIS, DE SI, NI DE ET »***		☐

Poser une feuille de papier sur le bureau, la montrer au sujet en lui disant : « Ecoutez bien et faites ce que je vais vous dire :

25. Prenez cette feuille de papier avec votre main droite, ☐
26. Pliez-la en deux, ☐
27. Et jetez-la par terre. »**** ☐

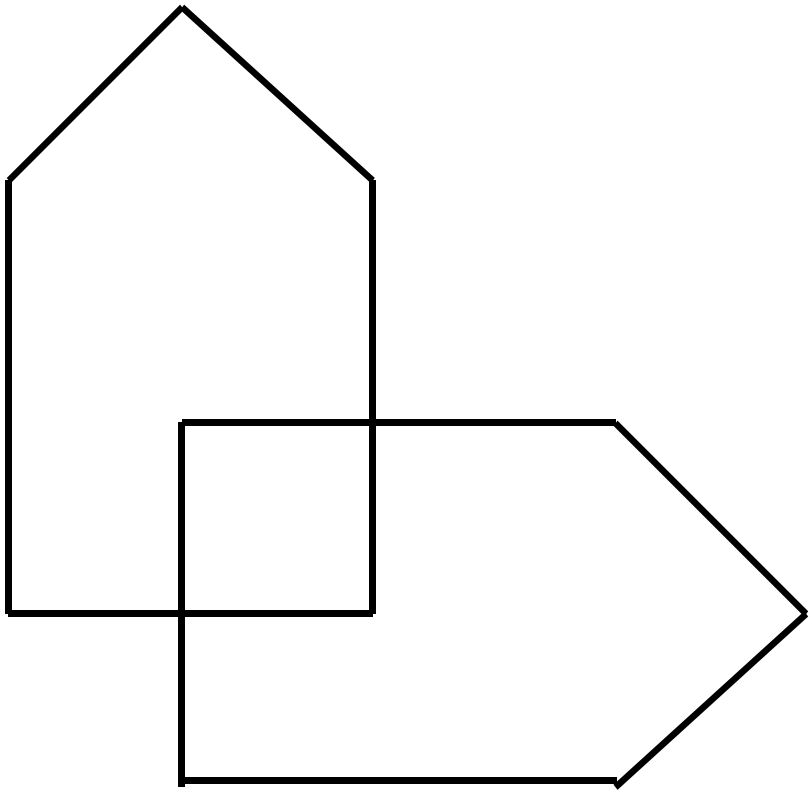
Tendre au sujet une feuille de papier sur laquelle est écrit en gros caractère : « FERMEZ LES YEUX » et dire au sujet :
28. « Faites ce qui est écrit ». ☐

Tendre au sujet une feuille de papier et un stylo, en disant :
29. « Voulez-vous m'écrire une phrase, ce que vous voulez, mais une phrase entière. »***** ☐

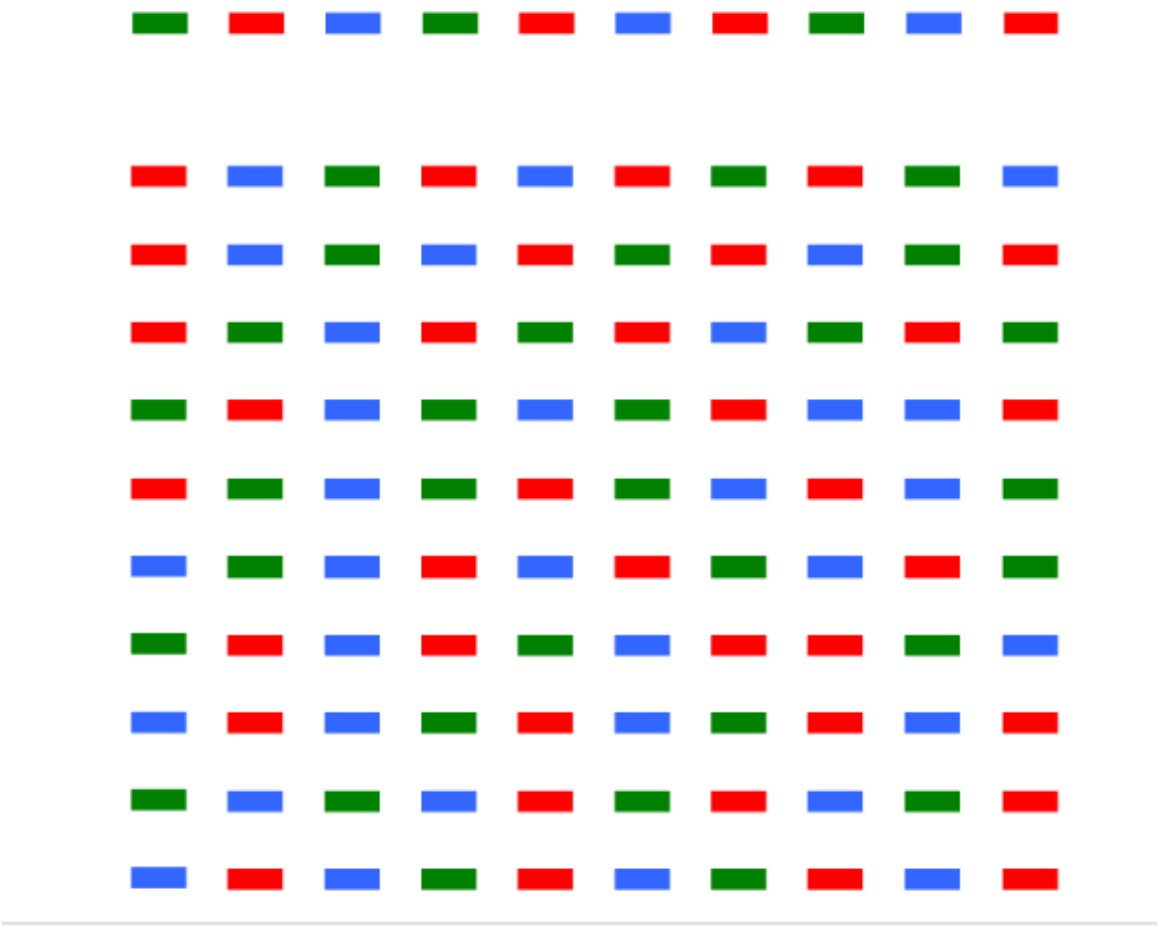
Praxies constructives **/ 1**

Tendre au sujet une feuille de papier et lui demander : 30. « Voulez-vous recopier ce dessin ? » ☐

« FERMEZ LES YEUX »



Appendix 2: Stroop test



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Appendix 3: Trial-Making Test

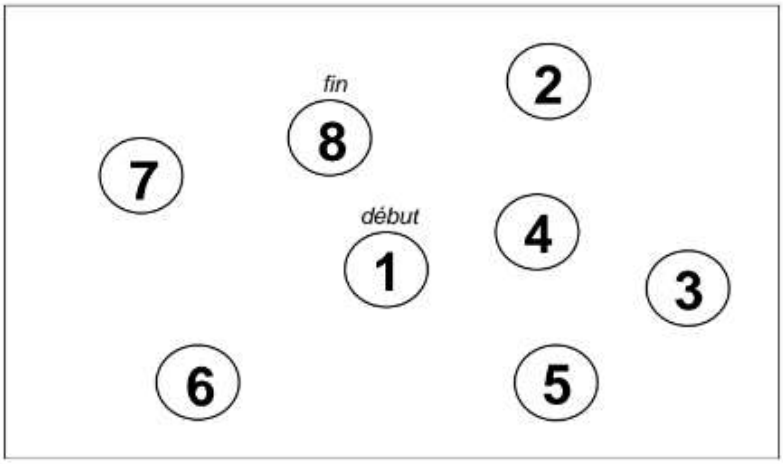
Code sujet : .....
Nom examinateur : .....

