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# Les troubles de l'initiation du mouvement dans la maladie de Parkinson : au-delà des symptômes moteurs de la dopamine

Charlotte Spay

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**Charlotte SPAY ROLLAND**

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**Les troubles de l'initiation du mouvement  
dans la maladie de Parkinson :**  
**Au-delà des symptômes moteurs de la dopamine.**

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## Résumé

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Les troubles de l'initiation du mouvement de la maladie de Parkinson sont invalidants et sans solution thérapeutique satisfaisante. Dans ce travail, nous nous intéressons à deux catégories de symptômes, classiquement explorées de façon indépendante : d'un côté, la lenteur à l'initiation du mouvement ou akinésie, et de l'autre, la difficulté à retenir l'initiation d'un mouvement ou impulsivité. En nous appuyant sur des avancées théoriques et méthodologiques récentes, nous tentons de revisiter ces troubles de l'initiation du mouvement en termes de dysfonctionnements exécutifs dans la maladie de Parkinson.

Dans ce but, nous avons : 1) recherché les liens entre marqueurs cliniques (akinésie et impulsivité) et marqueurs comportementaux des troubles du contrôle inhibiteur ; 2) identifié les dysfonctionnements cérébraux associés au moyen de méthodes électroencéphalographiques innovantes permettant de localiser les sources et d'observer la dynamique des processus cérébraux ; et 3) sondé l'origine neurochimique de cette fonction en combinant stimulations pharmacologique et cérébrale et enregistrement des modifications de l'activité électroencéphalographique résultantes.

Nos résultats suggèrent que l'impulsivité et l'akinésie sont les deux faces d'une même pièce, aux origines d'un dysfonctionnement du contrôle inhibiteur proactif. Ils indiquent également que ce contrôle exécutif est sous-tendu par l'activité du noyau sous-thalamique et d'un réseau cortical médian comprenant le précuneus et l'aire motrice supplémentaire. Un rôle du système noradrénergique a été mis en évidence dans ces troubles exécutifs. Ces travaux ouvrent donc la voie à de nouvelles perspectives thérapeutiques pour la maladie de Parkinson.

**Mots clés :** maladie de Parkinson, inhibition, contrôle proactif, akinésie, impulsivité, TCI, dopamine, noradrénaline, stimulation cérébrale profonde, noyau sous-thalamique, précuneus, aire motrice supplémentaire, électroencéphalographie, analyse spectrale, oscillations *alpha*, oscillations *beta*.

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# Movement initiation disorders in Parkinson's disease: Beyond motor symptoms and dopamine.

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## Abstract

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Movement initiation disorders in Parkinson's disease are multifaceted, are debilitating and have no satisfying therapeutic option. On the one hand, slowness and difficulties initiating voluntary movements contribute to akinesia, a cardinal symptom of the disease which is usually considered to be motor in origin and which is not fully alleviated by current medication. On the other hand, difficulties refraining voluntary movements contribute to impulsivity, a frequent side effect of current dopaminergic and neurosurgical therapies. Here, based on systematic analyses of the clinical neuroimaging literature, we suggest that these opposite forms of movement initiation disorders might be executive, not purely motor, in origin.

To empirically test this hypothesis, we: 1) related clinical markers of the disease (akinesia and impulsivity) to behavioral indexes of inhibitory control impairment; 2) identified associated cerebral dysfunctions by means of advanced electroencephalographic (EEG) methods; and 3) investigated the neurochemical origin of these dysfunctions by combining pharmacological and cerebral stimulations with EEG recordings.

Results suggest that impulsivity and akinesia are the two sides of the same coin. Indeed, they were found to be associated with opposite inhibitory control disorders, and dysfunctions of subthalamic cortical loops involving medial executive areas. Importantly, it was also found that restoring normal behavior and normal activity within these loops by means of deep brain stimulation depends on the level of noradrenergic tonus, opening the way for new therapeutic approaches for Parkinson's disease.

**Key words:** Parkinson's disease, inhibition, proactive control, akinesia, impulsivity, ICDs, dopamine, noradrenaline, deep brain stimulation, subthalamic nucleus, precuneus, supplementary motor area, electroencephalography, spectral analysis, *alpha* oscillations, *beta* oscillations.

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---

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## Glossaire

AMS : aire motrice supplémentaire

5-HT : sérotonine

CCA : cortex cingulaire antérieur

CCP : cortex cingulaire postérieur

CIC : comportements impulsifs-compulsifs

COMT : Cathécol-O-méthyltransférase

DA : dopamine

DAAAs : agonistes dopaminergiques

dIPFC : cortex préfrontal dorso-latéral

dmFC : cortex frontal dorso-médial

*DMN: default mode network*

DSM : manuel diagnostique et statistique des troubles mentaux

EEG : electroencéphalographie

*ERD: event-related desynchronisation*

*ERS: event-related synchronisation*

GPe : globus pallidus externe

GPi : globus pallidus interne

IPC : cortex pariétal inférieur

IPL : lobule pariétal inférieur gauche

IRMf : imagerie par résonance magnétique fonctionnelle

LC : locus coeruleus

*LFP: local field potential*

M1 : cortex moteur primaire

MAO-B : Monoamine oxydase B

*MIDI: the Minnesota Impulsive Disorders Interview*

NA : noradrénaline

NST : noyau sous-thalamique

MEG : magnéto-encéphalographie

OFF : absence de traitement

ON : présence de traitement

PD : patients atteints de la maladie de Parkinson

PE : potentiels évoqués

Pré-AMS : aire pré-motrice supplémentaire

*QUIP: questionnaire for impulsive-compulsive disorders in Parkinson's disease*

rIFG : gyrus frontal inférieur droit

SAS : séparation aveugle de source

SCP : stimulation cérébrale profonde

SN : substance noire

*SAST: sexual addiction screening test*

*SOGS: south oaks gambling screen*

*SSRT: stop-signal reaction time*

TCI : troubles du contrôle des impulsions

tDCS : stimulation transcrânienne à courant directe

TEP : tomographie par émission de positons

TMS : stimulation magnétique transcrânienne

TR : temps de réaction

*UPDRS: Unified Parkinson's Disease Rating Scale*

Vim : noyau intermédiaire du thalamus

vIPFC : cortex préfrontal ventro-latéral

*« Je ne perds jamais. Soit je gagne, soit j'apprends. »*

*Nelson Mandela*

# CHAPITRE 1 : LA MALADIE DE PARKINSON – DE L'ORIGINE DOPAMINERGIQUE AUX SYMPTOMES

Dans ce chapitre, nous allons commencer par présenter la maladie de Parkinson : son origine et sa symptomatologie. Notre objectif est de révéler son hétérogénéité clinique et de mieux cerner la neuropathophysiologie de cette maladie.

## A. DE L'ORIGINE DOPAMINERGIQUE...

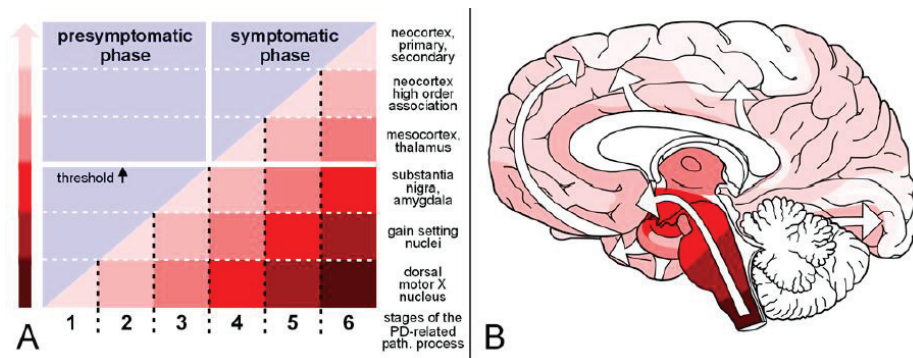
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### 1. ORIGINE DE LA MALADIE DE PARKINSON

La maladie de Parkinson est une pathologie neurodégénérative, la plus fréquente après la maladie d'Alzheimer. Sa prévalence est estimée à 1,6% après 65 ans et augmente progressivement avec l'âge jusqu'à atteindre près de 4% après 80 ans (Lau & Breteler, 2006). La maladie de Parkinson est une affection chronique, progressive et lentement évolutive, qui constitue un facteur de risque de mauvaise qualité de vie, de dépendance pour les actes de la vie quotidienne, et de mortalité (Driver et al., 2008; Marras et al., 2002; Muslimovic et al., 2008; Soh et al., 2011). De ce fait, la compréhension des mécanismes étiopathogéniques et physiopathologiques à l'origine des symptômes de la maladie relève d'un enjeu de santé publique.

La maladie de Parkinson est une maladie neurodégénérative progressive touchant le système nerveux central. Initialement, elle résulte d'une dégénérescence majeure des neurones dopaminergiques de la substance noire partie compacte (SNpc) (Hornykiewicz, 2006) entraînant une disparition progressive et irréversible des neurones (Agid, 1991). La substance noire est une petite structure nerveuse composée d'environ 400.000 neurones dopaminergiques. Elle envoie des projections en direction d'une autre structure cérébrale sous-corticale, le striatum, appartenant aux ganglions de la base. Dans la maladie de Parkinson, la déplétion des neurones dopaminergiques de la SNpc empêche l'activation du striatum et entrave le bon fonctionnement des boucles ganglio-thalamo-corticales à l'origine des symptômes de la maladie.

Dans une approche plutôt descriptive, Braak et al. (2003, 2004) proposent un modèle topographiquement organisé des processus neuropathologiques de la maladie de Parkinson (Figure 1). Il débiterait par le dysfonctionnement des structures non-dopaminergiques du noyau moteur dorsal du nerf vague et des structures olfactives antérieures. L'affection progresserait ensuite selon un gradient caudo-rostral et ventro-dorsal vers les noyaux gris centraux puis le cortex cérébral. L'apparition d'une symptomatologie motrice et la dégénérescence de la SNpc, souvent présentées comme caractéristiques centrales de la maladie, n'interviendraient en fait qu'à partir du troisième ou quatrième stade. Ce modèle permet ainsi d'expliquer l'apparition précoce de symptômes non-moteurs (hyposmie, dépression) et les signes de perturbation du système nerveux autonome et des symptômes démentiels tardifs.



**Figure 1 : Expansion topographique des lésions histopathologiques au cours de la maladie de Parkinson.**

**A. Diagramme simplifié. B. Vue médiale.** La phase pré-symptomatique est marquée par l'apparition de corps de Lewy sans symptôme chez les patients. Dans la phase symptomatique, le seuil neuropathologique est dépassé et les symptômes cliniques apparaissent. Les lésions intéressent initialement le noyau moteur des nerfs IX/X et fréquemment le noyau olfactif antérieur (stade 1). Ensuite, d'autres structures cérébrales sont progressivement impliquées. La pathologie s'étend plus rapidement au niveau du tronc cérébral que du bulbe olfactif. Elle implique ainsi le raphé, la formation réticulée, et le locus coeruleus (stade 2). Elle atteint ainsi les noyaux gris centraux, en particulier la substance noire (stade 3). Les lésions corticales débutent au niveau du mésocortex temporal antéromédian (stade 4) puis s'étendent vers les aires préfrontales et les aires sensorielles associatives de haut niveau (stade 5). Les aires prémotrices, motrices, et sensorielles primaires sont les plus tardivement affectées (stade 6). L'intensité de la couleur indique la sévérité de l'atteinte aux différents stades ; les flèches blanches indiquent le sens de propagation du processus dégénératif. *Illustration issue de Braak et al. (2004).*

**On considère classiquement que la maladie de Parkinson est à l'origine d'une symptomatologie motrice sous-tendue par une dégénérescence dopaminergique. Pourtant, la physiopathologie de la maladie s'avère plus complexe et se doit d'être plus amplement étudiée.**



## 2. ANATOMIE DES GANGLIONS DE LA BASE

D'un point de vue anatomique, les ganglions de la base sont composés de plusieurs noyaux. Le striatum est constitué du putamen, du noyau caudé et du striatum ventral, ce dernier comprenant le noyau accumbens. Le striatum, forme le point d'entrée des ganglions de la base en recevant les informations provenant de nombreuses aires corticales. Les informations transitent par la suite en direction du pallidum (interne -GPi- et externe -GPe-), qui reçoit les afférences du putamen ; et de la partie réticulée de la substance noire (SNr), qui reçoit les afférences du noyau caudé. Ces deux noyaux sont les noyaux de sortie de l'information des ganglions de la base qui projettent ensuite sur le thalamus et le colliculus supérieur, puis sur le cortex (Albin et al., 1989; DeLong, 1990).

D'un point de vue fonctionnel, les ganglions de la base ont pour rôle de supprimer les mouvements non-désirés, et de déclencher l'initiation du mouvement (Marsden, 1982; Mink, 1996). Actifs avant et pendant les mouvements, ils jouent un rôle moteur permettant le déclenchement des mouvements volontaires en communiquant avec les aires cérébrales motrices. Dans ce but, le système des ganglions de la base fonctionne selon un ensemble de boucles d'inhibitions et d'activations (Parent & Hazrati, 1995). Le striatum projette sur le GPi via deux voies différentes :

- la voie indirecte striato-GPe-NST-GPi qui inhibe le mouvement

Le globus pallidus et la substance noire sont toujours actifs de façon tonique au repos (i.e., lorsqu'aucun mouvement volontaire n'est déclenché). Ils reçoivent des projections excitatrices du noyau sous-thalamique (NST). Par défaut, avant l'initiation d'un mouvement, le GPi envoie des projections inhibitrices au thalamus, pour diminuer l'activité de ses cibles thalamo-corticales. Cette inhibition tonique permet d'éviter le déclenchement de réponses inappropriées ou non désirées.

- la voie directe striato-pallidal qui facilite le mouvement

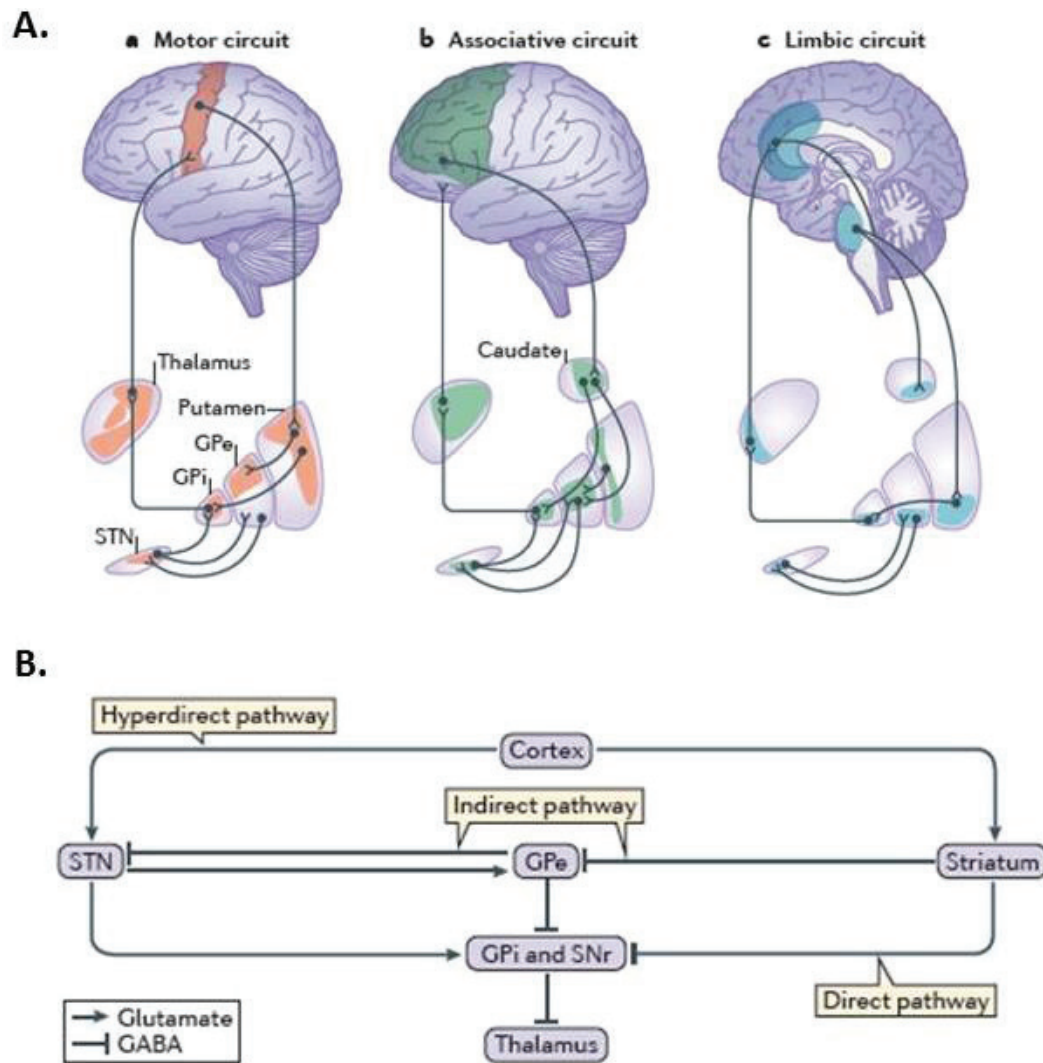
A l'inverse, lorsqu'un mouvement doit être initié, l'activation du putamen par les structures corticales permet d'inhiber le GPi, et donc de lever l'inhibition tonique du thalamus sur les neurones moteurs corticaux pour initier le mouvement.

Au contraire, s'il convient d'inhiber une réponse motrice suite à un stimulus, le cortex présente des projections directes sur le NST. Il s'agit d'une troisième voie au sein des ganglions de la base (Mathai & Smith, 2011) :

- la voie hyperdirecte NST-GPi

Le NST va activer le GPi ce qui entraîne une inhibition du thalamus et des cibles thalamo-corticales permettant d'inhiber l'action motrice en cours.

Les ganglions de la base sont initialement connus pour leur rôle dans le contrôle moteur (Parent, Lévesque, & Parent, 2001). Pour autant, au-delà de leur fonction initiale liée au traitement de l'information sensori-motrice, ils participent également au traitement des informations des circuits associatif et limbique (Jahanshahi et al., 2015b; Temel et al., 2005; Tremblay et al., 2015). A ce jour, les boucles cortico-ganglio-thalamo-corticales semblent plus complexes et dissociées en trois domaines fonctionnels selon les projections frontales associées. Elles sont impliquées, respectivement, dans la sélection et l'exécution du mouvement (circuit moteur), la sélection de l'action (circuit associatif) et la sélection du but ou des processus motivationnels en amont de toutes ces fonctions (circuit limbique).



**Figure 2 : Description des voies des ganglions de la base.**

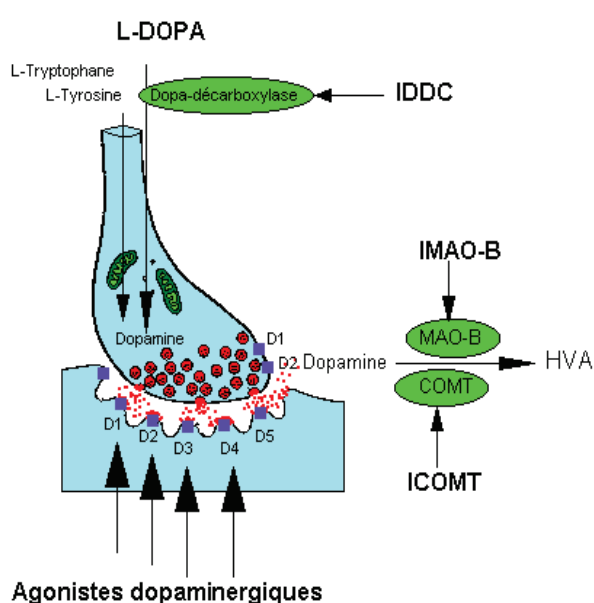
A. Subdivision des circuits cortico-striataux sensorimoteur, associatif et limbique. Les ganglions de la base présentent des connexions avec le circuit moteur mais influencent également un grand nombre d'aires non-motrices. B. Par défaut, le GPi inhibe de manière tonique le thalamus ce qui limite l'excitabilité corticale. La voie directe est excitatrice dans le sens où elle limite l'effet inhibiteur du GPi sur le thalamus. A l'inverse, les deux autres voies sont inhibitrices et favorisent l'effet inhibiteur du GPi sur le thalamus. STN = noyau sous-thalamique ; GPe = globus pallidus externe ; GPi = globus pallidus interne ; SNr = substance noire partie réticulaire. *Illustration tirée de Jahanshahi et al., 2015b.*

Les ganglions de la base jouent un rôle essentiel dans les circuits moteurs et permettent l'intégration et le couplage des boucles motrices et exécutives corticales.

### 3. LA MÉDICATION PHARMACOLOGIQUE

#### a. Traitements dopaminergiques

Les recherches du XXème siècle ont permis de comprendre que la maladie de Parkinson relevait d'une dégénérescence dopaminergique à l'origine d'un dysfonctionnement de la voie nigro-striée (Hornykiewicz, 2006). Ce déficit en dopamine (DA) nécessite donc de rétablir le tonus dopaminergique afin de réduire les symptômes. Pour ce faire, trois types de traitements dopaminergiques sont donc proposés.



**Figure 3 : Effet de la médication dopaminergique au niveau de la fente synaptique.**

- Tout d'abord, il est possible d'utiliser comme traitement un précurseur de la DA, la L-DOPA ou Levodopa, qui par prise orale passe la barrière hémato-encéphalique et agit au niveau présynaptique. La découverte et l'utilisation de la médication dopaminergique dans la maladie de Parkinson ont constituées une révolution thérapeutique (Cotzias et al, 1967). Son efficacité sur la symptomatologie extrapyramidale est très importante (on parle de « Lune de miel » au début du traitement) et constitue même un facteur de diagnostic de la maladie. Néanmoins, la demi-vie de la Levodopa est très courte et nécessite un grand nombre de prises journalières par

les patients dont les neurones dopaminergiques poursuivent leur dégénérescence pendant que la maladie progresse. Son action est donc forte mais son effet est pulsatile.

- L'utilisation d'inhibiteurs des enzymes qui dégradent la DA (COMT dans la fente synaptique, MAO-B sur les membranes mitochondriales des astrocytes et des neurones) est également possible pour potentialiser l'efficacité de la Levodopa. Malheureusement, ils sont difficiles à tolérer pour les patients donc leur utilisation n'est pas toujours favorable.

- Enfin, des agonistes dopaminergiques (DAAs) qui agissent cette fois au niveau post-synaptique sur les récepteurs dopaminergiques D1/D2/D3 peuvent être proposés. Ses agonistes ont pour avantage de présenter une demi-vie plus longue que la Levodopa donc minimise le nombre de prises journalière et les fluctuations motrices associées. Néanmoins, ils provoquent des effets secondaires et agissent de façon moins physiologique que la Levodopa. Leur utilisation permet donc principalement de retarder le début du traitement par la Levodopa et peut constituer un traitement de première intention.

Le choix du traitement et des doses administrées dépend du patient et reste entre les mains du neurologue. Les stratégies thérapeutiques ne seront donc pas discutées dans ce manuscrit (Fox et al., 2011).

#### b. Effets secondaires

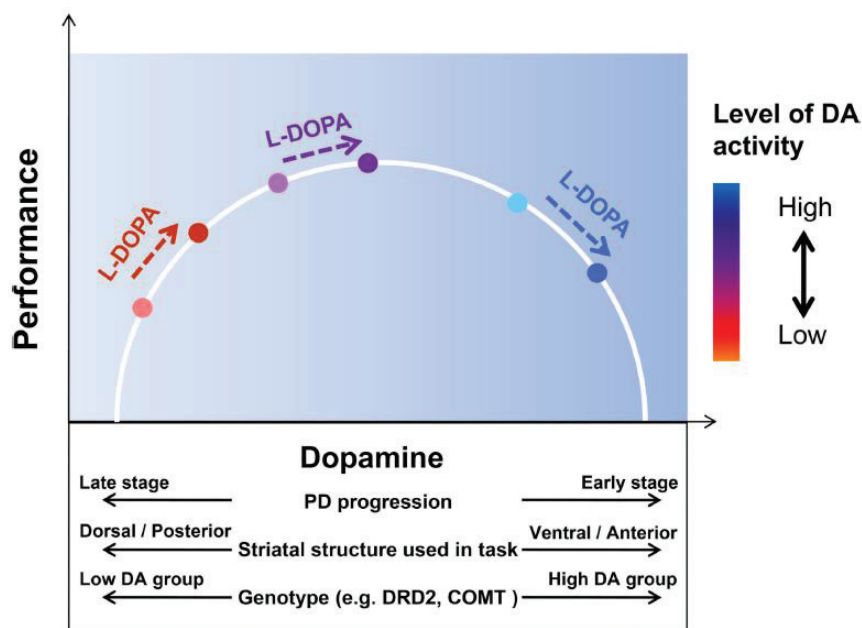
L'utilisation des traitements dopaminergiques expose les patients à des effets secondaires indésirables. On voit en effet apparaître des fluctuations motrices et des dyskinésies (Hauser et al., 2007; Mizuno et al., 2018; Vidailhet et al., 1999). Il s'agit de mouvements rapides anormaux et incontrôlés de certaines parties du corps, qui sont très invalidants pour les patients. De même, la thérapie dopaminergique, et plus particulièrement les DAAs, peut provoquer des troubles du contrôle des impulsions (TCI) (Cilia & van Eimeren, 2011; Weintraub et al., 2010). Ces effets

secondaires sont extrêmement invalidants pour les patients et obligent à une modification des doses de médication dopaminergique, faute de solution thérapeutique satisfaisante.

Enfin, l'effet de la dopathérapie est variable car la perte neuronale est hétérogène. Elle est massive et caractéristique dans la SNpc, moindre dans la partie latérale de la substance noire et de l'aire tegmento-ventrale, et absente dans la région périacqueducule (Hirsch et al., 1988). Les neurones de la SNpc, à l'origine de la voie nigrostriée, sont principalement la cible de la dégénérescence dans la maladie de Parkinson (Dahlstroem & Fuxe, 1964). Au contraire, les neurones de l'aire tegmentale ventrale (ATV) donnent naissance aux voies méso-limbiques et méso-corticales qui innervent le système limbique et le néocortex (Bjorklund & Lindvall, 1984). L'hypothèse d'une overdose dopaminergique (Cools et al., 2001; Dirnberger & Jahanshahi, 2013; Vaillancourt et al., 2013) pourrait alors expliquer un certain nombre d'effets secondaires indésirables. En effet, alors que les traitements dopaminergiques améliorent les fonctions du striatum dorsal et permettent de restaurer l'activité des circuits moteurs et exécutifs dorsaux ; le striatum ventral subit par contre une surdose de DA, ce qui nuit à son bon fonctionnement et peut provoquer l'apparition de symptômes cognitifs (Cools, 2006; MacDonald et al., 2011; Morrish et al., 1996). Ainsi, les traitements dopaminergiques ont un effet délétère sur différents processus d'apprentissage, notamment en vue d'une prise de décision (MacDonald et al., 2011; Miah et al., 2012; Swainson et al., 2000) et d'une prise de risque (Mimura et al., 2006; Molina et al., 2000). Au contraire, ils favoriseraient l'utilisation de stratégies exécutives notamment dans les situations conflictuelles (Macdonald & Monchi, 2011; Miah et al., 2012). Cette hypothèse de surdosage pourrait expliquer l'apparition de comportements impulsifs-compulsifs –CIC- suite à une stimulation anormale par les DAAs de la voie méso-cortico-limbique (Evans et al., 2009; Napier et al., 2015). Pour certains auteurs, cet effet de surdosage peut intervenir directement au niveau du cortex préfrontal via la surstimulation de la voie dopaminergique méso-corticale (Kehagia et al., 2010). Enfin,

l'hétérogénéité de la dénervation peut également expliquer l'apparition de certains symptômes non moteurs. En effet, des études récentes témoignent d'une dénervation de l'ATV plus importante que jusqu'à lors considérée (Alberico et al., 2015). Or, l'ATV est impliquée dans un grand nombre de comportements comme la dépression, l'anxiété, l'addiction et la récompense (Callaghan et al., 2018; Ranaldi, 2014).

L'hétérogénéité des profils cognitifs dans la maladie rend la compréhension des bases neuronales et neurochimiques de ces symptômes difficile. L'hypothèse d'un surdosage rejoint la notion plus générale selon laquelle l'effet de la DA cérébrale sur le comportement et la cognition suit une courbe en U inversé, un défaut et un excès de DA ayant tous deux un effet délétère (Vaillancourt et al., 2013).



**Figure 4 : Courbe de réponse à l'administration de L-Dopa chez les patients parkinsoniens.**

Courbe en U inversé qui révèle les performances des patients en réponse à l'administration de L-Dopa selon différents facteurs clés de la maladie : le stade de la maladie, la structure des ganglions de la base testée dans la tâche, le génotype. Une combinaison de ces trois facteurs peut expliquer que l'administration d'un même traitement dopaminergique puisse améliorer, aggraver ou ne pas modifier les performances d'un patient. *Illustration tirée de Vaillancourt et al., 2013.*

**Les traitements dopaminergiques constituent la seule médication pharmacologique à ce jour disponible pour améliorer les symptômes de la maladie de Parkinson. Néanmoins, ils exposent les patients à des effets secondaires invalidants et ne restaurent pas de façon satisfaisante l'ensemble des symptômes de la maladie.**

#### 4. LA STIMULATION CEREBRALE PROFONDE

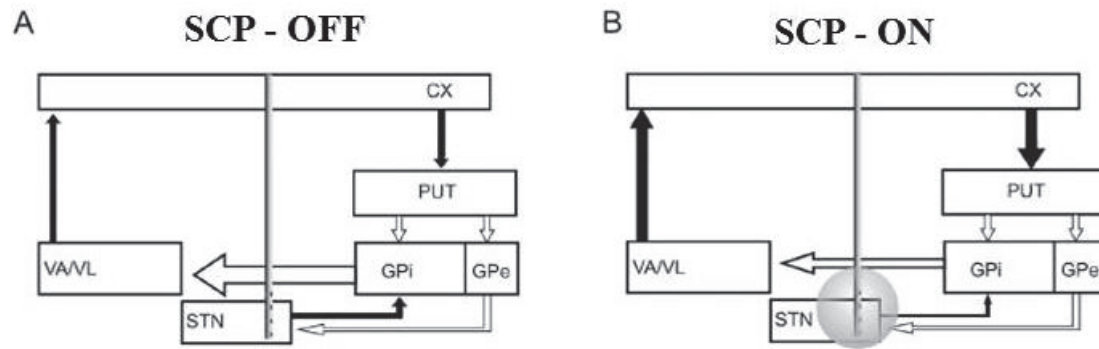
Depuis 1987, la stimulation cérébrale profonde (SCP) a été proposée dans le traitement de la maladie de Parkinson (Benabid et al., 1987). Ce traitement consiste à implanter des électrodes de stimulation à haute fréquence dans le NST, le GPi ou le noyau intermédiaire du thalamus – Vim- des patients (Benabid et al., 1998). La SCP-Vim a principalement un effet sur le tremblement essentiel et la SCP-GPi sur les dystonies. Ainsi, la cible privilégiée pour le traitement de la maladie de Parkinson est le NST. Le but de la SCP est de réduire les symptômes et de restaurer les fonctions motrices (Deuschl et al., 2006; Rodriguez-Oroz et al., 2005). Elle permet également de réduire de 50% les doses en DA, diminuant ainsi indirectement les dyskinésies (Limousin et al., 1998). L'avantage de cette technique est d'être réversible, continue, adaptable et avec une faible morbidité. Depuis les années 2000, elle constitue donc une technique très prometteuse pour les patients parkinsoniens dont les traitements pharmacologiques ne sont plus suffisants pour améliorer les symptômes ou présentant des effets secondaires indésirables à la médication (dyskinésies). A ce jour, de nombreuses avancées cliniques et techniques ont profondément modifié l'utilisation de cette technique. En effet, la SCP-NST peut être aujourd'hui proposée comme une alternative précoce dès l'apparition de fluctuations motrices et premiers signes de complications de la médication dopaminergique (deSouza et al., 2013; Deuschl et al., 2013; Lhommée et al., 2018; Schuepbach et al., 2013; Woopen et al., 2013). De plus, le développement de nouvelles électrodes de stimulation, de



générateurs permettant par exemple le stockage de données électrophysiologiques ou l'avènement de la stimulation adaptative ouvre de nouvelles perspectives à l'utilisation de cette technique (Little et al., 2013, 2014). Elle est par contre exclue lorsque les patients présentent des signes de démence ou des troubles psychiatriques, au risque de voir s'aggraver les symptômes. En effet, alors que la SCP-NST présente des effets positifs sur les symptômes moteurs, son effet sur la symptomatologie parkinsonienne non motrice reste débattu. Les symptômes non moteurs comme la dépression, l'apathie, l'anxiété ou l'impulsivité, peuvent être aggravés ou améliorés selon les paramètres de la stimulation, la localisation des électrodes ou les modifications de médication post-chirurgie (Kim et al., 2015).

L'effet positif de la SCP-NST sur la triade motrice indique que le NST est fortement impliqué dans la physiopathologie de la maladie de Parkinson (Blandini et al., 2000). Les neurones du NST, qui révèlent chez les sujets sains un pattern de décharge tonique, présentent en effet des bouffées anormales chez les patients parkinsoniens (Bergman et al., 1994). Selon le modèle anatomo-fonctionnel des ganglions de la base présenté précédemment, ce pattern pathologique induirait une inhibition du thalamus via le GPi et, à terme, une réduction des projections excitatrices thalamocorticales. La SCP-NST permettrait de rétablir le bon fonctionnement des boucles ganglio-thalamo-corticales (Figure 5).

Pour autant, le rôle du NST au sein des circuits anatomo-fonctionnels reliant le cortex et les ganglions de la base n'est à ce jour toujours pas élucidé (Aron & Poldrack, 2006; Benis et al., 2014). L'absence de consensus concernant le rôle du NST entrave ainsi la compréhension des mécanismes par lesquels s'opère la SCP-NST.



**Figure 5 : Représentation schématique de l'effet de la SCP-NST sur le fonctionnement des ganglions de la base.**

A. Schéma tiré des modifications du taux de décharge des différentes structures des ganglions de la base chez les patients parkinsoniens. Selon ce modèle, une hyperactivation pathologique de la voie indirecte est à l'origine d'une plus forte inhibition du thalamus associée à une lenteur à l'initiation du mouvement. B. Schéma illustrant l'effet de la SCP-NST qui restaure la balance au sein du réseau des ganglions de la base, possiblement par une inhibition du STN par la SCP. Il convient de noter que cette représentation simpliste ne prend pas en compte les effets complexes encore à l'étude de la SCP mais la considère comme mimant une lésion du NST. L'effet net est une levée de l'inhibition pathologique du thalamus. *Illustration tirée de Stefani et al., 2017.*

**Le NST est donc une structure pivot dans la physiopathologie de la maladie de Parkinson mais son rôle, ainsi que les mécanismes qui sous-tendent la SCP-NST, restent mal compris (cf. Chapitre 2 ; Stefani et al., 2017).**

## B. ... AUX SYMPTOMES

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### 1. LES SYMPTOMES MOTEURS

La conséquence directe de la déplétion dopaminergique est une dénervation massive du striatum à l'origine d'une triade de symptômes caractéristiques de la maladie de Parkinson

(Jankovic, 2008). Cette triade dite motrice a été décrite pour la première fois par James Parkinson en 1817 : les tremblements de repos, la rigidité et l'akinésie/bradykinésie.

#### a. Les tremblements

Les tremblements de repos constituent le premier signe de la maladie dans 60 à 70% des cas. Ils affectent les extrémités des membres lorsqu'ils sont en position de relâchement musculaire partiel mais cessent lors de l'exécution de mouvements volontaires. Ils correspondent à des mouvements oscillatoires réguliers de faible amplitude et de rythme lent (4-6 Hz). Ils touchent généralement les mains en premier lieu, puis la tête et les jambes, souvent de façon unilatérale ou asymétrique.

#### b. L'hypertonie

L'hypertonie ou rigidité est liée à un tonus musculaire excessif et entraîne des raideurs et des tensions au niveau des membres lors de la mobilisation passive des articulations du patient (Rodriguez-Oroz et al., 2009). Elle peut concerner l'ensemble des muscles du corps mais elle est prédominante à l'extrémité où débute les tremblements.

#### c. L'akinésie

L'akinésie est classiquement définie comme une réduction de la motricité volontaire et automatique (en l'absence de toute paralysie) et qui se traduit par un ralentissement, voire parfois l'impossibilité, à initier un mouvement (Hallett, 1990). Elle est presque toujours associée à l'hypertonie, les deux symptômes constituant le syndrome akinéto-rigide (par opposition au syndrome tremblant dominant).

L'akinésie est considérée comme l'un des symptômes moteurs les plus caractéristiques et les plus invalidants de la maladie de Parkinson (Schrag et al., 2000). Pourtant, l'akinésie est

également le symptôme le moins bien compris (Rodriguez-Oroz et al., 2009). Ceci peut s'expliquer par la difficulté à distinguer clairement les symptômes d'appauvrissement des mouvements par une simple observation clinique.

L'échelle d'évaluation des symptômes de la maladie de Parkinson la plus reconnue et utilisée est l'Unified Parkinson Disease Rating Scale (UPDRS) proposée par la Movement Disorder Society. Sa partie III permet une évaluation clinique des symptômes moteurs (Goetz et al., 2008) dont l'utilité en clinique est largement démontrée. Toutefois, bien qu'elle permette d'évaluer globalement la vitesse et l'amplitude des mouvements, elle ne permet pas de mesurer le retard d'initiation des mouvements (i.e. akinésie à proprement parler). Certains auteurs proposent alors de calculer des sous-scores qui reflèteraient l'akinésie (Stebbins et al., 1999). En particulier, (Wenzelburger et al., 2003) ont utilisé des items de l'UPDRS-III pour calculer un sous-score d'akinésie. Il inclut l'évaluation du tapotement des doigts (mouvements rapides de rapprochement / éloignement du pouce et de l'index), du mouvement des mains (ouverture / fermeture des mains), des mouvements rapides alternatifs des mains (mouvement de pronosupination des deux mains simultanément) et de l'agilité de la jambe (levée / abaissement du pied jusqu'au sol). Buck et al. (2011) ajoutent à ce sous-score les items de la bradykinésie et hypokinésie corporelle (lenteur, hésitation, diminution de l'amplitude et pauvreté des mouvements) pour révéler un score de bradykinésie. Welter et al. (2014) proposent de considérer également l'item d'évaluation de l'apathie (perte de motivation, d'initiative) de la Partie I pour constituer un score d'akinésie. Ces exemples illustrent bien l'importante confusion terminologique qui existe (Schilder et al., 2017) et l'absence d'évaluation clinique consensuelle.

L'akinésie peut être également mesurée via une tâche de tapotement dans laquelle le patient doit réaliser le plus de mouvements de pression possibles en un temps donné. Par exemple, le protocole informatisé nommé BRAIN Test a été validé dans la maladie de

Parkinson (Giovannoni et al., 1999; Homann et al., 2000; Noyce et al., 2014). Il permet en outre de distinguer l'akinésie (durée pendant laquelle le bouton n'est pas pressé) d'une mesure plus globale de la pauvreté des mouvements (nombre de fois que le bouton est pressé). Enfin, des travaux plus expérimentaux mesurent l'akinésie par des tâches de temps de réaction -TR-. En utilisant une tâche motrice, le temps global mesuré peut être décomposé en TR (délai entre apparition du stimulus et initiation du mouvement) et temps de mouvement (TM, délai entre le début du mouvement et l'atteinte de la cible) qui seraient respectivement plus sensibles à l'akinésie et la bradykinésie des patients parkinsoniens (Ballanger et al., 2007; Gauntlett-Gilbert & Brown, 1998; Marsden, 1989). Ainsi, l'akinésie chez les patients serait relative à un plus long TR que chez les sujets contrôles (i.e., lenteur à initier le mouvement).

**Au vu du rôle pivot des ganglions de la base dans les circuits moteurs (DeLong, 1990), une origine purement motrice des symptômes cardinaux de la maladie de Parkinson a semblé évidente. Pourtant, l'évaluation clinique traditionnelle ne permet d'obtenir qu'une mesure composite non spécifique de l'akinésie. Ainsi, les fonctions neuropsychologiques à l'origine de l'akinésie restent à étudier.**

## 2. HÉTÉROGENEITE CLINIQUE ET SYMPTÔMES NON MOTEURS

Si le diagnostic de la maladie est principalement fondé sur la présence de symptômes moteurs caractéristiques, ceux-ci s'accompagnent de nombreux troubles non-moteurs qui débent parfois même en amont des symptômes moteurs. Alors que ces derniers ont longtemps été au centre de l'attention, le diagnostic et la prise en charge des symptômes non moteurs restent aujourd'hui difficile (Chaudhuri et al., 2006; Sprenger & Poewe, 2013; Titova & Chaudhuri, 2018). Largement inexplorés, l'attention se porte aujourd'hui sur une meilleure

compréhension de ces symptômes non-moteurs (Langston, 2006) et une reconnaissance de la maladie de Parkinson comme un syndrome complexe (Titova et al., 2017). Une classification récente propose de séparer les symptômes non moteurs selon leur origine dopaminergique ou non dopaminergique (Titova & Chaudhuri, 2018; Todorova et al., 2014). Nous en réalisons ici une présentation sélective centrée sur notre question du contrôle de l'action.

#### a. Troubles non-moteurs d'origine dopaminergique

##### L'apathie

L'apathie se caractérise généralement par une perte d'intérêt, un manque d'initiative, une tendance à l'abandon prématuré des activités, une indifférence à soi et aux autres, et un émoussement affectif (Aarsland et al., 2009; Marin, 1991). Sa prévalence varie de 16 à 42% selon les études, et est souvent sous-évaluée au profit de la dépression (Dujardin et al., 2007). La perte d'intérêt se retrouve à la fois dans les définitions de l'apathie et de la dépression, rendant ainsi leur distinction difficile (Kirsch-Darrow et al., 2011), ce qui explique une étiologie parfois confondue de ces symptômes (Aarsland et al., 2011; Vriend et al., 2014). Selon les critères diagnostiques proposés par (Starkstein & Leentjens, 2008), l'apathie peut être décrite comme une diminution des comportements orientés vers un but, à la fois au niveau cognitif, comportemental et émotionnel. Un déficit des circuits fronto-subcorticaux impliqués dans la motivation et la récompense liée au système dopaminergique jouerait alors un rôle clé dans le développement de ce symptôme (Cummings, 1993; Wen et al., 2016). Ainsi, l'apathie et l'impulsivité (i.e., les TCI) ont été proposés comme constituant les deux extrêmes opposés de déficits DA-dépendant de la prise de décision et de la motivation (Sierra et al., 2015; Sinha et al., 2013). Pourtant, ces auteurs rapprochent l'apathie de la difficulté à initier les actions et proposent le terme d'apathie motrice (Sinha et al., 2013). Cette définition se rapproche de celle de l'akinésie présentée précédemment (Welter et al., 2014) et renforce l'absence de définition

consensuelle de ce symptôme. De même, face à l'absence de relation dose-dépendante de la médication dopaminergique avec ce symptôme, d'autres systèmes de neurotransmetteurs comme la sérotonine (5-HT) semblent être impliqués (Maillet et al., 2016; Schrag & Politis, 2016; Thobois et al., 2017).

## Troubles cognitifs légers

Le concept de trouble cognitif léger est utilisé pour caractériser un stade d'atteinte cognitive prédéméntielle (Petersen et al., 1999). Sa prévalence est de 19 à 38% des patients (Litvan et al., 2011) et son apparition se fait le plus souvent précocement dans la maladie (Muslimovic et al., 2008). Néanmoins, l'évaluation de ces troubles cognitifs dans la maladie de Parkinson reste aujourd'hui difficile (Litvan et al., 2011). La Movement Disorder Society a donc récemment proposé des critères diagnostiques du trouble cognitif léger (Litvan et al., 2012) qui sont en cours de validation (Geurtsen et al., 2014; Szeto et al., 2015) dans la maladie de Parkinson.

### b. Les troubles non-moteurs d'origine non dopaminergique

#### La démence parkinsonienne

La prévalence de la démence est estimée à environ 30-40% dans la population de patients parkinsoniens (Aarsland et al., 2005; Emre, 2003). Les facteurs de risque principaux sont l'âge et la durée de la maladie. En effet, elle augmente très largement avec la durée d'évolution de la maladie, passant de 28% entre 5 et 10 ans après le diagnostic à près de 80% entre 17 et 20 ans après le diagnostic (Aarsland et al., 2003). Le sexe masculin constitue également un facteur de risque de démence (Cereda et al., 2016). La démence est progressive, de survenue tardive, souvent associée à un syndrome akinéto-rigide et caractérisée par une

majoration du syndrome dysexécutif (Emre et al., 2007). La démence n'est pas améliorée par les traitements antiparkinsoniens, ce qui renforce l'hypothèse d'une origine non dopaminergique de ce symptôme. La démence peut être diagnostiquée en routine clinique en suivant les recommandations de la Movement Disorders Society proposant l'évaluation des fonctions cognitives à l'aide d'une batterie de tests cognitifs (Dujardin et al., 2010). Sa prise en charge fait intervenir des traitements inhibiteurs de la cholinestérase (ibid). Leur efficacité rend le diagnostic précoce de la démence particulièrement importante en clinique bien que l'amplitude de l'effet reste modeste (Horstink et al., 2006).

### c. Troubles induits par la médication ou comorbidité

Dans cette catégorie se retrouve les symptômes non moteurs dont l'origine reste à ce jour mal comprise ou qui sont induits par la médication dopaminergique ou son arrêt.

#### Syndrome de sevrage

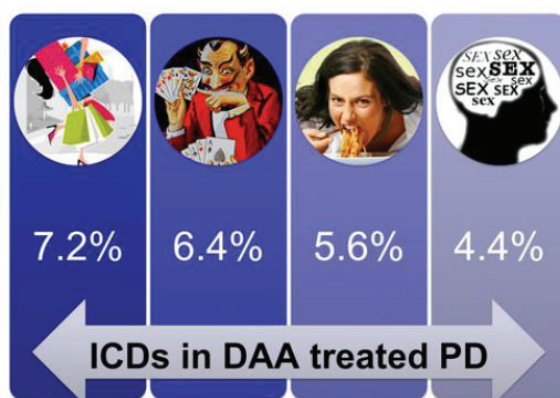
Ce syndrome de sevrage semble survenir chez 15 à 33% des patients lors de la réduction ou l'arrêt des doses de DAAs avec l'apparition d'attaques de panique, d'anxiété, de symptômes dépressifs et dysphoriques, de douleurs et une recherche compulsive du traitement (craving) (Rabinak & Nirenberg, 2010). Son apparition limite les possibilités d'interrompre le traitement (Bastiaens et al., 2013; Pondal et al., 2013; Rabinak & Nirenberg, 2010).

#### Comportements impulsifs - compulsifs

Les TCI sont fréquents dans la maladie de Parkinson incluant le jeu pathologique, l'hypersexualité, les achats compulsifs et la frénésie alimentaire (Cilia & van Eimeren, 2011). Le jeu pathologique est caractérisé par une préoccupation excessive pour le jeu, une augmentation progressive des sommes d'argent mises en jeu et une incapacité à arrêter de jouer



même après une perte importante. L'hypersexualité est caractérisée par une augmentation du désir et une modification significative du comportement sexuel par rapport aux habitudes antérieures. Les achats compulsifs sont ressentis comme un besoin répété, inadapté et irrésistible éprouvé par le patient. Enfin, les compulsions alimentaires sont caractérisées par une perte du contrôle sur l'alimentation conduisant à des épisodes répétés de frénésie alimentaire malgré l'absence de faim et des sensations d'inconfort liées aux quantités ingérées.



**Figure 6 : Prévalence des TCI dans la maladie de Parkinson.**

La prévalence des TCI chez les patients parkinsoniens sous DAAs est indiquée selon l'étude DOMINION (Weintraub et al., 2010). De gauche à droite : achats compulsifs, jeu pathologique, compulsions alimentaires et hypersexualité. *Illustration tirée de Cilia & van Eimeren (2011).*

Les CIC regroupent les comportements impulsifs – TCI - et incluent également des comportements compulsifs, le punding/hobbysm (comportement répétitif sans but apparent et dont le patient ne retire pas de satisfaction, collectionnisme), et l'addiction au traitement dopaminergique (Weintraub, 2008). Ces différents symptômes peuvent survenir isolément ou en association chez les patients (Averbeck et al., 2014). Bien que les TCI soient souvent associés aux troubles compulsifs sous le terme de CIC, il convient de noter que l'impulsivité est un phénomène complexe (*cf. Chapitre 2*) qui se distingue de la compulsion dans le sens où cette dernière implique la répétition de comportements sans but apparent (Dalley et al., 2011). Toutefois, ces deux phénomènes sont souvent observés conjointement. En effet, le jeu

pathologique comprend par exemple à la fois une dimension impulsive (prise de risque) et compulsive (mouvements répétitifs stéréotypés) (Averbeck et al., 2014). Les troubles impulsifs et compulsifs sont ainsi souvent regroupés et étudiés ensemble dans la maladie de Parkinson (Weintraub et al., 2009) malgré l'hétérogénéité des symptômes observés, ce qui accentue la difficulté de caractériser les bases neuropsychologiques de ces troubles.

Les CIC affectent environ 13 à 46% des patients (Antonini et al., 2017; Corvol et al., 2018; Weintraub et al., 2010) et leur prise en charge est difficile car il n'existe aucune solution thérapeutique satisfaisante à ce jour (Connolly & Fox, 2014). En effet, couramment considérés comme des effets secondaires des traitements dopaminergiques (Weintraub et al., 2010), la prise en charge de ces troubles se fait en diminuant, voir même en supprimant, la dose de DAAs (Samuel et al., 2015). Mais cette réduction se fait au risque de voir réapparaître les symptômes moteurs (Rabinak & Nirenberg, 2010) et nécessitent souvent de majorer la dose de lévodopa. Qui plus est, la réduction des DAA ne permet pas toujours de faire disparaître les CIC chez les patients (Ávila et al., 2011). De plus, l'arrêt des DAAs peut entraîner un syndrome de sevrage.

Actuellement, l'origine du développement des CIC reste débattue (*cf. Chapitre 2*). Seuls des facteurs de risque ont été identifiés comme participant à l'apparition des TCI : les traitements par DAAs, avec des doses élevées de lévodopa, par amantadine, un âge jeune, le sexe masculin, un début précoce de la MP, le tabagisme, une consommation de caféine, des antécédents familiaux d'alcoolisme ou de jeu pathologique, des traits de personnalité impulsive ou d'intérêt pour la nouveauté, une alexithymie et des troubles du sommeil paradoxal (Fantini et al., 2018; Poletti et al., 2013; Voon et al., 2011b; Weintraub et al., 2010). Des facteurs de susceptibilité génétique ont également été mis en évidence récemment (Kraemmer et al., 2016) et pointent, par exemple, les gènes codant pour les récepteurs dopaminergiques (Cormier et al., 2013). En l'absence de bases neuropsychologiques claires, les CIC ont donc longtemps été considérés dans le DSM-IV-TR (Diagnostic and statistical manual of Mental Disorders) comme

une catégorie non classifiée de symptômes. A ce jour, le DSM-V propose une nouvelle catégorie pour les CIC qui sont classiquement associés aux « addictions comportementales » (Marques et al., 2018). En effet, les CIC comprennent typiquement une dimension addictive, à une substance (traitement dopaminergique) ou à un comportement. L'existence d'efforts répétés, mais infructueux, de contrôle de ce comportement a conduit à proposer l'hypothèse de bases neuronales communes entre les CIC et l'addiction (Ray & Strafella, 2013). Ils peuvent avoir des conséquences cliniques, psycho-affectives, sociales, économiques voire judiciaires dramatiques (Dodd et al., 2005; Evans et al., 2004).

L'évaluation des CIC et de l'impulsivité dans la maladie de Parkinson reste aujourd'hui limitée. L'approche la plus classique consiste en l'utilisation d'auto-questionnaires ou d'entretiens semi-structurés qui permettent d'évaluer la présence de ces comportements, mais également leur fréquence et leur impact sur la vie quotidienne. Certaines études (Hälbig et al., 2009) utilisent la Minnesota Impulsive Disorders Interview (Christenson et al., 1994) qui est notamment basée sur les critères diagnostiques du DSM-IV-TR (American Psychiatric Association, 2000). Néanmoins, l'absence d'instructions dans la conduite de l'échelle et la façon d'établir un score rend difficile son utilisation (Weintraub et al., 2012). A ce jour, son utilisation a été validée chez des patients présentant différentes pathologies psychiatriques mais pas dans la maladie de Parkinson (Grant et al., 2005). Il existe également des échelles spécifiques à la maladie de Parkinson. On peut citer la QUIP (Questionnaire for Impulsive-Compulsive Disorders) qui permet d'évaluer la présence des CIC ; ainsi que sa version QUIP-Rating Scale qui permet d'évaluer la sévérité de ces comportements (Weintraub et al., 2009, 2012). L'échelle française d'Ardouin dissocie les comportements hypo- et hyperdopaminergiques dans la maladie de Parkinson dont certains correspondent aux TCI (Ardouin et al., 2009). L'avantage de cette dernière est de se baser sur un entretien semi-structuré approfondi qui permet de mesurer de façon quantitative l'évolution des comportements dans le

temps ce qui autorise à s'affranchir de l'influence des traits de personnalité. Certaines études se réfèrent également à des questionnaires évaluant spécifiquement certains types de symptômes comme le jeu pathologique avec la South Oaks Gambling Screen (SOGS) (Antonini et al., 2011; Isaias et al., 2008) ou l'hypersexualité avec le Sexual Addiction Screening Test (SAST) (Pereira et al., 2013).

Une seconde approche consiste à utiliser des questionnaires de mesure des traits de personnalité permettant de mettre en évidence indirectement les CIC. On peut citer principalement les échelles d'impulsivité (Antonini et al., 2011; Hälbig et al., 2009; Isaias et al., 2008) comme la Barratt Impulsiveness Scale (Barratt, 1994; Patton et al., 1995) ou la UPPS Impulsive Behavior Scale (Whiteside & Lynam, 2003). Mais ces échelles, moins spécifiques, ne révèlent pas l'hétérogénéité des CIC dans la maladie de Parkinson.

**L'expression des comportements impulsifs et compulsifs dans la maladie de Parkinson est hétérogène et composite. Concernant les bases neuropsychologiques de ces troubles, les fonctions neuropsychologiques à l'origine de l'impulsivité restent mal comprises. Leur prise en charge est alors difficile car il n'existe aucune solution thérapeutique satisfaisante à ce jour. Qui plus est, l'absence de consensus concernant le rôle des DAAs dans leur développement soulève la question d'une origine non dopaminergique de ces symptômes.**

## **Conclusion - Chapitre 1**

L'hypothèse explicative communément admise à l'origine de la maladie de Parkinson est une dégénérescence de la voie dopaminergique nigro-striée à l'origine d'une triade de symptômes moteurs : akinésie, rigidité et tremblements de repos. Toutefois, face à l'hétérogénéité des symptômes et l'absence d'efficacité de la médication dopaminergique, certains troubles restent encore mal compris et sans traitement satisfaisant. Ceci suggère que :

1) une partie des symptômes parkinsoniens pourrait ne pas avoir une origine purement motrice ;

2) d'autres systèmes de neurotransmetteurs que la DA doivent être impliqués dans l'étiologie des symptômes moteurs et non moteurs de la maladie de Parkinson ;

3) la maladie de Parkinson pourrait être revisitée en termes de syndrome multifacette (Titova et al., 2017).

# CHAPITRE 2 : LA MALADIE DE PARKINSON –

## AU-DELA DE LA BOUCLE MOTRICE ET DE LA DOPAMINE

Dans ce second chapitre, nous allons aborder plus spécifiquement les troubles de l'initiation du mouvement dans la maladie de Parkinson : de leurs fonctions neuropsychologiques à leurs bases neurophysiologiques et neurochimiques. Pour ce travail, nous allons considérer deux catégories de symptômes classiquement étudiés de façon indépendante (*cf. Chapitre 1*). D'un côté, les troubles liés à la difficulté ou la lenteur pour initier un mouvement, définis sous le terme d'akinésie. De l'autre côté, ceux liés aux difficultés à réprimer un mouvement, connus sous le terme générique d'impulsivité. Notre objectif est d'identifier les obstacles à une meilleure compréhension de ces troubles, actuellement sans solution thérapeutique satisfaisante.

### A. LA DIFFICULTE A CARACTERISER LES FONCTIONS NEUROPSYCHOLOGIQUES A L'ORIGINE DES TROUBLES DE L'INITIATION DES MOUVEMENTS

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#### 1. ORIGINE DE L'AKINESIE

##### a. Bases neuropsychologiques de l'akinésie

L'akinésie est considérée comme l'un des symptômes moteurs les plus caractéristiques et les plus invalidants de la maladie de Parkinson (Schrag et al., 2000) car il affecte un grand nombre d'actions (Gauntlett-Gilbert & Brown, 1998). Pourtant, l'akinésie est également le symptôme le moins bien compris (Rodriguez-Oroz et al., 2009). Ceci peut s'expliquer par

l'absence de consensus concernant les fonctions neuropsychologiques atteintes à l'origine de l'akinésie (Berardelli et al., 2001; Evarts et al., 1981; Schilder et al., 2017). En effet, la terminologie générale d'akinésie est souvent utilisée pour rendre compte de trois phénomènes pourtant distincts : la lenteur à l'initiation du mouvement (i.e. akinésie à proprement parler), le ralentissement de l'exécution du mouvement (i.e. bradykinésie), et la diminution de l'amplitude des mouvements (i.e. hypokinésie) (Marsden, 1989; Rodriguez-Oroz et al., 2009).

Au niveau comportemental, les patients parkinsoniens réagissent plus lentement que les sujets contrôles (TR plus lents) et ceci contribue clairement à l'akinésie (Evarts et al., 1981). L'akinésie est donc classiquement considérée comme un symptôme moteur, caractéristique de la triade motrice de la maladie de Parkinson (Hallett, 1990; Jahanshahiet al., 1992b, 1993). Berardelli et al. (2001) ont formulé l'hypothèse selon laquelle l'akinésie résulterait d'un déficit de l'output des ganglions de la base vers les mécanismes corticaux qui préparent, initient et exécutent la commande motrice. En d'autres termes, l'akinésie pourrait être due à une lenteur à formuler ou à déclencher l'instruction du mouvement (programmation) et/ou à une lenteur à exécuter et initier cette instruction (exécution). Dans le cadre d'une tâche de TR simple, la lenteur à l'initiation/exécution de la commande motrice est un facteur important à l'origine de l'akinésie parkinsonienne. Des expériences utilisant la stimulation magnétique transcrânienne (TMS) ont, en effet, confirmé, que l'excitabilité motrice avant le mouvement augmente plus lentement chez les patients parkinsoniens que chez les contrôles (Pascual-Leone et al., 1994). Ainsi, le seuil d'excitabilité pour le déclenchement du mouvement est atteint plus tard que la normale.

L'hypothèse d'une origine motrice de l'akinésie a conduit les auteurs à occulter l'influence potentielle d'autres facteurs, perceptuels et cognitifs, concourant possiblement à l'origine de ce symptôme. Pourtant, Ballanger et al. (2007) ont montré un déficit perceptif de haut niveau à l'origine de l'akinésie (mesurée de façon comportementale sur les TR) chez les

patients parkinsoniens. De façon intéressante, ce déficit perceptif était observé chez les patients parkinsoniens à la fois OFF et ON médication, ce qui semble rejeter la possibilité d'une origine purement dopaminergique de ce trouble.

Concernant le déficit moteur à l'origine de l'akinésie, les difficultés des patients parkinsoniens lors de l'initiation motrice diffèrent sensiblement selon l'origine du mouvement, à savoir spontané et initié par le patient lui-même, ou en réponse à un stimulus externe. Pour certains auteurs, des mécanismes distincts du contrôle de l'action sont à l'œuvre (Nachev & Hacker, 2014; Nachev & Husain, 2010), alors que d'autres sont en faveur de l'existence d'interactions entre ces deux types de processus (e.g. Stuss & Alexander, 2000). Ainsi, les processus réellement mesurés ne sont pas forcément comparables. En effet, alors que des difficultés ont été observées lors de l'exécution automatique des programmes moteurs des mouvements appris (Marsden, 1982), les patients parkinsoniens akinétiques présentent la capacité d'utiliser des amorces externes pour déclencher l'initiation du mouvement (Burleigh-Jacobs et al., 1997; Favre et al., 2013; Praamstra et al., 1998; Siegert et al., 2002). Ce phénomène est appelé kinésie paradoxale (Jankovic, 2008) et fait référence à la capacité du système moteur à améliorer les performances motrices en réponse à un stimulus externe ou dans des situations d'urgence. Il semble que ce processus constitue une propriété du système moteur, observé à la fois chez les patients parkinsoniens et chez les sujets sains, et ne soit donc pas constitutif de la maladie de Parkinson (Ballanger et al., 2006). L'akinésie serait donc spécifiquement caractérisée par une difficulté à initier volontairement et automatiquement un mouvement.

Dans ce sens, il a récemment été proposé que l'origine de l'akinésie pourrait plutôt être d'origine exécutive. En effet, un déficit des processus d'inhibition de réponse a été observé chez les patients parkinsoniens (Obeso et al., 2011) et suggère un rôle du contrôle exécutif de l'action à l'origine de l'akinésie. Plus précisément, l'akinésie pourrait avoir pour origine un



déficit de contrôle des mécanismes de verrouillage anticipé de l'action (Favre et al., 2013). Cette étude a montré que les patients parkinsoniens seraient bloqués dans un mode de verrouillage par défaut (i.e., contrôle exécutif de l'action ; (Criaud et al., 2012) et présenteraient des difficultés à passer à un mode automatique d'initiation du mouvement. Malheureusement, ces mécanismes ne sont que peu étudiés dans la littérature de l'akinésie parkinsonienne puisque leurs bases psychologiques sont encore à l'étude chez le sujet sain (*cf. Chapitre 3*).

### b. Bases neuro-fonctionnelles de l'akinésie

Afin d'éclairer le débat sur l'origine de l'akinésie, nous avons choisi de nous intéresser aux bases neuro-fonctionnelles de ce symptôme. Pour cela, nous avons procédé à une revue systématique de la littérature utilisant la neuroimagerie (Tomographie par Emission de Positons –TEP– ou Imagerie par Résonance Magnétique fonctionnelle –IRMf–) pour révéler les mécanismes neuropathologiques qui sous-tendent l'akinésie. Notre critère d'inclusion principal portait sur l'existence d'un contraste entre un groupe de patients parkinsoniens akinétiques et un groupe de sujets contrôles.

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## Functional imaging correlates of akinesia in Parkinson's disease: Still open issues



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### ABSTRACT

Akinesia is a major manifestation of Parkinson's disease (PD) related to difficulties or failures of willed movement to occur. Akinesia is still poorly understood and is not fully alleviated by standard therapeutic strategies. One reason is that the area of the clinical concept has blurred boundaries referring to confounded motor symptoms. Here, we review neuroimaging studies which, by providing access to finer-grained mechanisms, have the potential to reveal the dysfunctional brain processes that account for akinesia. It comes out that no clear common denominator could be identified across studies that are too heterogeneous with respect to the clinical/theoretical concepts and methods used. Results reveal, however, that various abnormalities within but also outside the motor and dopaminergic pathways might be associated with akinesia in PD patients. Notably, numerous yet poorly reproducible neural correlates were found in different brain regions supporting executive control by means of resting-state or task-based studies. This includes for instance the dorsolateral prefrontal cortex, the inferior frontal cortex, the supplementary motor area, the medial prefrontal cortex, the anterior cingulate cortex or the precuneus. This observation raises the issue of the multidimensional nature of akinesia. Yet, other open issues should be considered conjointly to drive future investigations. Above all, a unified terminology is needed to allow appropriate association of behavioral symptoms with brain mechanisms across studies. We adhere to a use of the term akinesia restricted to dysfunctions of movement initiation, ranging from delayed response to freezing or even total abolition of movement. We also call for targeting more specific neural mechanisms of movement preparation and action triggering with more sophisticated behavioral designs/event-related neurofunctional analyses. More work is needed to provide reliable evidence, but answering these still open issues might open up new prospects, beyond dopaminergic therapy, for managing this disabling symptom.

### 1. Introduction

The terms akinesia, hypokinesia, and bradykinesia are classically used to describe the wide range of motor dysfunctions characteristic of Parkinson's disease (PD). According to their etymology, akinesia refers to the total absence of movement, hypokinesia to decreased amplitude of movement, and bradykinesia to slowness in movement execution. However, the terminologies have evolved over time and are now inconsistently used in the literature (Schilder et al., 2017). Among these clinical manifestations, akinesia is certainly the most problematic term

and the least understood feature of PD (Rodriguez-Oroz et al., 2009). It is particularly disabling, affects a wide range of actions and has no satisfying therapeutic option (Gauntlett-Gilbert and Brown, 1998; Schrag et al., 2000).

At a clinical level, akinesia is often used interchangeably with the terms bradykinesia and hypokinesia (Abdo et al., 2010; Berardelli et al., 2001; Donaldson et al., 2012; Fahn, 2003; Ling et al., 2012; Rodriguez-Oroz et al., 2009; Schilder et al., 2017). Notably, bradykinesia often represents an umbrella term for all these motor symptoms, as encouraged by the UPDRS. However, to establish the link between these

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motor symptoms and the associated pathophysiological mechanisms, it is necessary to refine terminologies so that they refer not only to the symptoms but also to the underlying neural mechanisms. The definition proposed by Hallett and colleagues (e.g., [Hallett, 1990](#)), a failure of willed movement to occur, has been successful for addressing this need. This definition clearly states that: (1) akinesia shall not be confounded with bradykinesia -slowness of movement that is ongoing-, (2) akinesia is related to dysfunctions of brain mechanisms that are responsible for movement preparation and initiation, and (3) akinesia is best characterized at a behavioral level by the time needed to initiate a movement. In other words, this definition refers to slowness or failure in movement initiation that can go up to the total abolition of movement (e.g., [Jahanshahi et al., 2015b](#); [Krack et al., 1999](#)). It is both an extension of the original greek terminology and a substantial limitation of the common clinical use of the term.

A common belief is that akinesia is mainly a motor deficit related to dopaminergic (DA) depletion ([Holtbernd and Eidelberg, 2012](#)). According to the traditional view, the main symptoms of PD are related to dysfunctions of the motor circuit, which links the motor cortices to specific territories within the basal ganglia (BG) nuclei ([Alexander and Crutcher, 1990](#); [DeLong, 1990](#); [Jahanshahi et al., 2015a, 2015b](#)). The loss of DA in PD may cause dysfunctions in the balance between the direct pathway (hypoactivation) and the indirect pathway (hyperactivation), resulting in increased subthalamic nucleus and internal globus pallidus activities, and consequent excessive thalamic inhibition. Accordingly, it has long been assumed that the resulting dysfunction of the thalamocortical loop produces akinesia through its action upon motor cortical regions ([Escola et al., 2003](#); [Haslinger et al., 2001](#); [Jahanshahi et al., 2015a, 2015b](#)). However, this view fails to explain several clinical and experimental observations, such as the fact that lesions of the motor thalamus do not result in akinesia ([Canavan et al., 1989](#)), that globus pallidus lesions do not improve it ([Marsden and Obeso, 1994](#)), or that akinesia is not fully alleviated by standard pharmacological treatments using levodopa or DA agonists ([Favre et al., 2013](#); [Fox, 2013](#); [Jahanshahi et al., 1992](#); [Schubert et al., 2002](#)). In other words, the classic pathophysiological model of the BG does not explain the origin of akinesia (see [Rodriguez-Oroz et al., 2009](#) for review).

In an attempt to understand these contradictions, some authors have suggested that akinesia might also have non motor or non DA origins ([Ballanger et al., 2007](#); [Criaud et al., 2016b](#); [Favre et al., 2013](#); [Rodriguez-Oroz et al., 2009](#)). In particular, it was suggested, mainly from behavioral laboratory studies, that executive dysfunction could play a role in akinesia ([Albares et al., 2015b](#); [Favre et al., 2013](#); [Jahanshahi and Rothwell, 2017](#); [Michely et al., 2012, 2015](#); [Obeso et al., 2011](#)). Executive processes refer to mechanisms dedicated to the higher-order control of behavior. This includes the ability to initiate, execute, monitor, and inhibit actions. However, the mechanisms underlying executive dysfunction are difficult to understand in PD because they are often masked by, or confounded with, motor features ([Rodriguez-Oroz et al., 2009](#)).

To sum up, the blurred borders of the clinical concept of akinesia and the difficulty to disentangle motor and executive processes make it particularly difficult to determine the neural bases of movement initiation disorders on the sole basis of clinical, neuropsychological and behavioral evaluations. By giving access to finer-grained mechanisms, functional imaging studies have the potential to reveal the dysfunctional brain processes that account for akinesia, within and beyond the motor circuitry. Here, we propose a critical review of the topic based on a systematic analysis of the available neuroimaging studies. Our hope is to identify common neural denominators across studies, despite the heterogeneous functions, definitions and methods used. No such review is currently available. It is intended to complement other recent reviews of the pathophysiology of akinesia focusing on DA denervation ([Antonelli and Strafella, 2014](#); [Jellinger, 2014](#)) and subthalamic beta oscillations ([Weinberger et al., 2009](#)).

## 2. Methods

### 2.1. Literature selection

An electronic search was performed using the Web of Science and PubMed databases to collect studies on the neurofunctional bases of akinesia in PD until November 2018. The following search terms were used: ((Akin\*) AND (Parkinson) AND (Imaging OR fMRI OR PET OR Activation OR Blood flow)) and all variants of these terminologies.

The inclusion criteria for this review were:

- 1) Brain activation abnormalities using PET rCBF or fMRI studies,
- 2) Including PD patients with akinetic-rigid subtypes (AR) or assessing akinetic symptoms,
- 3) Including a control group with healthy subjects (HC) and/or tremor-dominant PD patients (TD).
- 4) Performing at least one of the four contrasts AR > HC, HC > AR, AR > TD or TD > AR.

The exclusion criteria were:

- 1) Review articles,
- 2) Behavioral studies,
- 3) Conference abstracts,
- 4) Animal studies,
- 5) Case reports,
- 6) Metabolism or neurotransmission PET studies,
- 7) Studies focusing only on treatment x group interactions.

### 2.2. Data extraction and criterion-referenced assessment

Papers were analyzed according to four sets of criteria:

#### 1) Characteristics of the Clinical groups

This includes the number of subjects, the clinical subtypes of PD patients (AR, TD), and the treatment status (ON/OFF Levodopa or Drug naïve).

#### 2) Neuroimaging methods

The neuroimaging methods used to characterize dysfunctional neural activity were analyzed as a function of:

- The neuroimaging tool used (fMRI/SPECT/PET) and the nature of the signal captured (BOLD or rCBF);
- The control group used to infer the neural correlates of akinesia in AR patients (HC and/or TD)
- The data processing method used to infer neural activity (functional connectivity, task-related activation/block design, event-related activation);
- The strategy of analysis of the neural correlates (whole brain or regions of interest).

#### 3) Characteristics of the behavioral task and rationale

Studies assessing the neural bases of akinesia associate clinical symptoms with discrete deficits in specific neural systems. This can rely on different strategies:

- Studies using no behavioral task: Resting state recordings allow linking clinical symptoms of akinesia to global and non-specific brain activity changes in defined neural systems, by assessing the intensity of spontaneous brain activity or resting state functional connectivity.
- Studies using a behavioral task: Task-based recordings allow

isolating the neural mechanisms of interest through specific behavioral designs, either by assessing specific event-related brain activity changes (event-related fMRI) or task-related motor activation (block designs) that differ between AR and HC.

We used several criteria informing about the strategy used by the authors: the author's explicit rationale and the behavioral task used to isolate the psychological mechanisms under scrutiny.

#### 4) Neuroimaging results

For each study, the list of brain regions including the global maxima of the significant clusters was reported for the contrasts HC > AR and AR > HC. When available, results of the contrasts TD > AR and AR > TD were also reported. Resting state studies were analyzed apart from studies using behavioral tasks for task-related or event-related neuroimaging designs.

### 3. Results

#### 3.1. Literature selection

1829 records were identified through database searching, including 1058 duplicates. 754 texts were excluded with respect to our criteria. Finally, only 17 full-texts (21 experiments) were included (Fig. 1).

#### 3.2. Systematic analysis

Detailed results are presented in Table 1.

##### 1) Characteristics of the Clinical groups

Most studies selected AR patients based on the mean AR score calculated with the corresponding items of the motor section of the Unified Parkinson's disease Rating Scale (UPDRS part III) ( $N = 8$ ) (#1–3; #5–7; #12, #14). The other studies simply excluded PD patients with tremor ( $N = 7$ ) (#9–11; #13; #15–17), considering akinesia as a major symptom of the disease. One study measured akinesia based on item #31 of the UPDRS-III (assessing global spontaneity of movements; #4). Only one study tested directly slowness in movement initiation in PD patients with a specific behavioral design (#8). Taken together, these studies comprised in average  $19.1 \pm 11.5$  AR patients and  $20.7 \pm 16.9$  HC. Detailed characteristics of the clinical groups are provided in Supplementary Table 1.

##### 2) Neuroimaging methods

Fourteen studies used fMRI, two used SPECT and one used PET imaging. Seven studies performed resting state fMRI recordings (#1–7), while two recorded event-related activity (#8–9) and eight recorded task-related activity (block-design) (#10–17). Eight studies searched for the neural bases of akinesia with no a priori about brain regions (#1–2; #6; #10–13; #17); while nine studies searched for alterations in specific regions of interest (ROI) based on their rationale (#3–5; #7–9; #14–16).

##### 3) Characteristics of the behavioral task and rationale

###### - Studies using no behavioral task:

Among the seven experiments collecting resting state data, three searched for alterations of intrinsic connectivity in akinetic PD patients with no a priori about specific psychological dysfunctions or brain regions (#1–2; #6), using Functional Connectivity Density (#1), Regional Homogeneity (ReHo) (#2) or Voxel-Mirrored Homotopic Connectivity (#6). One experiment searched for connectivity changes of regions

involved in movement initiation (#4 – seed-based functional connectivity). One experiment focused on the functional connectivity of the BG network (#5). Two experiments probed the functional integrity of default mode network (DMN-), either by assessing the intensity of its spontaneous activity (#7) or by measuring its functional connectivity at rest (#3 – seed-based functional connectivity). These last two studies clearly assumed cognitive dysfunctions in akinetic PD patients (#3; #7).

###### - Studies using a behavioral task:

Most studies ( $N = 10$ ) set-up behavioral experiments specifically designed to test the hypothesis that akinesia is a motor symptom. These studies used a motor task to reveal movement-related activations (joystick movements/sequential finger-to-thumb opposition movements/sequential finger tapping task/thumb pressing movements/timed movements), either by means of task-related (#10–17a) or event-related (#9) neuroimaging designs. Motor alterations associated with akinesia were evidenced using the HC > AR contrast in 8 experiments. Compensatory mechanisms of akinesia were revealed using the AR > HC contrast in 8 experiments.

Only two experiments tested the hypothesis that akinesia includes both motor and executive components (#8, #17b). Both studies focused on the pre-movement phase in order to capture the brain activity associated with motor preparation and executive control of movement initiation. One of the two experiments (whole brain PET) used a motor imagery task (#17b) while the other (ROI event-related fMRI) used a real, simple motor task (#8).

#### 4) Neuroimaging results

Detailed clinical scores and neuroimaging data are displayed in Table 1.

###### - Studies using no behavioral task:

Resting state alterations in AR with respect to HC are found in a widely distributed, poorly reproducible network including the cerebellum, various frontal areas (primary motor cortex -M1-, medial prefrontal cortex -mPFC-, middle frontal gyrus -midFG-, inferior frontal gyrus -iFG-), parietal areas (inferior parietal cortex -IPC-, angular gyrus, cuneus), and different subcortical regions (putamen, caudate nucleus, thalamus, amygdala) (Fig. 2). The precuneus (#2–3, #5a), the posterior cingulate gyrus -PCC- (#2–3; #7), the occipital lobe (#3-5a), the thalamus (#2, #4-5a) and the insula (#2–4) were detected more consistently. Whole brain studies (#1–2, #6) with no a priori on the brain regions failed to find reproducible areas accounting for akinesia, with the exception of the midFG evidenced in two studies (#1–2). The two studies focusing on the DMN to test cognitive integrity in AR patients also failed to reveal reproducible dysfunctional brain regions, with the exception of the PCC (#3–7).

The direction of the effect in AR with respect to HC is also variable. Among the brain regions found in at least two different studies, contradictory results are reported in nine out of 15 cases. For instance, among the studies showing brain activity differences in the IPC, one reports increased activity in AR with respect to HC while two others report increased activity in HC with respect to AR.