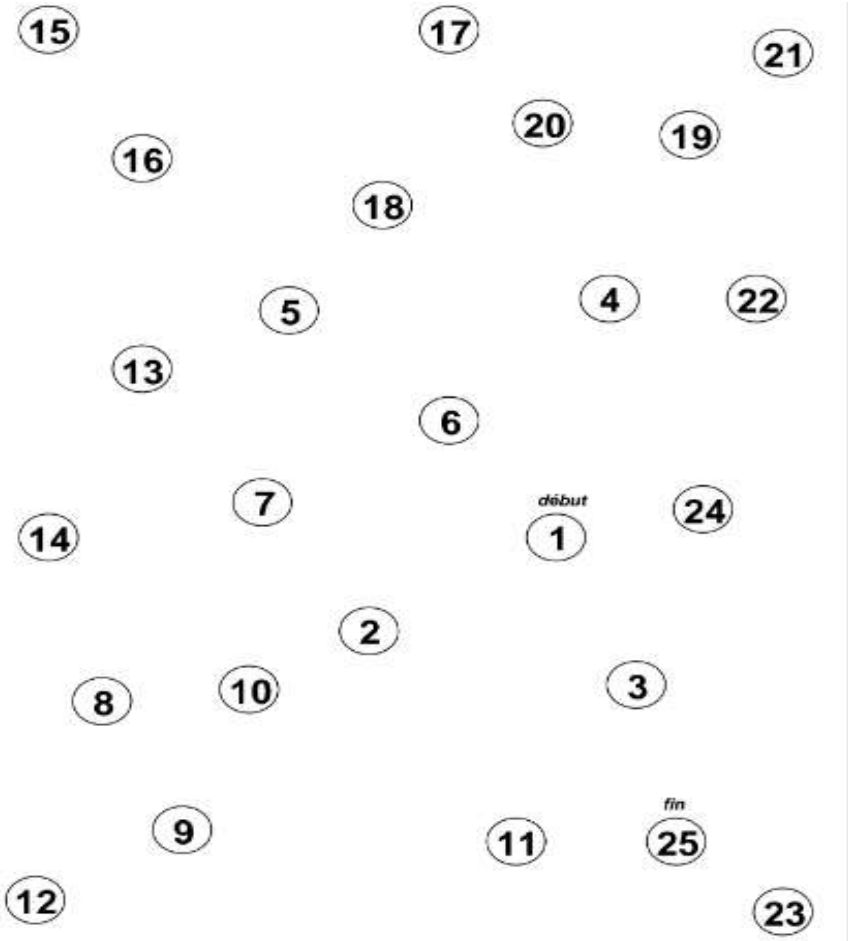
TRAIL-MAKING

Date : .....

Partie A

EXEMPLE

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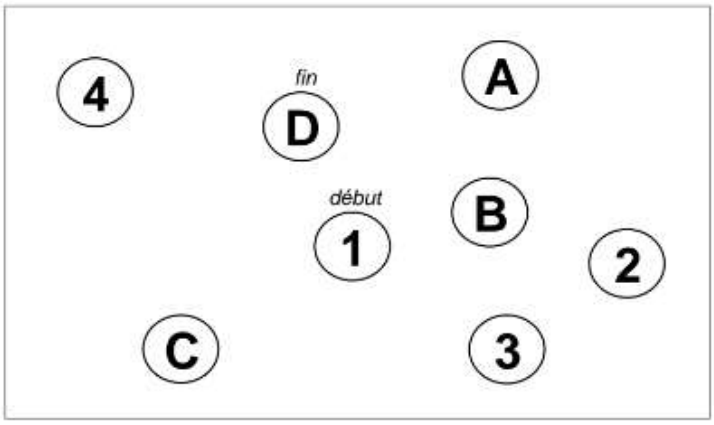
Code sujet : .....
Nom examinateur : .....

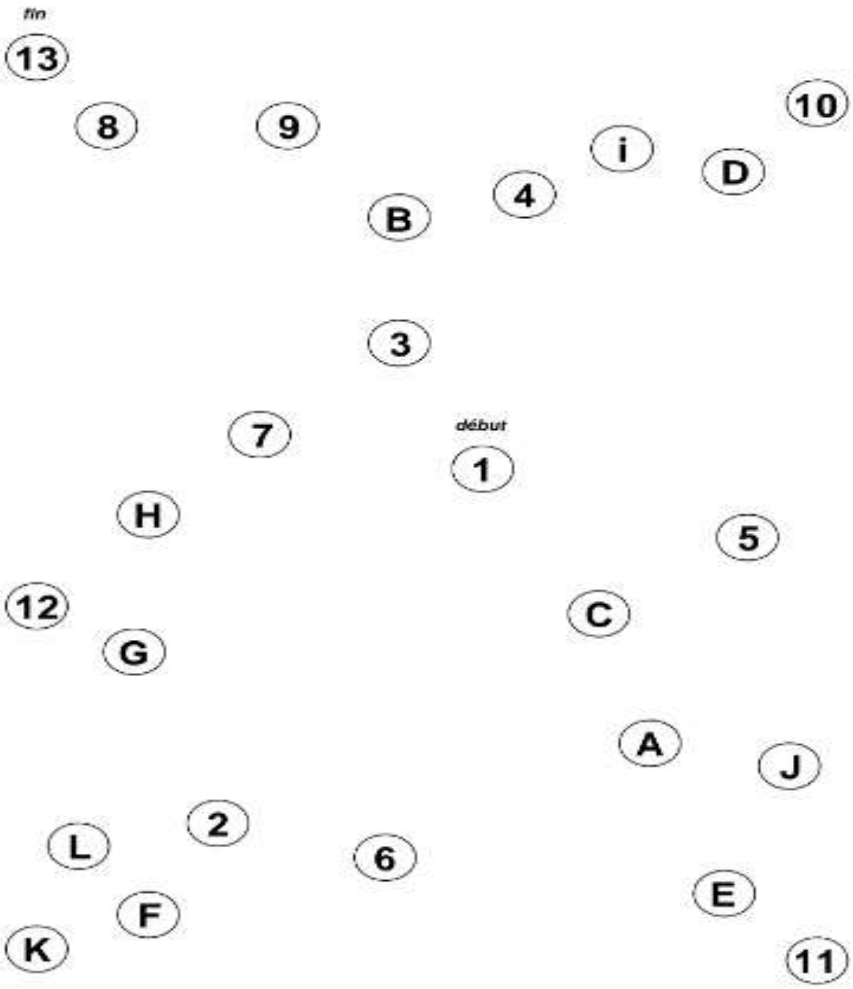
TRAIL-MAKING

Date : .....

Partie B

EXEMPLE

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Appendix 4: The Digit Span Forward and Backward Test

8. Mémoire des chiffres

REGLE D'ARRET
Ordre direct et Ordre inverse
Echec à 2 essais d'un même item.
Pour Ordre direct et Ordre inverse, administrer les 2 essais d'un même item, même si l'essai 1 est réussi. Administrer Ordre inverse, même si le sujet a échoué à Ordre direct.