An overlapping network is observed when considering TD patients rather than HC as a control population. Differences are found in the cerebellum, the PCC, the IPC, the primary somatosensory cortex, the superior and the inferior frontal gyri (only brain regions observed at least in two different studies are listed. For complete results, see Fig. 3). The direction of the effect is, however, as variable as in the AR vs. HC comparisons. There are two notable exceptions: The hypoactivity or hypoconnectivity of the cerebellum in AR found in four different studies (while the opposite pattern was found only once), and the hypoactivity

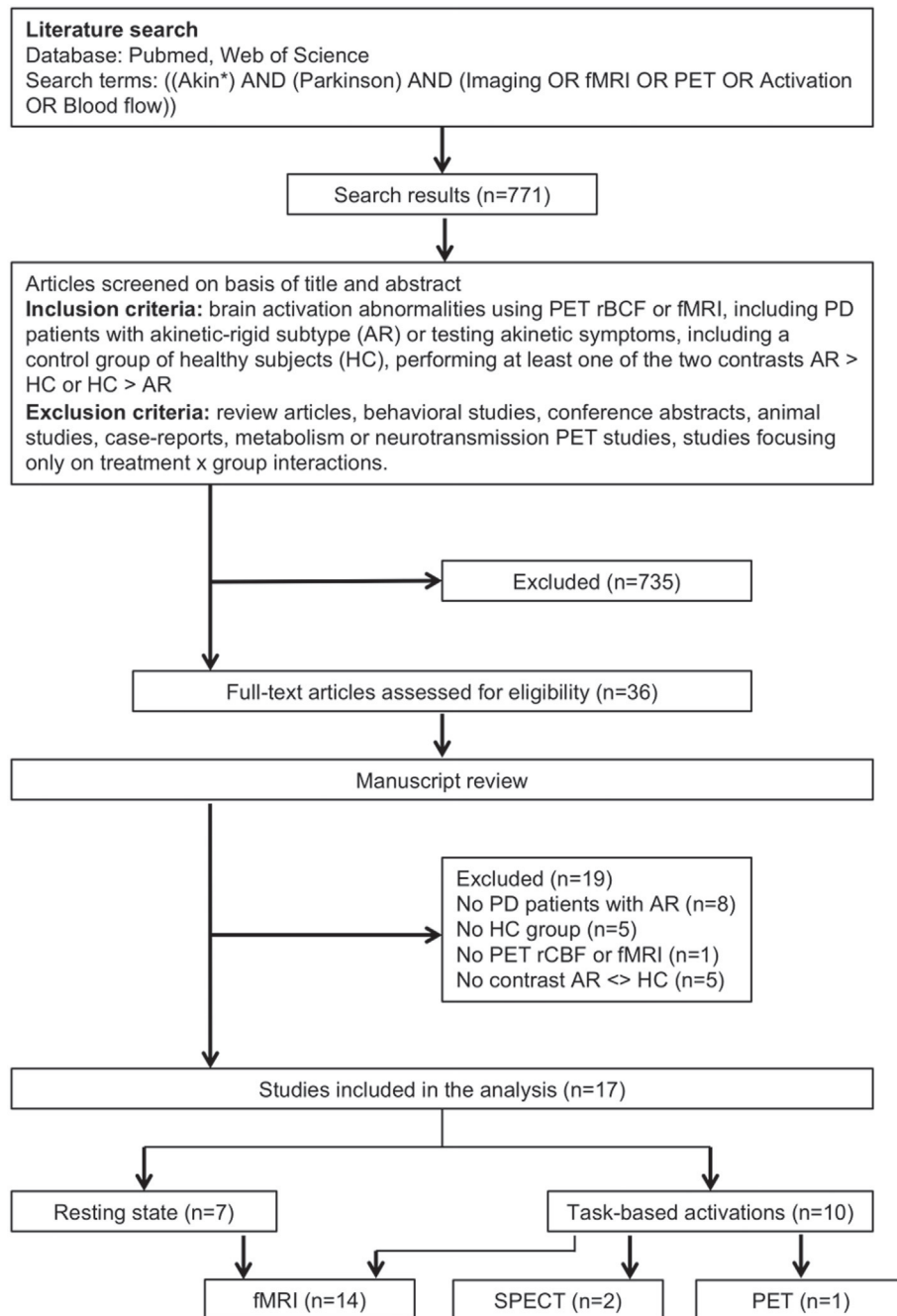


Fig. 1. Flow chart of publication selection for review, following PRISMA guidelines (Liberati et al., 2009).

of the PCC (reported in two different studies).

- Studies using a behavioral task:

Movement-related brain activity changes were found in a large network including the motor and supplementary motor cortices, the medial cortex (ACC, precuneus), the prefrontal cortex (dlPFC, iFG, frontal operculum), the visual cortex (lingual gyrus), the insula, the cerebellum, and subcortical regions (thalamus, insula, BG). Yet, these observations are poorly reproducible (Fig. 4). Consistent results were reported only for the cerebellum and the dlPFC, respectively found more activated in AR than HC (in four experiments; #12a-13; #16) and more activated in HC than AR (in four experiments; #11; #13; #17a-b). While changes in SMA activity were frequently reported (nine times; #8-13; #15-16), results are not fully consistent regarding the direction

of the effect.

Only one study using a behavioral task has considered TD patients rather than HC as a control population (#14). No significant result was reported.

#### 4. Discussion

The present systematic review pinpoints incompleteness and confounds that impede the identification of the neurofunctional bases of akinesia.

##### 4.1. The terminology of akinesia

The first thing to come out from the present systematic analysis is that most papers (15 out of 17) are not backed up by a clear definition

**Table 1**  
Systematic analysis of the functional neuroimaging studies included in the review.

Study #	1st Author Year	Population			Neuroimaging			Methods		Results	
		Definition of alkenesia. Symptoms. Subjects (AR/ HC/TD)	Treatment status	Tool. Signal	Type of activity. Data processing	Authors' rationale	Behavioral task	Regions of interest	Contrast	Brain regions showing significant differences	
#1	Hu 2017	(-) AR dominant 25/26/25 HC/TD	OFF	fMRI BOLD	Intrinsic activity Functional connectivity density (FCD)	"to investigate the altered functional connectivity patterns of TD and AR subtypes"	(-)	Whole brain	AR > HC . HC > AR	(a) Increased global FCD in the frontal lobe (right inferior frontal gyrus/bilateral middle frontal gyrus); temporal cortex (right middle temporal gyrus) and left posterior lobe of the cerebellum in AR compared to HC. ∅ (a) Higher global FCD in AR in the left inferior frontal gyrus, right middle frontal gyrus, right superior frontal gyrus. (a) Lower global FCD in AR in the left cerebellum anterior lobe. ∅ (b) Lower FC in AR between the left cerebellum anterior lobe and the left primary somatosensory cortex, left superior frontal gyrus, right insula, right orbital inferior frontal gyrus. Increased ReHo in AR in the right amygdala, left putamen, bilateral angular gyrus, bilateral medial prefrontal cortex, bilateral middle frontal gyrus, right middle cingulate cortex and right supramarginal gyrus. Decreased ReHo in the left middle and posterior cingulate gyrus/precuneus, right insula, left fusiform gyrus, vermis 4/5 and bilateral thalamus.	
#2	Zhang 2015	(-) AR dominant 27/26/20	OFF	fMRI rCBF	Intrinsic activity Functional connectivity, Regional Homogeneity (ReHo)	"to explore regional brain activity in TD and AR types during resting state to reveal distinct neural network in PD"	(-)	Whole brain	AR > HC TD > AR	Higher ReHo in AR in the left putamen, left primary somatosensory cortex, right superior temporal gyrus, right inferior frontal gyrus, left inferior parietal lobe. Lower ReHo in AR in the left thalamus, left superior frontal gyrus, left primary motor cortex, bilateral cerebellum.	

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Table 1 (continued)

Study #	1st Author Year	Population	Neuroimaging			Methods		Results		
			Treatment status	Tool, Signal	Type of activity, Data processing	Authors' rationale	Behavioral task		Regions of interest	Contrast
#3	Hou 2017	(-) AR dominant Subjects (AR/ HC/TD)	Drug naïve	fMRI .BOLD	Intrinsic activity Functional connectivity (FC) – Seed-based	“to test the functional connectivity of the DMN in cognitively unimpaired akinetic PD patients”	(-)	Seeds and ROI: DMN	. AR > HC HC > AR	Increased FC between the left medial prefrontal cortex, left posterior inferior parietal lobule and the cerebellum. Decreased FC between the posterior DMN and the cuneus, lingual gyrus and fusiform gyrus. Decreased FC between the anterior DMN and the middle and inferior frontal gyri, inferior parietal lobule and insula. ∅
#4	Hensel 2018	Impairment to initiate spontaneous movements . PD patients . 60/72	ON	fMRI BOLD	Intrinsic activity Functional connectivity (FC) – Seed-based	“we hypothesized that akinesia was particularly related to connectivity changes with regions involved in movement initiation”	(-)	Seeds: Bilateral putamen, bilateral primary motor cortex, posterior medial frontal cortex – ROIs: seed-specific networks	. AR > HC HC > AR	[Within the putamen-specific network] Decreased FC between the putamen and the thalamus, putamen, pallidum. [Within the posterior medial frontal cortex-specific network] Decreased FC between the putamen and the bilateral intraparietal sulcus, posterior medial frontal cortex, dorsolateral prefrontal cortex, left inferior parietal lobule – Decreased FC between the posterior medial frontal cortex and the bilateral anterior insula, left dorsolateral prefrontal cortex – Decreased FC between the primary motor cortex and the pre-supplementary motor area. [Within the primary motor cortex-specific network] Decreased FC between the putamen, the primary motor cortex; and the bilateral supplementary motor area, primary motor and somatosensory cortex, superior parietal lobule, intraparietal sulcus, extrastriate visual cortex -Decreased FC between the putamen and the right dorsal premotor cortex – Decreased FC between the posterior

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Table 1 (continued)

Study		Population			Neuroimaging		Methods		Results	
#	1st Author Year	Definition of akinesia. Symptoms. Subjects (AR/ HC/TD)	Treatment status	Tool. Signal	Type of activity. Data processing	Authors' rationale	Behavioral task	Regions of interest	Contrast	Brain regions showing significant differences
#5	Guan 2017	(-) AR dominant 49/52/57	Drug naive or OFF	fMRI BOLD	Intrinsic activity Functional connectivity (FC) -Network-based	"differences of functional connectivity connecting with BG would be observed between the PD-AR and PD-TD"	(-)	Basal Ganglia Network identified by ICA	. AR > HC . HC > AR	medial frontal cortex and the bilateral primary somatosensory cortex, right superior parietal lobe. Negative correlation between akinesia scores and FC between the posterior medial frontal cortex and the right inferior parietal lobe within the posterior medial frontal AR dominant. Ø (a) [Voxel-wised analysis] Reduced network-based FC in the bilateral thalamus, occipital lobe, precuneus [ROI-based analysis] Reduced network-based FC in the bilateral thalamus. Ø (a) [Voxel-wised analysis] Lower network-based FC in AR in the bilateral occipital lobe and right cerebellum posterior lobe [ROI-based analysis] Ø (b) Enhanced eigenvector centrality in the right caudate nucleus and right thalamus. Ø Ø Ø Decreased VMHC values in the primary motor cortex. Higher VMHC in AR in the cerebellum posterior lobe. Ø Decreased spontaneous brain activity in the left and right inferior parietal cortex and in the left posterior cingulate cortex within the DMN in AR compared to HC. Ø Ø Lower spontaneous brain activity in AR in the left and
#6	Hu 2015	(-) AR dominant 29/26/21	OFF	fMRI BOLD	Intrinsic activity Voxel-Mirrored Homotopic Connectivity (VMHC)	"we hypothesized that the VMHC alterations in motor-related cortical areas can be found in AR-PD group"	(-)	Whole brain	. AR > HC . HC > AR AR > TD TD > AR	
#7	Karunana- yaka 2016	(-) AR dominant 17/24/15	ON	fMRI BOLD	Intrinsic activity	"to test the hypothesis that DMN integrity is different between TD and AR subtypes in PD"	(-)	ROI: DMN	. AR > TD TD > AR . HC > AR . AR > HC AR > TD TD > AR	



Table 1 (continued)

Study #	1st Author Year	Population	Neuroimaging			Authors' rationale	Methods	Regions of interest	Results
			Tool	Signal	Type of activity, Data processing				
#8	Craud 2016	Slowness in movement initiation PD patients without tremor . 12/15	fMRI BOLD	Task-based activations Event-related	"to test the hypothesis that akinesia in PD is related to executive dysfunction (abnormal proactive inhibitory control)"	Motor Task Ext. Simple reaction time task	ROI: Proactive Inhibitory Network	. AR > HC	
#9	Haslinger 2001	(-) AR without tremor 8/8	fMRI BOLD	Task-based activations Event-related	"to study BOLD cortical signal changes in M1/premotor areas associated with volitional limb movements in akinetic PD patients"	Motor Task Ext. Paced single joystick movements in a freely chosen direction	ROI: M1, Parietal and Frontal Motor Association Cortex	. AR > HC	
#10	Buhmann 2003	(-) AR without tremor 8/10	fMRI BOLD	Task-based activations Block design (Modelling finger movements > delta functions convolved with HRF)	"to explore movements' activations in akinetic PD patients"	Motor Task Ext. Simple paced random finger opposition task	Whole brain	. HC > AR HC > AR	
#11	Sabatini . 2000	(-) AR without tremor . 6/6	fMRI BOLD	Task-based activations . Block design	"to study differences in activation between akinetic PD patients and HC"	Motor Task Ext. Complex sequential motor task	Whole brain	. AR > HC HC > AR	
#12	Cerasa . 2006	OFF	fMRI BOLD	Task-based activations Block design	"to explore motor entrainment ability of akinetic PD patients"	Motor Task Ext./Int.	Whole brain	. AR > HC . HC > AR	

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Table 1 (continued)

Study	Population	Neuroimaging	Authors' rationale	Methods	Regions of interest	Results
#	1st Author Year	Tool. Signal	Type of activity. Data processing	Behavioral task	Contrast	Brain regions showing significant differences
	Definition of akinesia. Symptoms. Subjects (AR/HC/TD)					
	(-) AR dominant . 10/11			Externally and internally timed movements		the cerebellum, frontostriatal circuit (putamen, SMA, thalamus) and specific areas (right inferior frontal gyrus, insula, left lingual gyrus) in AR compared to HC. (b) During the continuation phase, increased activity in the cerebellum and the thalamus in AR compared to HC.
#13	Yu . 2007	fMRI BOLD	Task-based activations Block design	Motor Task Ext. . Automatic vs. cognitively controlled thumb pressing movements	Whole brain (ROI mask based on group comparison)	. AR > HC  . HC > AR
	(-) PD patients without tremor . 8/8		"to examine whether cerebellar and motor cortex hyperactivation is a compensatory mechanism for hypoactivation in the basal ganglia or is a pathophysiological response that is related to the sign of the disease"			Hyperactivation of the cerebellum and the left primary motor cortex in AR compared to HC. Hypoactivation of the left putamen/right caudate, SMA and pre-SMA, right dlPFC in AR compared to HC.
#14	Lewis . 2011	fMRI BOLD	Task-based activations Block design	Motor Task Int. . Internally-guided sequential finger tapping task	ROI: CTC/STC circuits	. AR > HC . AR > TD
	(-) AR dominant . 8/14/9		"to understand the clinical heterogeneity between TD and AR subtypes"			After adjusting for age, significant increase of the % of voxels activated in contralateral CTC circuits in AR compared to HC. Post-hoc t-tests within the CTC revealed no significance for any of the ROIs. After adjusting for age and side of symptom onset, significant increase of the % of voxels activated in ipsilateral STC and CTC circuits in AR compared to TD. Post-hoc t-tests revealed no significance for any of the ROIs.
#15	Rascol . 1994	SPECT . rCBF	Task-based activations Block design	Motor Task Int. . Sequential finger-to-thumb opposition movements	ROI: SMA, S1 M1	. AR > HC  . HC > AR
	(-) AR without tremor . 15;11/15		"to assess whether the motor activation in the SMA is impaired or not when aknetic PD patients are treated with levodopa"			Hyperactivation of the ipsilateral S1 M1 in AR-ON compared to AR-OFF and HC. Hypoactivation of the SMA in AR-OFF compared to HC and AR-ON dopa. No changes on contralateral S1 M1 between AR and HC.
#16	Rascol . 1997	SPECT . rCBF	Task-based activations Block design	Motor Task Int. . Sequential finger-to-thumb	ROI: CerebellumS1 M1, SMA	. AR > HC
	(-) AR without tremor . 12;16/12		"to compare rCBF changes induced by a motor task in the cerebellar hemisphere of"			Overactivation in the ipsilateral cerebellum in AR-OFF compared to HC and AR-ON.

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Table 1 (continued)

Study #	Ist Author Year	Population Definition of akinesia. Symptoms. Subjects (AR/ HC/TD)	Neuroimaging			Methods		Results		
			Treatment status	Tool. Signal	Type of activity, Data processing	Authors' rationale	Behavioral task	Regions of interest	Contrast	Brain regions showing significant differences
#17	Samuel . 2001	(-) PD patients without tremor . 6/6	OFF	PET . rCBF	Task-based activations . Block design	akinetic PD or HC receiving or not levodopa" "to explore what is less activated in PD than in HC when executing or imaging movements"	opposition movements Motor Task Ext. . Paced single joystick movements in a freely chosen direction. . Motor Imagery Task	Whole brain	. HC > AR . HC > AR	Hypoactivation in the SMA in AR-OFF compared to HC and AR-ON. (a) For execution, reduced activation of the right dorsolateral prefrontal cortex and lateral premotor cortex, and bilateral thalamus and basal ganglia in AR compared to HC. (b) For imagery, reduction in dorsolateral and mesial frontal activation in the AR group compared to HC.

AR: Akinesic-Rigid dominant. HC: Healthy Controls. PD: Parkinson Disease. TD: Tremor Dominant. (-): no explicit definition of akinesia is provided. ON:ON levodopa – hyperdopaminergic state. OFF: from 6 to 24 h withdrawal of dopaminergic medication –hypodopaminergic state. Drug naive: Patients who never experienced dopaminergic medication. Ext.: Externally driven. Int.: Internally driven –self-initiated-. AH: Affected –Akinesic- Hand. UAH: Unaffected –non-akinesic- Hand. CTC: Cerebello-Thalamo-Cortical Circuits. DMN: Default Mode Network. S1 M1: Primary Sensorimotor Cortex. SMA: Supplementary Motor Area. STC: Striato-Thalamo-Cortical Circuits. ACC: anterior cingulate cortex. Ø: No significant modification of activity/connectivity.

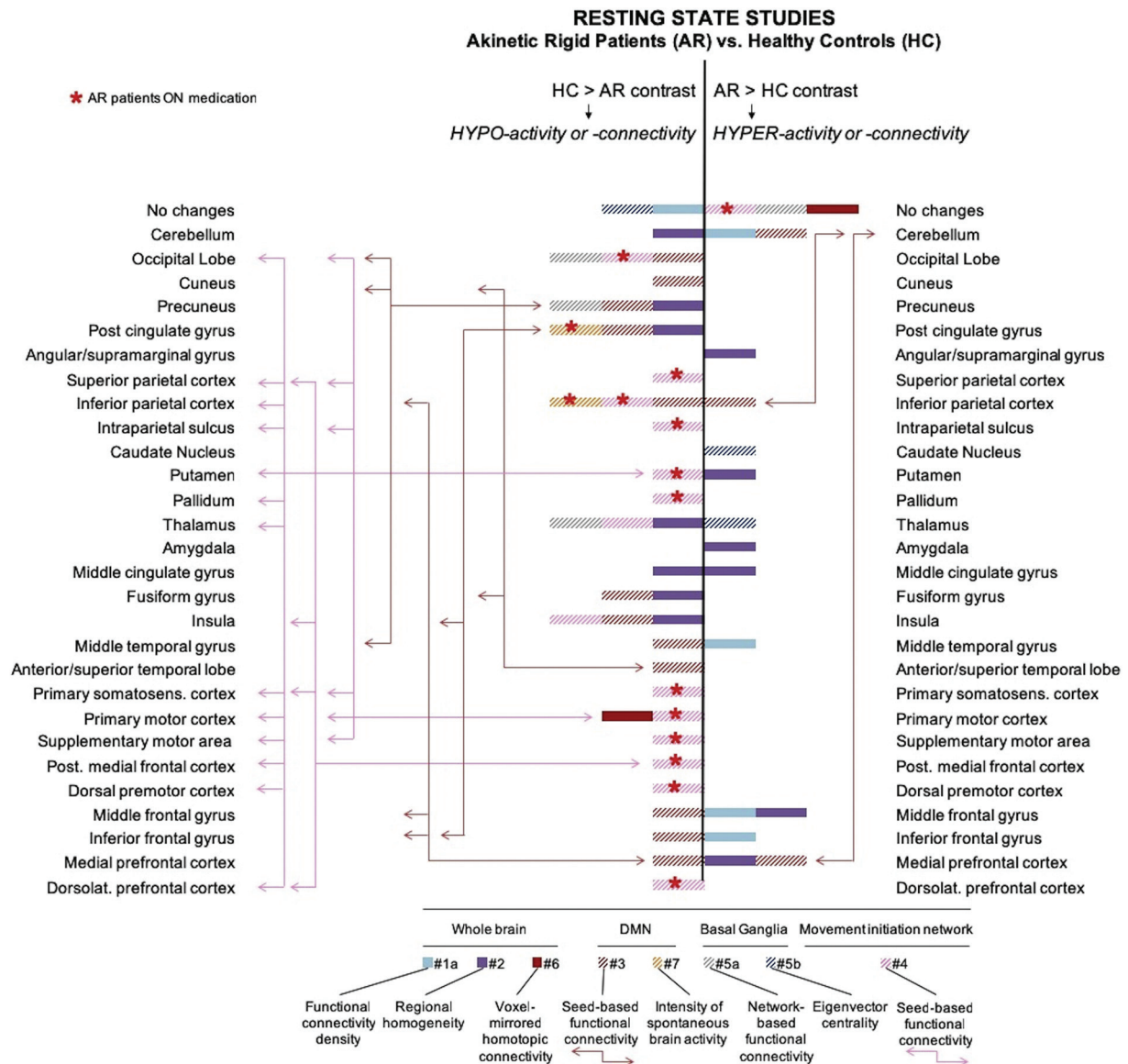


Fig. 2. Results of the neuroimaging studies using resting state approaches and comparing AR to HS subjects to assess the neural bases of akinesia. Arrows between two distinct brain regions indicate abnormal connectivity in seed-based functional connectivity studies. Studies assessing AR patients ON medication are indicated by red stars.

of akinesia (Table 1, supplementary Table 2). Rather, akinetic symptoms are just considered along with other predominant motor signs (Zaidel et al., 2009) to roughly distinguish AR from HC or AR from TD subtype of patients with PD (Buhmann et al., 2003; Cerasa et al., 2006; Guan et al., 2017; Haslinger et al., 2001; Hou et al., 2017; Hu et al., 2015, 2017; Karunanayaka et al., 2016; Lewis et al., 2011; Rascol et al., 1994, 1997; Sabatini et al., 2000; Samuel et al., 2001; Yu et al., 2007; Zhang et al., 2015). Most of the studies reviewed here were intended to assess the neural correlates of these two disparate clinical subtypes of PD. In that respect, the use of derivatives of the term akinesia in these papers does not require, indeed, more detailed description. It is, however, still a problem for our purpose that the mean AR score confounds bradykinesia, hypokinesia and akinesia, and that it is not always computed from the same items across studies. A considerably more circumscribed definition is mandatory when it comes to relate specific akinetic clinical symptoms to behavioral markers and to neural and psychological mechanisms. On the one hand, studies comparing AR to TD and even more AR to HC highlight brain functional differences that cover a wide range of dysfunctions, beyond akinesia. That certainly

explains part of the variability and contradictions regarding the dysfunctional neural networks associated with akinesia identified in the present review (Figs. 2–4). On the other hand, only one study has used a clear terminology based on Hallett's definition (Hallett, 1990) in combination with a behavioral design intended to capture specific markers of movement initiation disorders (Criaud et al., 2016b). Obviously, the results issued from this single study need to be reproduced to reach stronger scientific evidence (see limitations in supplementary Table 2). To summarize, although akinesia is considered a major feature of one of the most common and well documented neurodegenerative diseases, a definitive and unambiguous picture of its neural bases cannot emerge so far from the current literature. But there are both common denominators and interpretable differences between studies that raise important issues for future investigations.

#### 4.2. Resting state modulations

The way networks are active or functionally connected during rest has the potential to inform about the functional integrity of human

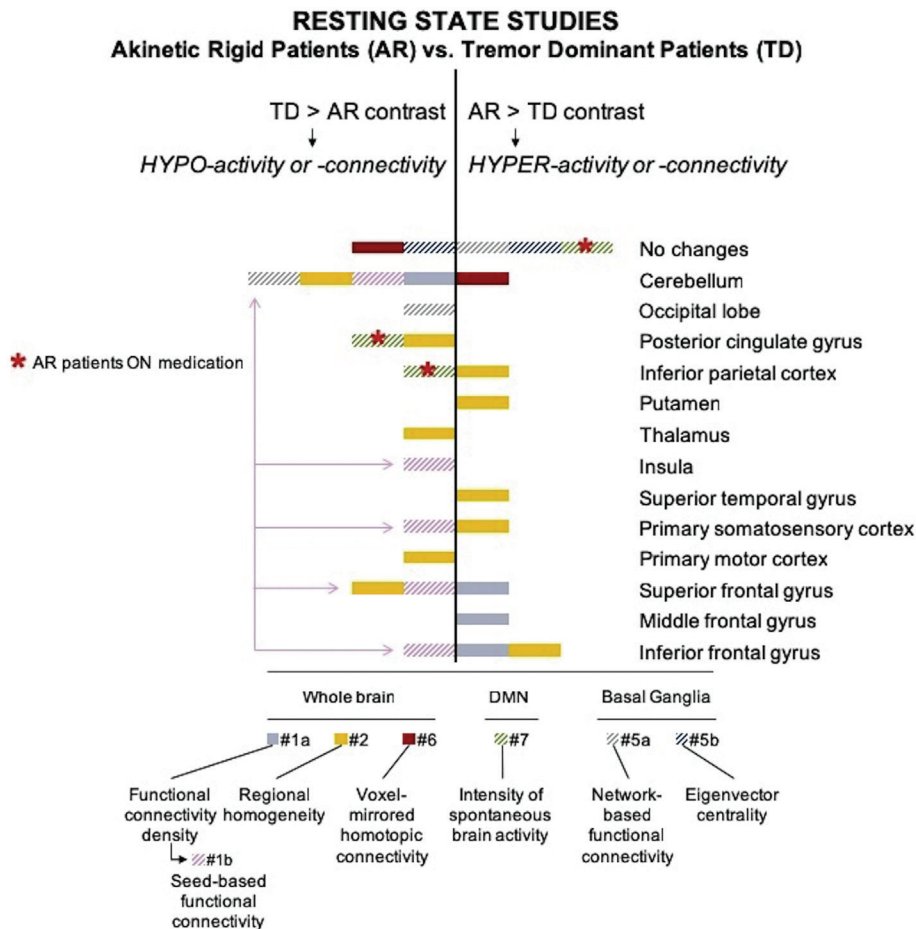


Fig. 3. Results of the neuroimaging studies using resting state approaches and comparing AR to TD subjects to assess the neural bases of akinesia. Arrows between two distinct brain regions indicate abnormal connectivity in seed-based functional connectivity studies. Studies assessing AR patients ON medication are indicated by red stars.

brain architecture in general, and about akinesia-related dysfunctional networks in PD in particular. We have identified only one study investigating spontaneous brain activity and six studies investigating different forms of functional connectivity at rest in AR patients.

Differences in the intensity of spontaneous brain activity between AR and HC but also AR and TD (Karunanayaka et al., 2016) can be observed in the left IPC and PCC (less intensity in AR). This represents an important advance with regard to former variable results about DMN functional integrity in PD (Delaveau et al., 2010; Ibarretxe-Bilbao et al., 2011; Krajcovicova et al., 2012; van Eimeren et al., 2009). Unfortunately, whole brain analyses have not been performed and differences have only been tested within the DMN. In other words, Karunanayaka's study (2016) has been very useful in identifying non-motor components of akinesia-related brain dysfunctions, but provided no clue about changes in the motor circuitry of AR patients with respect to other PD patients, which is not a closed issue.

Differences between AR and HC (or TD) in functional connectivity are observed in distributed but poorly reproducible brain areas, with the notable exception of the precuneus/PCC node, the insula, the thalamus and the occipital lobe. Besides common problems of imaging (heterogeneous data processing and paradigms, sample size, etc. See supplementary Table 2), the variability in the goals and methods used to probe altered intrinsic connectivity in AR patients (Table 1) is likely to explain part of the variability observed in the list of dysfunctional brain regions supporting differences between PD subtypes or between akinetic PD patients and matched controls. Abnormal local synchronization of spontaneous fMRI signals (ReHo) was found within various clusters in the medial cortical wall (mPFC, midFG, middle cingulate gyrus, supramarginal gyrus, PCC, precuneus, fusiform gyrus) and in subcortical regions (amygdala, putamen, thalamus) (Zhang et al.,

2015). Alterations of large scale functional connectivity of the DMN (seed-based approach) were found between the mPFC and the IPC with the cerebellum, between the iFG and the mPFC, between the PCC with the insula and the iFG, between the precuneus and both the middle temporal gyrus and the lingual gyrus/cuneus (Hou et al., 2017). Quantitative aspects of synchronization as measured by means of functional connectivity density also highlight differences between AR and HC patients (Hu et al., 2017). Increased functional connectivity density in AR was found in the frontal lobe (midFG, iFG), in the temporal lobe (middle temporal gyrus), and in the cerebellum. Decreased connectivity between the hemispheres was found in AR at the level of the precentral gyrus (Hu et al., 2015). Reduced global connectivity -the correlation of each voxel time course with all other voxel time courses- was observed in the thalamus, the occipital lobule, and the precuneus within the BG network (Guan et al., 2017). Enhanced connectivity as indexed by eigenvector centrality values (i.e., the relative influence of a node in a network) was observed in the right caudate nucleus and the right thalamus (Guan et al., 2017). Although all these measures clearly represent different aspects of abnormal functional connectivity, one observation emerges from the global map provided these studies (Figs. 2, 3): it is likely that akinesia is not just a purely motor dysfunction, as all studies have identified AR-related dysfunctions that go way beyond the motor circuitry. The fact that the most reproducible results pinpoint dysfunctions of integrating hubs interacting with multiple brain networks involved in nonmotor aspects of behavioral control, like the precuneus/PCC node, the insula or the thalamus, is particularly supportive of this hypothesis. These key regions play a significant role in PD (e.g., Criaud et al., 2016a). Moreover, since an overlapping ensemble of brain regions has been identified in the studies which tested not only AR vs. HC contrasts but also AR vs. TD contrasts

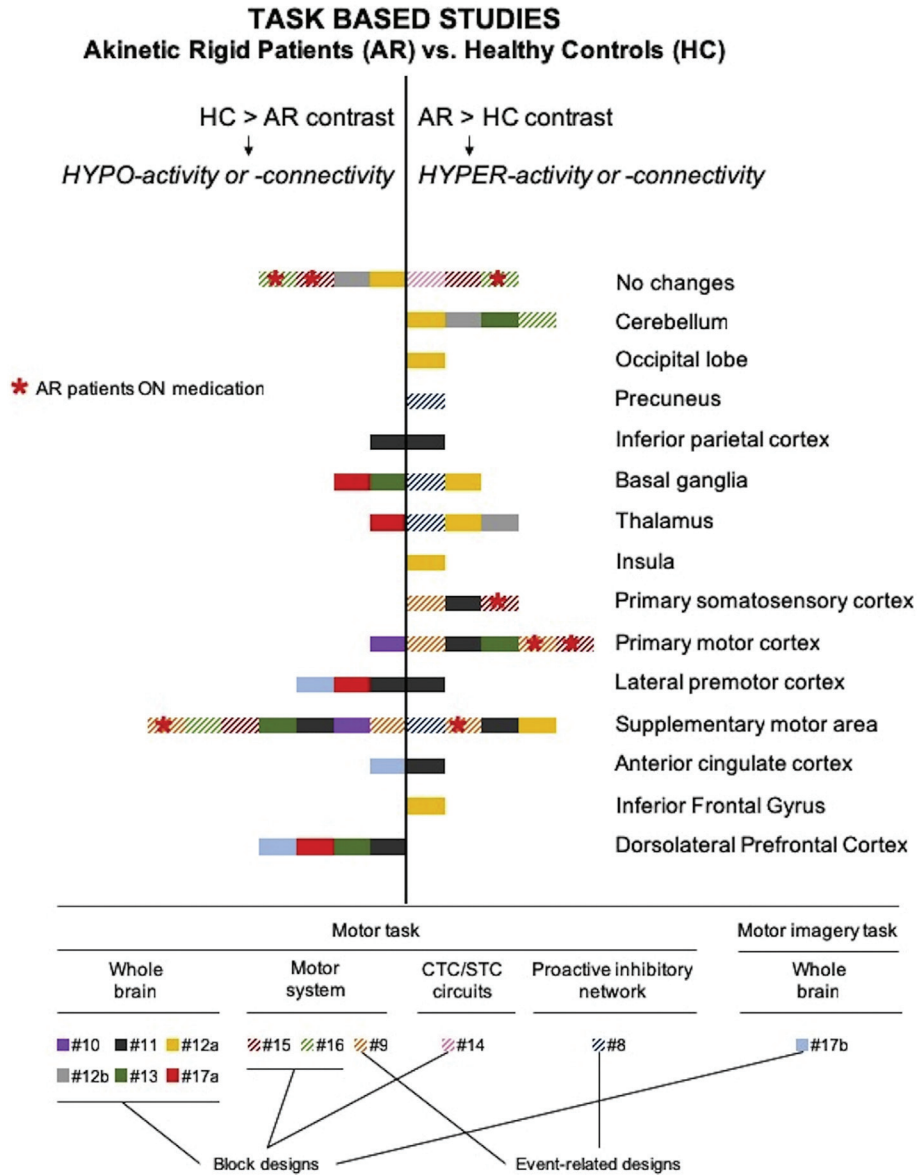


Fig. 4. Results of the neuroimaging studies using task-based approaches and comparing AR to HS subjects to assess the neural bases of akinesia. Studies assessing AR patients ON medication are indicated by red stars.

(Fig. 3), it is likely that the changes described above are not simply a broad effect of the disease, but actually an effect of PD subtype. Besides, studies performing whole-brain analyses (Hu et al., 2017; Hu et al., 2015; Zhang et al., 2015) did not even evidence consistent changes in the motor system.

4.2.1. Dysfunctional vs compensatory mechanisms

For a substantial part of the observations, resting activity and intrinsic functional connectivity results may appear contradictory between AR > HC and HC > AR contrasts (Fig. 2) or AR > TD and TD > AR contrasts (Fig. 3). However, these patterns are not necessarily in contradiction. Indeed, while decreased activity/functional connectivity is usually interpreted as a direct effect of the disease or condition, increased activity/functional connectivity is most often interpreted as the result of compensatory mechanisms by which BG-thalamo-cortical loop dysfunctions are overcome by the recruitment of other pathways (Hou et al., 2017). According to this debatable interpretation (Blesa et al., 2017), compensatory mechanisms would involve a widely distributed and poorly reproducible network (Fig. 2), including notably the cerebellum, the mPFC and the midFG (two

occurrences each).

4.2.2. Treatment status

It is tempting to speculate that part of the inconsistencies mentioned above might be accounted for essentially by the treatment status: three studies tested patients OFF medication (Hu et al., 2015, 2017; Zhang et al., 2015), one study tested drug naïve de novo patients (Hou et al., 2017), one tested patients OFF medication or drug naïve (Guan et al., 2017), and two studies tested patients ON medication (Hensel et al., 2018; Karunanayaka et al., 2016). This is a substantial issue. Indeed, on the one hand DA medication is known to modulate the metabolism of the functional circuits subserving akinesia and rigidity (globus pallidus, thalamus, premotor cortex -PMC-, SMA and parietal association regions; Holtbernd and Eidelberg, 2012), and to improve the motor functions that partly contribute to reduce movement initiation latency (e.g., Favre et al., 2013). But on the other hand DA medication is also known for not reinstating a full normal pattern of movement initiation (Favre et al., 2013). The recent neuroimaging studies reviewed here testing AR patients ON medication (Hensel et al., 2018; Karunanayaka et al., 2016) report that DA medication does not reinstate a normal

pattern of brain activity and functional connectivity either (Figs. 2, 3). In other words, it is likely that there are other, non-DA dysfunctional neural mechanisms that contribute to akinesia (Albares et al., 2015b; Spay et al., 2018). Much more pharmacological neuroimaging investigations of resting states modulations building on the papers identified here are required to clarify this point, in particular studies testing directly the effect of DA medication.

#### 4.2.3. Conclusion

The variability observed in the methods and in the results of resting state studies does not allow for any overall conclusions regarding the neural bases of akinesia. However, various clues are reported that raise the idea that abnormalities outside the motor network might be related to executive deficits in akinetic PD patients. Indeed, results pinpoint brain regions which are known to support executive control of movement initiation, including notably the PCC/Precuneus (Chikazoe et al., 2009; Criaud et al., 2017), the IPC (Criaud et al., 2017; Jaffard et al., 2008; Zandbelt et al., 2013), the insula (Chikazoe et al., 2009; Criaud et al., 2017), the mPFC (Jaffard et al., 2008) and the iFG (Aron, 2011; Aron et al., 2003; Jahfari et al., 2012; Zandbelt et al., 2013). Interestingly, most of these regions are also known to involve non-DA systems when engaged in these functions (Borchert et al., 2016; Buddhala et al., 2015; Chamberlain et al., 2009; Fox, 2013; Spay et al., 2018; Ye et al., 2015). This tentative explanation is consistent with previous studies on the neural bases of executive deficits in PD (Huang et al., 2007; Mattis et al., 2016; Pereira et al., 2014; van Eimeren et al., 2009).

### 4.3. Task-related and event-related brain activity changes

#### 4.3.1. Dysfunctional mechanisms (akinesia-related hypoactivation)

Most experiments that recorded task-based modulations (eight out of twelve) searched for motor alterations, based on the common belief that akinesia is mainly a motor deficit (Buhmann et al., 2003; Cerasa et al., 2006; Haslinger et al., 2001; Rascol et al., 1994, 1997; Sabatini et al., 2000; Samuel et al., 2001; Yu et al., 2007). According to the BG-thalamocortical circuit model, DA depletion in the nigrostriatal system induces hypoactivation in the motor and premotor circuits in akinetic PD patients compared to healthy controls, including the SMA, the lateral PMC and M1 (Alexander et al., 1990; Holtbernd and Eidelberg, 2012). This hypothesis has been tested in the eight experiments mentioned above by means of the HC > AR contrast, akinesia being simply associated with the absence of tremor. Results are quite inconsistent for most of the brain regions showing task-based and event-related brain activity changes (Fig. 4). Motor alterations are found in a widely distributed, poorly reproducible network including the motor/premotor cortices and associated subcortical areas (thalamus, BG), but also in the cerebellum, in different prefrontal areas (dlPFC, iFG) as well as in the ACC and in the insula. In these experiments, akinesia-related motor dysfunctions (hypoactivation in AR patients) are only consistent for the SMA across 6 experiments (Buhmann et al., 2003; Haslinger et al., 2001; Rascol et al., 1994, 1997; Sabatini et al., 2000), and for the dlPFC across half of the whole brain experiments (Sabatini et al., 2000; Samuel et al., 2001; Yu et al., 2007). Again, despite inconsistencies about the extent of the observed modulations, studies using motor tasks to probe task-related and event-related brain activity changes in AR patients suggest that akinesia is not a purely motor dysfunction.

Only two experiments (out of twelve) considered the hypothesis that akinesia includes both motor and executive components. By focusing on the preparatory phase of movement (Criaud et al., 2016b; Samuel et al., 2001), they revealed akinesia-related alterations in the motor system (including the caudate nucleus and the lateral PMC), but also in other brain regions embracing the precuneus, the thalamus, the ACC and the dlPFC. Importantly, these regions are known to be part of an executive network involved in the inhibitory control of movement initiation (Blasi et al., 2006; Chikazoe et al., 2009; Jaffard et al., 2008; van Belle et al., 2014; Zandbelt et al., 2013). More precisely, Criaud and

collaborators (2016b) proposed that akinesia in PD is associated with abnormal proactive inhibitory control, an executive function which supports the gating of movement triggering to avoid inappropriate or premature responses in uncertain contexts (Jahanshahi et al., 2015a; 2015b). According to this view, akinesia could be considered as a de-automation symptom resulting partly from an impairment of the ability to switch from controlled to automatic action (Albares et al., 2015b; Favre et al., 2013; Hikosaka and Isoda, 2010; Isoda and Hikosaka, 2007; Jahanshahi et al., 1995; Jahanshahi et al., 2015a; 2015b; Siegert et al., 2002). However, this hypothesis has been overlooked so far in neuroimaging studies of PD akinesia and requires further evidence.

An important part of the observed variability may be due to differences in the nature of the behavioral tasks used in the different studies. In particular, the differences observed between studies based on simple motor tasks (self-paced or internally triggered) and stimulus-response tasks (externally triggered) might be enlightening (Table 1). Simple motor tasks seem to induce effects confined to the SMA (hypoactivation in AR patients), the cerebellum and the primary sensorimotor cortex (hyperactivation in AR patients), or no changes at all (Cerasa et al., 2006; Lewis et al., 2011; Rascol et al., 1994, 1997). Conversely, stimulus-response tasks (externally triggered) involve a variety of brain regions outside the motor network (Cerasa et al., 2006; Criaud et al., 2016b; Samuel et al., 2001; Yu et al., 2007). Unfortunately, there is a strong bias, as identified in the quality check section (Supplementary Table 2). Studies using a simple motor task also applied ROI analyses centered on the motor system, making it impossible to conclude that only the more complex stimulus-response tasks involve dysfunctions outside the motor network.

It is noteworthy that most of the reviewed studies (Buhmann et al., 2003; Cerasa et al., 2006; Sabatini et al., 2000; Samuel et al., 2001; Yu et al., 2007) have been performed in the OFF-medication state. Only three studies have compared ON and OFF states but reported discordant results. Two of these studies (Rascol et al., 1994, 1997) suggest that DA restores normal SMA activity patterns in patients ON medication state with respect to OFF medication state and to healthy control subjects. The third one conversely suggests that residual deficits in M1 activity can be observed in the ON medication state (Haslinger et al., 2001). This, again, raises the issue of the purely motor and DA origins of akinesia. On the one hand, if one considers as Rascol et al. (1994, 1997) that DA restores normal activity in motor circuits, then the fact that akinesia is unsuccessfully alleviated by standard pharmacological treatments at a behavioral level (Favre et al., 2013; Fox, 2013; Jahanshahi et al., 1992; Schubert et al., 2002) strongly suggests a non-motor origin. On the other hand, if one considers as Haslinger et al. (2001) that the functional cortical deafferentation of motor regions associated with decreased input from the subcortical motor loop (see also Escola et al., 2003) is only partly reversible by levodopa treatment, then it is likely that non-DA dysfunctions are involved in akinesia. Unfortunately, all of these studies have used ROI approaches and focused on motor cortical dysfunctions. Future studies combining pharmacological approaches, whole brain analyses, and behavioral designs disentangling executive and motor functions might help addressing this open issue.

#### 4.3.2. Compensatory mechanisms (akinesia-related hyperactivation)

Many studies which recorded task-based activations (eight out of twelve) also looked for hyperactivation of brain regions in akinetic PD patients compared to healthy subjects (contrast AR > HC), assuming that BG-thalamo-cortical loops dysfunctions are compensated for by the recruitment of parallel pathways (Sabatini et al., 2000). Again, some results are poorly reproducible (Fig. 4), like those pinpointing the motor cortex (M1, lateral PMC), the prefrontal cortex (iFC, dlPFC), the lateral and medial parietal cortex (iPC and precuneus), the visual cortex (lingual gyrus), the ACC and the insula. Yet, highest reproducibility is observed for the cerebellum (4 occurrences out of six studies performing cerebellar recordings: Cerasa et al., 2006; Lewis et al., 2011;

Rascol et al., 1997; Sabatini et al., 2000; Yu et al., 2007). These data are consistent with more general observations about compensatory mechanisms (Blesa et al., 2017). They are also consistent with the hyperconnectivity of the cerebellum observed at rest (Hou et al., 2017; Hu et al., 2017; Fig. 2). However, as highlighted in the recent review from Blesa et al. (2017), the substantiation of putative compensatory mechanisms remains weak. This might especially be the case for motor dysfunctions. For instance, Ballanger et al. (2009) observed that PD patients are able to improve dramatically motor performance, including movement initiation, by recruiting the contralateral cerebellum in externally driven urgent situations. However, by testing healthy controls, the authors also demonstrated that this form of compensatory mechanism, so-called paradoxical kineses, are not a hallmark of PD but a general property of the motor system (Ballanger et al., 2006). In other words, how specific to the disease and how specific to akinesia these mechanisms are is still highly disputable.

#### 4.3.3. Conclusion

Although task-related and event-related brain activity changes are not highly reproducible across studies, results suggest that abnormalities within but also outside the motor pathways might induce motor and executive deficits that could contribute jointly to akinesia in PD patients.

## 5. Limitations

The reviewed studies represent a useful step towards refining the concepts and methods classically used to assess akinesia. However, the following limitations should be kept in mind as findings are interpreted.

Despite the scale of the problem and the total number of papers on the general topic of akinesia, few studies reached the criteria for being included (Fig. 1). This prevented us from performing any quantitative meta-analysis. The conclusions of this systematic analysis cannot rely on the use of statistical techniques for summarizing the results of all available studies into a single estimate. This weakens interpretation when common denominators are found between studies (i.e., movement-related hypoactivation in the motor cortex of AR patients). However, meta-analytical statistical methods would have ignored the brain activity which is poorly reproducible in terms of location, but which makes sense regarding the frequency of observation of the phenomenon (e.g., functional changes in different parts of the executive system). Often, variability in the exact location of brain functional differences is likely to be accounted for by the variability of the nature of the modulations that were assessed (e.g., intensity of intrinsic activity vs. functional connectivity density vs. ReHo vs. seed-based functional connectivity for resting state studies).

Due to the level of inaccuracy and confusion related to the terminology of akinesia, there are strong potential confounds in the imaging results. Most studies are referring to the AR subtype of PD, defined by paucity and slowness of movement accompanied by muscle stiffness. However, the set of dysfunctions which are specific of this subtype form a syndrome (Donaldson et al., 2012) that includes more disorders than the sole dysfunction of movement initiation mechanisms. Yet, there is no mean to disentangle these confounds in the reviewed studies. Accordingly, the results pinpoint neural correlates rather than comprehensive neural bases of akinesia, and the causal links between brain dysfunctions and clinical symptoms inferred from these studies remain speculative.

## 6. Open issues and future directions

Given the inconsistency of concepts and results, tentative conclusions on the neural bases of akinesia would be somewhat hazardous. However, the clues provided by the neural correlates analyzed in this review raise major issues for future studies.

### 6.1. Characteristics of the clinical group: how to define akinesia?

A consensus on the neurofunctional bases of akinesia requires a unified use of terminology for this specific disturbance of voluntary movement, but there are still obstacles to overcome. First, the term akinesia is used at different conceptual levels: as a classifying term to identify subtypes of movement disorder like most of the studies reviewed here, and as a descriptive term to depict particular symptoms. Second, from a clinical point of view there is a tendency to group clinical signs, and consequently to use unique terminology whereas these signs represent clusters of symptoms (Schilder et al., 2017; Pellegrino and Thomasma, 1981). From an epistemological point of view, this contributes to form a substantial obstacle (Smith, 2016) in clinical research. This is often the case, for instance, when direct links between DA depletion and movement disorders are assessed. A clear definition of akinesia would help targeting more precisely the multiple mechanisms that are potentially dysfunctional in this multifaceted disease. It would help developing more sophisticated models for assessing brain-behavior relationships in PD neuroimaging studies.

### 6.2. Neuroimaging methods: How to reveal akinesia?

Appropriate behavioral designs and markers are required to isolate the neural mechanisms that play a direct role in movement initiation, and to measure their efficiency. Using advanced psychological models and associated designs- of movement preparation and executive control should help making predictions about the nature, the dynamics or the localization of the brain signals that are most likely to inform about the neural correlates of akinesia (e.g., Criaud et al., 2017). This is crucial for setting-up adapted event-related neuroimaging designs. In particular since the present review has pinpointed: (1) the underuse of this type of approach, and (2) the possibility that akinesia does not only rely on motor dysfunctions. For instance, assessing the executive mechanisms that gate movement initiation in uncertain contexts in order to avoid premature or erroneous responding – a function which might cause akinesia when disturbed (Jahanshahi et al., 2015a, 2015b)- requires: (1) the manipulation of the relative probability of the stimuli in the experimental design, and (2) the analysis of the brain activity occurring before a movement is initiated (e.g., Criaud et al., 2016b). Additionally, specific behavioral markers like reaction time or omission rate can be used as covariates in functional data processing in order to select the brain modulations that play a direct role in behavioral changes (e.g., Albares et al., 2015a; Albares et al., 2014). The same rationale applies to standard clinical scores, which must also be included in data processing models in order to relate the clinical severity of PD symptoms to behavioral manifestations and specific brain activity changes. Only then should the large and inconsistent inventory of neural correlates of akinesia be reduced to a shorter list of reliable candidates forming the neural bases of akinetic symptoms.

Finally, the hypothesis of an executive origin of akinesia raised in the present review calls for using complementary neuroimaging tools. Indeed, executive control strongly relies on inhibitory functions (Heyder et al., 2004; Hofmann et al., 2012; Miyake et al., 2000; Norman and Shallice, 1986). However, no single neuroimaging method based on blood flow measurements can disentangle the time-course of concurrent excitatory and inhibitory mechanisms (Logothetis, 2008). Disentangling the executive and motor dysfunctions of akinetic symptoms may require the use of other techniques such as MEG and EEG, which offer the possibility to identify inhibitory activity through spectral analyses (Albares et al., 2015a). Since recent developments now offer optimal solutions for separating and localizing the brain electrical sources of activity that are mixed on the scalp (e.g., Lio and Boulinguez, 2013, 2018), EEG might represent a promising alternative to the standard neuroimaging methods reviewed here, at least for identifying cortical dysfunctions.



### 6.3. Pharmacological neuroimaging: How to reveal the neurochemical bases of akinesia?

It is clear that other neurotransmitters than DA play a role in the pathophysiology of PD (Bohnen et al., 2018; Braak et al., 2004; Delaville et al., 2012; Faggiani and Benazzouz, 2017; Fornai et al., 2007; Pahapill and Lozano, 2000; Politis et al., 2014). Yet, non-DA therapeutic strategies are still difficult to develop (Fox, 2013; Freitas and Fox, 2016). It is likely that the lack of neurocognitive footing in clinical neuroimaging studies does not help for distinguishing the neural mechanisms that rely on DA neurotransmission from those that rely on other systems. We especially think about the noradrenergic system, which might be involved in the functioning of BG-thalamocortical loops and executive functions (Albares et al., 2015b; Chamberlain et al., 2009; Faggiani and Benazzouz, 2017; Spay et al., 2018), but also about the serotonergic (Carli and Invernizzi, 2014; Miguelez et al., 2014) and the cholinergic (Bohnen and Albin, 2011) systems. Here, we suggest that future pharmacological neuroimaging designs, whatever goal they are intended for –e.g., testing dose-dependent effects in DA-medicated patients or non-DA pharmacological agents in healthy subjects–, should comply with the general recommendations described above to reveal the neurochemical bases of movement initiation and related disorders. Given the multidimensional complexity of movement disorders in general, and akinesia in particular, future neuroimaging studies should not settle on linking vague clinical subtypes and/or pharmacological challenges to broad and un-specific brain activity modulations. Rather, future studies should target specific neural mechanisms by means of adapted empirical designs and behavioral markers. More sophisticated behavioral tasks (e.g., Criaud et al., 2016b, Criaud et al., 2017) combined with the use of movement analysis technologies (e.g., Dai et al., 2015; Salimi-Badr et al., 2017; Varriale et al., 2018) to detect and quantitate akinesia might prove useful to better isolate, and then image, the processes that are directly linked to movement initiation disorders. With these conditions in place, future studies will get more chances to extricate the complex interactions that form the neural and neurochemical bases of akinesia.

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### Supplementary data

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## SUPPLEMENTARY FILE 1

Spay C, Meyer G, Welter ML, Lau B, Boulinguez P, Ballanger B. Functional imaging correlates of akinesia in Parkinson's disease: still open issues. *Neuroimage: Clinical*.

**Supplementary Table 1: Patient Demographics and Characteristics.**

Studies (1 <sup>st</sup> author – year)	Age (Mean ± SD)	Disease duration (Mean ± SD)	Sex (M/F)	Cognitive status (Criterion)	UPDRS (OFF)
Hu, 2017	65.1 ± 10.1	6.7 ± 5.1	9/16	Non-demented (MMSE > 28, MoCA > 26)	35.8 ± 14.0
Zhang, 2015	63.4 ± 9.5	4.2 ± 4.1	16/11	Non-demented (MMSE > 28, MoCA > 26)	19.9 ± 6.7
Hou, 2017	54.8 ± 8.3	2.5 ± 2.4	11/10	(MoCA = 25.6 ± 3.3)	20.0 ± 9.3
Hensel, 2018	61.6 ± 10.2	6.5 ± 5.5	37/23	(MMSE = 28.6 ± 1.2 or MDRS = 136.8 ± 5.8)	NR <sup>2</sup>
Guan, 2017	56.0 ± 9.9	4.4 ± 4.0	23/26	Non-demented <sup>1</sup> (MMSE = 27.6 ± 2.2)	28.8 ± 14.8
Hu, 2015	62.3 ± 8.7	5.0 ± 5.2	18/11	Non-demented (MMSE > 26)	20.8 ± 8.8
Karunanayaka, 2016	59.1 ± 7.4	3.7 ± 4.6	9/8	Non-demented (MMSE > 26)	20.8 ± 12.9
Criaud, 2016	56.2 ± 8.9	6.1 ± 2.3	8/4	Non-demented (MDRS > 130)	12.7 ± 4.8
Haslinger, 2001	60.8 ± 7.7	1.8 ± 1.3	7/1	NR	15.8 ± 6.3
Buhmann, 2003	54 ± 12	13 ± 6 months	7/1	NR	NR
Sabatini, 2000	61 ± 8	5 ± 2	4/2	NR	16 ± 4
Ceresa, 2006	64.2 ± 13.6	7.2 ± 3.5	5/5	(MMSE = 28.4 ± 1.6)	27.5 ± 8.8
Yu, 2007	59.4 ± 8.4	5.9 ± 2.6	3/5	Non-demented (MMSE > 27)	31.1 ± 10.8
Lewis, 2011	51.3 ± 10.2	16.0 ± 23.8 months	NR	Non-demented (NR)	9.5 ± 3.9
Rascol, 1994	60 ± 8 / 63 ± 6 <sup>2</sup>	6 ± 4 / 7 ± 6 <sup>2</sup>	17/9	Non-demented (NR)	23 ± 10 / 25 ± 7 <sup>3</sup>
Rascol, 1997	61 ± 3 / 60 ± 2 <sup>2</sup>	6 ± 1 / 8 ± 1 <sup>2</sup>	NR	Non-demented (NR)	26 ± 4 / 22 ± 3 <sup>3</sup>
Samuel, 2001	62 ± 6	10 ± 8	NR	Non-demented (MMSE > 28)	24 ± 13

MDRS: Mattis dementia rating scale – MMSE: Mini Mental State Examination – MoCA: Montreal Cognitive Assessment – NR – Non-Reported – <sup>1</sup>Patients with cognitive impairment were excluded according to MMSE and the criteria suitable for Chinese population – <sup>2</sup>UPDRS-III ON medication: 20.0 ± 13.2 – <sup>3</sup>Non-treated group / ON medication group

## SUPPLEMENTARY FILE 2

Spay C, Meyer G, Welter ML, Lau B, Boulinguez P, Ballanger B. Functional imaging correlates of akinesia in Parkinson's disease: still open issues. *Neuroimage: Clinical*.

**Supplementary Table 2:** Main sources of potential bias identified in the reviewed studies.

Study	Definition of akinesia	Assessment of akinesia	Potential demographic-related bias	Sample size	Potential data processing-related bias	Statistics
#1 Hu et al., 2017	Unclear	UPDRS Ratio derived from mean AR and tremor score based on UPDRS-III				
#2 Zhang et al., 2015	Unclear	UPDRS Ratio derived from mean AR and tremor score based on UPDRS-III				
#3 Hou et al., 2017	Unclear	UPDRS Ratio derived from tremor and non tremor score based on UPDRS-III			Seeds and ROI (DMN)	
#4 Hensel et al., 2018	UPDRS UPDRS-III it 31	Potential confounds between the effects of disease and akinesia	No exclusion criteria regarding dementia		Potential omission of effects outside the regions of interest Seeds and ROIs (seed-specific networks)	Potential omission of effects outside the regions of interest
		Potential confounds between akinesia,	Potential confound with the effect of dementia			Potential omission of effects outside the regions of interest

	<i>bradykinesia and hypokinesia</i>				
#5 Guan et al., 2017	Unclear UPDRS Ratio derived from 2 tremor and 7 AR items	ROI (Basal ganglia network)			<i>Potential omission of effects outside the regions of interest</i>
#6 Hu et al., 2015	Unclear UPDRS Ratio derived from tremor and PIGD items				
#7 Karunanayaka et al., 2016	Unclear UPDRS Ratio derived from 9 tremor and 14 AR items	ROI (DMN)	17 AR / 15 TD / 24 HC		
#8 Criaud et al., 2016	<i>Potential confounds between the effects of disease and akinesia</i>	<i>Potential omission of effects outside the regions of interest</i>	<i>Insufficient sampling</i> 12 PD / 15 HC	<i>Potential omission of effects outside the regions of interest</i> ROIs (Proactive inhibitory network)	
#9 Haslinger et al., 2001	Unclear Unclear	No statistical testing of between groups match. No data on dementia	8 AR / 8HC	<i>Insufficient sampling</i> ROI (M1, parietal and frontal motor association cortex)	No statistical correction for multiple comparisons
#10 Buhmann et al., 2003	Unclear Unclear	<i>Possible confounds with the effects of age and dementia</i> No data on dementia	8 AR / 10 HC	<i>Insufficient sampling</i> <i>Potential omission of effects outside the regions of interest</i>	<i>Possible source of spurious associations</i> No statistical correction for multiple comparisons
#11 Sabatini et al.,	Unclear Unclear	<i>Possible confound with the effect of dementia</i> No statistical testing of between groups match.	6 AR / 6 HC	<i>Insufficient sampling</i> <i>Potential omission of effects outside the regions of interest</i>	<i>Possible source of spurious associations</i> No statistical correction for multiple comparisons

2000	No data on dementia						
#12 Ceresa et al., 2006	Potential confounds between the effects of disease and akinesia	Possible confound with the effects of dementia and age	Insufficient sampling	possible source of spurious associations	possible source of spurious associations	possible source of spurious associations	
	Unclear	No exclusion criteria regarding dementia	10 AR / 11 HC				
#13 Yu et al., 2007	Potential confounds between the effects of disease and akinesia	Possible confound with the effect of dementia	Insufficient sampling				
	Unclear		8 AR / 7 HC				
#14 Lewis et al., 2011	Potential confounds between the effects of disease and akinesia		Insufficient sampling				
	Unclear	UPDRS Ratio based on 9 tremor and 12 AR items	8 AR / 9 TD / 14 HC	ROI (CTC/STC circuits)	No statistical correction for multiple comparisons	No statistical correction for multiple comparisons	
#15 Rascol et al., 1994	Potential confounds between the effects of disease and akinesia		Insufficient sampling	Potential omission of effects outside the regions of interest	Possible source of spurious associations	Possible source of spurious associations	
	Unclear	?	15 ON / 11 OFF / 15 HC	No motion correction ROI (SMA, SIM1)	No statistical correction for multiple comparisons	No statistical correction for multiple comparisons	
#16 Rascol et al., 1997	Potential confounds between the effects of disease and akinesia	"AR syndrome without tremor"	Insufficient sampling	Possible source of spurious associations	Possible source of spurious associations	Possible source of spurious associations	
	Unclear			Potential omission of effects outside the regions of interest			
#17 Samuel et al., 2001	Potential confounds between the effects of disease and akinesia	Groups unmatched for age and sex	Insufficient sampling	Possible source of spurious associations	Possible source of spurious associations	Possible source of spurious associations	
	Unclear		6 AR / 6 HC	Potential omission of effects outside the regions of interest	No motion correction ROI (SMA, SIM1)	No statistical correction for multiple comparisons	
#17 Samuel et al., 2001	Potential confounds between the effects of disease and akinesia	Possible confound with the effect of age	Insufficient sampling	Possible source of spurious associations	Possible source of spurious associations	Possible source of spurious associations	
	Unclear			Potential omission of effects outside the regions of interest			

AR: akineto-rigid subtype. HC: healthy controls. TD: tremor-dominant subtype.

### c. Synthèse & Perspectives

Notre revue de la littérature révèle l'existence de 16 études qui se sont intéressées en imagerie à caractériser une population de patients akinétiques vs. un groupe de sujets contrôles. Plusieurs résultats émergent de cette revue :

1/ L'absence de terminologie claire concernant les dysfonctionnements du mouvement dans la maladie entraîne des confusions fortes sur les bases neurofonctionnelles de ce symptôme. En effet, Schilder et al (2017) ont révélé l'absence de distinction claire entre akinésie, bradykinésie et hypokinésie dans la littérature. De même, 15 études sur 16 se sont intéressées à des patients akinéto-rigides, sans tester spécifiquement l'akinésie au niveau clinique et comportemental. Pourtant, les sous-types de patients akinéto-rigides et tremblements-dominant se réfèrent à une dichotomie clinique selon les signes moteurs prédominants observés chez les patients. Il convient de tester comportementalement l'akinésie à proprement parlé chez ces patients si l'on veut prétendre révéler les bases neurofonctionnelles de ce symptôme.

2/ L'hétérogénéité des méthodes utilisées empêche la réalisation d'une méta-analyse et participe à la difficulté de compréhension de ce trouble. En effet, 6 études se sont intéressées aux corrélats de l'akinésie à l'état de repos, permettant uniquement de révéler la fonctionnalité des réseaux neuronaux chez les patients akinéto-rigides (Hou et al., 2017; Hu et al., 2017; Karunanayaka et al., 2016; Zhang et al., 2015). Seules 2 études ont utilisé une tâche motrice avec un protocole lié aux événements qui permettent d'accéder spécifiquement aux processus neuropsychologiques impliqués (Criaud et al., 2016; Haslinger et al., 2001). De même, la moitié des études ont réalisé des analyses en régions d'intérêt, ciblant le circuit moteur (boucles ganglio-thalamo-corticales motrices) ce qui restreint les observations à l'hypothèse motrice dominante. Enfin, seules 2 études (Criaud et al., 2016; Samuel et al., 2001) ont utilisé une



méthode adaptée pour démêler les hypothèses à la fois motrice et exécutive sur l'origine de l'akinésie.

3/ Lorsque l'on aborde plus concrètement les bases neurofonctionnelles de l'akinésie, ces deux freins terminologique et méthodologique imposent un constat : il n'existe à ce jour pas de consensus clair sur l'origine de ce symptôme. En effet, les études sur la fonctionnalité des réseaux neuronaux à l'état de repos échouent à révéler des régions cérébrales consistantes entre les études. De même, les études ayant utilisé une tâche motrice pour révéler les altérations motrices relatives à l'akinésie révèlent un large réseau, qui s'avère être peu reproductible entre les études. L'hypothèse d'une origine motrice de l'akinésie a été étudiée par la plupart des études (n=8) et révèle que seule l'hypoactivation de l'aire motrice supplémentaire (AMS) et celle du cortex préfrontal dorso-latéral (dlPFC) sont en partie cohérentes pour la moitié des études. Alors que l'AMS joue un rôle clé dans les boucles ganglio-thalamo-corticales, le dysfonctionnement du cortex préfrontal remet en cause l'hypothèse d'une origine purement motrice de l'akinésie. En effet, son rôle dans la préparation et le contrôle exécutif de l'action ne peut être ignoré (Jahanshahi et al., 1995; Jenkins et al., 2000). Ces études sont également en faveur d'une hyperactivation du cervelet chez les patients akinétiques, interprétée comme un mécanisme de compensation mis en place dans la physiopathologie de la maladie pour faire face à la dégénérescence des voies motrices dopaminergiques. Une hyperactivité du réseau par défaut (ou Default Mode Network (DMN)) a également été révélée à l'état de repos chez les patients akinéto-rigides et associée à des mécanismes de compensation (Hu et al., 2017). Ce dysfonctionnement du DMN a également été associé à un déficit exécutif des patients parkinsoniens (van Eimeren et al., 2009b). Des arguments en faveur d'une hypothèse exécutive ont également été proposés par 2 études (Criaud et al., 2016; Samuel et al., 2001) révélant une altération de certaines régions clés du réseau de l'inhibition de réponse (Blasi et al., 2006; Jaffard et al., 2008; van Belle et al., 2014; Zandbelt et al., 2013).

**Alors que l'akinésie est un symptôme cardinal de la maladie de Parkinson, notre analyse systématique révèle que les processus neuropsychologiques et les bases neuro-fonctionnelles qui sous-tendent ce trouble sont à ce jour encore mal compris. Alors que l'hypothèse d'un symptôme moteur et d'origine dopaminergique semble être établie, un déficit en partie exécutif semble également jouer un rôle dans le développement de l'akinésie parkinsonienne. L'entremise du contrôle exécutif de l'action pourrait permettre de revisiter ce trouble. De nombreuses questions restent néanmoins en suspens à ce jour concernant les bases neurochimiques de ce trouble. Cette hypothèse nécessite donc d'être plus largement explorée.**

## 2. ORIGINE DES TROUBLES DU CONTROLE DES IMPULSIONS

### a. Bases neuropsychologiques de l'impulsivité

L'impulsivité est classiquement définie comme une large variété d'actions qui sont réalisées de façon prématurée, risquée, inappropriée à la situation ou sans considération des conséquences négatives (Evenden, 1999). D'un point de vue clinique, l'impulsivité peut même conduire à des TCI (Isaias et al., 2008), pouvant avoir des conséquences dramatiques sur la qualité de vie des patients (Dodd et al., 2005). Pourtant, leurs corrélats neurologiques sont à ce jour encore à l'étude (*cf. Chapitre 1*). En effet, l'impulsivité est multi-facette et regroupe de nombreux processus cognitifs. A ce jour, les bases neuropsychologiques de l'impulsivité, à l'étude chez le sujet sain (Bari & Robbins, 2013; Bechara et al., 2000), ont permis d'ouvrir la voie de l'identification des mécanismes psychologiques sous-tendant différentes pathologies neuropsychiatriques (Dalley & Robbins, 2017).

D'un point de vue neuropsychologique, on peut distinguer l'impulsivité cognitive (i.e., choix impulsifs) et l'impulsivité motrice (i.e., actions impulsives) (Bari & Robbins, 2013;

Bechara et al., 2000; Dalley & Robbins, 2017). L'impulsivité motrice fait référence à un dysfonctionnement des mécanismes d'inhibition de réponse et regroupe des processus moteurs et exécutifs. L'impulsivité cognitive est complexe (Harnishfeger, 1995) et regroupe des dysfonctionnements de processus divers menant à la prise de décision. Alors que l'impulsivité cognitive a été largement investiguée (Voon et al., 2017a), la plupart des études sur l'impulsivité motrice ont échoué à mettre en évidence un déficit chez les patients parkinsoniens avec TCI (Bentivoglio et al., 2013; Claassen et al., 2015; Leroi et al., 2013; Pineau et al., 2016; Ricciardi et al., 2017; Rossi et al., 2010; Yoo et al., 2015). Brevers et al. (2012) ont pourtant montré qu'un déficit de l'impulsivité de choix caractérisait l'ensemble des joueurs pathologiques, alors que des dysfonctionnements de l'impulsivité d'action expliqueraient la sévérité de la maladie.

Face à l'hétérogénéité des TCI, il a alors été proposé que l'impulsivité chez le patient parkinsonien ne soit pas à l'origine d'un seul déficit du contrôle inhibiteur mais qu'il existerait plutôt de multiples formes d'impulsivité avec des processus psychologiques, des bases anatomo-fonctionnelles et des bases pharmacologiques distinctes (Nombela et al., 2014).

#### b. Bases neuro-fonctionnelles de l'impulsivité

Afin d'éclairer le débat sur l'origine des TCI dans la maladie de Parkinson, nous avons choisi de nous intéresser aux bases neuro-fonctionnelles de ces symptômes. Pour cela, nous avons procédé à une revue systématique de la littérature utilisant la neuroimagerie (TEP rCBF ou IRMf) pour révéler les mécanismes neuropathologiques qui sous-tendent les TCI. Notre critère d'inclusion principal portait sur l'existence d'un contraste entre deux populations de patients parkinsoniens avec (TCI+) et sans (TCI-) TCI.

**Article 2** : Meyer\*, G., Spay\*, C., Ballanger, B., Sescousse, G., Boulinguez, P. (under revision). Functional imaging studies of Impulse Control Disorders in Parkinson's disease need a stronger neurocognitive footing. *Neuroscience and Biobehavioral Review*. (\*=co-first author)



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## Review article

## Functional imaging studies of Impulse Control Disorders in Parkinson's disease need a stronger neurocognitive footing

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## ABSTRACT

Impulse control disorders (ICDs) in Parkinson's disease (PD) are associated with dopaminergic dysfunction and treatment, but have no satisfactory therapeutic solution. While studies assessing the neurofunctional bases of ICDs are important for advancing our understanding and management of ICDs, they remain sparse and inconsistent. Based on a systematic analysis of the neuroimaging literature, the present review pinpoints various abnormalities beyond the mesocorticolimbic circuit that supports reward processing, suggesting possible dysfunction at the sensorimotor, executive and affective levels. We advocate that: 1) Future studies should use more sophisticated psychological models and behavioral designs that take into account the potentially multifaceted aspect of ICDs; this would allow a more accurate assessment of the underlying neurocognitive processes, which are not all dependent on the dopaminergic system. 2) Future neuroimaging studies should rely more strongly on task-based, event-related analyses to disentangle the various mechanisms that can be dysfunctional in ICDs. We believe these guidelines constitute a prerequisite towards distinguishing causes, correlates and individual susceptibility factors of PD patients with ICDs.

## 1. Introduction

Impulse control disorders (ICDs) include pathological gambling, hypersexuality, compulsive eating and compulsive shopping (Cilia and van Eimeren, 2011; Weintraub et al., 2015). ICDs are common in Parkinson's disease (PD) (Antonini et al., 2017; Weintraub et al., 2010) and affect from 13.6% to 46% of patients (Corvol et al., 2018; Weintraub et al., 2010), with potentially dramatic consequences such as huge financial losses or disintegration of family relationships (Dodd et al., 2005). Recent reviews focusing on the neurochemical and pharmacological underpinnings of ICDs have made it abundantly clear that they are associated with dopaminergic dysfunction and treatment (Aracil-Bolaños and Strafella, 2016; Cilia and van Eimeren, 2011; Corvol et al., 2018; Jiménez-Urbietta et al., 2015; Marques et al., 2018; Probst and van Eimeren, 2013; Voon et al., 2017; Vriend, 2018; Weintraub et al., 2015). As a consequence, the management of ICDs involves mainly

discontinuing or decreasing dopamine agonists, with the risk of worsening motor symptoms or developing dopamine agonist withdrawal syndrome (Connolly and Fox, 2014; Samuel et al., 2015). This lack of satisfying therapeutic strategy for handling ICDs calls for a better understanding of the underlying mechanisms (Antonelli et al., 2011; Cilia and van Eimeren, 2011).

## 1.1. The major contribution of molecular imaging studies

ICDs have many similarities with substance abuse and are increasingly being conceptualized as behavioral addictions (Aracil-Bolaños and Strafella, 2016; Leeman and Potenza, 2012; Ray and Strafella, 2013). Notably, in the DSM-V (<http://www.dsm5.org>) gambling disorder has been included in "substance-related and addictive disorders". This change reflects the similarity in clinical symptoms, as well as the fact that gambling activates similar brain reward-related regions as of

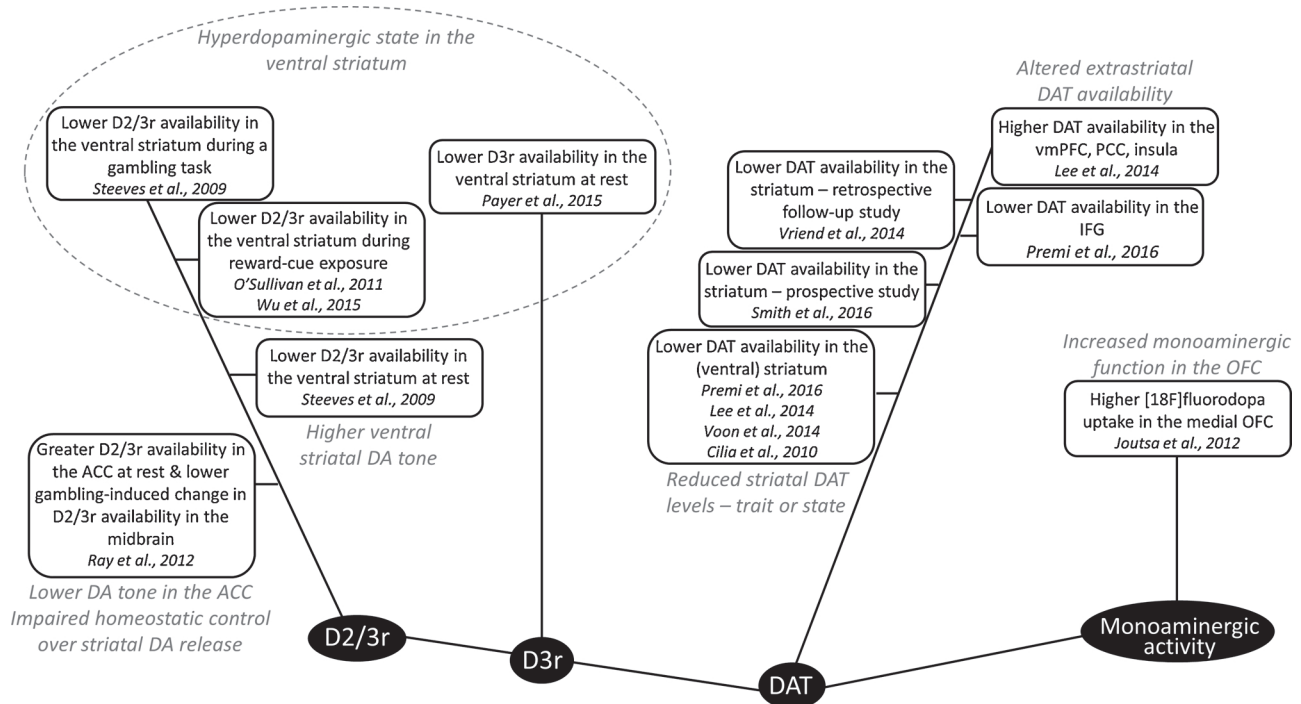
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## DOPAMINERGIC ALTERATIONS IN PD-ICDS

**Fig. 1.** Molecular imaging findings in PD-ICDS. This literature provides important insights on PD-ICDS etiology by revealing various dopaminergic alterations in ICDs + compared to ICDs- (see Aracil-Bolaños and Strafella, 2016; Vriend, 2018; Weintraub and Claassen, 2017 for extensive reviews). At the postsynaptic level, lower D2/3 dopamine receptor (D2/3r) availability in the ventral striatum was demonstrated using [<sup>11</sup>C]Raclopride during performance of a gambling task (Steeves et al., 2009), exposure to reward-related cues (O'Sullivan et al., 2011; Wu et al., 2015) but also at baseline (Steeves et al., 2009). One study showed lower D3r availability in the ventral striatum in ICDs + using [<sup>11</sup>C]-(+)-PHNO (Payer et al., 2015). These observations are consistent with higher endogenous DA release or higher DA tone in the ventral striatum, i.e., a “hyperdopaminergic state”. Yet, this could also reflect reduced D2/3r density or more pronounced DA degeneration. One study using [<sup>11</sup>C]-FLB-457 found greater D2/3r availability in the anterior cingulate cortex (ACC) in ICDs both at rest and during a gambling task, possibly due to lower DA tone or increased D2/3r expression. There was also a lower gambling-induced change in D2/3r availability in the midbrain, where auto-receptors dominate, suggesting impaired homeostatic control over striatal DA release (Ray et al., 2012). At the presynaptic level, lower DAT availability in the striatum (Premi et al., 2016; Voon et al., 2014), and more specifically in the ventral striatum (Cilia et al., 2010; Lee et al., 2014) is a consistent finding in [<sup>123</sup>I]-FP-CIT SPECT studies. This is often interpreted as reduced striatal DAT levels rather than advanced degeneration, since reduced striatal DAT levels better account for the hyperdopaminergic state observed in [<sup>11</sup>C]Raclopride studies (Dreyer, 2014; Steeves et al., 2009; Voon et al., 2014). These alterations have been shown to predate ICD development in retrospective (Vriend et al., 2014a) and prospective studies (Smith et al., 2016). Abnormalities of extra-striatal DAT availability were also identified in two studies (Lee et al., 2014; Premi et al., 2016) in the ventromedial prefrontal cortex (vmPFC), the posterior cingulate cortex (PCC), the insula and the inferior frontal gyrus (IFG). Finally, one study using [<sup>18</sup>F]Fluorodopa showed higher tracer uptake at rest in the medial orbitofrontal cortex (OFC) in ICDs+ (Joutsa et al., 2012).

drugs of abuse (but see Kardefelt-Winther et al., 2017 for a critical discussion of the conceptualization of behavioral addiction). The evidence underlying this insight on PD-ICDS pathophysiology mostly come from molecular imaging studies (Aracil-Bolaños and Strafella, 2016). The state of the art has been thoroughly reviewed elsewhere (Aracil-Bolaños and Strafella, 2016; Callesen et al., 2013; Jiménez-Urbietta et al., 2015; Marques et al., 2018; Voon et al., 2017; Vriend, 2018; Vriend et al., 2014b; Weintraub and Claassen, 2017) and is summarized schematically in Fig. 1. While dopaminergic treatment allows restoring pathological dopaminergic (DA) activity in the dorsal striatum with subsequent benefits on the motor system, it would lead to uncontrolled activation of the reward system whose pivotal structure is the less damaged ventral striatum. This DA “overdose” of ventral striatal-cortical circuitry would induce increased sensitization to reward cues and abnormal reward seeking (Steeves et al., 2009; Weintraub, 2008). Molecular imaging has been essential to delineate the whole network impacted by this hyper-dopaminergic state, and to understand the interactions between neurotransmitters, transporters and receptors of the dysfunctional DA system (Aracil-Bolaños and Strafella, 2016). It has become clear from PET studies that ICDs are associated with low ventral striatal D2/D3 receptor availability (e.g., Steeves et al., 2009), with

low dopamine transporter (DAT) expression in ventral striatum (e.g., Cilia et al., 2010) and with low midbrain dopamine autoreceptor function (Ray et al., 2012). These dopaminergic changes have respectively been associated with altered transmission of reward signals, compensatory downregulation and increased sensitivity to rewards. However, molecular imaging studies have limitations. First, available studies have mostly focused on the dopaminergic system. Yet, there are some clues indicating that non-dopaminergic dysfunctions may contribute to PD-ICDS (Callesen et al., 2013; Napier et al., 2015; Vriend, 2018). Second, available studies have mostly focused on the reward system. Yet, a wealth of research indicates that impulsivity and compulsivity are non-unitary traits mediated by various psychological and neural mechanisms beyond those underlying reward processing (Antonelli et al., 2014; Dalley et al., 2011; Nombela et al., 2014). Third, PET does not allow the identification of the specific neural mechanisms that are potentially dysfunctional in ICDs, since it cannot disentangle the time-course of numerous concurrent activations. Thus, although available molecular imaging studies have provided major theoretical and therapeutic insights by associating clinical symptoms to dysregulation of DA neurotransmission, they cannot draw a clear and complete picture of the potential neurocognitive dysfunctions leading to PD ICDs.