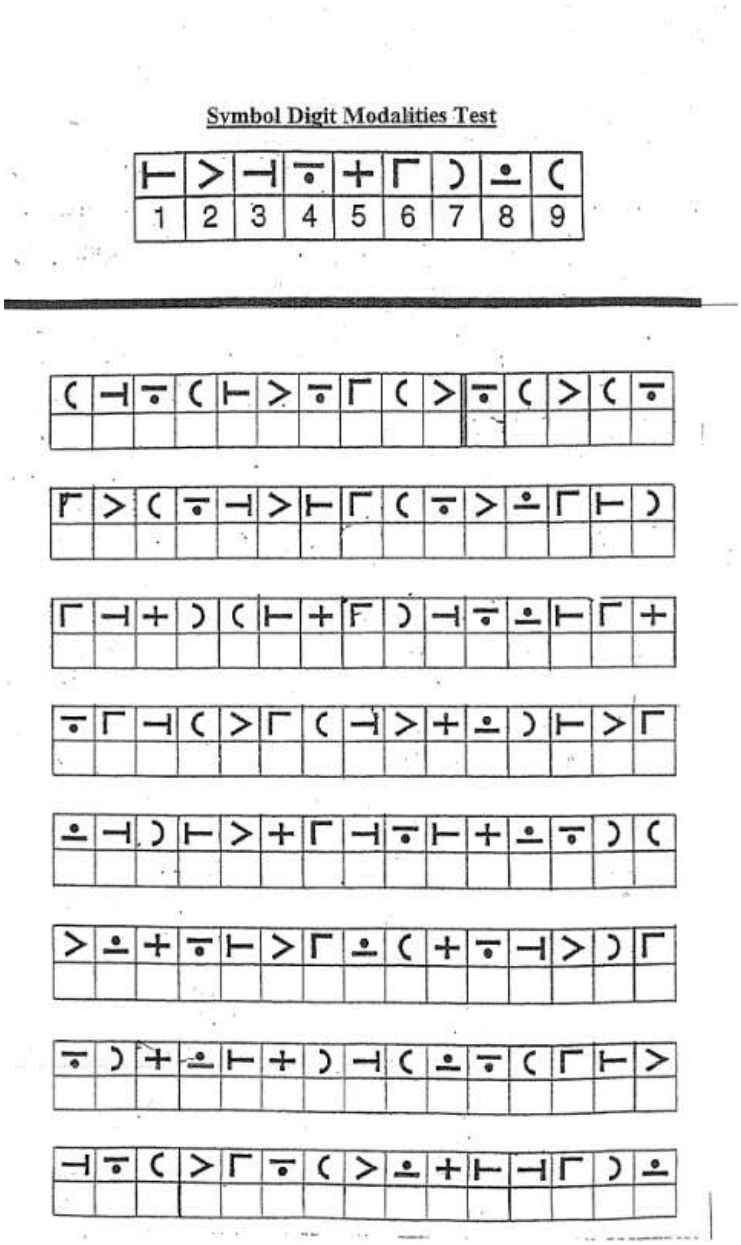
REGLE DE COTATION
Chaque essai : 0 ou 1 point.
Note à l'item : Essai 1 + Essai 2.

	Ordre direct Essai / Réponse	Note à l'essai	Note à l'item (0, 1 ou 2)
DÉBUT 1.	1 1-7		
	2 6-3		
2.	1 5-8-2		
	2 6-9-4		
3.	1 6-4-3-9		
	2 7-2-8-6		
4.	1 4-2-7-3-1		
	2 7-5-8-3-6		
5.	1 6-1-9-4-7-3		
	2 3-9-2-4-8-7		
6.	1 5-9-1-7-4-2-8		
	2 4-1-7-9-3-8-6		
7.	1 5-8-1-9-2-6-4-7		
	2 3-8-2-9-5-1-7-4		
8.	1 2-7-5-8-6-2-5-8-4		
	2 7-1-3-9-4-2-5-6-8		
	Total Ordre direct (Note maximum = 16)		

	Ordre inverse Essai / Réponse	Note à l'essai	Note à l'item (0, 1 ou 2)
1.	1 2-4		
	2 5-7		
2.	1 6-2-9		
	2 4-1-5		
3.	1 3-2-7-9		
	2 4-9-6-8		
4.	1 1-5-2-8-6		
	2 6-1-8-4-3		
5.	1 5-3-9-4-1-8		
	2 7-2-4-8-5-6		
6.	1 8-1-2-9-3-6-5		
	2 4-7-3-9-1-2-8		
7.	1 9-4-3-7-6-2-5-8		
	2 7-2-8-1-9-6-5-3		
	Total Ordre inverse (Note maximum = 14)		

Direct	+	Inverse	=	(Maximum = 30)

Annex 5: The symbol digit modalities test



Appendix 6 : New cognitive reserve questionnaire

CR QUESTIONNAIRE

IDENTIFICATION

NOM : .....**PRENOM** : .....
SEXE : ❑ F ❑ M
Statut civil: ❑ Célibataire ❑ Concubinage ❑ Marié (e) ❑ Divorcé (e) ❑ Veuf (ve)
Date de naissance : JJ/MM/AAAA :..... ...../...../ Nationalité :.....
Pays de naissance : .....
Prématuré : ❑ **OUI** ❑ NON
Nombre d'années de scolarisation : ❑ de 0 à 3 ans ❑ de 4 à 7 ans ❑ de 8 à 11 ans ❑ > 12 ans

ENFANCE (6ans/12ans)

I. QUESTIONS SUR VOS PARENTS

	Mère	Père
Niveau d'études de vos parents	☐ Inférieur au Brevet d'Etude ☐ Brevet d'Etudes ☐ Niveau collège ou lycée ☐ Baccalauréat général ou technologique ☐ Entre Bac+1 et Bac+3 ☐ Entre Bac+3 et Bac+5 ☐ Au delà de Bac+5	☐ Inférieur au Brevet d'Etude ☐ Brevet d'Etudes ☐ Niveau collège ou lycée ☐ Baccalauréat général ou technologique ☐ Entre Bac+1 et Bac+3 ☐ Entre Bac+3 et Bac+5 ☐ Au-delà de Bac+5
Profession de vos parents	☐ Travail manuel non qualifié [1] ☐ Travail manuel qualifié [2] ☐ Travail qualifié non manuel [3] ☐ Profession intermédiaire [4] ☐ Cadre ou professionnel à grandes responsabilités [5]	☐ Travail manuel non qualifié [1] ☐ Travail manuel qualifié [2] ☐ Travail qualifié non manuel [3] ☐ Profession intermédiaire [4] ☐ Cadre ou professionnel à grandes responsabilités [5]

[1] Ex : Ouvrier non spécialisé, travail à la campagne, serveur, opérateur de call center, baby-sitter, domestique, jardinier, femme au foyer, etc.
[2] Ex : Artisan ou ouvrier spécialisé, commis, coiffeur, simple employé, tailleur, infirmier, représentant, cuisinier, etc.
[3] Ex : Commerçant, maîtresse d'école maternelle, agent immobilier, prêtre, moine/sœur, musicien, etc.
[4] Ex : Dirigeant d'une petite entreprise, médecin, enseignant, avocat, entrepreneur, ingénieur, psychologue, etc.
[5] Ex : Professions intellectuelles et scientifiques de haute spécialisation, magistrat, directeur d'entreprise, etc.

Niveau de revenus de vos parents	☐ Très Bas ☐ Bas ☐ Moyen ☐ Haut ☐ Très haut	☐ Très Bas ☐ Bas ☐ Moyen ☐ Haut ☐ Très haut
Loisirs de vos parents	❑ Artistiques [6] ❑ Sportifs [7] ❑ Intellectuels [8] ❑ Sociale [9] ❑ Voyage ❑ Volontariat ❑ Aucun	❑ Artistiques [6] ❑ Sportifs [7] ❑ Intellectuels [8] ❑ Sociale [9] ❑ Voyage ❑ Volontariat ❑ Aucun

[6] Ex : Activités artistiques (jouer d'un instrument, arts plastiques) etc.
[7] Ex : Marche, natation, course, danse, jardinage, sports avec balle (football, handball, tennis…) etc.
[8] Ex : Écrire, lecture, collecte de timbres, musée, cinéma, théâtre, expositions, concerts, etc.
[9] Ex : Visites familiales et amicales, jeux de cartes, jeux de sociétés, billard, échecs, etc.

II. VOTRE STATUT LINGUISTIQUE PENDANT L'ENFANCE

Vos parents étaient-ils originaires du pays où vous habitiez entre 6 et 12 ans ? ❑ OUI ❑ NON

Si NON: ❑ PERE ❑ MERE ❑ LES DEUX

Quel était son (leurs) pays d'origine: ……

Parlez-vous la langue maternelle de vos parents au quotidien ? ❑ OUI ❑ NON

Avez-vous étudié une ou des langues étrangères durant cette période ? ❑ OUI ❑ NON

Si OUI la ou lesquelles : ……

Particularité(s) spécifiez :

……

A quelle fréquence pratiquiez-vous la (ou les) langue(s) de vos parents:

☐ Quotidienne ❑ Hebdomadaire

❑ Saisonnière ❑ Autre(s) ……..

Particularité(s) spécifiez :

……

A quel âge avez-vous entamé l'apprentissage d'une seconde langue ?

❑ 6 - 8 ans ❑ 10- 12 ans

❑ 8- 10 ans

Particularité(s) spécifiez :

……

Au cumulé pendant combien de temps (environ) ?

☐ Entre 1 an et 2 ans

❑ Entre 2 ans et 4 ans ❑ Au-delà de 4 ans

❑ Autre(s) ……..

Particularité(s) spécifiez :

……

Avez-vous effectué des séjours ou formations linguistiques ? ❑ OUI ❑ NON

Si oui, au cumulé pendant combien de temps (environ) ?

☐ En dessous d'un mois ❑ Entre 1 mois et 2 mois

❑ Entre 2 mois et 4 mois ❑ Au-delà de 4 mois

❑ Autre(s) ……..

En général, quelles sont vos compétences linguistiques durant cette période ?

❑ Compréhension écrite ❑ Faible ❑ Moyenne ❑ Très bonne ❑ Excellente

❑ Compréhension orale ❑ Faible ❑ Moyenne ❑ Très bonne ❑ Excellente

❑ Expression écrite ❑ Faible ❑ Moyenne ❑ Très bonne ❑ Excellente

❑ Expression orale ❑ Faible ❑ Moyenne ❑ Très bonne ❑ Excellente

❑ Bilingue ou trilingue

Si vous avez pratiqué plus d'une longue étrangère, veillez préciser vos compétences dans la partie ci-dessous

……

……

……

……

……

…….

III. VOS ACTIVITES PARASCOLAIRES PENDANT L'ENFANCE

Le tableau ci-dessous est à compléter de la manière suivante : une ligne correspond à une seule activité parascolaire. Exemple : Entre 9 et 12 ans vous avez pratiqué une activité sportive et deux activités sociales veuillez cocher chaque activité dans une ligne différente, vous aurez alors trois lignes de remplies.

Activités	De façon	Durée	Fréquence
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelle [8] ❑ Sociales [9] ❑ Voyages ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..

[6] Ex : Faire de la peinture, poésies, jouer d'un instrument, etc.
[7] Ex : Marche, natation, course, danse, sports avec balle (football, handball, tennis…) etc.
[8] Ex : Écrire, lecture de livres, collecte de timbres, musée, cinéma, théâtre, concerts, etc.
[9] Ex : Visites familiales et amicales, jeux de sociétés, etc.

IV. VOTRE SCOLARITE PENDANT L'ENFANCE (ENTRE 6 ET 12 ANS)

Quelles étaient vos performances scolaires ?

☐ Très faibles
☐ Faibles ❑ Bonnes
☐ Moyennes ❑ Excellentes

Quelle note donnez-vous de 0 à 20 : ……/20

Avez-vous obtenu un diplôme ? ☐ OUI ☐ NON
Si OUI, lequel : ……

Avez-vous arrêté l'école pendant votre enfance : *(Partie à remplir* si la scolarité n'est pas obligatoire dans votre pays*)*

☐ OUI ☐ NON

Si OUI, à quel âge vous êtes-vous arrêté ?

❑ 6 - 8 ans ❑ 8 - 10 ans
❑ 10 - 12 ans

V. VOS ACTIVITES PROFESSIONNELLES PENDANT L'ENFANCE *(Partie à remplir uniquement si vous aviez exercé une activité professionnelle entre 6 et 12 ans)*

☐ OUI ☐ NON

Avez-vous exercé une activité professionnelle pendant votre enfance ?

Si OUI, ❑ 1 ❑ 2

☐ dans le même domaine ☐ dans des domaines différents

☐ 3 ou plus

☐ dans le même domaine ☐ dans des domaines différents

De quelle(s) nature(s) ?

❑ Manuelle (ex : maçon, charpentier, restauration, etc.) ❑ Sociale (ex : animation)

❑ Sportive (ex : joueur du football) ❑ Commerciale (ex : vente)

A quelle fréquence ?

☐ Quotidienne ❑ Hebdomadaire

☐ Mensuelle ❑ Saisonnière

Pendant combien de temps (au cumulé) avez-vous travaillé pendant votre enfance ?

❑ Moins de 6 mois ❑ Entre 2 et 4 ans

❑ Entre 1 et 2 ans ❑ Autre(s) ……..

VI. VOTRE RESEAU SOCIAL PENDANT VOTRE ENFANCE (ENTRE 6 ET 12 ANS)

Avec qui viviez-vous pendant votre enfance ?

☐ Parents ☐ Membre de famille ☐ Centre d'accueil pour orphelins ☐ Autre(s) ……

Durant cette période étiez-vous d'une nature :

❑ Insociable (rapports humains extrêmement restreints)

❑ Peu sociable (ex : limitée aux parents, frères/sœurs)

❑ Sociable (ex : voisins, amis, camarades)

❑ Très sociable (ex : facilité à aller parler à des inconnus)

VII. VOTRE QUALITE DE VIE PENDANT VOTRE ENFANCE

Comment perceviez-vous votre vie pendant votre enfance ?

☐ Insatisfait ☐ Peu satisfait ☐Satisfait ☐ Très satisfait

Adolescence (13 ans/ 19 ans)

I. SCOLARITE ET FORMATIONS *(Partie à remplir si vous poursuiviez un parcours scolaire durant cette période)*

Au collège, quelles étaient vos performances scolaires ?

- ☐ Très faibles
- ❑ Faibles
- ☐ Moyennes
- ❑ Bonnes
- ☐ Très bonnes
- ❑ Excellentes

Quelle note donnez-vous de 0 à 20 : ……/20

Avez-vous obtenu un ou des diplômes ? ☐ OUI ☐ NON

Si OUI, le ou lesquels : ……

Au lycée, quelles étaient vos performances scolaires :

- ☐ Très faibles
- ❑ Faibles
- ☐ Moyennes
- ❑ Bonnes
- ☐ Très bonnes
- ❑ Excellentes

Quelle note donnez-vous de 0 à 20 : ……/20

Quelle orientation aviez-vous choisi ?