## 1.2. The neurocognitive footing of ICDs

Entering the neurocognitive “black box” represents the opportunity to separate different possible sources of dysfunction, to evaluate their respective dependency on the DA system (or on other systems), and their respective contribution to the surfacing behavioral signs and verbal reports of patients on which clinical diagnosis is based. Although challenging to translate into clinical practice (Ekhtiari et al., 2017; Lo et al., 2015), recent developments in the understanding of the distinct psychological, neural and neurochemical mechanisms of decision making and impulsivity have proven useful for the study and treatment of certain neuropsychiatric disorders such as substance use disorders, obsessive-compulsive disorder (OCD) or attention deficit hyperactivity disorder (Bari and Robbins, 2013; Dalley and Robbins, 2017; Fineberg et al., 2014; Robbins et al., 2012; Robbins, 2017; Chamberlain and Robbins, 2013; Cuthbert and Insel, 2013). In PD, it may be useful for instance to evaluate the susceptibility of patients to develop a drug-induced ICD prior to the onset of treatment on the basis of neurocognitive markers (e.g., Nombela et al., 2014; Santangelo et al., 2017). Similarly, identifying the genetic underpinnings of ICDs in PD and the neurocognitive endophenotypes accounting for comorbidities and commonalities across disorders (Napier et al., 2015; Robbins et al., 2012) may help uncover new therapeutic opportunities (e.g., targeting ICDs with noradrenergic agents: Kehagia et al., 2014; Rae et al., 2016).

Recent reviews and modeling studies based on neuropsychological approaches (Dawson et al., 2018; Nombela et al., 2014; Santangelo et al., 2017) have highlighted two important points about the cognitive correlates of PD ICDs. First, the fact that ICDs in PD are multi-dimensional (e.g., Nombela et al., 2014; see also Napier et al., 2015). Second, the fact that cognitive dysfunctions associated with ICDs are heterogeneous and difficult to identify (e.g., Dawson et al., 2018), especially when cognition is only measured by means of global neuropsychological batteries (Santangelo et al., 2017). It comes out of these reviews that ICDs reflect dysfunctions in various aspects of decision making and motivation involving the reward system (choice impulsivity), but also possibly in various aspects of motor and executive control (action impulsivity). Dysfunctions in the control of value- or reward-based responding can be due to irrational preference for small, immediate rewards versus larger but delayed rewards –i.e. temporal discounting-, irrational estimation of probabilistic gains –i.e. probabilistic discounting-, or irrational ill-timed decision without adequate accumulation and consideration of available evidence –i.e. reflection impulsivity. Dysfunctions of motor and executive control could rely on clusters of mechanisms related to response conflict/interference processing, time estimation and response inhibition (Nombela et al., 2014). More broadly, the neurocognitive correlates of drug-induced ICDs in PD might also depend on affective states, apathy and depression (Dawson et al., 2018; Vriend et al., 2014b). It is a major issue to identify more precisely the neurocognitive dysfunctions potentially involved in addiction in general (Ekhtiari et al., 2017) and in ICDs in particular (Napier et al., 2015). For instance, as revealed by a meta-analysis from Santangelo and colleagues (2017), persistence of an impulsive and maladaptive behavior in people with PD could depend on executive dysfunction (set-switching) rather than on the rewarding nature of decision-making. This is in line with the broader idea that vulnerability to stimulant addiction may depend on an impulsivity endophenotype (Dalley et al., 2011; Miller et al., 2018; Ray and Strafella, 2013). However, the corresponding ensemble of cognitive processes and discrete deficits in defined neural systems still needs to be precisely identified in PD ICDs.

Here, we provide a critical perspective on the current state of this endeavor, informed by a systematic review of the functional imaging studies examining the brain mechanisms that differentiate PD patients with ICDs from those without ICDs. The hope is that neural-based evidence will reduce the heterogeneity and confounds observed in neuropsychological and behavioral approaches. Indeed, psychological

functions are overlapping concepts that integrate, and sometimes share, a variable number of computational processes. Functional neuroimaging has the potential to provide access to finer-grained mechanisms, and to identify common denominators and discrepancies across psychological functions. This aspect has been only peripherally tackled in most recent reviews (Dawson et al., 2018; Santangelo et al., 2017), and is the central topic of our analysis below.

## 2. Neurocognitive bases of ICDs in PD: current state of knowledge

We performed a systematic review of the functional neuroimaging studies assessing the neural correlates of PD-ICDs. Molecular imaging studies centered on DA neurotransmission and reward (Fig. 1) were excluded from the analysis because their scope was considered too narrow with regards to the present goal of surveying all potential neurocognitive mechanisms underlying ICDs (see above).

### 2.1. Methods

#### 2.1.1. Literature selection

We searched the Web of Science and Pubmed databases on 11/10/2018 using the keywords “impuls\* AND Parkinson” combined with “fMRI” OR “PET” OR “imaging” OR “blood flow” (and all variants of these terminologies). Additionally, we used “gambl\*” instead of “impuls\*” as pathological gambling (PG) is often studied alone. The inclusion criteria for this review were:

- 1) PET regional cerebral blood flow (rCBF) or fMRI studies,
- 2) Including PD patients with current ICDs (ICDs+),
- 3) Including a control group comprised of PD patients without ICDs (ICDs-),
- 4) Reporting at least one of the two contrasts ICDs+ > ICDs- and ICDs- > ICDs+.

The exclusion criteria were:

- 1) Review articles,
- 2) Conference abstracts,
- 3) Animal studies,
- 4) Case reports,
- 5) Metabolism or neurotransmission PET studies.

A flow chart summarizing the literature search and selection can be found in Fig. 2.

#### 2.1.2. Data extraction

Selected papers (n = 14) were scrutinized to extract the following information:

- 1) Characteristics of the clinical groups

This includes the number of subjects, the ICD subtypes, the treatment status, as well as the clinical scores on the MIDI (Minnesota Impulsive Disorders Interview), QUIP-RS (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale) or SOGS (South Oaks Gambling Screen).

- 2) Neuroimaging methods

The neuroimaging methods used to characterize dysfunctional neural activity were categorized as a function of:

- The neuroimaging tool used and the nature of the signal captured.
- The data processing method used to infer neural activity (functional connectivity, block design, event-related design).

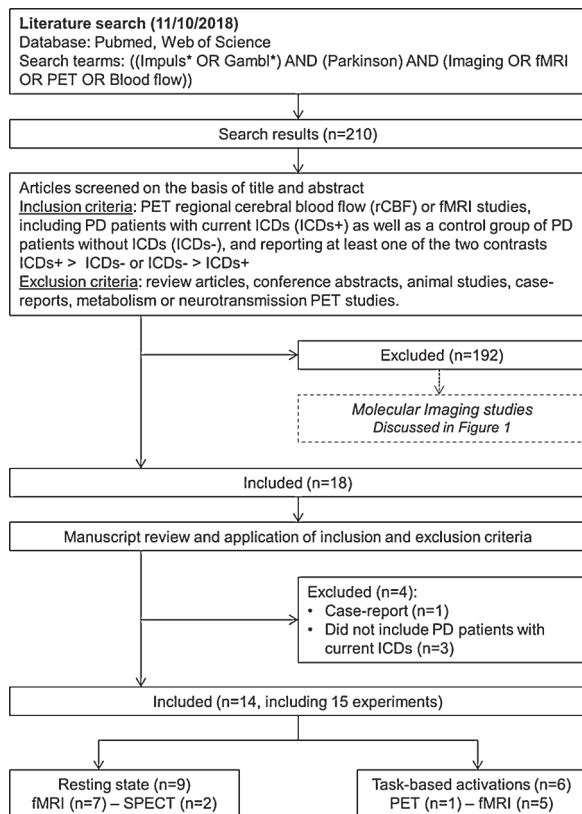


Fig. 2. Flow chart of publication selection procedure based on PRISMA guidelines ([www.prisma-statement.org](http://www.prisma-statement.org)).

### 3) Characteristics of the behavioral task and targeted neurocognitive functions

Assessing the neural bases of ICDs consists in associating clinical symptoms with changes in cognitive processes and discrete deficits in specific neural systems. This can rely on different strategies:

- Linking clinical symptoms to global and non-specific brain activity changes in defined neural systems (e.g., identifying the modulations of functional connectivity at rest that account for a clinical score of impulsivity within the reward circuitry).
- Isolating neurocognitive mechanisms of interest through specific behavioral designs, and associate event-related brain activity changes that differ between ICD+ and ICD- patients (e.g., identifying the brain regions showing abnormal gambling cue-induced activation in PD patients with pathological gambling (PG) vs without PG).

In order to characterize the strategies used by the authors, we extracted the following information: the theoretical rationale, the neurocognitive mechanism of interest, the behavioral task used to isolate it, and the brain regions of interest.

#### 4) Results

The clinical, behavioral and neuroimaging main results were extracted for each study.

## 2.2. Results

### 2.2.1. Literature selection

298 records were identified through database searching, including 88 duplicates. Among the 210 uniquely identified studies, 196 were

excluded based on our inclusion/exclusion criteria. The remaining 14 studies (corresponding to 15 experiments) were included (Fig. 2).

### 2.2.2. Systematic review of selected studies

Detailed results are presented in Table 1. Studies are referenced with numbers, from #1 to #14.

#### 1) Characteristics of the clinical groups

Seven studies did not select a specific ICD subtype, while four focused on pathological gambling, two on pathological gambling and compulsive buying and one on hypersexual patients. Studies included on average  $15.0 \pm 7.3$  ICDs+ and  $18.6 \pm 12.8$  ICDs-. Three studies reported QUIP-RS scores (ICDs+ =  $31.5 \pm 8.3$ ; ICDs- =  $19.0 \pm 0.1$ ) and one reported MIDI scores (ICDs+ =  $6.8 \pm 3.2$ , ICDs- =  $0.4 \pm 0.5$ ). Five studies (#6,8,10,11,14) investigated the interaction between medication (ON vs OFF dopamine replacement therapy) and group (ICDs+ vs ICDs-).

#### 2) Neuroimaging methods

Eleven studies used fMRI, two used SPECT imaging, and one used PET. Most experiments (#1-9a) recorded resting state data, while five of them recorded task-related activity using block-designs (#11-13) or event-related designs (#9b-10). The last study (#14) reported activations based on computational modelling.

#### 3) Characteristics of the behavioral tasks and targeted neurocognitive functions:

Nine experiments searched for alterations of intrinsic activity in ICDs+. Among these experiments, four formulated no a priori hypotheses about specific psychological dysfunctions or brain regions (#1-4), using for instance SPECT rCBF or ICA to separate independent components corresponding to (dys)functional brain networks. Four studies searched for alterations of intrinsic activity specifically in the mesocorticolimbic system of ICDs+, assuming dysfunction in the reward system, but without probing it directly by means of a behavioral task (#5-6, #8-9a). The last one focused on affective and sensorimotor striatal circuitries based on the rationale that both can contribute to impulsivity (#7).

Six experiments used task-based imaging. Among these experiments, three used block-designs, assessing cue-induced motivation in PD patients with pathological gambling (#13) or hypersexuality (#12), or assessing risk taking by means of a computerized card selection task (#11). Two experiments used event-related designs focusing on risk taking by entering risk level as a linear parametric modulation of the hemodynamic response function (HRF) triggered by the stimuli or the behavioral responses of the subjects (#9b-10). One study used computational modelling to probe incentive value and prediction error signals in a probabilistic gain and loss learning task (#14).

#### 4) Results

Mean clinical scores and main behavioral results are displayed in Table 1. Neuroimaging results are reported in Table 1 and summarized in Fig. 3. Abnormal activity or abnormal functional connectivity were found in a widely distributed, poorly replicable network including the limbic system, the sensorimotor network, the visual network, the default mode network, the attentional network, the cerebellum, the striatum and numerous prefrontal areas.

## 2.3. Discussion

Three main results emerge from this review. First, and surprisingly given the scale of the problem and the total number of papers on the



topic (922 articles in PubMed at the time of writing using the keywords Impuls\* AND Parkinson), very few studies ( $N = 14$ ) have examined the functional brain correlates of PD-ICDs according to our criteria (Fig. 2). This, in addition to the heterogeneity of the methods employed, prevents us from performing any quantitative meta-analysis. Second, results are largely inconsistent, as illustrated in Fig. 3. Third, among selected studies, only a few have targeted specific neurocognitive mechanisms by combining appropriate behavioral tasks and event-related analyses (Table 1). As a result, it is difficult to extract a clear and coherent picture from this literature.

Even the abnormalities in mesocorticolimbic circuits in PD-ICDs predicted by current neurobiological hypotheses (Aracil-Bolaños and Strafella, 2016; Callesen et al., 2013; Voon et al., 2017; Vriend, 2018; Vriend et al., 2014b) present an overall lack of consensus about their location and direction (Fig. 3). Even in comparable studies and brain regions, the comparison of ICDs + vs. ICDs- reveals inconsistent results showing either decreased or increased activity/functional connectivity. The most striking example is the ventral striatum. Most fMRI resting state studies seem in agreement with molecular imaging studies targeting the DA system, in the sense that they report increased activity/connectivity in the ventral striatum of ICD + patients (4 hyperactivity pattern against 1 hypoactivity pattern). However, functional studies based on task-related activations report as many decreases (Rao et al., 2010; Voon et al., 2010) as increases (Frosini et al., 2010; Politis et al., 2013) in activity. This might suggest that the hyperactivation pattern of the ventral striatum accounts for motivational aspects guiding sexual and gambling disorders (as specifically tested by Frosini et al., 2010 and Politis et al., 2013), but not for risk-taking or incentive learning (as specifically tested by Rao et al., 2010 and Voon et al., 2010). More generally, this reminds us that the uncontrolled DA activation of the ventral striatum measured at rest in medicated patients developing ICDs+ (as tested in 8 out of the 12 molecular imaging studies identified in Fig. 1) does not represent a direct marker of increased functional activation of the ventral striatum for all the neurocognitive mechanisms that this key structure contributes to. Unfortunately, given the small number of available studies, further functional imaging investigations are warranted to disentangle the cognitive mechanisms whose dysfunction actually 1) accounts for ICDs and 2) is due to, and not just co-occurs with, ventral striatum DA overdose.

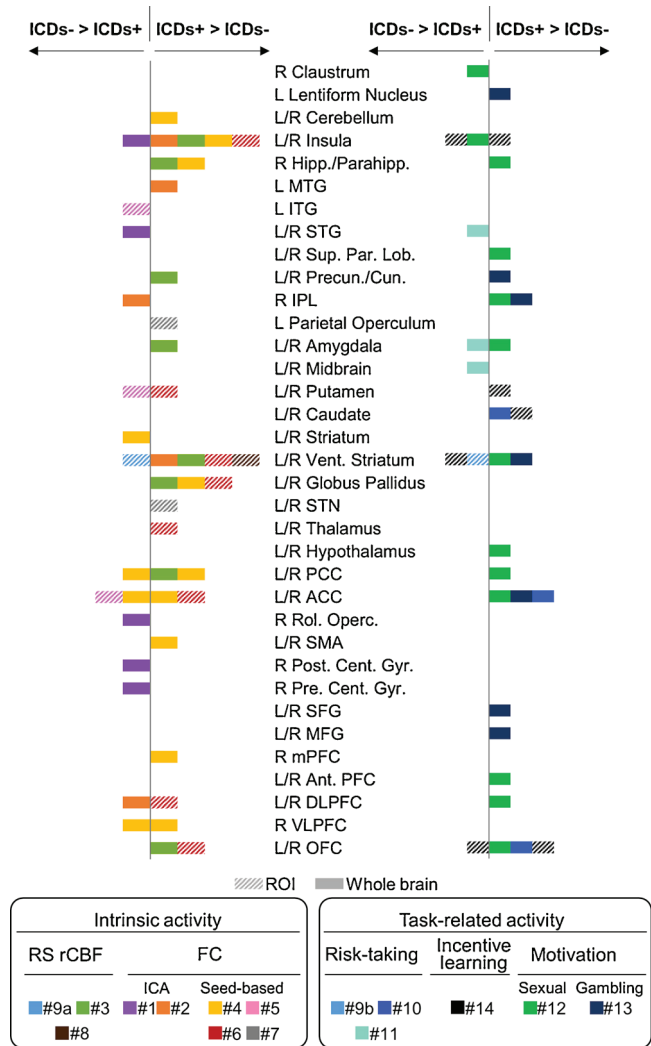
Additionally, inconsistent results are observed in numerous spots of the large mesocorticolimbic circuit, and beyond. Abnormal activity or abnormal functional connectivity were found in a widely distributed, poorly replicable network including the limbic system, the sensorimotor network, the visual network, the default mode network, the attentional network, the cerebellum, the striatum and numerous prefrontal areas. In other words, in contrast to our hope to find common denominators between studies, the present analysis did not identify a reliable brain map of ICDs (Fig. 3). This further underlines that there are still numerous unanswered questions about ICD-related abnormalities, both within and outside the reward system (Aracil-Bolaños and Strafella, 2016; Napier et al., 2015). It is for instance unlikely that there exists a single common reward system. It is more probable that there are reward type-dependent brain structures (Sescousse et al., 2013) that would explain part of the observed variability. It is even possible that increased sensitivity to rewards or troubles computing the experienced value of rewards are not always the most important triggers of impulsive actions. Incentive salience (cue-triggered ‘wanting’, Lades, 2012) can induce impulsive choices of smaller sooner rewards instead of larger later rewards regardless of the nature or value of these rewards. Furthermore, it is well known from studies outside the field of PD that a variety of action control mechanisms (including in particular different processes of motor response inhibition) are dysfunctional in impulsivity and addiction (Bari and Robbins, 2013; Dalley and Robbins, 2017). Similar dysfunctions could play a direct, substantial role in PD ICDs, as suggested by recent investigations (Antonelli et al., 2011; Kehagia et al., 2014; Nombela et al., 2014; Ye et al., 2015). This could

account for some ICD-related brain activity changes in sensorimotor, prefrontal, default mode and basal ganglia networks highlighted in the present analysis. However, knowledge about the neural bases of action impulsivity in PD ICDs is still largely incomplete and requires direct assessment for each single mechanism. Finally, there are also strong comorbidity issues related to cognitive or affective disorders that are likely to blur the overall picture (Dawson et al., 2018; Ekhtiari et al., 2017; Goerlich-Dobre et al., 2014; Jaakkola et al., 2014; Santangelo et al., 2017; Vriend et al., 2014b; Weintraub and Claassen, 2017). In sum, without overlooking the influence of demographic/clinical confounders in neuroimaging studies (e.g., clinical stage, age at onset of PD, disease duration; Ekhtiari et al., 2017; Santangelo et al., 2017) and common problems of imaging (heterogeneous data processing and paradigms, sample size, etc), it seems that improving neurofunctional analyses requires a more careful consideration of the cognitive functions of interest.

### 3. The need for a stronger neurocognitive footing

The existing literature on the neural bases of PD-ICDs faces challenges of consistency and validity (e.g., Ekhtiari et al., 2017), but has nonetheless provided important theoretical and therapeutic insights. In particular, it now seems obvious that ICDs have no unitary explanation. It is therefore necessary to disentangle and identify the neural and neurochemical bases of each potentially dysfunctional process underlying ICDs. This constitutes a prerequisite towards understanding the interactions among different functional networks and distinguishing causes, correlates and individual susceptibility factors of PD ICDs.

To this aim, a stronger neurocognitive footing is necessary. There are important confounds in the available literature because psychological functions are conceptual and flexible constructs that integrate a variable number of computational processes. The only way to control the involvement of these processes is to use sophisticated psychological (i.e., neurocomputational) models in combination with sophisticated behavioral tasks. Various behavioral protocols have been developed and are now used routinely in clinical investigations to define sub-components of impulsivity in other pathologies. Examples are Temporal Discounting and probability discounting tasks assessing different aspects of impulsive choice, Stop Signal Reaction Time and Go-NoGo tasks assessing different aspects of response inhibition, Choice Serial Reaction Time tasks assessing premature responding, etc (Dalley and Robbins, 2017; Napier et al., 2015; Voon et al., 2017). These protocols have been used in the study of Obsessive Compulsive Disorders, Attention Deficit Hyperactivity Disorder and Substance Use Disorders (Fineberg et al., 2014; Voon, 2014). It is very surprising that only a few studies on PD-ICDs ( $N = 6$ ) have combined standard behavioral protocols with neuroimaging methods targeting precisely the underlying psychological processes. The majority of the available studies rather searched for non-specific correlates of ICDs clinical scores. However, neither the MIDI (Minnesota Impulsive Disorders Interview; Christenson et al., 1994), the QUIP (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; Weintraub et al., 2009), or the BIS-11 (Barratt Impulsiveness Scale-11; Patton et al., 1995) provide clinical scores that reflect the multidimensional nature of impulsivity in terms of dysfunctional neurocognitive mechanisms (Ekhtiari et al., 2017). This calls for more neuroimaging research using event-related fMRI or electromagnetic recordings for their potential to provide access to fine-grain processes, provided that advanced and valid psychological models are used for design and interpretation. In that sense, the main limitation of the approach we are promoting is the inherent limit of cognitive work in humans. There are conflicting models and the use of one or another may lead to conflicting results with the risk of introducing even more confusion in clinical investigations (e.g., Ballanger et al., 2009). However, combining brain activity recordings with appropriate behavioral tasks precisely allows testing the physiological plausibility of the underlying psychological models



**Fig. 3.** Differences in functional connectivity (A) or task-related activation (B) between PD patients with (ICDs+) or without ICDs-. For the sake of clarity, only regions involved in Group effects (and not Group x Medication effects) are reported. The heterogeneity of the methods as well as the results (in terms of location and direction of group differences) makes it difficult to extract a clear and coherent picture.

(e.g., [Criaud et al., 2017](#); [Criaud and Boulinguez, 2013](#)), which neuropsychological batteries or purely behavioral studies cannot achieve. To that extent, any future improvement, refutation or enrichment of a psychological model will provide an opportunity for neuroimaging studies to further disentangle actual confounds in clinical research.

Separating all possible sources of dysfunction may be highly valuable in uncovering new therapeutic opportunities. This might help clarifying the complex link between PD-ICDs and DA dysfunction and treatment (e.g., [Antonelli et al., 2014](#)), and might open possible perspectives for the major issue of non-DA therapeutic solutions in PD ([Fox et al., 2008](#); [Fox, 2013](#)). For instance, recent work on the neural and neurochemical bases of response inhibition has identified the key role of the noradrenergic (NA) system ([Albares et al., 2015b](#); [Chamberlain et al., 2009, 2006](#); [Chamberlain and Robbins, 2013](#); [Chamberlain and Sahakian, 2007](#); [Robbins and Arnsten, 2009](#); [Spay et al., 2018](#)). Other clues point to the involvement of the serotonergic (5HT) system ([Dalley and Robbins, 2017](#); [Eagle et al., 2008](#); [Paterson et al., 2012](#)). Dysfunction of specific inhibitory processes in PD patients with ICDs might thus be treated with NA or 5HT pharmacological agents ([Kehagia et al., 2014](#); [Rae et al., 2016](#); [Ye et al., 2015, 2016](#)). To illustrate how entering into detailed neural mechanisms of response

control can be fruitful, let's mention the case of proactive inhibitory control, a central mechanism controlling the initiation of response, that has recently been modeled in healthy subjects (e.g., [Criaud et al., 2017, 2012](#); [Jaffard et al., 2008, 2007](#); [Wardak et al., 2012](#)). The function of this gating mechanism is to lock movement initiation processes in order to avoid automatic responses to external or internal stimuli in uncertain contexts, or when the situation requires saving time to settle on the best option. A dysfunction of this basic motor inhibitory mechanism can induce not only action impulsivity, but also choice impulsivity. Its neural substrates involve brain regions that have been identified in many of the studies reviewed here (supplementary motor area, medial prefrontal cortex, precuneus, striatum, subthalamic nucleus). Using appropriate behavioral protocols and brain recordings, it has been possible to demonstrate the alteration of this pivotal mechanism in PD and the associated dysfunction of the NA system ([Albares et al., 2015b](#); [Ballanger et al., 2009, 2014](#); [Criaud et al., 2016](#); [Spay et al., 2018](#)). Based on this insight, a phase 2 clinical trial testing the efficacy of clonidine for the treatment of ICDs in PD is currently running (ClinicalTrials.gov Identifier: NCT03552068). This is a potentially promising approach, that would avoid fiddling with the dopaminergic treatment, and thus reduce the risk of worsening motor symptoms or developing dopamine agonist withdrawal syndrome ([Samuel et al., 2015](#)).

Nonetheless, another key source of confusion arises from the fact that all these neurocognitive processes strongly interact (e.g., [Antonelli et al., 2011](#); [Antonelli and Strafella, 2014](#); [Bari and Robbins, 2013](#); [Criaud and Boulinguez, 2013](#); [Dalley and Robbins, 2017](#); [Robbins et al., 2012](#)). This means that identifying each possible dysfunction independently of all others by means of specific behavioral protocols will not be enough. The next step should consist in assessing interactions between processes, trying to build mechanistic models integrating possible sources of dysfunction leading to ICDs and states favoring the development of ICDs. The identification of sources and modulators is a prerequisite for future studies which will then have the opportunity to implement computational approaches to understand these interactions. In this effort, electroencephalography (EEG) may be useful. First because EEG provides a direct measure of brain activity, by contrast with blood flow imaging ([Logothetis, 2008](#)). Second because EEG has the necessary temporal resolution for distinguishing processes that are close in time. Third because EEG offers high functional discrimination power by means of spectral analyses. Indeed, distinct cortical functions are expressed in distinct frequency bands ([Albares et al., 2015a](#); [Siegel et al., 2012](#)). Since recent methods now offer efficient source separation and localization solutions, EEG is certainly a highly suitable tool for future neurocomputational investigations of the multidimensional system supporting various forms of impulsive and compulsive behaviors ([Albares et al., 2015a](#)).

#### 4. Conclusion

There is much to gain from incorporating strong psychological models and methods into clinical and neuroimaging studies of PD-ICDs. Indeed, PD-ICDs are multidimensional and remain difficult to understand thoroughly by simply linking global clinical scores to overall changes in brain activity or connectivity with paradigms that do not allow the targeting of specific neurocognitive mechanisms. A lot of work still needs to be done to explore more efficiently the possible ways in which pioneering studies in the field may help managing ICDs in PD. In this respect, identifying patients at high risk of developing drug-induced ICDs is of tremendous importance. As inspired by extensive investigations in psychiatric conditions ([Bari and Robbins, 2013](#); [Dalley and Robbins, 2017](#); [Robbins et al., 2012](#)) neurocognitive subtypes could be differently associated with the DA, NA and 5HT systems. Characterizing ICDs-related neurocognitive dysfunctions using more sophisticated behavioral paradigms and brain activity recordings might thus offer the possibility to improve personalized therapeutic pharmacological approaches.

**Table 1**  
Functional neuroimaging studies examining the brain mechanisms that differentiate PD patients with ICDs from PD patients without ICDs.

Studies	Populations		Neuroimaging		Behavioral tasks and targeted neurocognitive mechanisms		Results		
	ICDs + /ICDs- /HC	PD-ICDs 35/50/50 Interview QUIP-RS = 21.9 ± 10.2/NR ON	Tool Signal	Processing methods	Authors' rationale	NOI BT	ROI		
#1 Imperiale, 2017	ICDs + /ICDs- /HC	PD-ICDs 35/50/50 Interview QUIP-RS = 21.9 ± 10.2/NR ON	fMRI BOLD	Intrinsic activity FC - ICA	"to investigate [...] functional alterations in PD-ICB patients compared with healthy controls and PD no-ICB cases"	/ /	Major RSNS	ICDs+ > ICDs- ICDs- > ICDs+ ICDs+ > HC	[FC within and between RSNS] $\emptyset$ [FC within Sensorimotor Network] R Precentral Gyrus - R Postcentral Gyrus - R Rolandic Operculum - R STG - L Insula [FC between RSNS] $\emptyset$ [FC within Visual Network] L and R Middle Occipital Gyrus - R Lingual Gyrus - L Fusiform Gyrus - R Cerebellum Vermis 4-5 - R Cerebellum Crus 1 [FC within and between RSNS] $\emptyset$ [FC within SN and DMN] L and R Insula - R Ventral Striatum - L Middle Temporal Gyrus [FC within Right CEN] R DLPFC - R IPL [FC within Right CEN] R Angular Gyrus [FC within SN and DMN] ACC - Precuneus
#2 Tessitore, 2017	PD-ICDs 15/15/24 Interview MIDI = 6.8 ± 3.2/ 0.4 ± 0.5 ON	PD-ICDs 15/15/24 Interview MIDI = 6.8 ± 3.2/ 0.4 ± 0.5 ON	fMRI BOLD	Intrinsic activity FC - ICA	"to assess whether the presence of ICD in PD patients may determine abnormalities in the intrinsic neural networks connectivity"	/ /	Major RSNS	HC > ICDs+ ICDs+ > ICDs- ICDs- > ICDs+ ICDs+ > HC HC > ICDs+	[FC within and between RSNS] $\emptyset$ [FC within SN and DMN] L and R Insula - R Ventral Striatum - L Middle Temporal Gyrus [FC within Right CEN] R DLPFC - R IPL [FC within Right CEN] R Angular Gyrus [FC within SN and DMN] ACC - Precuneus
#3 Cilia, 2008	PD-PG <sup>1</sup> 11/40/29 DSM-IV SOGS = 7.6 ± 2.8/ 1.1 ± 0.4 ON	PD-PG <sup>1</sup> 11/40/29 DSM-IV SOGS = 7.6 ± 2.8/ 1.1 ± 0.4 ON	SPECT rCBF	Intrinsic activity RS activation	"to determine whether PD patients with PG exhibit differential brain activity compared with matched PD controls and healthy controls"	/ /	Whole brain	PG+ > PG- PG- > PG+ PG+ > HC	[rCBF peak/extended to] R OFC/Insula - R Hippocampus/Parahippocampal Gyrus - R Amygdala - R Ventral Pallidum/Nucleus Accumbens - L Insula - R and L Precuneus/ Cuneus/PCC [rCBF] $\emptyset$ [rCBF peak/extended to] R Hippocampus/ Parahippocampal Gyrus - R Insula/OFC/ Striatum - R Caudate/Insula - R Putamen/ Insula
#4 Cilia, 2011	PD-PG <sup>1</sup> 15/15/15 DSM-IV SOGS = 7.5 ± 2.7/ 0.9 ± 0.5 ON	PD-PG <sup>1</sup> 15/15/15 DSM-IV SOGS = 7.5 ± 2.7/ 0.9 ± 0.5 ON	SPECT rCBF	Intrinsic activity FC	"to identify the critical neural interactions that differentiated PD gamblers from matched controls"	/ /	Seeds: regions whose activity correlated with SOGS scores	HC > PG+ PG+ > PG- PG- > PG+ PG+ < PG-/ HC	[Covariance between regions not functionally connected in PG-] R ACC and Insula, SMA, Cerebellum - R VLPFC and Ventral Pallidum - R mPFC and PCC - R Parahippocampal Gyrus and Insula [Lack of covariance between] R VLPFC and ACC, PCC - R ACC and Striatum [Main finding] Disconnection of the Striatum from ACC
				Intrinsic activity Effective connectivity			Seeds: R VLPFC, R mPFC, R ACC, R PCC, L Striatum, R Insula, R Parahippocampal Gyrus	PG+ < PG-/ HC	Activity correlated with SOGS scores: [positive correlation] R VLPFC, R mPFC, R ACC, R PCC, R Rostral SMA, R Anterior Superior Temporal Gyrus, L Striatum, L and R Insula, R Parahippocampal Gyrus - [negative correlation] L Fusiform Gyrus, Cerebellum.

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Table 1 (continued)

Studies	Neuroimaging			Behavioral tasks and targeted neurocognitive mechanisms		Results
	Populations	Tool Signal	Processing methods	Authors' rationale	ROI	
#5 Carriere, 2015	PD-ICDs 19/17/16 Interview QUIP = NR ON	fMRI BOLD	Intrinsic activity FC - Seed- based	"ICDs would be associated with alterations in corticostriatal connectivity and especially the connectivity between the ventral striatum and cortical limbic regions" <sup>6</sup>	Seeds: Bilateral Dorsal Caudate, Ventral Striatum, Anterior and Posterior Putamen	ICDs- > ICDs+ L ACC <sup>6</sup> ICDs+ > ICDs- ICDs+ < > $\emptyset$ <sup>6</sup> HC
#6 Petersen, 2018	PD-ICDs 19/18 Interview QUIP-RS = 35.9 ± 9.7/ 18.9 ± 11.1 ON DAA + OFF L-DOPA / OFF	fMRI BOLD	Intrinsic activity FC - Seed- based	"we hypothesized that DAA-treated PD patients with this behavioral phenotype [ICDs] have increased functional connectivity between the ventral striatum and components of the limbic striato-pallido-thalamo-cortical loop" <sup>6</sup> - "Because amygdala activity has also been linked with reward-motivated behaviors [...], we additionally examined amygdala connectivity with reward network components." <sup>6</sup>	Seeds: Bilateral Ventral Striatum, Bilateral Amygdala	ICDs+ > ICDs- ICDs+ > ICDs- ICDs- > ICDs+ ICDs+ > ICDs- ICDs- > ICDs+ Group x Medication
#7 Ruitenberg, 2018	PD-ICDs 21/30 QUIP = NR ON	fMRI BOLD	Intrinsic activity FC - Seed- based	"The present study aimed to investigate differences in both affective and sensorimotor striatal circuitries between PD patients with and without ICDs and their association with impulsive behaviors" <sup>6</sup>	Seeds: L Putamen, Caudate, GPI, GPe, STN, Parietal	ICDs+ > ICDs- ICDs- > ICDs+  [Behavioral results] More proficient reward learning in ICDs + compared to ICDs- ( $p < 0.01$ , ICDs+ = 90%, ICDs- = 73% correct responses) [Incentive learning and LASSO regression] Ventral striatum to ACC connectivity positively correlated with reward learning performance ( $\rho = 0.43$ , $p < 0.01$ ) <sup>5</sup> [FC from STN, increased] L Parietal Operculum <sup>6</sup> $\emptyset$ <sup>6</sup>
#8 Claassen, 2017	PD-ICDs 17/17 Interview QUIP-RS = 36.6 ± 9.6/19.0 ± 11.4 ON/OFF	fMRI rCBF	Intrinsic activity RS activation	"we hypothesized that impulsive control behaviors patients would have different CBF responses to dopamine agonist in mesocorticolimbic regions than PD patients without impulse control behaviors" <sup>6</sup>	ROIs: Hippocampus, Amygdala, Pallidum, Ventral Striatum, Putamen, Caudate	ICDs+ > ICDs- ICDs- > ICDs+ Correlation analysis  [Behavioral results] No group effect <sup>5</sup>
#9a Rao, 2010	PD-ICDs 9/9 Interview	fMRI rCBF	Intrinsic activity RS activation	"we hypothesized that PD patients without an ICD, would demonstrate diminished neural activity in mesolimbic-prefrontal cortex brain regions, particularly in the ventral striatum." <sup>6</sup>	Ventral Striatum	ICDs- > ICDs+ [rCBF, voxel-wise and ROI analysis] Ventral Striatum
#9b	MIDI/MGS/DSM-IV <sup>2</sup> ON	fMRI rCBF	Task-related activity Event-related	HRF on balloon inflation with risk level as a linear parametric modulation	Ventral Striatum	ICDs- > ICDs+ [Risk-taking related activation, voxel-wise and ROI analysis] Ventral Striatum [Average adjusted number of pumps for unexploded balloons] ICDs+ = 5.6 ± 1.0, ICDs- = 5.8 ± 0.9, $p = 0.63$

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Table 1 (continued)

Studies	Populations		Neuroimaging		Behavioral tasks and targeted neurocognitive mechanisms		Results
	ICDs+ /ICDs- /HC	ICDs- /HC	Tool Signal	Processing methods	Authors' rationale	ROI	
#10 Voon, 2011	PD-PG/CB 11/11 DSM-IV/ McElroy criteria ON/OFF DAAs		fMRI BOLD	Task-related activity Event-related	"we hypothesized that dopamine agonists would be associated with greater risk taking and lower ventral striatal activity in patients with ICD relative to Parkinson's disease controls."	Whole brain Risk Taking Gambling Task Box-car convolved with HRF on decision phase (4 s) with risk as a parametric regressor	ICDs+ > ICDs- Group effect ICDs- > ICDs+ Group effect Group x Medication [Risk-taking related activation] L and R ACC, L and R Caudate, L OFC [Risk-taking related activation] Ø [Risk-taking related activation - Increased ON versus OFF in ICDs- but decreased activity ON versus OFF in ICDs+ ] L and R Ventral Striatum [Proportion of risky choices] No Group effect (p = 0.96)– No Medication x Group effect (p = 0.19) Behavioral results <sup>5</sup>
#11 Van Eimeren, 2010	PD-PG 7/7 DSM-IV ON/OFF DAAs		PET rCBF	Task-related activity Block-design	"we reasoned that in contrast to controls, gamblers may show DA-induced hypoactivity of inhibitory frontolimbic networks encompassing the lateral OFC and the rostral cingulate zone."	Whole brain Risk Taking Card selection game with probabilistic feedback, neutral and financial variant Task > Rest Motivation Watching sexual cues <sup>3</sup> Sexual cues > Neutral cues, Sexual cues > Other cues <sup>4</sup>	ICDs- > ICDs+ Group effect Group x Medication L and R Midbrain, L and R Superior Temporal Gyrus, R Amygdala [Increased activity ON versus OFF in ICDs- but decreased activity ON versus OFF in ICDs+ ] L lateral OFC, R Rostral Cingulate Zone, R Amygdala, L Ventral Anterior External Pallidum [Sexual versus neutral, ON and OFF] L and R OFC - L and R ACC - L and R PCC - L Amygdala - L and R Ventral Striatum - L and R Hypothalamus [Sexual versus others, ON and OFF] L and R OFC - L and R ACC - L and R PCC - L and R Ventral Striatum - L and R Hypothalamus [Sexual versus neutral, ON and OFF] L and R OFC - L and R ACC - L and R PCC - L Amygdala - L and R Ventral Striatum - L and R Hypothalamus - L and R Anterior PFC - L and R Superior Parietal Lobule - R IPL [Sexual versus others, ON and OFF] L and R OFC - L and R ACC - L and R PCC - L and R Ventral Striatum - L and R Hypothalamus - R and L DLPFC - R anterior PFC - R Parahippocampal Gyrus [Sexual versus neutral, OFF] L and R Insula - R Claustrum [Sexual desire after-before sexual stimuli exposure] OFF: HypS = 0.28 ± 0.26, HypS+ = 1.04 ± 0.32, p = 0.08; ON: HypS = 0.80 ± 0.52, HypS+ = 3.23 ± 0.51, p < 0.01 [Gambling cues related activation] L and R ACC - L and R Medial Frontal Gyrus - L and R Superior Frontal Gyrus - L and R Precuneus - R IPL - L Ventral Striatum - L Lentiform Nucleus [Gambling urge after gambling stimuli exposure] PG+ = 7.10 ± 1.8, PG- = 1.3 ± 0.9, p < 0.05.
#12 Politis, 2013	PD-Hyps <sup>1</sup> 12/12 Based on Voon, 2006 ON/OFF		fMRI BOLD	Task-related activity Block-design	"hypersexuality in Parkinson's disease could be associated with increased processing in brain regions linked to sexual motivation and cue reactivity"	Whole brain Motivation Watching sexual cues <sup>3</sup> Sexual cues > Neutral cues, Sexual cues > Other cues <sup>4</sup>	Hyps+ > Hyps- Hyps+ > Hyps- Behavioral results
#13 Frosini, 2010	PD-PG <sup>1</sup> 7/7 DSM-IV OFF		fMRI BOLD	Task-related activity Block-design	Gambling related cues would result in activation patterns similar to those related to craving in drug addictions	Whole brain Motivation Watching gambling cues <sup>3</sup> Gambling cues > Neutral cues	PG+ > PG- Behavioral results [Gambling urge after gambling stimuli exposure] PG+ = 7.10 ± 1.8, PG- = 1.3 ± 0.9, p < 0.05.

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Table 1 (continued)

Studies	Populations		Neuroimaging		Behavioral tasks and targeted neurocognitive mechanisms		Results
	ICDs+ /ICDs- /HC	PD-PG/CB 11/11/16 DSM-IV/ McElroy criteria ON/OFF DAAs	Tool Signal	Processing methods	Authors' rationale	NOI BT	
#14 Voon, 2010			fMRI BOLD	Task-related activity Computational modelling	"dopamine agonists would be associated with faster learning from gain outcomes along with greater ventral striatal positive $\delta$ activity in [ICDs] compared to PD controls"	Incentive Learning Probabilistic gain and loss learning task PE and PO activity: PE entered as a parametric modulator for the outcome phase (3 s) – PO entered as a parametric modulator for the stimulus phase (3 s)	<p>ICDs+ &gt; ICDs- Group effect</p> <p>ROIs: Striatum, Amygdala, OFC, Insula</p> <p>ICDs- &gt; ICDs+ Group effect</p> <p>Group x Medication</p> <p>[PO activity, gain condition] L and R OFC [Positive PE activity, gain condition] R Posterior Putamen – L OFC [Negative PE activity, gain condition] <math>\emptyset</math> [PO activity, loss condition] L Dorsolateral Striatum [Positive PE activity, loss condition] <math>\emptyset</math> [Negative PE activity, loss condition] L Anterior Insula – L Dorsomedial Caudate – L Dorsolateral Striatum [PO activity, gain condition] <math>\emptyset</math> [Positive PE activity, gain condition] <math>\emptyset</math> [Negative PE activity, gain condition] R Ventral Striatum – R OFC [PO activity, loss condition] L and R OFC – R Anterior Insula [Positive PE activity, loss condition] L/R OFC [Negative PE activity, loss condition] L and R OFC, R Anterior Insula [PO activity, gain condition] Greater increase under DAAs in L Ventral Striatum and lower decrease under DAAs in R Posterior Insula in ICDs+ than in ICDs- [Positive PE activity, gain condition] Greater increase under DAAs in L and R Posterior Putamen, R Insula and L Dorsomedial Striatum and lower decrease under DAAs in L and R OFC in ICDs+ than in ICDs- [Negative PE activity, gain condition] <math>\emptyset</math> [PO activity, loss condition] Lower decrease under DAAs in L Dorsomedial, Ventral Striatum and L and R Anterior Insula in ICDs+ than in ICDs- [Positive PE activity, loss condition] Greater increase under DAAs in L and R Anterior Insula and R Ventral Striatum in ICDs+ than in ICDs- [Negative PE activity, loss condition] Lower decrease under DAAs in L and R Anterior Insula, R OFC and L Putamen in ICDs- than in ICDs+</p>

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Table 1 (continued)

Studies	Populations	Neuroimaging	Behavioral tasks and targeted neurocognitive mechanisms	Results
	ICDs+ /ICDs- /HC	Tool Signal Processing methods	Authors' rationale	ROI NOI BT
				Behavioral results

<sup>1</sup> with other ICD co-occurrence in some patients. – <sup>2</sup>: ICD status was determined using the MGS (Massachusetts Gambling Screen) for pathological gambling, the MIDI for hypersexuality and buying, and the DSM-IV-TR research criteria for compulsive eating. – <sup>3</sup>: No responses required – <sup>4</sup>: Gambling, food, and dopaminergic cues – <sup>5</sup>: The reader is referred to the complete results – <sup>6</sup>: The reader is referred to the whole article for the results of the exploratory analysis using a less stringent criteria for significance – ICDs+/–: PD patients with/without hypersexuality – ICDs-/–: PD patients with/without ICDs – PG+/–: PD patients with/without PG – CB: Compulsive Buying – HC: Healthy Controls – MIDI: Minnesota Impulsive Disorders Interview – QUIP-RS: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale – DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – MGS: Massachusetts Gambling Screen – SOGS: South Oaks Gambling Screen – DAAS: Dopamine Agonists – NR: Non-Reported – FC: Functional Connectivity – RS: Resting state – BT: Behavioral task – NOI: Neurocognitive processes Of Interest – ROI: Regions Of Interest approach – RSs: Resting State Networks – BART: Balloon Analogue Risk Task – PE: Prediction Error – PO: Predicted Outcome – ACC: Anterior Cingulate Cortex – CEN: Central Executive Network – DJLPC: Dorsolateral Prefrontal Cortex – DMN: Default Mode Network – GPe: External portion of the Globus Pallidus – GPi: Internal portion of the Globus Pallidus – IPL: Inferior Parietal Lobule – mPFC: Medial Prefrontal Cortex – OFC: Orbitofrontal Cortex – PCC: Posterior Cingulate Cortex – SMA: Supplementary Motor Area – SN: Substantia nigra – STG: Superior Temporal Gyrus – VLPFC: Ventrolateral Prefrontal Cortex – Ø : No areas concerned by significant modification of activity/connectivity for the corresponding contrast.

[Gain learning] No main effects – Group x medication interaction: Higher percentage of gain cue choices and faster learning rate under DAAs in ICDs+ but not in ICDs-<sup>5</sup> [Loss learning] No main effects – Group x medication interaction: Lower percentage of correct responses and lower learning rate under DAAs in ICDs- but not in ICDs+<sup>5</sup>

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## Declarations of interest

None.

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### c. Synthèse & Perspectives

Alors que les mécanismes neuropsychologiques sous-tendant les TCI sont actuellement à l'étude, les bases neuro-fonctionnelles de ces troubles n'en sont finalement que plus complexes. Notre analyse systématique révèle que :

1/ Malgré le nombre grandissant d'études sur le sujet (843 articles référencés sur PubMed), seules 11 études se sont intéressées aux bases neurales des TCI en comparant des patients parkinsoniens TCI+ et TCI- en IRMf ou SPECT. La plupart (7/11) a enregistré l'activité cérébrale au repos ; les autres ont utilisé des tâches comportementales en se focalisant sur les processus liés à la motivation et à la prise de risque. La disparité des méthodes utilisées ne nous permet pas de réaliser une méta-analyse sur le sujet.

2/ Les études actuelles présentent des résultats inconsistants et ne permettent pas de conclure sur les bases fonctionnelles des TCI.

3/ La plupart des études (9/11) n'a pas cherché d'altérations associées à des processus neurocognitifs spécifiques. Les études qui le font se sont uniquement focalisées sur les processus liés à la motivation ou à la prise de risque. Aucune étude ne s'est attelée à révéler l'aspect multi-facette de l'impulsivité.

Finalement, de nombreuses altérations sont observées dans le circuit méso-cortico- limbique, en lien avec les hypothèses neurobiologiques classiques sur l'origine des TCI. Néanmoins, la direction et la localisation précise de ces altérations ne sont pas reproductibles entre les études ne permettant pas de consensus sur les bases neurofonctionnelles des TCI. Au contraire, les altérations sont observées dans un réseau largement distribué et peu reproductible incluant le circuit méso-cortico- limbique mais également de nombreuses autres aires cérébrales regroupant les circuits sensorimoteurs, visuels, le DMN, le réseau attentionnel, le cervelet et de nombreuses aires préfrontales. En conclusion, les bases neurofonctionnelles des TCI semblent

rejeter l'hypothèse d'un déficit purement associé à la voie méso-cortico-limbique et appellent à approfondir l'origine de ces symptômes.

Cette revue systématique nous permet de révéler plusieurs points méthodologiques à l'origine des inconsistances observées dans la littérature et qui devront être considérés dans les futures études neuro-fonctionnelles afin de révéler l'origine des TCI dans la maladie de Parkinson. 1/ Bien que la littérature ait permis de révéler des indices forts sur les bases neurales des TCI, il est à ce jour nécessaire d'utiliser des modèles psychologiques plus sophistiqués et des designs expérimentaux qui permettent de circonscrire l'aspect multi-facette de l'impulsivité. L'évaluation des processus cognitifs sous-tendant les TCI permettrait de révéler l'hétérogénéité de leurs bases neurales, qui reposent probablement d'ailleurs sur des bases neurochimiques distinctes (Nombela et al., 2014). 2/ Des analyses ciblées sur le stimulus (event-related) doivent être réalisées pour distinguer les activités neurales concurrentes et révéler les dysfonctionnements des mécanismes neuropsychologiques à l'origine des TCI.

**L'absence de consensus concernant les bases neuro-fonctionnelles des TCI entravent le développement de solutions thérapeutiques satisfaisantes. Dissocier les fonctions neuropsychologiques qui sous-tendent ces symptômes est aujourd'hui un prérequis pour une meilleure compréhension de ces troubles.**

## B. LA DIFFICULTE A CARACTERISER LES EFFETS DES TRAITEMENTS DE LA MALADIE DE PARKINSON

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En l'absence de traitement curatif, la prise en charge thérapeutique de la maladie de Parkinson comprend principalement des traitements symptomatiques pharmacologiques, chirurgicaux (*cf. Chapitre 1*). A ce jour, les effets de ces traitements sur l'ensemble des symptômes sont encore débattus.

### 1. LA MEDICATION DOPAMINERGIQUE

#### a. Effet de la médication sur l'akinésie

La médication dopaminergique constitue le traitement de référence de la maladie de Parkinson sur la triade motrice dont l'akinésie (*cf. Chapitre 1*). Alors que l'akinésie a été associée avec une hypo-activation de l'AMS suite à l'inhibition anormale des boucles thalamo-corticales (Grafton, 2004; Haslinger et al., 2001; Playford et al., 1992 ; voir Spay et al., submitted - *Chapitre 2* pour revue), la L-Dopa permettrait en effet de normaliser l'activité de l'AMS (Buhmann et al., 2003; Haslinger et al., 2001), ce qui corrèle avec une amélioration des performances motrices chez les patients. Un effet similaire a été observé avec l'apomorphine (agoniste DA) sur l'activation de l'AMS et l'amélioration de l'akinésie et de la bradykinésie (Jenkins et al., 1992).

Mais, à ce jour, l'akinésie n'est pas entièrement restaurée par ces traitements pharmacologiques classiques (Ballanger et al., 2007; Favre et al., 2013; Fox, 2013; Jahanshahi et al., 1992a; Schubert et al., 2002). En effet, il semble que l'effet de la médication DA ait un effet positif sur les tâches de choix (Schubert et al., 2002) ou le TR global dans des tâches d'amorçage (Jahanshahi et al., 1992a), mais ne présente pas d'effet, voire présente même un effet délétère, sur les tâches simples de TR. Ceci pourrait être expliqué par l'absence de bases

neuropsychologiques claires à l'origine de l'akinésie défendue précédemment. En effet, la distinction des différents processus neurocognitifs sous-tendant l'akinésie pourrait permettre une meilleure compréhension de l'effet des traitements. Cette hypothèse est défendue par des travaux récents proposant une origine motrice et exécutive de ce symptôme. En effet, les travaux de (Favre et al., 2013) montrent que si la médication dopaminergique a un effet global probablement d'origine motrice sur le TR (Vaillancourt et al., 2004), elle ne permet pas de restaurer un comportement normal de déverrouillage dans les situations ne nécessitant pas de contrôle exécutif de l'action (*cf. Chapitre 3*). Ainsi, l'effet de cette médication est variable (Espay et al., 2011; Schubert et al., 2002) et ne semble pas améliorer les dysfonctionnements exécutifs à l'origine de l'initiation de l'action chez les patients parkinsoniens (Rowe et al., 2008; Weintraub et al., 2006).

#### b. Effet de la médication sur les TCI

Concernant les effets de la médication dopaminergique sur les TCI, il apparaît important de distinguer les différents traitements. En effet, il semble que les DAAs sont plus susceptibles de produire des TCI que la Levodopa. Dans ce sens, van Eimeren et al. (2009) proposent une dissociation de l'action de ces traitements dans la fente synaptique. Alors que le taux de DA varie de façon naturelle selon la valence d'une action, les DAAs provoquent une augmentation continue de l'activité dopaminergique en agissant sur les récepteurs post-synaptiques, responsable d'une baisse de sensibilité aux conséquences des actions. A l'inverse, la Levodopa présente un effet phasique qui ne perturberait donc pas la modulation du taux de DA suite à la réalisation d'une action.

Une autre explication est proposée, basée sur l'affinité des différents traitements dopaminergiques aux récepteurs dopaminergiques. En effet, les DAAs se lient particulièrement aux récepteurs D3 surtout exprimés au niveau du système limbique (Sokoloff et al., 1990) et

sont responsables de la survenue de TCI (Brusa et al., 2013; Seeman, 2015). Au contraire, la Levodopa présente une affinité pour les récepteurs D1/D2 (Ahlskog, 2011; Gerlach et al., 2003) moins enclins à provoquer des TCI. Néanmoins, la physiopathologie des TCI et leur survenue dans la maladie de Parkinson sont encore débattues. Ainsi, la prise en charge des TCI reste à ce jour très complexe (*cf. Chapitre 1*).

Concernant les processus impliqués, il semble établi que les DAA entraînent une modification de la neurotransmission dans le système de la récompense (hyperactivation dopaminergique méso-cortico-limbique) provoquant une plus forte sensibilité au développement des TCI (Abler et al., 2009; Claassen et al., 2017; Rao et al., 2010; Voon et al., 2011b). Ainsi, il a été proposé que les DAA présentent un impact sur l'impulsivité cognitive mais pas sur l'impulsivité motrice (Antonelli et al., 2014; Leroi et al., 2013). L'utilisation de tâches testant la prise de décision (Delay-discounting task) a montré une plus grande impulsivité cognitive (Leroi et al., 2013; Voon et al., 2010), des TR plus courts (Voon et al., 2010) et une augmentation de la prise de risque (Claassen et al., 2011; Voon et al., 2011a) chez les patients parkinsoniens avec TCI. La médication dopaminergique potentialiserait alors le risque de déclenchement des TCI chez certains patients parkinsoniens (Piray et al., 2014). Or, la DA est impliquée dans le codage de la valence des stimuli et des actions en encodant le signal d'erreur de prédiction. Ainsi, les patients avec TCI sous médication sont plus sensibles aux récompenses et présentent un plus faible apprentissage des erreurs de prédictions négatives et ainsi sous-estiment les conséquences négatives (van Eimeren et al., 2009a). L'effet des DAA semblerait potentialiser un apprentissage par le gain chez les patients souffrant de TCI (Voon et al., 2010). Il semble donc que les DAA aient un effet sur l'impulsivité cognitive chez des patients présentant déjà une susceptibilité aux TCI en induisant des comportements addictifs (Dawson et al., 2018). Il semblerait en revanche que d'autres systèmes de neurotransmetteurs soutiennent l'impulsivité motrice.

### c. La difficulté de dissocier les effets des traitements de l'effet de la maladie

En tant que traitement de référence de la maladie de Parkinson, tous les patients sont sous médication dopaminergique et la réponse à ce traitement constitue même un facteur de diagnostique de la maladie. De ce fait, il est difficile de dissocier l'effet réel de la maladie de l'effet des traitements. L'effet de la maladie est classiquement évalué en testant les patients ON vs. OFF Levodopa. Le statut OFF Levodopa correspond en fait à un retrait de la médication dopaminergique (entre 6 et 12h classiquement) avant l'évaluation des symptômes. Pourtant, les patients sous traitement depuis des années, même OFF Levodopa depuis plusieurs heures, sont sujets à des mécanismes d'habituation aux traitements qui modulent clairement l'expression de la maladie. Pour s'affranchir de ces mécanismes et dissocier l'effet réel de la maladie de l'effet des traitements, il convient de tester des patients de novo, donc récemment diagnostiqués mais pas encore traités (Tahmasian et al., 2015). Ces patients sont difficiles à recruter ce qui explique qu'il existe très peu d'études avec ces patients. Néanmoins, les études ayant testé ce type de patients remettent en cause les hypothèses communément admises sur l'origine des troubles de l'initiation des mouvements.

Ainsi, le lien entre médication dopaminergique et TCI n'est aujourd'hui pas clair. En effet, tous les patients parkinsoniens sous DAAs ne développent pas de TCI (Isaias et al., 2008) ; alors que des TCI sont observées chez des patients de novo qui ne sont pas encore sous traitement (Antonini et al., 2011). Il apparaît alors que les DAAs augmentent le risque de développer des TCI (Weintraub et al., 2006) mais aucun argument ne permet d'affirmer sans équivoque que les DAAs causent les TCI (Evans et al., 2005; Grall-Bronnec et al., 2018; Voon et al., 2007). Il semble donc que : 1/ certains facteurs de risque puissent prédisposer les patients parkinsoniens au développement des TCI ou 2/ que la physiopathologie de ces troubles soient plus complexes et impliquent d'autres systèmes de neurotransmetteurs. Alors que certains

facteurs de risque ont été évoqués (*cf. Chapitre 1*), des prédispositions individuelles pourraient être en rapport avec une topographie différente des lésions de la maladie de Parkinson ou des prédispositions génétiques. A ce jour, des études sont nécessaires afin de révéler des endophénotypes de vulnérabilité et de déterminer leur influence réelle sur la physiopathologie des TCI dans la maladie de Parkinson (Marques et al., 2018; Robbins et al., 2012). De même, bien que des avancées fondamentales ait été faites dans notre compréhension des TCI, d'autres recherches sont nécessaires pour aller au-delà de la DA (Callesen et al., 2013; Williams & Potenza, 2008).

**A ce jour, alors que l'akinésie n'est pas entièrement restaurée par la médication dopaminergique et, face à l'absence de consensus concernant le rôle des DAAs dans le développement des TCI, la prise en charge de ces troubles reste sans solution thérapeutique satisfaisante. D'autres systèmes de neurotransmetteurs sont donc possiblement impliqués (Borchert et al., 2016).**

## 2. LA STIMULATION CEREBRALE PROFONDE

### a. Effet de la SCP sur l'akinésie

Un grand nombre d'études cliniques s'est intéressé à l'effet de la stimulation cérébrale profonde (pallidum ou NST) sur l'akinésie. Elles semblent indiquer qu'une lésion, de même que la SCP du NST ou du GPi, réduisent les activités inhibitrices excessives sur le thalamus et améliorent l'akinésie (Obeso et al., 2009; Wichmann et al., 2011). La plupart des études révèlent que la SCP-NST semble plus efficace que la SCP-GPi sur l'akinésie (Fukaya & Yamamoto, 2015). En effet, la SCP-GPi présente des résultats controversés, dépendant de la localisation au sein du GPi (Krack et al., 1998; Schubert et al., 2002). Au contraire, la SCP-NST présente un effet positif sur les scores moteurs de bradykinésie OFF-traitement (Limousin



et al., 1998) et semble réduire l'akinésie de 57% (Brown et al., 1999; Kumar et al., 1998). Pourtant, comme la médication dopaminergique, la SCP améliore le déficit moteur à l'origine de la bradykinésie mais ne restaure pas complètement la lenteur à l'initiation du mouvement (Vaillancourt et al., 2004).

Pour mieux comprendre ces effets, il est crucial de s'appuyer sur les modèles anatomo-fonctionnels des ganglions de la base et de mieux comprendre le rôle du NST par exemple. Dans ce sens, le travail de (Favre et al., 2013) a permis de révéler que seule la SCP du NST a un effet positif sur le déficit exécutif observé à l'origine de l'akinésie. En effet, la SCP-NST rétablit un pattern normal du contrôle de l'action, i.e., restaure l'akinésie observée chez les patients parkinsoniens. Une meilleure compréhension du contrôle exécutif de l'action pourrait permettre de démêler le rôle du NST et les effets de la SCP-NST chez les patients (*cf. Chapitre 3*).

#### b. Effet de la SCP sur les TCI

L'effet de la stimulation cérébrale profonde sur les TCI est également controversé (Kasemsuk et al., 2017; Kim et al., 2018). Alors que certains auteurs rapportent l'apparition ou une aggravation des TCI suite à l'instauration d'une SCP-NST (Hälbig et al., 2009; Lim et al., 2009; Smeding et al., 2007) ; d'autres ont montré que la SCP-NST pourrait améliorer les TCI, probablement en permettant de réduire les doses de traitements dopaminergiques (Abbes et al., 2018; Amami et al., 2015; Ardouin et al., 2006; Eusebio et al., 2013; Kim et al., 2018; Knobel et al., 2008; Lhommée et al., 2017, 2012; Merola et al., 2017; Weaver et al., 2012; Witjas et al., 2005). Ces résultats contradictoires renforcent le besoin de mieux comprendre le rôle du NST pour démêler l'origine des TCI (Rossi et al., 2015).

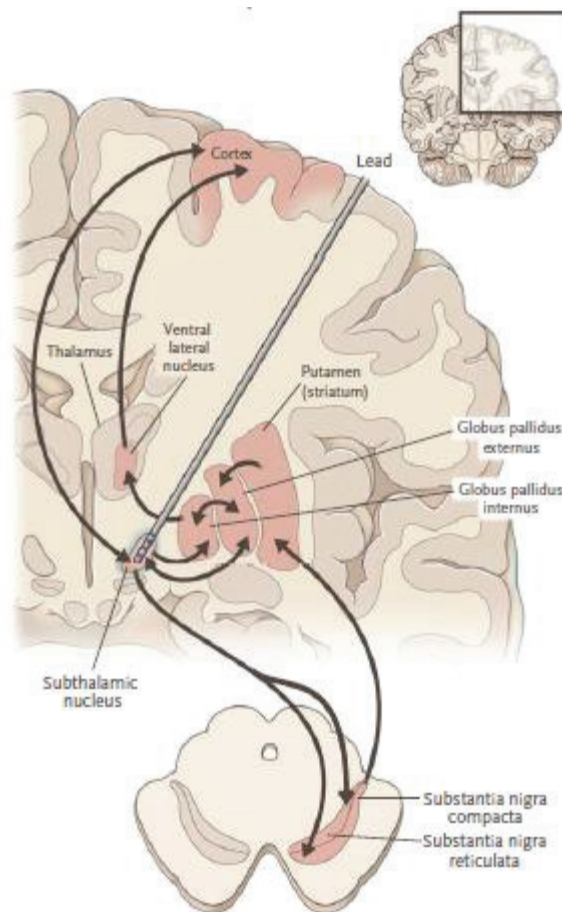
Il reste difficile d'appréhender les effets de la SCP face à l'hétérogénéité des TCI. Il convient de prendre en compte le caractère multi-facette de l'impulsivité en dissociant

l'impulsivité cognitive (choix impulsifs) et l'impulsivité motrice (actions impulsives). Comme proposé par (Antonelli et al., 2014), il apparaît que la médication dopaminergique et la stimulation cérébrale profonde (SCP-NST) influencent différentes formes d'impulsivité. Alors que les DAAs semblent agir essentiellement sur l'impulsivité cognitive, la SCP-NST provoquerait moins de contrôle inhibiteur entraînant plus d'impulsivité motrice chez les patients parkinsoniens (Ray, Antonelli, & Strafella, 2011). Plus précisément, la SCP-NST améliorerait l'impulsivité de choix (Adams et al., 2017; Boller et al., 2014) mais favoriserait l'impulsivité motrice. En d'autres termes, la SCP-NST agirait ainsi positivement sur le contrôle inhibiteur en améliorant l'activation des réponses automatiques (Plessow, Fischer, Volkmann, & Schubert, 2014; van Wouwe et al., 2017), favorisant le risque de développer des réponses impulsives (Frank et al., 2007a; Pote et al., 2016; Rossi et al., 2017; Wylie et al., 2010). Les différentes formes d'impulsivité à l'origine des TCI pourraient ainsi être sous-tendues par des processus cognitifs, des corrélats neuronaux et des bases neurochimiques potentiellement distinctes (Nombela et al., 2014). Ces résultats renforcent le besoin de fractionner l'impulsivité pour mieux comprendre l'origine des TCI.

### c. La difficulté de caractériser les effets de la SCP

La stimulation cérébrale profonde peut aujourd'hui s'opérer sur plusieurs noyaux : principalement, le NST, le GPi, le noyau intermédiaire du thalamus (Vim). La SCP-Vim montre des effets principalement sur les tremblements (Benabid et al., 1987) et ne fera donc pas l'objet de ce travail. De même, la SCP-GPi présente des effets contradictoires (Krack et al., 1998). Nous nous intéresserons donc ici uniquement à la SCP-NST au vu des résultats cliniques observés à la fois sur l'akinésie et sur les TCI, et motivé par le rôle pivot du NST au sein des ganglions de la base. En effet, le NST est un noyau à l'interface entre de multiples circuits cortico-basal ganglio-thalamo-corticaux sous-tendant les fonctions motrices, cognitives et

limbiques (Nambu, 2005). Il est aujourd'hui nécessaire d'identifier les processus neurocognitifs qui sous-tendent l'akinésie et l'impulsivité afin de mieux comprendre les effets spécifiques de la SCP-NST sur ces différentes fonctions. En effet, la SCP-NST semble avoir des effets distincts sur les fonctions motrices et le contrôle exécutif sous-tendant l'akinésie et paraît influencer les différentes formes d'impulsivité (Jahanshahi et al., 2015a). L'effet de la SCP-NST renforce l'idée d'un rôle clé du NST dans le contrôle exécutif de l'action (Jahanshahi, 2013).



**Figure 7 : Effet de la stimulation cérébrale profonde du NST.**

Hypothèses sur les effets de la SCP-NST sur les circuits ganglio-thalamo-corticaux. La stimulation électrique du NST est supposée normaliser l'activité du thalamus vers le cortex  
*Illustration tirée de Okun (2014).*

Pourtant, la compréhension des mécanismes qui sous-tendent la SCP-NST reste à ce

jour imparfaite (*cf. Chapitre 1* ; Fukaya & Yamamoto, 2015). Au niveau cellulaire, les résultats sont contradictoires et il est aujourd'hui débattu de savoir si la SCP a pour effet de réduire ou d'inhiber (Meissner et al., 2005; Welter et al., 2004), d'exciter (Reese et al., 2011) ou de perturber (Chiken & Nambu, 2014, 2016; Rosenbaum et al., 2014) les terminaisons nerveuses. Au niveau des réseaux neuronaux, l'évaluation de l'effet clinique de la SCP-NST sur l'activité neurale est difficile (Ballanger et al., 2009; Obeso et al., 2011). En effet, la SCP-NST produit des effets neurophysiologiques diffus qui s'expliquent par une possible activation de multiples voies et mécanismes (Lozano & Lipsman, 2013). Des effets non spécifiques s'ajoutent à cette complexité en provoquant des mécanismes compensatoires ou compétiteurs entre les activités corticales (Grafton et al., 2006). L'effet de la SCP-NST, qui est censé être inhibiteur, pourrait donc normaliser l'activité des boucles thalamo-corticales en réduisant l'hyperactivité pathologique du NST (Benabid et al., 2000) et en restaurant la balance fonctionnelle entre inhibition et facilitation du réseau fronto-striatal (Jahanshahi & Rothwell, 2017). Une autre hypothèse concerne la possibilité pour la SCP-NST d'agir de façon antidromique sur les réseaux corticaux en modulant l'excitabilité du réseau moteur et en bloquant ainsi l'activité oscillatoire caractéristique des réseaux corticaux dans la maladie de Parkinson (Dejean et al., 2009; Li et al., 2007). Gradinaru et al. (2009) ont, en effet, montré que l'effet thérapeutique bénéfique de la SCP-NST était associé à une activation des afférences de la voie subthalamo-corticale alors qu'aucune activation des efférences du STN n'était observée.

Il est aujourd'hui essentiel d'aller au-delà des modulations électrophysiologiques au niveau du NST pour mieux comprendre les modulations globales des réseaux neuronaux induits par la SCP (Okun, 2014). Pourtant, les opportunités d'évaluer les effets de la SCP sur l'activité cérébrale sont limitées. Ceci s'explique par les limites inhérentes aux méthodes de neuroimagerie, comme l'IRMf qui n'est pas autorisée pour les patients implantés pour des raisons de sécurité, ou comme la TEP dont la résolution temporelle la rend aveugle aux

dynamiques neurales permettant l'accès aux modulations critiques de la SCP. L'utilisation de l'EEG à haute résolution ouvre en revanche aujourd'hui la voie à une meilleure compréhension des modulations corticales de la SCP. En effet, de récentes méthodes de filtrage des artéfacts ont été développées et autorisent l'utilisation de l'EEG avec des patients stimulés (Allen et al., 2010; Lio et al., 2018) en combinaison avec des méthodes avancées de traitement du signal (*cf. Chapitre 3*). Combiné à un logiciel de sur-échantillonnage du signal EEG, cette méthode est en mesure de supprimer les artéfacts liés à la SCP, tout en préservant l'information dans les fréquences d'intérêt.

#### d. Le rôle clé du NST dans la maladie de Parkinson

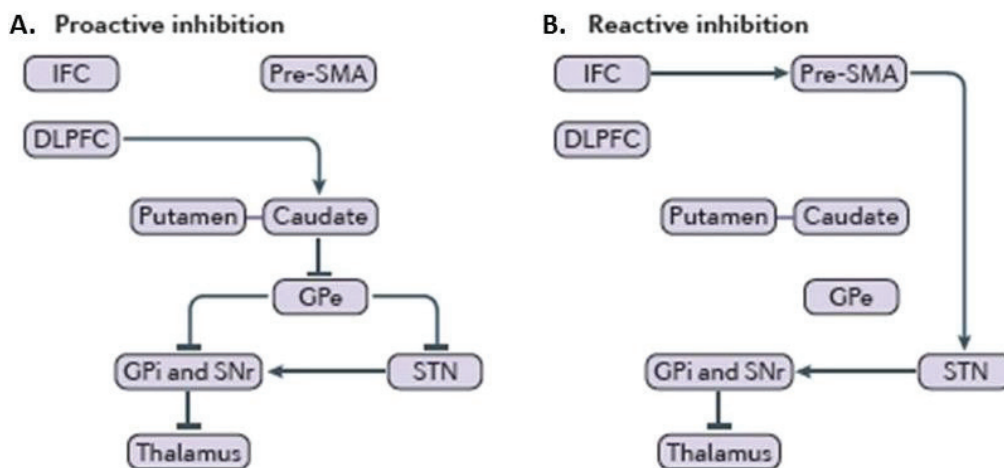
Au sein des ganglions de la base, le GPi et la SNr reçoivent des projections excitatrices du NST. Ce dernier joue donc un rôle essentiel mais mal compris au sein ce réseau.

Un rôle du NST dans l'inhibition de réponse a été mis en évidence par des études de lésions (Baunez et al., 1995; Eagle et al., 2008) et électrophysiologiques (Isoda & Hikosaka, 2008; Schmidt et al., 2013; Yoshida & Tanaka, 2009) chez l'animal, mais également chez l'homme en imagerie fonctionnelle (Aron et al., 2007; Aron & Poldrack, 2006; Chikazoe et al., 2009; Rae et al., 2015; Schel et al., 2014; Zandbelt et al., 2013) et dans la maladie de Parkinson (Gauggel et al., 2004; Obeso et al., 2011; Vriend et al., 2015; Ye et al., 2014). Plus précisément, le NST jouerait différents rôles dans le contrôle inhibiteur de l'action (Baunez & Lardeux, 2011) :

- un rôle phasique via la voie hyperdirecte en relayant le signal d'inhibition de la réponse motrice non désirée de façon réactive au stimulus (Aron, 2011; Frank et al., 2007a).
- un rôle tonique via la voie indirecte pour empêcher de façon proactive le déclenchement de réponses motrices inappropriées (Alegre et al., 2013; Benis et al., 2014; Jaffard et al., 2007, 2008; van den Wildenberg et al., 2006).

- un rôle phasique via la voie hyperdirecte en relayant cette fois le signal de levée de l'inhibition de façon à répondre automatiquement au stimulus dans des situations où le sujet sait par avance (proactif) qu'il devra répondre (Ballanger et al., 2009).

Le NST peut donc être considéré comme le point de convergence entre fonctions motrices et exécutives (Aulická et al., 2014; Nambu, 2005; Temel et al., 2005). Il permet le passage de traitements sensorimoteurs contrôlés à automatiques, une fonction qui requiert une interaction fine entre les mécanismes inhibiteurs toniques et phasiques (Favre et al., 2013).



**Figure 8 : Synthèse des voies ganglio-thalamo-corticales impliquées dans le contrôle inhibiteur.**

Nous formulons ainsi l'hypothèse d'un rôle pivot du NST et du réseau fronto-striato-subthalamo-pallidal dans le contrôle exécutif de l'action (Jahanshahi et al., 2015a, b; *cf. Chapitre 3*) que ce soit à l'origine d'une incapacité à lever le contrôle inhibiteur entraînant une lenteur à l'initiation des mouvements (i.e., akinésie) ou pouvant conduire à une incapacité à réprimer les réponses non désirées conduisant à de l'impulsivité. L'entremise du contrôle exécutif de l'action pourrait donc permettre de revisiter ces symptômes (*cf. Chapitre 4*).

**Les résultats de l'effet de la SCP-NST sur l'akinésie et les TCI renforcent la nécessité : 1/ de mieux comprendre le rôle du NST et les mécanismes de la SCP-NST sur les modulations des réseaux neuronaux ; 2/ de fractionner les processus neurocognitifs à l'origine des troubles de l'initiation du mouvement ; 3/ de revisiter ces symptômes à la lumière du contrôle exécutif de l'action.**

## C. LA DIFFICULTE A CARACTERISER LES BASES NEUROCHIMIQUES DE LA MALADIE DE PARKINSON : NEUROPATHOPHYSIOLOGIE

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### 1. LE SYSTEME DOPAMINERGIQUE

Le système dopaminergique a été largement étudié afin de révéler l'origine des troubles de l'initiation du mouvement dans la maladie (Haber, 2014). L'étude des bases neurochimiques a été facilitée par l'existence des méthodes d'imagerie permettant, au moyen de différents ligands (Thobois et al., 2001), d'étudier la neurobiologie de l'akinésie et des TCI.

#### a. Akinésie et dopamine

Selon le modèle classique, l'akinésie s'explique par un dysfonctionnement du système dopaminergique au sein du circuit moteur, qui relie le cortex moteur aux ganglions de la base (Albin et al., 1989; Alexander & Crutcher, 1990; DeLong, 1990; DeLong & Wichmann, 2007; DeLong & Wichmann, 2009; Michely et al., 2015; Obeso et al., 2008). La dégénérescence dopaminergique serait donc responsable d'altérations de la balance entre la voie directe (hypoactivation) et la voie indirecte (hyperactivation), qui entraîneraient une augmentation de l'activité du NST et du GPi et auraient pour conséquence une augmentation de l'inhibition thalamo-corticale (i.e., une lenteur à l'initiation des mouvements) (Obeso et al., 2008). Ainsi, l'akinésie résulterait de la dégénérescence dopaminergique au niveau des boucles thalamo-corticales. Ce consensus s'appuie sur des études TEP permettant au moyen de différents ligands d'étudier le système dopaminergique. Dans ce sens, l'utilisation du [<sup>123</sup>I]-FP-CIT en SPECT a permis de montrer que la sévérité de l'akinésie était corrélée avec l'intégrité des terminaisons nerveuses dopaminergiques au niveau du striatum chez des patients akinéto-rigides ou



bradykinétiques (Benamer et al., 2000; Rossi et al., 2010; Schillaci et al., 2011; Spiegel et al., 2007). Néanmoins, l'interprétation des résultats utilisant le [<sup>123</sup>I]FP-CIT reste délicate au vu de son affinité à la fois pour les transporteurs de la 5-HT et de la DA. Mais l'origine dopaminergique de l'akinésie a été confirmée par des études utilisant la 6-L-[<sup>18</sup>F]Fluorodopa, permettant d'évaluer la fonctionnalité des voies dopaminergiques nigrostriatales, qui observent une corrélation entre le score de bradykinésie et une diminution de la recapture dopaminergique au niveau du striatum (Otsuka et al., 1996; Vingerhoets et al., 1997).

Pour autant, ces études ne sont pas exemptes des limites méthodologiques soulevées dans notre analyse systématique (Spay et al., submitted – *Chapitre 2*) concernant la définition de l'akinésie et la caractérisation du sous-type akinéto-rigide qui ne révèle pas spécifiquement l'akinésie mais seulement des corrélats d'une forme prédominante de la maladie. Qui plus est, ce modèle impliquant uniquement les ganglions de la base et le système dopaminergique ne permet pas d'expliquer certaines observations cliniques. En effet, bien que la dénervation dopaminergique striatale provoquée expérimentalement chez l'animal altère l'initiation de l'action (Carli et al., 1985) et constitue un argument en faveur de l'origine dopaminergique de ce symptôme, les données chez le patient parkinsonien sont plus contradictoires. Par exemple, le fait que les lésions du thalamus moteur n'entraînent pas d'akinésie (Canavan et al., 1989), et l'absence d'amélioration de ce symptôme par les lésions du globus pallidus (Marsden & Obeso, 1994) remettent en cause ce modèle.

A ce jour, il semble plus probable que le système dopaminergique soit impliqué dans la physiopathologie de la bradykinésie dont les sous-scores de l'UPDRS-III ont été corrélés avec la déplétion dopaminergique au niveau striatale. Des études précurseurs avaient révélé une distinction entre la sévérité de l'akinésie et de la bradykinésie chez les patients parkinsoniens, dissociant la physiopathologie de ces symptômes (Evarts et al., 1981).

**L'absence de distinction claire dans la littérature entre bradykinésie et akinésie stricto sensu remet aujourd'hui en cause le lien entre le système dopaminergique et la physiopathologie de l'akinésie. Il semble donc que d'autres systèmes de neurotransmetteurs puissent être impliqués.**

#### b. TCI et dopamine

L'utilisation des différents traceurs en TEP, présentant des affinités pour des récepteurs différents, a également permis d'appréhender les bases neurochimiques des TCI (Verger et al., 2018). L'utilisation de traceurs se fixant aux récepteurs post-synaptiques permet de révéler la libération de DA dans la fente synaptique. Ainsi, l'utilisation du [<sup>11</sup>C]-(+)-PHNO (ligand des récepteurs dopaminergiques D3) au niveau des ganglions de la base, a permis à Payer et collaborateurs (2015) de révéler une plus faible fixation du traceur chez les patients parkinsoniens avec des TCI au niveau du striatum ventral (Payer et al., 2015). Ces résultats sont consistants avec ceux de Steeves et collaborateurs (2009) qui ont montré une plus forte diminution du potentiel de liaison du [<sup>11</sup>C]Raclopride (antagoniste des récepteurs dopaminergiques D2), au niveau du striatum ventral chez les patients avec TCI (Steeves et al., 2009). Un autre radio-ligand le [<sup>11</sup>C]-FLB-457, qui présente une forte affinité pour les récepteurs dopaminergiques D2/D3 extra-striataux, a de son côté permis de mettre en évidence une augmentation du potentiel de liaison du traceur chez les joueurs pathologiques parkinsoniens au niveau du cortex cingulaire antérieur -CCA- lors d'une tâche de récompense (Ray et al., 2012). Les résultats de ces études suggèrent une plus forte libération de DA au niveau du striatum ventral chez les patients avec TCI, associée à une plus faible libération de DA au niveau extra-striatal.