- ☐ Scientifique
- ❑ Littéraire
- ❑ Autre(s)……..
- ☐ Economique et sociale
- ❑ Technique

Durant cette période, avez-vous fait une ou des formations **supplémentaires à votre cursus scolaire ?**

☐ OUI ☐ NON

Si OUI

- ❑ 1
  - ☐ dans le même domaine
  - ☐ dans des domaines différents
- ☐ 3 ou plus
  - ☐ dans le même domaine
  - ☐ dans des domaines différents

De quelle(s) nature(s) ?

- ❑ Manuelle (ex : maçon, charpentier, restauration, etc.)
- ❑ Sociale (ex : animation)
- ❑ Sportive (ex : coaching, sauvetage)
- ❑ Commerciale (ex : vente)
- ❑ Sciences informatiques (ex : programmation, secrétariat)
- ❑ Médicale (ex : cadre de santé)
- ❑ Sciences économiques (ex : gestion d'entreprises)
- ❑ Autres : ……

Pendant combien de temps (au cumulé) a (ont) duré la ou les formation(s) ?

- ☐ Entre 1 mois et 3 mois
- ☐ Entre 3 mois et 6 mois
- ☐ Entre 6 mois et 1 an
- ☐ 1 an et 2 ans
- ☐ 2 ans et plus
- ☐ Autre (s) : ……

Avez-vous arrêté le collège ou le lycée ? *(Partie à remplir uniquement si vous aviez arrêté le collège ou le lycée)*

☐ OUI ☐ NON

Si OUI, à quel âge avez-vous arrêté le collège ou le lycée ?

- ❑ 13 - 15 ans
- ❑ 17 - 19 ans
- ❑ 15 - 17 ans

Durant cette période, avez-vous fait une ou des formations **hors cursus scolaire** ? *(Partie à remplir si vous avez arrêté votre parcours scolaire durant cette période)*

- ❑ 1
  - ☐ dans le même domaine
  - ☐ dans des domaines différents
- ☐ 3 ou plus
  - ☐ dans le même domaine
  - ☐ dans des domaines différents

Pendant combien de temps (au cumulé) a (ont) duré la ou les formation(s) ?

- ☐ Entre 1 mois et 3 mois
- ☐ Entre 3 mois et 6 mois
- ☐ Entre 6 mois et 1 an
- ☐ 1 an et 2 ans
- ☐ 2 ans et plus
- ☐ Autre (s) : ……

Cette ou ces formations avaient pour objectif final d'obtenir :

☐ Un travail manuel non qualifié [1] ☐ Un travail manuel qualifié [2]

☐ Un travail qualifié non manuel [3] ☐ Une profession intermédiaire [4]

☐ Autre (s) : ……

[1] Ex : Ouvrier non spécialisé, travail en campagne, serveur, opérateur de call center, baby-sitter, domestique, jardinier, femme au foyer, etc.
[2] Ex : Artisan ou ouvrier spécialisé, commis, coiffeur, simple employé, tailleur, infirmier, représentant, cuisinier, etc.
[3] Ex : Commerçant, maîtresse d'école maternelle, agent immobilier, employé de concept, prêtre, moine/sœur, musicien, etc.
[4] Ex : Dirigeant d'une petite entreprise, médecin, enseignant, avocat, entrepreneur, ingénieur, psychologue, etc.

II. ACTIVITES PROFESSIONNELLES PENDANT L'ADOLESCENCE (ENTRE 13 ET 19 ANS)

Avez-vous exercé une activité professionnelle durant cette période ? ☐ OUI ☐ NON

Si OUI, ☐ 1 ☐ 2

☐ dans le même domaine ☐ dans des domaines différents

☐ 3 ou plus

☐ dans le même domaine ☐ dans des domaines différents

De quelle(s) nature(s) :

☐ Intellectuelle (ex : aide au devoir) ☐ Manuelle (ex : maçon, charpentier, restauration, etc.)

☐ Sociale (ex : animation) ☐ Sportive (ex : coaching)

☐ Commerciale (ex : vente) ☐ Médicale

☐ Autres : ……

A quelle fréquence ?

☐ Quotidienne ☐ Hebdomadaire

☐ Mensuelle ☐ Saisonnière

Pendant combien de temps (au cumulé) avez-vous travaillé ?

☐ Entre 1 et 2 ans ❑ Entre 4 et 6 ans

☐ Entre 2 et 4 ans ❑ Autre(s) ……..

III. STATUT LINGUISTIQUE PENDANT L'ADOLESCENCE (ENTRE 13 ET 19 ANS)

Avez-vous étudié une ou des langues étrangères durant cette période ? ☐ OUI ☐ NON

Si OUI la ou lesquelles : ……

A quelle fréquence pratiquiez-vous la (ou les) langue(s) :

☐ Quotidienne ❑ Hebdomadaire

❑ Saisonnière ❑ Autre(s) ……..

Avez-vous effectué des séjours ou formations linguistiques ? ☐ OUI ☐ NON

Si OUI, au cumulé, pendant combien de temps (environ) ?

☐ En dessous d'un mois ❑ Entre 1 mois et 2 mois

❑ Entre 2 mois et 4 mois ❑ Au-delà de 4 mois

En général, quelles sont vos compétences linguistiques durant cette période **?**

❑ Compréhension écrite	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente
❑ Compréhension orale	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente
❑ Expression écrite	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente
❑ Expression orale	❑ Faible	❑ Moyenne	❑ Très bionne	❑ Excellente

❑ Bilingue ou trilingue

Si vous avez pratiqué plus d'une longue étrangère, veillez préciser vos compétences dans la partie ci-dessous

……
……
……
……
……

IV. ACTIVITES PARASCOLAIRES PENDANT L'ADOLESCENCE

Activités	De façon	Durée	Fréquence
❑ Artistiques [1] ❑ Sportives [2] ❑ Intellectuelles [3] ❑ Voyages [4] ❑ Volontariat [5] ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [1] ❑ Sportives [2] ❑ Intellectuelles [3] ❑ Voyages [4] ❑ Volontariat [5] ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [1] ❑ Sportives [2] ❑ Intellectuelles [3] ❑ Voyages [4] ❑ Volontariat [5] ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [1] ❑ Sportives [2] ❑ Intellectuelles [3] ❑ Voyages [4] ❑ Volontariat [5] ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [1] ❑ Sportives [2] ❑ Intellectuelles [3] ❑ Voyages [4] ❑ Volontariat [5] ❑ Aucune	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre : ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..

[6] Ex : Faire de la peinture, jouer d'un instrument, etc.
[7] Ex : Marche, natation, course, danse, musculation, sports avec balle (football, handball, tennis…) etc.
[8] Ex : écrire, lecture de journaux et de livres, collecte de timbres, musée, cinéma, théâtre, Expositions, concerts, conférences, etc.
[9] Ex : Visites familiales et amicales, jeux de cartes, jeux de sociétés, billard, échecs, etc.

Pratiquiez-vous une activité de façon particulièrement soutenue (ex : classe sportive) :
De quelle nature ?

❑ Artistique ❑ Sportive
❑ Intellectuelle ❑ Autres : ……

V. RESEAU SOCIAL PENDANT L'ADOLESCENCE

Avec qui viviez-vous pendant cette période?

☐ Parents ☐ Amis ☐ Membre de famille ☐ Centre d'accueil pour orphelins

Durant cette période êtes-vous d'une nature :

☐ Insociable (rapports humains extrêmement restreints) ☐ Peu sociable (ex : limitée aux parents, frères/sœurs)
☐ Sociable (ex : voisins, amis, camarades) ☐ Très sociable (ex : facilité à aller parler à des inconnus)

VI. AISANCE FINANCIERE ENTRE 13 ET 19 ANS

☐ Très Bas ☐ Bas ☐ Moyen ☐ Haut ☐ Très haut

VII. QUALITE DE VIE PENDANT L'ADOLESCENCE

Comment perceviez-vous votre vie à cette époque ?

☐ Insatisfait ☐ Peu satisfait ☐ Satisfait ☐ Très satisfait

Jeune adulte (20 ans/ 40 ans)

I. EDUCATION ET FORMATIONS ENTRE 20 ET 40 ANS

Avez-vous fait des études supérieures : ☐ OUI ☐ NON

Si OUI, dans quel domaine :

- ☐ Sciences Humaines et sociales
- ☐ Sciences économiques
- ☐ Sciences et techniques des activités physiques et sportives
- ☐ Sciences physiques, mathématiques
- ☐ Sciences biologiques et médicales
- ☐ Sciences de l'ingénieur
- ❑ Artistiques

Jusqu'à quel niveau :

- ☐ Entre BAC+1 et BAC+3
- ☐ Entre BAC+4 et BAC +5
- ☐ Au delà de BAC+5

Diplômes obtenus dans l'enseignement supérieur : ……
……

Avez-vous suivi des formations hors du cursus universitaire : ☐ OUI ☐ NON

Si OUI ❑ 1 ❑ 2

- ☐ dans le même domaine ☐ dans des domaines différents
- ☐ 3 ou plus
  - ☐ dans le même domaine ☐ dans des domaines différents

De quelle(s) nature(s) ?

- ❑ Manuelle (ex : maçon, charpentier, restauration, etc.)
- ❑ Sociale (ex : animation)
- ❑ Sportive (ex : coaching, sauvetage)
- ❑ Commerciale (ex : vente)
- ❑ Sciences informatiques (ex : programmation, secrétariat)
- ❑ Médicale (ex : cadre de santé)
- ❑ Sciences économique (ex : gestion d'entreprises)
- ☐ Autres : ……

Pendant combien de temps (au cumulé) a (ont) duré la ou les formation(s) ?

- ☐ Entre 1 mois et 3 mois
- ☐ Entre 3 mois et 6 mois
- ☐ Entre 6 mois et 1 an
- ☐ 1 an et 2 ans
- ☐ 2 ans et plus
- ☐ Autre (s) : ……

II. Statut linguistique ENTRE 20 ET 40 ANS

Avez-vous étudié une ou des langues étrangères durant cette période ? ☐ OUI ☐ NON

Si OUI, la ou lesquelles : ……

A quelle fréquence pratiquiez-vous la (ou les) langue(s) :

- ☐ Quotidienne
- ☐ Hebdomadaire
- ☐ Saisonnière
- ☐ Autre (s) : ……

Avez-vous effectué des séjours ou formations linguistiques ? ☐ OUI ☐ NON

Si oui, pendant combien de temps (environ) ?

- ☐ En dessous d'un mois
- ☐ Entre 1 mois et 2 mois
- ☐ Au-delà de 2 mois

Avez- vous exercé une activité professionnelle à l'étranger ? ☐ OUI ☐ NON

Avez-vous appris la langue du pays ? ☐ OUI ☐ NON

Quelle longue avez-vous pratiqué et pendant combien de temps ? ……

En général, quelles sont vos compétences linguistiques durant cette période ?

❑ Compréhension écrite	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente
❑ Compréhension orale	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente
❑ Expression écrite	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente
❑ Expression orale	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente

❑ Bilingue ou trilingue

Si vous avez pratiqué plus d'une longue étrangère, veillez préciser vos compétences dans la partie ci-dessous

……
……
……
……
……

III. VOTRE QUALITE DE VIE ENTRE 20 ET 40 ANS

Comment perceviez-vous votre vie à cette époque ?

☐ Insatisfait ☐ Peu satisfait ☐ Satisfait ☐ Très satisfait

IV. VOS ACTIVEES DE LOISIR ENTRE 20 ET 40 ANS:

Le tableau ci-dessous est à compléter de la manière suivante : une ligne correspond à une seule activité de loisir. Exemple : Vous avez pratiqué une activité sportive et deux activités sociales. Veuillez cocher chaque activité dans une ligne différente, vous aurez alors trois lignes de remplies.

Activités	Nombre	De façon	Durée	Fréquence
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	☐ Aucune ☐ 1 ☐ 2 ☐ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle

❑ Volontariat ☐ Autre : ……..
❑ Aucune

[6] Ex : Faire de la peinture, poésies, jouer d'un instrument, etc.
[7] Ex : Marche, natation, course, danse, musculation, sports avec balle (football, handball, tennis…) etc.
[8] Ex : Écrire, lecture de journaux et de livres, collecte de timbres, musée, cinéma, théâtre, concerts, conférences, etc.
[9] Ex : Visites familiales et amicales, jeux de cartes, jeux de sociétés, billard, échecs, etc.

Pratiquiez-vous une ou plusieurs activité(s) de façon particulièrement soutenue : ☐ OUI ☐ NON
Si OUI de quelle nature ?
❑ Artistique ☐ Sportive
❑ Intellectuelle ☐ Sociale
❑ Volontariat ☐ Autres : ……

Enfants : Aviez- vous des enfants pendant cette période ? ☐ OUI ☐ NON
Si oui : ☐ Nombre……

IV. VOTRE PROFESSION ENTRE 20 ET 40 ANS

Avez-vous exercé un travail professionnel durant cette période ? ☐ OUI ☐ NON
Si OUI, à quel âge avez-vous commencé à travailler ?
☐ 20-25 ans ☐ 30-35 ans
☐ 25-30 ans ☐ 35-40 ans
De quel type ? (*remplissez le tableau ci-dessous)*

Profession	☐ Travail manuel non qualifié[1] ☐ Travail manuel qualifié[2] ☐ Travail qualifié non manuel[3] ☐ Profession intermédiaire[4] ☐ Cadre ou professionnel à grandes responsabilités[5]

[1] Ex : Ouvrier non spécialisé, travail à la campagne, serveur, opérateur de call center, baby-sitter, domestique, jardinier, femme au foyer, etc.
[2] Ex : Artisan ou ouvrier spécialisé, commis, coiffeur, simple employé, tailleur, infirmier, représentant, cuisinier, etc.
[3] Ex : Commerçant, maîtresse d'école maternelle, agent immobilier, prêtre, moine/sœur, musicien, etc.
[4] Ex : Dirigeant d'une petite entreprise, médecin, enseignant, avocat, entrepreneur, ingénieur, psychologue, etc.
[5] Ex : Professions intellectuelles et scientifiques de haute spécialisation, magistrat, directeur d'entreprise, etc.

Pendant combien de temps (au cumulé) avez-vous travaillé durant cette période ? (pour chaque métier exercé)
☐ Entre 1 et 5 ans ☐ Entre 5 et 10 ans
☐ Entre 10 et 15 ans ☐ Entre 15 et 20 ans

☐ dans le même domaine ☐ dans des domaines différents
Précisez:
……

Avez-vous suivi des formations dans le cadre de votre profession ? ☐ OUI ☐ NON
Si OUI ❑ 1 ❑ 2
☐ dans le même domaine ☐ dans des domaines différents
☐ 3 ou plus
☐ dans le même domaine ☐ dans des domaines différents

De quelle(s) nature(s) ?
❑ Manuelle (ex : maçon, charpentier, restauration, etc.) ❑ Sociale (ex : animation)
❑ Sportive (ex : coaching) ❑ Commerciale (ex : vente, marketing)
❑ Sciences informatiques (ex : programmation, secrétariat) ❑ Médicale (ex : cadre de santé)
❑ Sciences économique (ex : gestion d'entreprises) ☐ Autres : ……

Pendant combien de temps (au cumulé) a (ont) duré la ou les formations ?