L'étude du système dopaminergique permet également d'explorer spécifiquement les transporteurs de la dopamine au niveau pré-synaptique, lié à la recapture de la DA. Au niveau striatal, l'utilisation du [<sup>123</sup>I]-FP-CIT a révélé que les patients joueurs pathologiques présentent une diminution de la fixation du traceur aux transporteurs dopaminergiques au niveau du striatum ventral par rapport à des patients parkinsoniens contrôles (Cilia et al., 2010). Une réduction similaire dans une population plus large de TCI a été observée dans le striatum de façon plus globale (Voon et al., 2014). Ces résultats, associés à l'observation d'une plus grande libération de DA au niveau du striatum ventral, sont en faveur d'une plus grande dénervation dopaminergique, d'une régulation négative du nombre de transporteurs de la DA au niveau pré-synaptique ou d'une expression membranaire des transporteurs diminuée de manière constitutive au niveau striatal. Au niveau extra-striatal, l'utilisation [<sup>18</sup>F]-FP-CIT permet également l'étude des transporteurs de la DA en dehors du striatum. Grâce à son utilisation, il a été démontré que les patients avec TCI présentent une fixation plus importante au niveau du cortex cingulaire postérieur -CCP- droit et du cortex ventromédial préfrontal droit (Lee et al., 2014). Ce résultat suggère une régulation positive des transporteurs dopaminergiques extra-striataux, ou une relative préservation des voies dopaminergiques méso-corticales, qui pourrait être un facteur de risque des TCI (*cf. Chapitre 1 – hypothèse de l'overdose*). Néanmoins, le [<sup>18</sup>F]-FP-CIT a une affinité croisée pour les transporteurs de la DA et de la 5-HT, rendant l'interprétation de ces résultats délicate.

Les études d'imagerie fonctionnelle centrées sur l'analyse des voies dopaminergiques soulignent l'implication du réseau dopaminergique méso-cortico-limbique dans la survenue des TCI au cours de la maladie de Parkinson. Néanmoins, les études ne parviennent pas à démêler la physiopathologie de ces troubles car les résultats s'avèrent difficiles à interpréter (Meyer\*, Spay\* et al., under revision). Des altérations du circuit méso-cortico-limbique ont été identifiées regroupant le cortex orbito-frontal, le CCA, l'amygdale et le striatum ventral (Frosini et al.,

2010a; Politis et al., 2013). De nombreuses études utilisant des tâches de récompense avec des stimuli motivationnels révèlent une hyperactivité du circuit méso-cortico-limbique qui modifierait l'appétence de la récompense et, au contraire, entraînerait une sous-estimation des pertes et conséquences négatives chez les patients avec TCI (Piray et al., 2014). Les études d'imagerie mettent en évidence une sensibilisation du striatum ventral aux stimuli appétitifs (Evans et al., 2006; O'Sullivan et al., 2011). Ces résultats sont compatibles avec la modélisation des comportements addictifs (dont les CIC) comme dysfonctionnement des mécanismes de traitement de la récompense (Berridge, 2007; Robinson & Berridge, 2008).

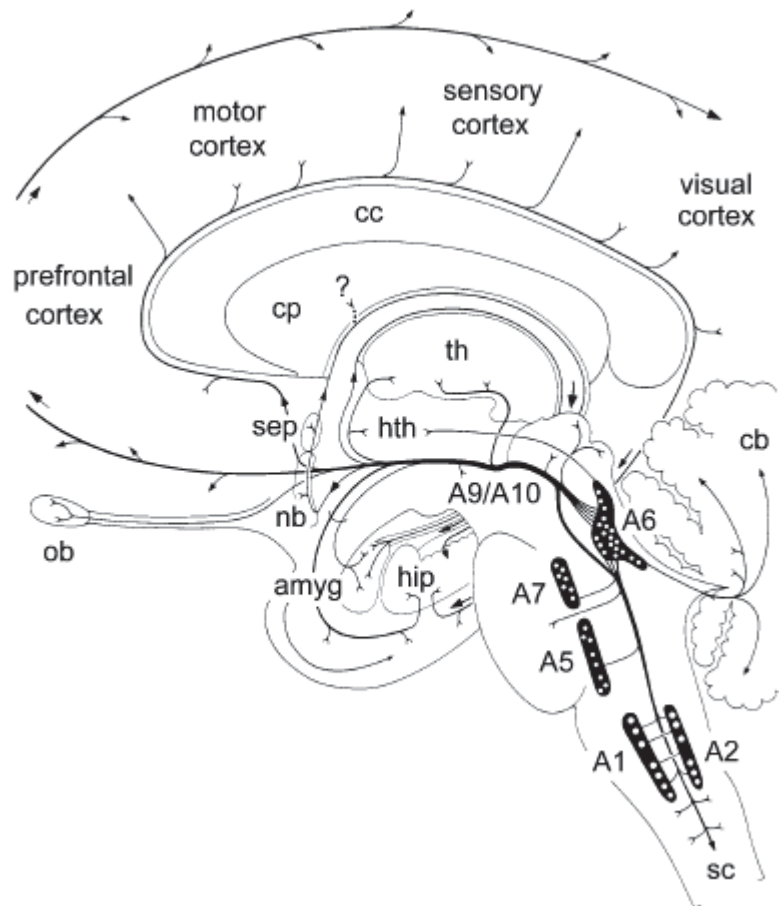
En conclusion, les études sur l'origine des TCI se sont principalement intéressées aux neuromodulations du système dopaminergique associées à la prise de décision et aux comportements de risque chez les TCI (Probst & van Eimeren, 2013; Williams & Potenza, 2008). Le circuit méso-cortico-limbique a été longuement investigué, avec un focus particulier sur le striatum ventral et le cortex préfrontal ventromédian (Lee et al., 2014; Payer et al., 2015; Ray et al., 2012; Steeves et al., 2009).

**Malgré l'étendu de la littérature disponible (cf. Aracil-Bolaños & Strafella, 2016; Cossu et al., 2018; Marques et al., 2018; Napier et al., 2015; Voon et al., 2017b; Vriend, 2018; Weintraub & Claassen, 2017 pour des revues extensives), il n'existe aujourd'hui pas de consensus clairs sur l'origine des TCI dans la maladie de Parkinson (Grall-Bronnec et al., 2018).**

## 2. L'HYPOTHESE NORADRENERGIQUE

L'atteinte du système noradrénergique (i.e., les neurones noradrénergiques du locus coeruleus –LC- ; Figure 9) jouerait un rôle clé dans la progression de la maladie de Parkinson, voir même précéderait la dégénérescence dopaminergique (Braak et al., 2004; Ferrer et al.,

2012; Marien et al., 2004; Zarow et al., 2003). La déplétion noradrénergique interagirait avec la pathophysiologie du système dopaminergique en favorisant la susceptibilité des neurones dopaminergiques à la dégénérescence (Fornai et al., 2007).



**Figure 9 : Groupes de neurones noradrénergiques et projections vers le cerveau chez l'Homme**

Le LC (A6) innerve de façon diffuse l'ensemble du cortex. Les noyaux dopaminergiques du mésencéphale, la SN (A9) et l'ATV (A10) sont également visibles. En effet, les projections noradrénergiques du LC influencent le fonctionnement du système dopaminergique nigro-striatal. *Illustration tirée de Marien et al., 2004.*

La noradrénaline (NA) est principalement connue pour son rôle non spécifique dans l'attention et l'éveil (Aston-Jones & Cohen, 2005; Sara, 2009). Mais la NA présente aussi un rôle spécifique sur de nombreuses fonctions cognitives et motrices (Borodovitsyna et al., 2017;

Chamberlain & Robbins, 2013). Le système LC-NA semble impliqué dans la prise de décision et la sélection de réponse (voir Aston-Jones & Cohen, 2005 pour revue) et associé au contrôle exécutif de l'action (Mückschel et al., 2017). Il a également été impliqué dans le jeu pathologique (Potenza et al., 2002). L'activité noradrénergique centrale est en effet augmentée chez les joueurs pathologiques. Ce résultat est cohérent avec l'observation d'une augmentation des comportements impulsifs dans la maladie de Parkinson suite à l'augmentation du tonus noradrénergique par un inhibiteur sélectif de la recapture de la NA (Atomoxétine) (Kehagia et al., 2014). Un rôle de la NA sur les fonctions exécutives a donc été proposé à l'origine de l'impulsivité chez les patients parkinsoniens (ibid). Mais peu d'études se sont intéressées à l'effet de la manipulation noradrénergique sur le contrôle inhibiteur chez les sujets sains (Chamberlain & Robbins, 2013 pour revue) et les patients parkinsoniens. De récentes études suggèrent un effet de la médication noradrénergique (Atomoxetine) sur l'inhibition de réponse chez les patients parkinsoniens (Rae et al., 2016; Ye et al., 2015) en restaurant la connectivité des réseaux préfrontaux liés aux fonctions exécutives (Borchert et al., 2016).

Anatomiquement, le LC, la structure majeure de synthèse de la NA, se projette sur le NST (Canteras et al., 1990). Des travaux récents chez l'animal ont mis en évidence un rôle direct de la NA dans le pattern de décharge du NST (Belujon et al., 2007; Delaville et al., 2012; Marien et al., 2004). Or, au vu du rôle pivot mais multifacette du NST dans l'inhibition de réponse, son implication est possible dans l'effet de la NA. De même, il a été récemment proposé que la NA pourrait jouer un rôle direct dans l'activité (pathologique et restaurée) du NST chez l'homme (Albares et al., 2015b). Cette étude comportementale a révélé un effet de la clonidine, qui réduit le tonus noradrénergique, sur l'effet positif de la SCP-NST sur les mécanismes exécutifs de verrouillage du contrôle de l'initiation de l'action (i.e., l'akinésie).

Néanmoins, des évidences directes chez l'homme d'une modulation de l'activité cérébrale induite par la NA ne sont à ce jour pas disponibles. En effet, le rôle du système

noradrénergique est difficile à cerner au moyen d'études directes chez l'homme car aucun traceur n'est à ce jour disponible en TEP (Lehto et al., 2015; Phan et al., 2015). Le système noradrénergique est donc étudié au moyen de manipulation pharmacologique combinée à des investigations en neuroimagerie ou électrophysiologie (Devos et al., 2007; Espay et al., 2011; Moreau et al., 2012). Néanmoins, certains agents pharmacologiques ne sont pas autorisés en France (e.g., Atomoxétine), ou ne sont pas sélectifs de la NA (e.g., Méthylphénidate, inhibiteur non sélectif de la recapture de la DA et de la NA).

**En conclusion, il semble que le système noradrénergique : 1/ joue un rôle crucial dans les dysfonctionnements de l'inhibition de réponse, 2/ pourrait être impliqué à la fois dans la symptomatologie de l'akinésie et de l'impulsivité, 3/ serait couplé à l'activité du NST. Mais à ce jour, le système noradrénergique et ses implications dans la physiopathologie de la maladie de Parkinson largement inexplorés.**

### 3. AUTRES SYSTEMES

Comme décrit par Braak et al (2004, 2008), la neuropathologie de la maladie de Parkinson impliquerait également la dégénérescence d'autres systèmes comme le système sérotoninergique (noyau du raphé), cholinergique (noyau basal de Meynert, locus subcoeruleus et noyau pédonculopontin), adrénérergique (medulla oblongata) dès le deuxième stade (Figure 1). La dégénérescence précoce de ces systèmes pourrait être à l'origine du développement de nombreux symptômes moteurs et non-moteurs de la maladie (Fox et al., 2008; Martínez-Fernández et al., 2016) incluant les troubles du sommeil, de l'humeur (anxiété, dépression) et de la cognition. Par exemple, les dysfonctionnements sérotoninergiques seraient impliqués dans le tremblement, la genèse des dyskinésies (Doder et al., 2003; Loane et al., 2013; Politis et al., 2014) mais également dans l'anxiété, la dépression et l'apathie (Maillet et al., 2016; Paulus &

Jellinger, 1991; Thobois et al., 2017). Les dysfonctionnements cholinergiques seraient eux impliqués dans la genèse des troubles de la marche et cognitifs (Bohnen & Albin, 2011; Müller & Bohnen, 2013).

L'intérêt de l'étude des systèmes non-dopaminergiques est donc grandissant en vue du développement de nouvelles stratégies thérapeutiques pour pallier aux symptômes résistants aux traitements dopaminergiques standards (Fox et al., 2008). A l'heure actuelle, il existe de nombreux radiotraceurs pour l'imagerie TEP des récepteurs sérotoninergiques (principalement pour les récepteurs 5-HT<sub>1A</sub> ; Halldin et al., 2001; Kumar & Mann, 2007; Pike et al., 2001 ; cf. Pagano et al., 2017 pour revue extensive) permettant l'étude de ce système dans la maladie.

**La physiopathologie de la maladie de Parkinson est donc plus complexe que la dégénérescence dopaminergique nigro-striée communément admise (Braak & Del Tredici, 2008).**



## Conclusion - Chapitre 2

Les troubles de l'initiation de l'action dans la maladie de Parkinson sont très invalidants et sans solution thérapeutique satisfaisante. Nous avons identifié dans la littérature trois obstacles à une meilleure compréhension de ces troubles :

- Les fonctions neuropsychologiques à l'origine de ces troubles sont difficiles à caractériser.
  - Les effets des traitements restent débattus et sont difficiles à évaluer.
  - Les bases neurochimiques semblent plus complexes que la seule dégénérescence dopaminergique communément admise mais le rôle des systèmes non-dopaminergiques reste difficile à appréhender.
- ➔ De récents travaux suggèrent que les troubles de l'initiation du mouvement qui sont DA-résistants, sont dus à un dysfonctionnement exécutif, non-moteur. Le contrôle exécutif de l'action pourrait jouer un rôle clé.

# CHAPITRE 3 : L'ENTREMISE DU CONTROLE EXECUTIF DE L'ACTION

Dans ce troisième chapitre, nous tenterons de mieux cerner la fonction d'inhibition de réponse – des modèles théoriques, aux marqueurs comportementaux et anatomo-fonctionnels. Notre objectif est d'appréhender le contrôle exécutif de l'action, possiblement impliqué dans les troubles de l'initiation du mouvement dans la Maladie de Parkinson.

## A. LA DIFFICULTE A CARACTERISER LA FONCTION D'INHIBITION DE REPONSE

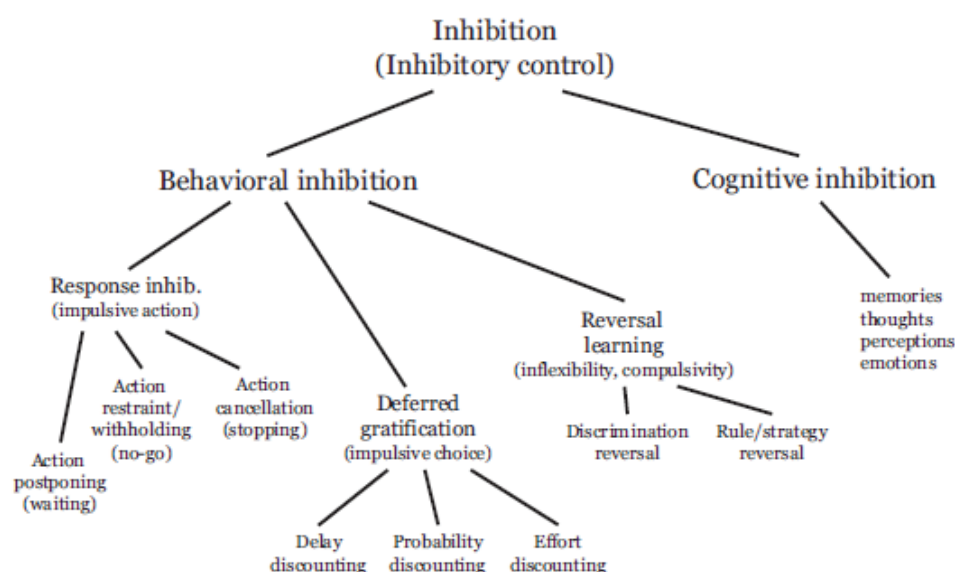
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Alors que nous recevons en permanence une multitude de stimulations, **l'inhibition de réponse** est la fonction qui nous permet de ne pas répondre à la plupart de ces stimuli et d'adopter, au contraire, un comportement adapté à la situation. Cette fonction a pour finalité d'empêcher le déclenchement d'une réponse motrice inappropriée ou non désirée (Bari & Robbins, 2013; Verbruggen & Logan, 2008b). Bien que cette fonction joue un rôle central dans le contrôle de l'action, le contrôle inhibiteur reste à ce jour difficile à appréhender et son rôle probablement sous-estimé. Ce travail de thèse repose pourtant sur l'hypothèse d'un rôle clé de ces processus inhibiteurs dans le contrôle de l'action dans la maladie de Parkinson. Nous analyserons tout d'abord différents aspects méthodologiques qui concourent à l'ambiguïté de la définition de l'inhibition de réponse dans le contrôle de l'action et de son étude. Nous proposerons alors des amendements méthodologiques pour revisiter ces dysfonctionnements dans la maladie de Parkinson.

## 1. MODELES DE L'INHIBITION DE REPONSE

Une première difficulté dans la caractérisation de la fonction d'inhibition de réponse repose sur la complexité de sa définition et de sa modélisation qui restent aujourd'hui incomplètes.

Concernant sa définition, différentes formes d'inhibition peuvent être dissociées (Figure 10 ; Bari & Robbins, 2013) mettant en évidence le caractère multi-facette de cette fonction.



**Figure 10 : Subdivision des différentes formes d'inhibition selon Bari & Robbins (2013).**

Les auteurs ont dissocié l'inhibition comportementale (regroupant 'response inhibition', 'reversal learning' et 'delay discounting') de l'inhibition cognitive. Dans le cas de l'inhibition de réponse (i.e., actions impulsives), l'action est restreinte au sens large, c'est-à-dire qu'elle est soit supprimée, soit retardée. Dans les deux autres types d'inhibition comportementale, il s'agit d'inhiber une réponse qui a précédemment été source de gratification (i.e., compulsivité) ou d'inhiber une réponse malgré une récompense immédiate pour se tourner vers un choix plus gratifiant mais sur le long terme (i.e., choix impulsifs). *Illustration tirée de Bari & Robbins, 2013.*

Certains auteurs se prémunissent de la nécessité de modéliser l'inhibition de réponse en considérant que l'inhibition est un processus intrinsèque des mécanismes de prise de décision ou de sélection de réponse (Koechlin et al., 2003; Siegel et al., 2011). Pourtant, l'inhibition de réponse ne se limite pas à cette fonction de sélection de réponse et il semble coexister deux

processus neurocognitifs distincts (Bender et al., 2016). Ainsi, l'inhibition de réponse est une fonction pivot du contrôle exécutif, un ensemble de processus cognitifs impliqués dans l'organisation d'actions complexes (Heyder et al., 2004; Hofmann et al., 2012; Norman & Shallice, 1986). Ainsi, l'inhibition de réponse peut également être impliquée dans le verrouillage des processus de déclenchement du mouvement, la décision de ne pas agir (Brass & Haggard, 2008), ou encore dans l'annulation d'une action en cours de préparation ou d'une action déjà engagée (Aron, 2011; Logan et al., 1984). Dissocier l'inhibition de réponse (concourant à l'impulsivité motrice) des mécanismes de prise de décision (concourant à l'impulsivité cognitive) pourrait permettre de révéler les dysfonctionnements des troubles du contrôle du mouvement (*cf. Chapitre 2*).

Lorsque l'on aborde l'inhibition de réponse, plusieurs types de modèles émergent de la littérature (Aron, 2011; Jaffard et al., 2008; Verbruggen & Logan, 2008b). Une distinction selon le niveau de contrôle de l'action dissocie des mécanismes inhibiteurs contrôlés vs automatiques (Jahanshahi et al., 2015b; Sumner et al., 2007; Verbruggen & Logan, 2008a). Alors que l'inhibition de l'action automatique n'est pas volontaire, l'inhibition contrôlée serait intentionnelle. Néanmoins, cette distinction n'est pas immuable, étant donné que l'inhibition volontaire peut devenir automatique par l'apprentissage (Verbruggen et al., 2014). Une autre distinction porte sur la sélectivité de ces mécanismes d'inhibition. L'inhibition est parfois supposée **non sélective** en ce sens qu'elle est censée s'appliquer à tout mouvement ; ou considérée comme **sélective** lorsqu'elle cible une représentation motrice particulière. Une autre distinction classique porte sur le caractère temporel de ces mécanismes d'inhibition. On distingue l'inhibition **réactive** qui permet de stopper une action engagée suite à un stimulus externe ; alors que l'inhibition **proactive** est prospective et nécessaire avant l'apparition du stimulus. Dans le cadre de ce travail de thèse, nous ne détaillerons pas l'ensemble des modèles

mais nous proposons de les catégoriser selon ces deux axes : leur sélectivité (sélectif vs. non sélectif) et leur temporalité (réactif vs. proactif).

#### a. Modèles réactifs sélectifs

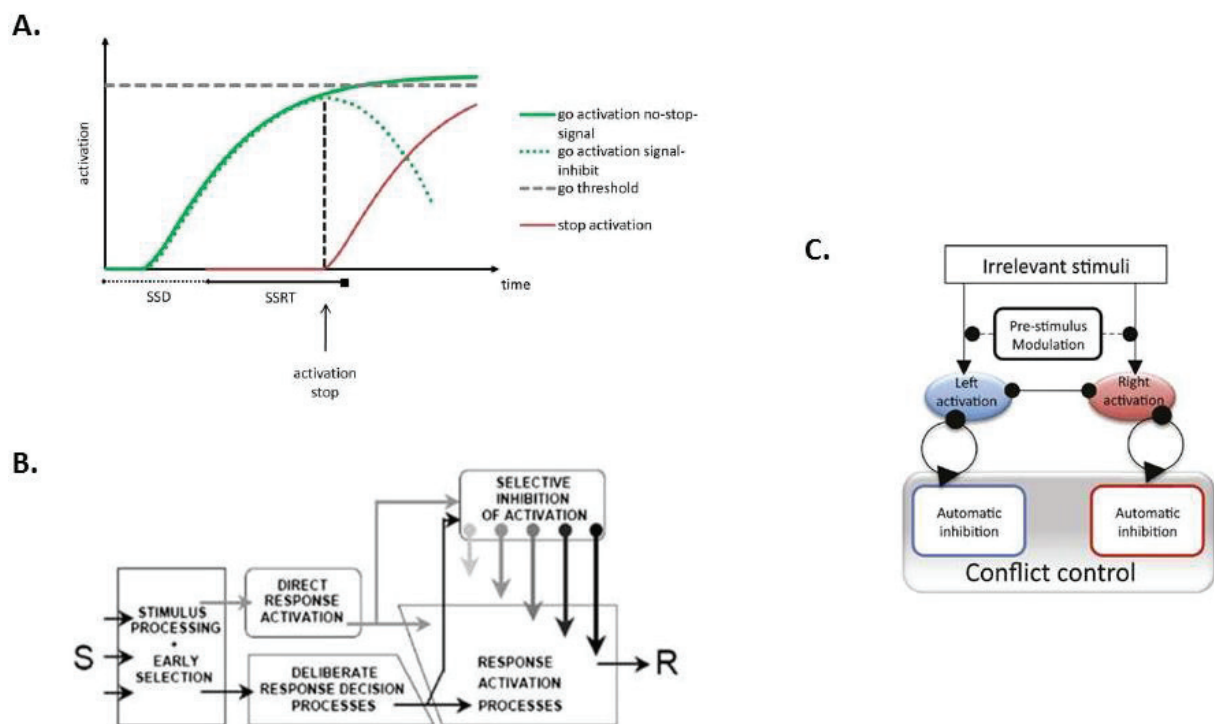
Les modèles dominants s'appuient sur l'hypothèse selon laquelle l'activité inhibitrice est spécifiquement déclenchée par l'identification du stimulus qui impose de supprimer l'action en cours (stop) ou auquel il convient de ne pas réagir (nogo). Dans ce sens, l'inhibition de réponse est assimilée à un processus phasique et sélectif déclenché par le stimulus auquel il ne faut pas répondre (post-stimulus). Cette condition d'inhibition de la réponse motrice est classiquement comparée à une condition de référence où l'inhibition n'est pas censée être mise en jeu. Cette condition de référence est constituée d'essais pour lesquels il convient de répondre (go). Les deux types d'essais (go vs. nogo/stop) sont présentés de façon aléatoire au sein de blocs d'essais (bloc mixte). Ainsi, une concurrence directe entre les mécanismes co-occurents excitateurs activateurs de la réponse motrice et inhibiteurs est donc supposée.

A ce jour, les modèles sélectifs réactifs regroupent (Figure 11) :

- Le **Race Model** : il s'agit du modèle le plus populaire qui reprend la métaphore d'une course entre ces mécanismes excitateurs et inhibiteurs qui entrent alors en compétition pour l'atteinte d'un seuil d'activation (Logan et al., 1984). L'objectif pour le processus inhibiteur est d'atténuer l'activation excitatrice de façon à ce que celle-ci ne dépasse pas le seuil de déclenchement du mouvement.
- Le **Dual Route Model** (Eimer, 1995; Forstmann et al., 2008; Kornblum et al., 1990; Ridderinkhof, 2002) suppose que tout comportement implique des activations motrices automatiques qu'il est nécessaire de réprimer. Il s'applique à des tâches complexes de TR de choix mettant en jeu un conflit entre plusieurs réponses possibles et impliquant des mécanismes de prise de décision. Une confusion entre les processus inhibiteurs et d'autres

processus inhérents aux tâches complexes pourrait remettre en cause l'application de ce modèle à des protocoles expérimentaux plus simples.

- Le **modèle d'inhibition sélective automatique** s'accorde sur l'idée d'activations motrices automatiques intrinsèques à tout comportement mais suggère par contre que l'inhibition sélective est automatique et inconsciente (Sumner, 2008; Sumner & Husain, 2008; Sumner et al., 2007).



**Figure 11 : Modèles réactifs sélectifs.**

**A. Race Model.** L'activation excitatrice est provoquée par la présentation d'un signal auquel le sujet doit répondre (go, vert). L'activation inhibitrice est déclenchée par la présentation soit d'un stimulus stop nécessitant de supprimer la réponse motrice quelques millisecondes plus tard, soit d'un stimulus nogo présenté séparément et auquel il convient de ne pas répondre. *Illustration tirée de Verbruggen et Logan, 2008.* **B. Dual Route Model.** Il existe un conflit entre des réponses automatisées de courte latence et des réponses contrôlées, volontaires et de longue latence représentées par deux voies co-occurentes. Lorsque la réponse correcte ne correspond pas à la réponse automatiquement activée, des processus inhibiteurs sont mis en jeu pour retenir cette dernière. L'inhibition est alors sélective et phasique et des processus moteurs engagés dans la réponse erronée. S = stimulus; R = réponse. *Illustration tirée de Ridderinkhof, 2002.* **C. Modèle de l'inhibition automatique sélective.** L'inhibition est ici une composante du contrôle cognitif. La modulation de la sensibilité de l'inhibition s'applique spécifiquement à chaque effecteur par l'attention et le but de la tâche. *Illustration tirée de Boy et al., 2010.*

## b. Modèles réactifs non sélectifs

Les modèles réactifs non sélectifs supposent, dans des tâches de prise de décision complexes, que toutes les réponses potentielles sont inhibées par un signal « nogo global » non sélectif, pour laisser le temps nécessaire pour décider du choix à faire.

- Le « **Hold your Horses** » **Model** (Frank, 2006, 2011; Frank et al., 2007b) est un modèle neuro-computationnel de prise de décision dans des situations dites « gagnantes-gagnantes », c'est-à-dire pour laquelle un choix doit être fait entre plusieurs options positives (e.g., de la glace ou un gâteau au chocolat en dessert ?). Alors que le domaine d'application de ce modèle se limite à des tâches probabilistiques complexes et n'est pas testé chez les patients, il serait pourtant susceptible de rendre compte d'une forme de contrôle exécutif mise en jeu dès lors que la situation exige un choix, ne serait-ce que le choix de répondre ou pas (i.e., comme lors d'un go/nogo).
- Le **What When Whether modèle** (Brass & Haggard, 2008) dissocie les différents mécanismes relatifs à la prise de décision de quelle action doit être exécutée (what), de quand l'initier (when), de ceux en lien avec le choix d'exécuter ou non cette action (whether).
- Le **Modèle du contrôle de l'impulsion** dissocie plusieurs mécanismes inhibiteurs co-occurrents dans le cadre de la préparation du mouvement (Duque & Ivry, 2009; Duque et al., 2012, 2010). Un premier mécanisme inhibiteur, appelé processus de « compétition-résolution », est impliqué dans la sélection de la réponse à produire vs. la réponse à inhiber. Un deuxième mécanisme inhibiteur, appelé « contrôle des impulsions » permet de contrôler le moment d'exécution de la réponse sélectionnée et d'empêcher l'initiation prématurée ou non désirée de la réponse motrice (Duque et al., 2012, 2010). Ces processus de contrôle des impulsions peuvent être assimilés à une forme de contrôle inhibiteur réactif

non-sélectif. Néanmoins, ce modèle s'applique également à des tâches de choix, ce qui augmente de fait la complexité de la tâche cognitive.

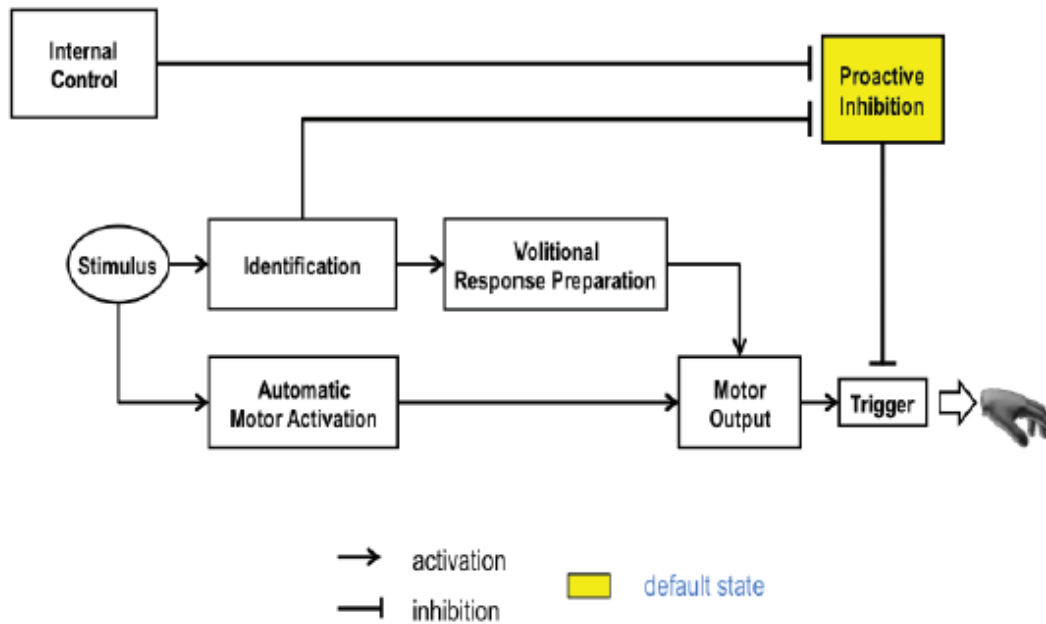
### c. Modèles proactifs sélectifs

Récemment, des modèles proactifs sélectifs ont émergé et entrevoyent la possibilité d'inhiber sélectivement une action avant même l'apparition du stimulus auquel il ne faut pas répondre (e.g., Aron, 2011). Ces processus inhibiteurs proactifs sélectifs sont retrouvés sous les termes de contrôle proactif (Aron, 2011; Cai et al., 2011; Stuphorn et al., 2010), parfois d'inhibition proactive (Benis et al., 2014; Zandbelt et al., 2011), ou de « préparation à stopper » (Aron, 2011; Jahfari et al., 2012). Ces mécanismes ne correspondraient pas à de l'inhibition à proprement parler mais concernent en fait une pré-activation de processus sélectifs comme une préparation anticipée d'une réponse motrice spécifique (Hu & Li, 2012). Ainsi, il pourrait plutôt s'agir d'une modulation proactive comme une activité préparatoire, tel que proposé par le modèle d'inhibition sélective automatique (Boy et al., 2010; Sumner et al., 2007).

### d. Modèles proactifs non sélectifs

Le **modèle proactif non-sélectif** est le négatif du modèle réactif sélectif classique. Il s'agit d'un modèle alternatif qui propose l'existence de mécanismes de verrouillage anticipé des processus d'initiation du mouvement lorsque le contexte est incertain. Les processus inhibiteurs seraient alors actifs, toniques et effectifs avant l'apparition des stimuli dans le but de verrouiller le déclenchement de tout mouvement. Ce contrôle inhibiteur proactif s'appliquerait de façon non sélective, il permettrait donc de refréner indifféremment tous les stimuli susceptibles d'être présentés et potentiellement inappropriés à la situation ou non désirés (Figure 12).





**Figure 12 : Le modèle du contrôle inhibiteur proactif.**

L'inhibition proactive non-sélective s'applique sur les mécanismes de déclenchement de l'initiation du mouvement en condition d'incertitude, et représenterait l'état par défaut du contrôle exécutif (Criaud et al., 2012). Ce verrouillage permet de prévenir les réponses automatiques, dans le but de laisser du temps pour la mise en place des mécanismes de préparation volontaire de la réponse motrice. C'est l'identification du stimulus auquel il faut répondre qui permet la levée de cette inhibition proactive non-sélective. Elle peut également être déverrouillée par anticipation par un contrôle interne (lorsque le contexte encourage les réactions automatiques rapides pour tout événement à venir), ou en réaction à un signal externe réduisant l'incertitude événementielle (par exemple, un signal d'alerte). *Illustration tirée de Favre et al., 2013.*

L'existence de ce contrôle inhibiteur non sélectif se base sur l'observation, au niveau du système moteur, d'activations excitatrices automatiques induites par tout stimulus (Go ou Nogo/stop/amorce) (Sumner et al., 2007). L'existence d'un contrôle inhibiteur non sélectif permettrait alors de les réprimer grâce à la capacité de verrouiller de façon anticipée les processus d'initiation du mouvement. L'objectif serait, comme pour le dual route model (Eimer, 1995; Forstmann et al., 2008; Kornblum et al., 1990; Ridderinkhof, 2002) et le « Hold your horses model » (Frank et al., 2007b) développé plus haut, de laisser le temps aux processus décisionnels de statuer sur la réponse motrice à déclencher. Mais contrairement aux autres modèles qui s'appliquent à des tâches complexes de choix, ce modèle proactif non sélectif a été

mis en évidence pour des tâches simples de TR (go/nogo). Ensuite, ce contrôle inhibiteur proactif serait levé pour permettre le déclenchement des réponses motrices volontaires, contrôlées, de longue latence.

Selon ce modèle, c'est précisément l'identification du signal go qui induirait une levée du contrôle inhibiteur et non le signal auquel il ne faut pas répondre (nogo) qui déclencherait des activations inhibitrices (Figure 12). Ce modèle est jusqu'à lors très largement ignoré. En effet, le modèle proactif non-sélectif suppose que ce contrôle inhibiteur n'est implémenté qu'en condition d'incertitude événementielle, en d'autres termes, que l'inhibition n'est pas implémentée lorsque le contexte ne recèle pas d'incertitude. Ainsi, la seule façon de mettre en évidence ce contrôle inhibiteur proactif non sélectif est d'utiliser une réelle condition de contrôle dans laquelle les sujets n'implémentent pas de contrôle inhibiteur. Dans cette condition, les sujets doivent être certains de devoir répondre à tous les essais et en absence d'incertitude événementielle, ils peuvent laisser libre court aux automatismes sensorimoteurs (Figure 12) via les processus d'activation directe supposés par le dual route model et d'autres auteurs (Boulinguez et al., 2008; McBride et al., 2012; Sumner & Husain, 2008). Néanmoins, cette condition de contrôle n'est que très rarement mise en œuvre dans la littérature.

Les travaux qui utilisent cette condition de contrôle révèlent une différence importante de TR entre les conditions avec et sans incertitude. Alors que certains travaux attribuent cette différence à la charge attentionnelle qui pèse sur la condition d'incertitude (Chikazoe et al., 2009; Tachibana et al., 1997), le modèle proactif non-sélectif suggère que cette différence indexe le temps nécessaire au déverrouillage des mécanismes d'initiation de l'action (Ballanger et al., 2009; Boulinguez et al., 2009; Jaffard et al., 2008). L'existence de ce contrôle inhibiteur non sélectif repose sur des travaux récents conduits chez le sujet sain (Albares et al., 2014; Boulinguez et al., 2009, 2008; Criaud et al., 2012; Jaffard et al., 2007, 2008), dans la maladie

de Parkinson (Ballanger et al., 2009; Criaud et al., 2016; Favre et al., 2013), et chez l'animal (Lo et al., 2009; Stuphorn et al., 2010).

**Il existe de nombreux modèles d'inhibition de réponse qui, bien que souvent présentés comme concurrents, ne sont en vérité pas nécessairement mutuellement exclusifs. Cette pluralité de mécanismes inhibiteurs se doit d'être explorée pour cerner la globalité de la fonction d'inhibition de réponse (Criaud et al., 2017). En effet, l'existence d'un contrôle inhibiteur proactif non sélectif pourrait permettre de revisiter les troubles de l'initiation du mouvement et mérite d'être plus largement explorée (Meyer & Bucci, 2016).**

## 2. METHODES D'ETUDE COMPORTEMENTALE DE L'INHIBITION DE REPONSE

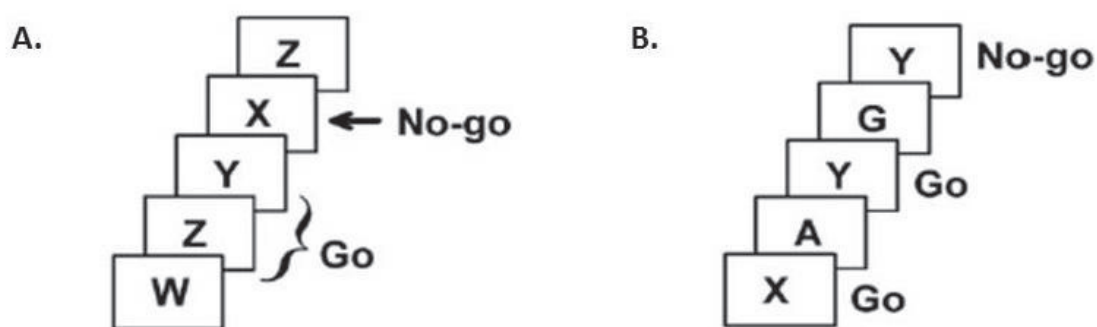
Différents paradigmes expérimentaux sont classiquement employés pour investiguer la fonction d'inhibition de réponse. Les plus couramment utilisés sont la tâche de go/nogo (Garavan et al., 1999; Picton et al., 2007), la tâche de stop (Logan, 1994; Verbruggen & Logan, 2009), et la tâche d'anti-saccades (Anderson et al., 2008; Butter et al., 1988; Hallett, 1978).

### a. Tâche de go/nogo classique

Le principe d'une tâche dite de Go/nogo est simple (Figure 13.A). Deux types de stimuli sont présentés : un stimulus go auquel le sujet doit répondre le plus rapidement possible, et un stimulus nogo auquel il ne doit pas répondre (e.g., Logan et al., 1984; Menon et al., 2001). La performance est estimée de façon globale au moyen du taux de réponse aux stimuli nogo, i.e., de la capacité à empêcher le déclenchement de réponses inappropriées. Ce taux d'erreurs dites

de commissions est alors un marqueur d'impulsivité (Ballanger et al., 2009; Trommer et al., 1988).