- ☐ Entre 1 mois et 3 mois
- ☐ Entre 3 mois et 6 mois
- ☐ Entre 6 mois et 1 an
- ☐ 1 an et 2 ans
- ☐ 2 ans et plus
- ☐ Autre (s) : ……

II. NIVEAU DE VOS REVENUS

- ☐ Très Bas
- ☐ Haut
- ☐ Bas
- ☐ Très haut
- ☐ Moyen

III. RESEAU SOCIAL

Avec qui viviez-vous durant cette période?

☐ Seul ☐ Conjoint(e) ☐ Enfants ☐ Amis

Durant cette période étiez-vous d'une nature :

- ☐ Insociable (rapport humains extrêmement restreint)
- ☐ Peu sociable (ex : limitée aux frères/sœurs)
- ☐ Sociable (ex : voisins, amis, camarades)
- ☐ Très sociable (ex : facilité à aller parler à des inconnus)

II. QUALITE DE VIE

Comment perceviez-vous votre vie à cette époque ?

☐ Insatisfait ☐ Peu satisfait ☐ Satisfait ☐ Très satisfait

Adulte (41 ans/ 60 ans)

Profession	☐ Travail manuel non qualifié [1] ☐ Travail manuel qualifié [2] ☐ Travail qualifié non manuel [3] ☐ Profession intermédiaire [4] ☐ Cadre ou professionnel à grandes responsabilités [5]

[1] Ex : Ouvrier non spécialisé, travail en campagne, serveur, opérateur de call center, baby-sitter, domestique, jardinier, femme au foyer, etc.
[2] Ex : Artisan ou ouvrier spécialisé, commis, coiffeur, simple employé, tailleur, infirmier, représentant, cuisinier, etc.
[3] Ex : Commerçant, maîtresse d'école maternelle, agent immobilier, employé de concept, prêtre, moine/sœur, musicien, etc.
[4] Ex : Dirigeant d'une petite entreprise, médecin, enseignant, avocat, entrepreneur, ingénieur, psychologue, etc.
[5] Ex : Professions intellectuelles et scientifiques de haute spécialisation, magistrat, directeur d'entreprise, etc.

Avez-vous suivi des formations dans le cadre de votre profession ? ☐ OUI ☐ NON

Si OUI

- ❑ 1
  - ☐ dans le même domaine
  - ☐ dans des domaines différents
- ❑ 2
  - ☐ dans le même domaine
  - ☐ dans des domaines différents
- ☐ 3 ou plus

De quelle(s) nature(s) ?

- ❑ Manuelle (ex : maçon, charpentier, restauration, etc.)
- ❑ Sociale (ex : animation)
- ❑ Sportive (ex : coaching)
- ❑ Commerciale (ex : vente)
- ❑ Sciences informatiques (ex : programmation, secrétariat)
- ❑ Médicale (ex : cadre de santé)
- ❑ Sciences économique (ex : gestion d'entreprises)
- ☐ Autres : ……

Pendant combien de temps (au cumulé) a (ont) duré la ou (les) formations ?

- ☐ Entre 1 et 3 mois
- ☐ Entre 3 et 6 mois
- ☐ Entre 6 mois et 1 an
- ☐ Entre 1 et 3 ans
- ☐ Entre 3 et 6 ans
- ☐ Autre (s) : ……

ACTIVITES DE LOISIRS :

Activités	Nombre	De façon	Durée	Fréquence
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	☐ Aucune ☐ 1 ☐ 2 ☐ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariats ❑ Aucunes	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..

[6] Ex : Faire de la peinture, poésies, jouer d'un instrument, etc.
[7] Ex : Marche, natation, course, danse, musculation, sports avec balle (football, handball, tennis…) etc.
[8] Ex : écrire, lecture de journaux et de livres, collecte de timbres, musée, cinéma, théâtre, concerts, conférences, etc.
[9] Ex : Visites familiales et amicales, jeux de cartes, jeux de sociétés, billard, échecs, etc.

Pratiquiez-vous une ou plusieurs activité(s) de façon particulièrement soutenue : ☐ OUI ☐ NON
Si OUI de quelle nature ?

❑ Artistique ☐ Sportive ☐ Intellectuelle
❑ Sociale ☐ Volontariat ☐ Autres : ……

Enfants : Aviez- vous des enfants pendant cette période ? ☐ OUI ☐ NON
Si oui : ☐ Nombre

III. RESEAU SOCIAL

Avec qui viviez-vous durant cette période ?

☐ Seul ☐ Conjoint(e) ☐ Enfants ☐ Amis

Durant cette période êtes-vous d'une nature :

- ☐ Insociable (rapport humains extrêmement restreints)
- ☐ Peu sociable (ex : limitée aux parents, frères/sœurs)
- ☐ Sociable (ex : voisins, amis, camarades)
- ☐ Très sociable (ex : facilité à aller parler à des inconnus)

IV. NIVEAU DE REVENUS

- ☐ Très Bas
- ☐ Bas
- ☐ Moyen
- ☐ Haut
- ☐ Très haut

Statut linguistique

Parliez-vous une ou des langues étrangères durant cette période ?

☐ OUI ☐ NON

Si OUI la ou lesquelles : ……

A quelle fréquence pratiquiez-vous la (ou les) langue(s) :

- ☐ Quotidienne
- ☐ Hebdomadaire
- ☐ Saisonnière

En général, quelles sont **vos** compétences linguistiques durant cette période ?

❑ Compréhension écrite	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente
❑ Compréhension orale	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente
❑ Expression écrite	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente
❑ Expression orale	❑ Faible	❑ Moyenne	❑ Très bonne	❑ Excellente

- ❑ Bilingue ou trilingue

Si vous avez pratiqué plus d'une longue étrangère, veillez préciser vos compétences dans la partie ci-dessous

……
……
……
……
……

IV. QUALITE DE VIE

- ☐ Insatisfait
- ☐ Peu satisfait
- ☐Satisfait
- ☐ Très satisfait

Personne âgée (entre 61 ans jusqu' à la retraite)

Profession	☐ Travail manuel non qualifié [1] ☐ Travail manuel qualifié [2] ☐ Travail qualifié non manuel [3] ☐ Profession intermédiaire [4] ☐ Cadre ou professionnel à grandes responsabilités [5]

[1] Ex : Ouvrier non spécialisé, travail en campagne, serveur, opérateur de call center, baby-sitter, domestique, jardinier, femme au foyer, etc.
[2] Ex : Artisan ou ouvrier spécialisé, commis, coiffeur, simple employé, tailleur, infirmier, représentant, cuisinier, etc.
[3] Ex : Commerçant, maîtresse d'école maternelle, agent immobilier, employé de concept, prêtre, moine/sœur, musicien, etc.
[4] Ex : Dirigeant d'une petite entreprise, médecin, enseignant, avocat, entrepreneur, ingénieur, psychologue, etc.
[5] Ex : Professions intellectuelles et scientifiques de haute spécialisation, magistrat, directeur d'entreprise, etc.

II. STATUT LINGUISTIQUE

Parliez-vous une ou des langues étrangères durant cette période ? ☐ OUI ☐ NON
Si OUI la ou lesquelles : ……
A quelle fréquence pratiquiez-vous la (ou les) langue(s) :
☐ Quotidienne ☐ Hebdomadaire ☐ Saisonnière

Avez-vous étudié une ou des langues étrangères durant cette période ? ❑ OUI ❑ NON
☐ Si OUI la ou lesquelles : ……
☐ Particularité(s) spécifiez :
……

III. ACTIVITES DE LOISIRS :

Activités	Nombre	De façon	Durée	Fréquence
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	☐ Aucune ☐ 1 ☐ 2 ☐ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistique9*-+ ❑ s [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..

❑ Volontariat ❑ Aucune				☐ Autre ……	
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ [7]Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..	

[6] Ex : Faire de la peinture, poésies, jouer d'un instrument, etc.
[7] Ex : Marche, natation, course, danse, musculation, sports avec balle (football, handball, tennis…) etc.
[8] Ex : Écrire, lecture de journaux et de livres, collecte de timbres, musée, cinéma, théâtre, concerts, conférences, etc.
[9] Ex : Visites familiales et amicales, jeux de cartes, jeux de sociétés, billard, échecs, etc.

Pratiquiez-vous une ou plusieurs activité(s) de façon particulièrement soutenue : ☐ OUI ☐ NON
Si OUI de quelle nature ?

- ❑ Artistique
- ❑ Intellectuelle
- ❑ Volontariat
- ☐ Sportive
- ☐ Sociale
- ☐ Autres : ……

III. RESEAU SOCIAL

Avec qui vivez-vous présentement ?

☐ Seul ☐ Conjoint(e) ☐ Enfants ☐ Amis

Durant cette période êtes-vous d'une nature :

- ☐ Insociable (rapport humains extrêmement restreint)
- ☐ Peu sociable (ex : limitée aux frères/sœurs)
- ☐ Sociable (ex : voisins, amis, camarades)
- ☐ Très sociable (ex : facilité à aller parler à des inconnus)

IV. NIVEAU DE REVENUS

☐ Très Bas ☐ Bas ☐ Moyen ☐ Haut ☐ Très haut

VI. QUALITE DE VIE

Comment percevez-vous votre vie en ce moment ?

☐ Insatisfait ☐ Peu satisfait ☐Satisfait ☐ Très satisfait

Personne âgée (À la retraite)

I. ÂGE DE RETRAITE

A quel âge avez-vous pris la retraite ?.....

II. LE STATUT D'ACTIVITE PROFESSIONNELLE

Comment perceviez-vous votre vie professionnelle durant cette période ?

- ❑ Inactif depuis 0 à 4 ans
- ❑ Inactif depuis 5 à 9 ans
- ❑ Inactif depuis 10 à 14 ans
- ❑ Inactif depuis 15 ans ou plus
- ❑ N'a pas eu d'activité

- ❑ Actif depuis 0 à 4 ans
- ❑ Actif depuis 5 à 9 ans
- ❑ Actif depuis 10 à 14 ans
- ❑ Actif depuis 15 ans ou plus
- ❑ Toujours actif (Depuis la retraite jusqu'au moment présent)

III. STATUT LINGUISTIQUE

Parliez-vous une ou des langues étrangères durant cette période ? ☐ OUI ☐ NON

Si OUI la ou lesquelles : ……

A quelle fréquence pratiquiez-vous la (ou les) langue(s) :

☐ Quotidienne ☐ Hebdomadaire ☐ Saisonnière

Avez-vous étudié une ou des langues étrangères durant cette période ? ❑ OUI ❑ NON

- ☐ Si OUI la ou lesquelles : ……
- ☐ Particularité(s) spécifiez :

  ……

IV. ACTIVITES DE LOISIRS :

Activités	Nombre	De façon	Durée	Fréquence
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	☐ Aucune ☐ 1 ☐ 2 ☐ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..

[6] ***Ex : Faire de la peinture, poésies, jouer d'un instrument, etc.***

❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..
❑ Artistiques [6] ❑ Sportives [7] ❑ Intellectuelles [8] ❑ Sociales [9] ❑ Voyages ❑ Volontariat ❑ Aucune	❑ Aucune ❑ 1 ❑ 2 ❑ 3 et plus	☐ Individuelle ☐ Collective	☐ Entre 1h et 2h ☐ Entre 2h et 3h ☐ Entre 3h et 4h ☐ Autre ……	☐ Quotidienne ☐ 2 fois par semaine ☐ Hebdomadaire ☐ Mensuelle ☐ Autre : ……..

[7] Ex : Marche, natation, course, danse, musculation, sports avec balle (football, handball, tennis…) etc.

[8] Ex : Écrire, lecture de journaux et de livres, collecte de timbres, musée, cinéma, théâtre, concerts, conférences, etc.

[9] Ex : Visites familiales et amicales, jeux de cartes, jeux de sociétés, billard, échecs, etc.

Pratiquiez-vous une ou plusieurs activité(s) de façon particulièrement soutenue : ☐ OUI ☐ NON

Si OUI de quelle nature ?

❑ Artistique ☐ Sportive
❑ Intellectuelle ☐ Sociale
❑ Volontariat ☐ Autres : ……

VI. RESEAU SOCIAL

Avec qui vivez-vous présentement ?

☐ Seul ☐ Conjoint(e) ☐ Enfants ☐ Amis

Durant cette période êtes-vous d'une nature :

☐ Insociable (rapport humains extrêmement restreint) ☐ Peu sociable (ex : limitée aux frères/sœurs)
☐ Sociable (ex : voisins, amis, camarades) ☐ Très sociable (ex : facilité à aller parler à des inconnus)

NIVEAU DE REVENUS

☐ Très Bas ☐ Bas ☐ Moyen ☐ Haut ☐ Très haut

QUALITE DE VIE

Comment percevez-vous votre vie en ce moment ?

☐ Insatisfait ☐ Peu satisfait ☐Satisfait ☐ Très satisfait

Votre santé (dès l'instant de votre naissance jusqu'au moment présent)

Comment percevez-vous votre santé physique ?

De 0 à 6 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
De 6 à 12 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
De 41 à 55 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
De 20 à 40 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
De 41 à 55 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
61 ans et plus ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne

Comment percevez-vous votre santé psychologique ?

De 0 à 6 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
De 6 à 12 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
De 41 à 55 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
De 20 à 40 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
De 41 à 60 ans ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne
61 ans et plus ❑ Mauvaise ❑ Moyenne ❑ Bonne ❑ Très Bonne

Appendix 7

CERSTAPS

Comité d'Ethique pour la Recherche en STAPS

Objet[1] : Avis sur le projet «Fonctions exécutives et contrôle posturo-locomoteur : Quelle interaction ?» présenté par Leslie Decker, Laboratoire Comète, U 1075 INSERM, Université de Caen.

Compte tenu des éléments fournis dans la demande déposée par Leslie Decker, le Comité d'Ethique pour la Recherche en STAPS émet l'avis suivant :

AVIS FAVORABLE

Numéro de l'avis : 2016-26-04-13

A Grenoble, le 26 avril 2016,

Le Président du CERSTAPS,

Vincent Nougier

[1] Le Comité d'Ethique pour les Recherches en STAPS (CERSTAPS), mis en place sous l'égide de la Conférence des Directeurs et Doyens STAPS (C3D) et de la 74ème section du CNU propose aux chercheurs qui le souhaitent d'examiner les aspects éthiques de leur protocole de recherche. Cette structure est à la disposition de tout chercheur relevant de la 74ème section (1) pour les recherches pluridisciplinaires impliquant des personnes et qui ne sont pas tenues pour l'instant par la loi 2004-806 du 9 août 2004 de passer en Comité de Protection des Personnes (CPP), c'est-à-dire notamment les projets de recherches non-interventionnelles impliquant la personne humaine et les recherches en sciences humaines et sociales ou assimilées et (2) comme une préparation et une facilitation au passage en CPP de projets de recherche biomédicale et en santé qui, de par la loi, se doivent de passer en CPP. Le CERSTAPS est surtout utile aux projets sans grands risques biomédicaux a priori.