Deux limites majeures à l'utilisation de cette tâche sont observées dans la littérature. Premièrement, alors que cette tâche se veut très simple en utilisant deux stimuli, les protocoles utilisés dans les faits sont en réalité très complexes (Figure 13.B ; Criaud & Boulinguez, 2013). Ainsi, les processus inhibiteurs sont confondus avec d'autres mécanismes de sélection de réponse (Rushworth et al., 2003; Rushworth & Taylor, 2007; Sumner et al., 2007), de planification de réponse (Coxon et al., 2007; De Jong & Paans, 2007) ou de monitoring de conflit et de détection d'erreur (Menon et al., 2001; Rushworth et al., 2007). Deuxièmement, la tâche de go/nogo présente l'inconvénient de ne pas offrir de marqueur comportemental chronométrique de l'inhibition étant donné qu'aucun TR n'est associé au stimulus nogo. Alors que les TR sont censés indexer la durée des processus cognitifs impliqués (Posner, 1978), la tâche de go/nogo se voit alors délaissée au profit de tâches permettant d'offrir un marqueur psychophysique chronométrique de l'inhibition.



**Figure 13 : Tâche de Go/NoGo**

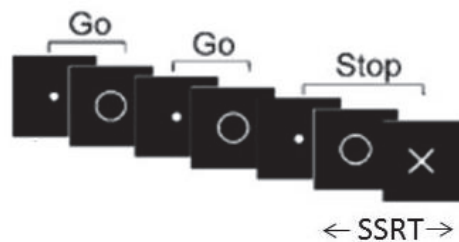
**A. Go/nogo simple** (réponse au stimulus go uniquement). **B. Protocole alternatif** couramment utilisé de la tâche de go/nogo introduisant une charge mnésique supplémentaire (le Nogo est à déterminer en fonction de quel stimulus go était préalablement présenté). *Illustration tirée de Chambers et al. (2009).*

## b. Tâche de stop

Dans une tâche de stop, le sujet doit toujours répondre le plus rapidement possible à l'apparition d'un stimulus go, mais un stimulus stop peut être présenté en de rares occasions à la suite du signal go. Le principe d'une tâche de stop (e.g., Aron, 2007; Verbruggen & Logan, 2008b) repose sur l'annulation d'une réponse motrice préalablement engagée (Figure 14). La manipulation du délai go-stop permet alors de dissocier dans le temps les processus de préparation de la réponse de ceux destinés à inhiber son déclenchement. L'avantage principal de la tâche de stop par rapport au Go/NoGo est ainsi l'existence d'un marqueur chronométrique des processus d'inhibition de réponse sur la base d'analyse essai par essai (SSRT). Cette variable chronométrique (SSRT) est calculée selon l'évolution du taux d'erreurs en fonction du délai go-stop. En effet, si le signal stop est présenté immédiatement après le go, il sera facile d'inhiber sa réponse. En revanche, si ce délai augmente, il sera plus difficile d'interrompre sa réponse, jusqu'à un point où cela deviendra impossible.

Mais le paradigme de stop recèle néanmoins un certain nombre de limites. Premièrement, alors que certains auteurs supposent que les deux types de paradigmes sondent les mêmes processus (Bari & Robbins, 2013; Chambers et al., 2009; Garavan et al., 1999; Rubia et al., 2001), le fait qu'il indexe des processus inhibiteurs de même nature que ceux sollicités dans la tâche de go/nogo est clairement remis en question (e.g., Eagle et al., 2008; Rubia et al., 2001; Swick et al., 2011). Ainsi, les conclusions issues de ce paradigme sondant des mécanismes très spécifiques (annulation d'une action en cours d'exécution) doivent être reconsidérées avec prudence alors qu'elles sont classiquement généralisées lorsque l'on aborde l'inhibition et l'impulsivité. Deuxièmement, l'interprétation du SSRT en tant que mesure comportementale de l'inhibition a été remise en cause (Boehler et al., 2012). En effet, la manipulation du délai go-stop oblige à une adaptation des stratégies de réponse des sujets qui rend difficile l'interprétation du SSRT. De plus, en fixant un taux d'erreurs à 50%, le protocole

induit un allongement des TR (Li et al., 2006) qui pourrait être dû à des mécanismes adaptatifs de préparation de la réponse motrice afin d'en faciliter la suppression peu après son initiation (Jahfari et al., 2012). Enfin, la critique concernant l'utilisation de tâches complexes (Criaud & Boulinguez, 2013) indexant des processus corollaires plus que l'inhibition a proprement parlé s'applique également à la tâche de stop pour laquelle des biais considérables sont observés (Eagle et al., 2008; Erika-Florence et al., 2014; Swick et al., 2011).



**Figure 14 : Tâche de stop**

Un stimulus go auquel il faut répondre est présenté. En de rares occasions, un stimulus stop apparaît peu de temps après l'apparition du go, le sujet doit alors réfréner sa réponse motrice préalablement préparée. *Illustration tirée de Manza et al. (2017).*

### c. Autres paradigmes

D'autres paradigmes expérimentaux (antisaccade, distracteurs, stroop, Simon...) mettent en jeu la concurrence entre une activité automatique (sollicitée par les stimuli) et une activité contrôlée (pertinente pour la tâche). Bien que ces méthodes impliquent clairement des mécanismes d'inhibition de réponse, leur complexité les rendent incapables de révéler spécifiquement les processus d'inhibition de réponse (Miyake et al., 2000; Nigg, 2000).

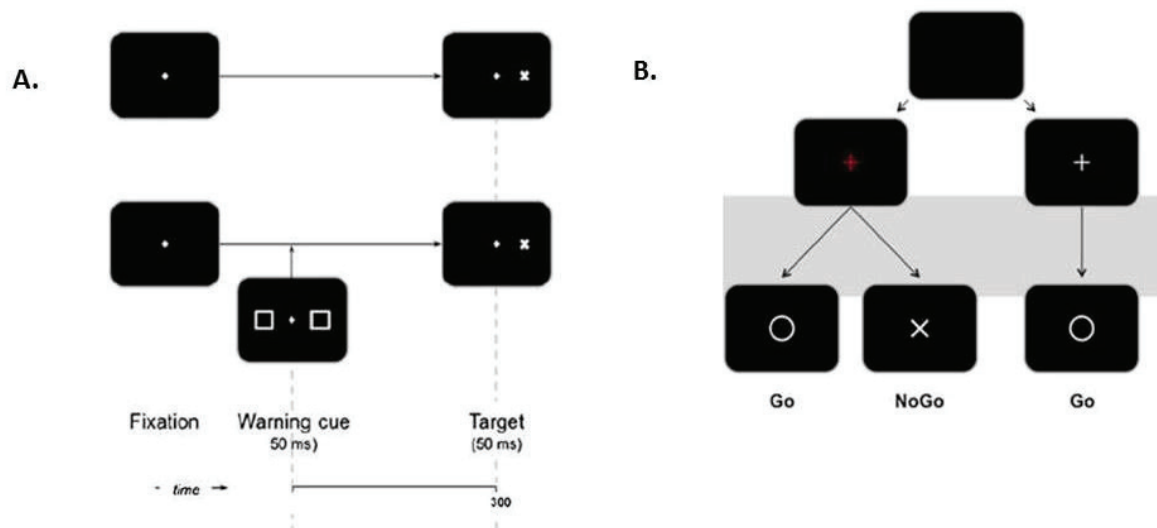
Néanmoins, l'utilisation de ces tâches peut s'avérer très intéressante pour révéler la dynamique du contrôle inhibiteur. En effet, la présentation aléatoire d'un indice évoque de l'incertitude quant à l'évènement à venir et oblige les sujets à implémenter un contrôle inhibiteur proactif non-sélectif pour prévenir le déclenchement de réponses à l'indice (Jaffard et al., 2007). Ce type de protocole offre un moyen d'estimer l'implication et la durée des

processus d'inhibition pour chaque essai individuel (ibid). Ce design permet ainsi de dissocier dans le temps les mécanismes d'activation motrice et d'implémentation du contrôle inhibiteur, ce qui le rend très complémentaire du go/nogo (Criaud et al., 2012).

### 3. AMENDEMENTS METHODOLOGIQUES PROPOSES

Les paradigmes expérimentaux utilisés pour évaluer le contrôle inhibiteur sont très variés et le plus souvent complexes. La complexité de ces paradigmes ne permet pas de dissocier les différentes fonctions impliquées et participe à la difficulté de caractériser les fonctions neuropsychologiques à l'origine des troubles de l'initiation de l'action (Criaud & Boulinguez, 2013). Par exemple, dans les tâches de sélection de réponse, une situation de choix entre plusieurs actions implique à la fois des processus liés à la prise de décision et l'activation de la réponse sélectionnée, en plus des mécanismes liés à l'inhibition des réponses concurrentes. Dans ce travail de thèse, un premier amendement concerne donc l'utilisation de tâches expérimentales simples afin de révéler spécifiquement les processus inhibiteurs.

Ensuite, il semble important de construire des protocoles qui permettent de tester en même temps la pluralité des modèles de l'inhibition de réponse. Alors que les mécanismes proactifs non-sélectifs sont classiquement ignorés dans la littérature, l'ajout d'une simple condition de contrôle à des protocoles classiques d'inhibition de réponse (i.e., condition de certitude pour laquelle l'implémentation d'un contrôle inhibiteur n'est pas requise) permet de contourner simplement cette limite (Figure 15).



**Figure 15 : Illustration de tâches adaptées à l'étude du contrôle inhibiteur proactif non-sélectif.**

**A. Tâche d'amorçage** (Favre et al., 2013). Dans cette tâche, le sujet doit répondre le plus rapidement à une cible. Dans certains cas, une amorce est présentée préalablement pour indiquer au sujet de l'arrivée imminente de la cible. Elle constitue donc un indice temporel permettant au sujet de préparer le déclenchement de la réponse motrice et permet de révéler la dynamique de levée du contrôle inhibiteur. Une condition de contrôle est ajoutée au moyen de protocoles en blocs, où sont présentés alternativement un bloc d'essais mixte (condition d'incertitude avec tous les types d'essais mélangés nécessitant l'implémentation d'un contrôle proactif non-sélectif) et un bloc contrôle (seuls des essais go sont présentés, condition de certitude événementielle permettant de laisser libre court aux automatismes sensorimoteurs). **B. Tâche de go/nogo** (Criaud et al., 2012). La condition de contrôle est ajoutée au moyen d'un design dans lequel un indice indique au début de chaque essai la condition dans laquelle il se trouve (rouge, incertitude ; blanc, contrôle).

Les paradigmes comportementaux classiques ont été érigés en standards pour tester l'inhibition de réponse mais ne sont pourtant pas exemptes de problèmes méthodologiques. A ce jour, ils ne permettent pas de révéler l'ensemble des modèles du contrôle de l'action proposés. L'utilisation d'une condition de contrôle (i.e., ne présentant pas d'incertitude événementielle) est la seule façon de mettre en évidence les mécanismes proactifs non-sélectifs afin de révéler les différents modèles de l'inhibition de réponse sans à priori.



## B. LA DIFFICULTE A IDENTIFIER LES BASES ANATOMO-FONCTIONNELLES DE L'INHIBITION DE REPONSE

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### 1. BASES ANATOMO-FONCTIONNELLES

#### a. Modèles réactifs sélectifs

A ce jour, les travaux d'imagerie se sont quasi exclusivement intéressés au modèle théorique dominant, à savoir réactif et sélectif. Selon ce modèle, l'activité inhibitrice réactive est déclenchée sélectivement par la présentation du stimulus auquel il ne faut pas répondre. Les contrastes utilisés sont donc généralement destinés à révéler l'activité réactive lors d'une inhibition réussie (nogo ou stop réussis), par rapport à une condition dans laquelle aucune inhibition n'est nécessaire (go), ou par rapport à une condition dans laquelle l'inhibition a échoué (nogo ou stop ratés). L'analyse de l'activité réactive se porte alors uniquement sur l'activité cérébrale phasique post-stimulus. Dans ce sens, l'IRMf a été largement privilégiée pour sa résolution spatiale et a permis de révéler un large réseau cortico/sous-cortical impliqué dans l'inhibition réactive et sélective (Alexander & Crutcher, 1990; Mink, 1996; Swick et al., 2011).

Au niveau sous-cortical, les différentes voies des ganglions de la base jouent un rôle essentiel dans les circuits moteurs (*cf. Chapitre 1*). Ainsi, le NST semble jouer un rôle clé (Aron & Poldrack, 2006; van den Wildenberg et al., 2006), ainsi que le striatum (Zandbelt & Vink, 2010). Mais la compréhension de leur rôle précis dans les boucles ganglio-thalamo-corticales nécessite encore d'être étayée. L'activation de l'insula (Rubia et al., 2001) a également été mise en évidence.

Au niveau cortical, l'inhibition réactive sélective semblent impliquer l'hémisphère droit de façon dominante (Swick et al., 2011). On observe principalement l'implication du cortex pré-frontal dorsolatéral (dlPFC) (Garavan et al., 2006; Hughes et al., 2014; Kelly et al., 2004),

et du gyrus frontal inférieur droit (rIFG) (Aron, 2007; Aron & Poldrack, 2006; Aron et al., 2004; Sebastian et al., 2013; Zheng et al., 2008). On retrouve également les structures pilotant les voies des ganglions de la base comme le complexe AMS et aire pré-motrice supplémentaire (pré-AMS) (Isoda & Hikosaka, 2007; Jahfari et al., 2011; Mostofsky et al., 2003; Sebastian et al., 2013; Sumner et al., 2007) et le cortex moteur primaire (M1) (Aron, 2011; Stinear et al., 2009) qui pilotent la voie directe. Le dlPFC, le cortex pré-frontal ventro latéral (vlPFC) (Garavan et al., 2006; Liddle et al., 2001), le cortex pariétal inférieur (IPC) (Garavan et al., 1999, 2006; Menon et al., 2001; Rubia et al., 2001) et le CCA (Dambacher et al., 2014; Garavan et al., 2006; Menon et al., 2001; Rubia et al., 2001) sont également impliqués dans le pilotage de la voie hyperdirecte.

Toutefois, il convient de noter que ces activations ont été retrouvées pour les deux types de tâches couramment utilisées pour sonder les bases de l'inhibition de réponse : la tâche de stop et la tâche de go/nogo. Or, contrairement à ce qui est affirmé par Chambers et collaborateurs (2009), les réseaux cérébraux supportant l'inhibition réactive sélective ne se recoupent que peu entre les tâches de stop et de go/nogo (Swick et al., 2011). Ces résultats laissent envisager l'idée que les structures identifiées séparément dans chacune des tâches ne joueraient pas de rôle direct dans l'inhibition de réponse réactive sélective, et que le cœur du processus commun d'inhibition se trouverait dans l'insula et l'AMS. Ceci est cohérent avec une récente méta-analyse (Criaud & Boulinguez, 2013) qui a mis en évidence que la grande majorité des régions identifiées dans ces tâches ne supporteraient que des processus corollaires, notamment attentionnels, décisionnels, liés au conflit ou à la mémoire de travail, et difficilement dissociables des mécanismes d'inhibition à proprement parler (Criaud & Boulinguez, 2013; Erika-Florence et al., 2014; Sharp et al., 2010).

### b. Modèles réactifs non sélectifs

Ces modèles réactifs non sélectifs présentent peu d'évidences anatomo-fonctionnelles. En effet, le modèle du contrôle des impulsions est issu de travaux en TMS qui n'offrent pas la possibilité d'une exploration anatomo-fonctionnelle complète. Ainsi, seuls le cortex latéral préfrontal dans les processus de « compétition-résolution » et le cortex pré-moteur dorsal dans les mécanismes de « contrôle des impulsions » (Duque & Ivry, 2009; Duque et al., 2012, 2010) semblent être impliqués. Quant à lui, le « Hold your horses model » (Frank et al., 2007) n'utilise pas non plus de données issues d'une méthode de neuroimagerie et est basé sur un travail de modélisation mathématique de données comportementales tirées notamment de travaux chez des patients parkinsoniens stimulés dans le NST. Il révèle un rôle pivot du NST dans l'inhibition de réponse et le contrôle de la sélection de réponse lors de situations conflictuelles. Ce rôle du NST dans le contrôle inhibiteur non-sélectif a récemment été confirmé chez des patients parkinsoniens sous SCP-NST (Benis et al., 2014). Cependant, en s'intéressant aux données fonctionnelles provenant des électrodes implantées dans le NST, cette étude ne permet pas d'inférer les modulations corticales associées. Une étude récente a proposé un lien entre contrôle inhibiteur réactif non-sélectif et contrôle proactif (Albares et al., 2014) dans l'AMS. Ceci est cohérent avec l'organisation anatomo-fonctionnelle des ganglions de la base, les voies indirecte et hyperdirecte étant considérées comme sous-tendant respectivement les contrôles proactif et réactif (Jahanshahi & Rothwell, 2017). Mais les bases neurofonctionnelles de ces modèles nécessitent d'être plus étayées.

### c. Modèles proactifs sélectifs

Les modèles proactifs sélectifs, plus récents, ont à ce jour été peu explorés. Les structures cérébrales mises en évidence correspondent aux rIFG (Aron, 2011; Aron et al., 2014; Jahfari et al., 2010), à la pré-AMS (Chikazoe et al., 2009) et au NST (Benis et al., 2014). Ces

structures sont ici souvent considérées comme s'activant par avance pour anticiper l'action à annuler. Pourtant, de façon intéressante, on peut noter que ces structures correspondent à celles précédemment mises en jeu dans la tâche de stop comme de l'inhibition réactive sélective. Ainsi, il semble que ces modèles fassent plutôt référence à une forme de pré-activation du réseau de l'inhibition réactive sélective pour ajuster le niveau de préparation motrice de la réponse, plutôt qu'à une inhibition motrice anticipée à proprement parler (Jahfari et al., 2012).

#### d. Modèles proactifs non sélectifs

Les corrélats neurofonctionnels de ce modèle alternatif sont encore à l'étude. En effet, le modèle proactif non-sélectif est récent et nécessite, pour être mis en évidence, l'utilisation d'une condition de contrôle qui est rarement utilisée dans la littérature (Criaud & Boulinguez, 2013). Chez le sujet sain, une seule étude a mis en évidence en IRMf des structures suractivées par ce contrôle : le cortex frontal dorso-médial (dmFC), le précunéus/CCP) et le lobule pariétal inférieur gauche (IPL)/gyrus temporal moyen, formant un réseau pariéto-frontal. A l'inverse, un circuit moteur incluant le M1, l'AMS et le putamen (Jaffard et al., 2008) serait hypoactivé par ce contrôle. Dans la maladie de Parkinson, un rôle central du NST a également été proposé dans ce contrôle inhibiteur proactif en manipulant directement l'activité des ganglions de la base au moyen de la SCP (Favre et al., 2013). Malheureusement, ce type d'étude comportementale avec des patients implantés n'est pas compatible avec la plupart des méthodes d'imagerie cérébrale et n'a pas encore permis à ce jour de révéler les modulations corticales associées.

**Les études des bases anatomo-fonctionnelles de l'inhibition de réponse sont contradictoires, controversées ou incomplètes. Seuls l'AMS et le STN semblent impliqués de façon consistante, mais leur rôle exact reste mal compris. De plus, l'hypothèse d'un contrôle proactif non-sélectif reste largement inexplorée.**

## 2. METHODES D'ETUDE DE L'ANATOMIE FONCTIONNELLE

Alors qu'il n'existe pas de consensus sur les modèles et les méthodes comportementales destinés à révéler les mécanismes d'inhibition de réponse, l'étude des bases neurofonctionnelles n'en est que plus complexe. Il convient tout d'abord d'évoquer les méthodes d'étude de l'anatomie fonctionnelle et les limites inhérentes à la nature des signaux enregistrés par chacune des méthodes.

L'IRMf, de par sa résolution spatiale, est l'outil privilégié pour aborder les bases anatomo-fonctionnelles. Mais il convient de rappeler les limites inhérentes à l'analyse du signal BOLD en neuroimagerie qui ne constitue qu'une mesure indirecte de l'activité neurale. Ainsi, les variations du niveau d'oxygénation sanguine par rapport à une condition de contrôle ne peuvent en aucun cas renseigner sur la nature excitatrice ou inhibitrice de l'activité neuronale (Buzsáki et al., 2007; Logothetis, 2008). Cette limite est critique lorsque l'on aborde des mécanismes inhibiteurs. De plus, l'IRMf ne possède pas la résolution temporelle suffisante pour distinguer la dynamique d'activités intervenant dans des fenêtres temporelles très courtes (de l'ordre du TR, c.à.d. quelques centaines de millisecondes). Cette critique est également valable pour la TEP qui ne permet pas de réaliser des analyses liées aux événements. L'IRMf et la TEP ne semblent donc pas constituer des techniques idéales pour dissocier la pluralité des modèles de l'inhibition de réponse et considérer des activités excitatrices et inhibitrices dans les périodes pré et post-stimulus.

L'EEG et la MEG présentent à cet égard deux avantages. Le premier concerne la nature même du signal électrique qui offre une mesure plus directe de l'activité neuronale. Le second est relatif à la résolution temporelle qui s'avère idéale pour étudier la dynamique des processus inhibiteurs opérant dans une fenêtre temporelle extrêmement courte ( $< 500\text{ms}$ ). Cette résolution permet de mieux caractériser des phénomènes purement phasiques et transitoires. Ainsi, l'analyse des potentiels évoqués (PE) a dès lors semblé idéale car elle indexe l'activité synchronisée d'une masse neuronale qui génère des variations de champ électrique sur le scalp dans une fenêtre temporelle stricte liée à l'événement d'intérêt. Ainsi, de nombreuses études se sont intéressées aux marqueurs psychophysiologiques des mécanismes réactifs d'inhibition de réponse au moyen de l'analyse des PE (e.g., Albert et al., 2013; Eimer, 1995; Falkenstein et al., 1999). Cependant, la nature du signal enregistré en EEG doit également être questionnée. En effet, l'activité EEG résulte essentiellement de l'activité post-synaptique (dendritique), et ne représente donc pas l'activité de sortie des neurones (Whittington et al., 2000). De plus, l'activité enregistrée à la surface du scalp est la résultante d'un mélange complexe de l'activité d'une multitude de sources (Kropotov & Ponomarev, 2009; Kropotov et al., 2011; Makeig et al., 1996). Ainsi, l'EEG offre une faible résolution spatiale, au départ incompatible avec une localisation optimale des sources d'activité (Koles, 1998).

On peut également citer d'autres méthodes indirectes d'étude des bases anatomo-fonctionnelles du contrôle inhibiteur. Par exemple, les études neuropsychologiques offrent une voie d'accès privilégiée à une région d'intérêt (Kehagia et al., 2014; Picton et al., 2007; Sumner et al., 2007). Néanmoins, les lésions sont très rarement circonscrites aux régions d'intérêt ce qui limite fortement la portée des résultats de ce genre d'études. Dans le cas de l'inhibition de réponse, le réseau impliqué semble être largement distribué rendant ce type de méthode inadapté.

Enfin, les méthodes de stimulation, comme la TMS (Duque et al., 2012, 2010), la SCP (Favre et al., 2013) ou la stimulation transcrânienne à courant directe –tDCS- (Hayduk-Costa et al., 2013; Hsu et al., 2011), permettent de moduler directement l'activité cérébrale de régions cibles. Néanmoins, ces méthodes ne permettent pas l'analyse de l'ensemble des régions cérébrales (e.g., TMS), sont restreintes à l'étude de patients implantés (SCP) ou sont d'une précision limitée (tDCS).

**Aucune des méthodes disponibles ne permet à ce jour de discerner la dynamique cérébrale de processus concurrents et co-occurrents qui régissent la fonction d'inhibition de réponse, tout en offrant une résolution spatiale adéquate pour accéder aux bases anatomo-fonctionnelles.**

### 3. AMENDEMENTS METHODOLOGIQUES PROPOSES

A ce jour, les bases anatomo-fonctionnelles de l'inhibition de réponse restent complexes et conflictuelles. Ceci s'explique par différentes raisons que nous avons évoqué dans le Chapitre 3 : 1/ Les paradigmes expérimentaux classiquement utilisés présentent des biais importants très susceptibles de bruyé les données anatomo-fonctionnelles ; 2/ La littérature est très influencée par les données d'imagerie basées sur le modèle dominant sélectif réactif et occulte la pluralité des modèles d'inhibition de réponse alors même que ces modèles ne sont pas mutuellement exclusifs et impliquent probablement des régions spécifiques ; 3/ Les méthodes d'imagerie sont incapables de distinguer les activités excitatrices des activités inhibitrices co-occurrentes tout en offrant une résolution spatiale adéquate pour localiser les régions impliquées. Plusieurs amendements méthodologiques sont donc nécessaires afin

d'entrevoir les bases anatomo-fonctionnelles de l'inhibition de réponse et ses possibles dysfonctionnements dans la maladie de Parkinson.

#### a. Contourner les limites de l'EEG

Alors que les méthodes d'imagerie classiquement utilisées possèdent des limites difficiles à contourner, les limites inhérentes aux méthodes MEG/EEG peuvent être plus facilement contournées en appliquant un ensemble de méthodes avancées de traitement du signal. En effet, alors que l'EEG est classiquement réputé pour sa faible résolution spatiale, sa limite se situe plus précisément dans la difficulté à isoler une activité localisée alors que l'EEG est la résultante d'un mélange spatial d'activités provenant de l'ensemble du cortex. Pour pallier à ce problème, des méthodes de séparation aveugle de sources (SAS) permettent aujourd'hui de démêler les différentes activités neurologiques corticales (Lio & Boulinguez, 2013). Plus précisément, des méthodes de SAS de groupe ont été mises au point pour se focaliser sur les sources présentant les modulations spectrales les plus reproductibles, consistantes entre les sujets et spécifiquement en relation avec le protocole testé (SOBI, UWSOBI). En optimisant les méthodes de séparation de source, combinées à des méthodes de localisation (permettant de localiser les sources identifiées), et d'analyse temps-fréquence (renseignant sur la nature de l'activité observée), il est aujourd'hui possible avec une résolution temporelle optimale et une très bonne résolution spatiale corticale, de discriminer des processus psychologiques co-occurents qui ne pouvaient jusqu'à présent être distingués.

#### b. Utiliser le potentiel discriminatif de l'EEG comme marqueur de l'inhibition de réponse

Fortement influencées par le modèle théorique dominant, les études EEG de l'inhibition de réponse ont isolé un indice électrophysiologique, la N2 (ou N200), censé rendre compte des



processus sous-tendant l'inhibition comportementale (Falkenstein et al., 1999). Cet indice est un potentiel évoqué (PE) par le stimulus auquel il convient de ne pas répondre. Il s'agit d'une onde négative ayant une topographie fronto-centrale qui apparaît environ 200 à 300 ms après la présentation du stimulus. La majorité des travaux qui l'ont observée ont été conduits au moyen de tâches de go/nogo et de stop, en utilisant les contrastes classiques entre essais go et nogo/stop (Bokura et al., 2001; Eimer, 1993). Ainsi, cet indice ne peut refléter que des mécanismes sélectifs et réactifs et occultent la pluralité des modèles d'inhibition de réponse. Qui plus est, face à une grande disparité des résultats, il n'existe pas de consensus clair sur le rôle et les régions cérébrales à l'origine de ce PE. En effet, sa latence (270ms) semble trop tardive pour indexer les processus inhibiteurs réactifs et correspondrait plutôt à des mécanismes de prise de décision pour le déclenchement de l'initiation de mouvements volontaires, de longue latence (Albares et al., 2015a; Albert et al., 2013; Enriquez-Geppert et al., 2010; Frank et al., 2007b). Ainsi, la N2 a récemment été remise en cause comme un indicateur peu fiable des mécanismes d'inhibition de réponse (Huster et al., 2013). Il convient donc d'aller au-delà des potentiels évoqués et de définir de nouveaux marqueurs de l'inhibition de réponse.

L'EEG offre la possibilité de réaliser des analyses de l'activité induite (e.g., via la puissance du signal dans une bande de fréquence) et de ses modulations induites par des événements précis (ERD/ERS). L'EEG a également le potentiel de discriminer les mécanismes excitateurs et inhibiteurs par l'intermédiaire d'analyses spectrales. Ainsi, les bandes de fréquence permettent de révéler des processus cognitifs distincts (Albares et al., 2015a; Jensen & Mazaheri, 2010; Siegel et al., 2012). Ceci semble idéal pour l'analyse des mécanismes proactifs, toniques d'inhibition de réponse (e.g., Mathewson et al., 2011; Mazaheri et al., 2009). L'utilisation de l'EEG pour notre problématique semble donc justifiée. Il s'agit essentiellement de permettre d'isoler l'activité inhibitrice en recherchant sa signature spectrale, et d'en

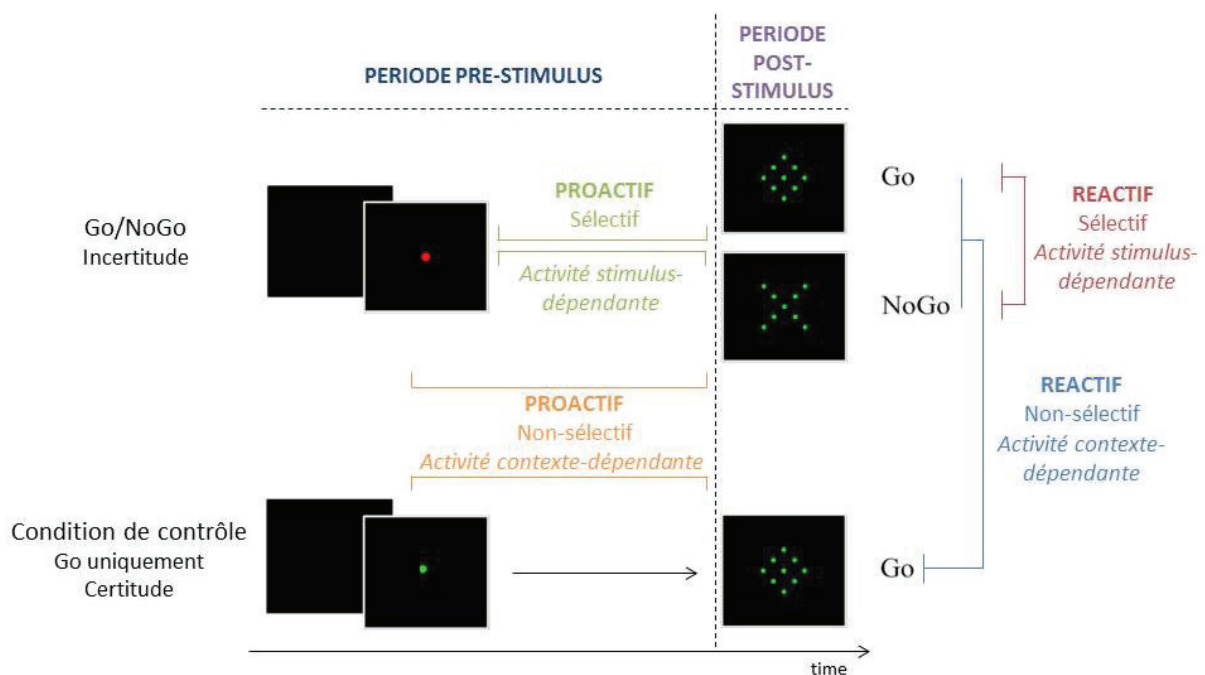
optimiser l'analyse de la dynamique temporelle afin de dissocier l'inhibition proactive et réactive (Liebrand et al., 2017).

Récemment, diverses bandes de fréquence ont été associées à l'inhibition de réponse : delta (1-4Hz) (Harmony, 2013), theta (4-8Hz) (Liu et al., 2014; Zavala et al., 2015), alpha (7-13Hz) (Haegens et al., 2011; Klimesch et al., 2007), beta (13-30Hz) (Engel & Fries, 2010; Kilavik et al., 2013) et gamma (> 30 Hz) (Alegre et al., 2013; Iijima et al., 2015). Un rôle clé des oscillations alpha et beta a principalement été mis en avant. La bande de fréquence alpha serait générée par des fluctuations rythmiques locales des interneurons inhibiteurs GABAergiques (Lorincz et al., 2009) et pourrait indexer des mécanismes actifs inhibiteurs (Jensen & Mazaheri, 2010). Les oscillations beta indexeraient plutôt le signal top-down et le contrôle de l'inhibition fonctionnelle sur les régions corticales sensori-motrices (Jensen et al., 2005). Il semblerait que l'activité beta pourrait conduire l'activité alpha (Hwang et al., 2014) et que ces deux bandes de fréquence indexeraient des processus distincts mais associés (Pani et al., 2014). De même, il semblerait que l'activité gamma soit inversement couplée à l'activité alpha et participe conjointement aux mécanismes d'inhibition du déclenchement de l'action (Bonfond & Jensen, 2015).

Qui plus est, d'un point de vue clinique, les oscillations dans la bande bêta sont particulièrement intéressantes car elles sont connues pour être augmentées dans la maladie de Parkinson (Brown & Williams, 2005; Hammond et al., 2007; Weinberger et al., 2009). Des études en LFP au niveau du NST chez des patients parkinsoniens suggèrent en effet qu'une augmentation de l'activité beta pourrait contribuer à la lenteur des mouvements (i.e., bradykinésie) (Brown, 2007). Dans ce sens, le niveau d'oscillations beta dans le NST est corrélé aux bénéfices comportementaux observés chez les patients sous traitement ; lié à la médication dopaminergique (Kühn et al., 2006; Levy et al., 2002; Priori et al., 2004; Silberstein et al., 2005) ou à la stimulation cérébrale profonde du NST (Brown et al., 2004).

c. Optimiser les contrastes pour révéler la pluralité des modèles de l'inhibition de réponse

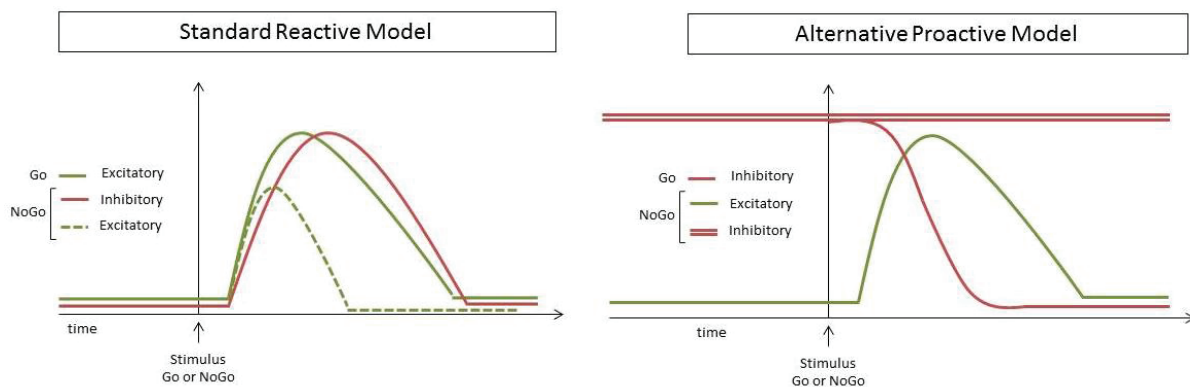
L'influence du modèle standard réactif sélectif a focalisé la recherche des bases anatomo-fonctionnelles de l'inhibition de réponse sur les contrastes destinés à révéler l'activité réactive (inhibition réussie vs. ratée) et dans la période post-stimulus. L'ajout de la condition de contrôle dans laquelle aucune incertitude ne pèse quant à la nature du stimulus à venir (i.e., aucune inhibition requise) permettra de mettre en évidence les mécanismes non-sélectifs. Le choix des contrastes permettra ensuite de révéler les différents modèles de l'inhibition de réponse sans à priori (Figure 16).



**Figure 16 : Contrastes permettant de révéler les 4 mécanismes de l'inhibition de réponse potentiellement engagés lors d'un protocole de GoNogo adapté.**

De plus, par sa résolution temporelle, l'EEG offre la possibilité de s'intéresser à la fois à l'activité réactive suite à la présentation de la cible d'intérêt mais également à l'activité proactive qui précède la présentation des stimuli. Ainsi, l'EEG permet de révéler l'existence

d'un contrôle exécutif automatique, proactif et non sélectif, en amont des stimuli, en condition d'incertitude (Albares et al., 2014; Criaud et al., 2017, 2012). Il s'agit ainsi de comprendre l'activité pré-stimulus, qu'elle soit spécifique d'un contexte (verrouillage en situation d'incertitude vs. déverrouillage lorsque l'incertitude contextuelle est levée) ou d'une action (suppression d'une activité préparatoire spécifique vs. pas d'inhibition). L'EEG offre donc la possibilité de sonder les différents modèles d'inhibition de réponse qui guident très différemment la recherche de leurs bases anatomo-fonctionnelles.



**Figure 17 : Mécanismes neuropsychologiques qui guident l'analyse de l'activité cérébrale à l'origine de l'inhibition de réponse.**

Les différents modèles guident très différemment la recherche des bases anatomo-fonctionnelles de l'inhibition de réponse. L'existence d'activations excitatrice (verte) et inhibitrice (rouge) nécessite l'analyse de processus co-occurents. **A. Modèle réactif standard** : Le modèle psychologique dominant (e.g., Verbruggen & Logan, 2008) suppose que les processus inhibiteurs sont sélectifs, phasiques et réactifs en réponse à un stimulus externe auquel il ne faut pas répondre. Selon ce modèle, tout stimulus entraîne des activations excitatrices automatiques qu'il convient de réprimer. C'est donc l'identification d'un stimulus auquel il ne faut pas répondre qui déclenche des activations inhibitrices co-occurentes pour contrer l'initiation du mouvement. Cette idée a guidé la plupart des études psychophysiques et de neuroimagerie vers l'analyse de l'activité post-stimulus et du contraste Nogo-Go. **B. Modèle proactif alternatif** : Le modèle alternatif propose que le contrôle inhibiteur peut s'opérer i) en l'absence d'instruction explicite pour prévenir le déclenchement de réponses prématurées, erronées ou non désirées (Franck, 2006 ; Franck et al., 2007 ; Jaffard et al., 2007, 2008), ii) par défaut dans un contexte d'incertitude événementielle (Criaud et al., 2012), et iii) avant même qu'un stimulus ne soit présenté (Boulinguez et al., 2008, 2009 ; Jaffard et al., 2007, 2008).

Selon ce modèle, le contrôle inhibiteur proactif induit une suppression anticipée des processus d'initiation du mouvement, et la suppression directe des activations motrices excitatrices automatiques. Il s'agirait de l'état de verrouillage par défaut des mécanismes d'initiation du mouvement pour éviter tout risque de réponses non désirées ou non appropriées. C'est l'identification d'un stimulus auquel il convient de répondre qui permet de lever cette inhibition et de transmettre l'activité motrice excitatrice au système moteur. Ce modèle appelle à analyser l'activité pré-stimulus et à utiliser une réelle condition de contrôle pour révéler le contrôle proactif. *Illustration adaptée de Verbruggen & Logan, 2008 et Jaffard et al., 2008.*

**En conclusion, différents amendements méthodologiques peuvent être proposés pour contourner les limites des travaux existants et revisiter la fonction d'inhibition de réponse : 1/ créer des protocoles expérimentaux adaptés, permettant de tester en même temps les différents modèles d'inhibition, 2/ utiliser des méthodes avancées de traitement du signal (séparation aveugle de sources) permettant de démêler les différentes activités neurologiques, 3/ procéder à des analyses temps/fréquence, qui renseignent sur la nature de l'activité observée, et 4/ localiser les sources cérébrales responsables de l'activité d'intérêt. Il est important d'insister sur le fait qu'il est nécessaire de coupler ces différentes techniques, qui sont complémentaires et interdépendantes.**

### **Conclusion - Chapitre 3**

L'inhibition de réponse est une fonction clé et pourtant encore mal comprise du contrôle de l'action. Nous avons identifié plusieurs obstacles à une meilleure compréhension de ces mécanismes et de leurs bases anatomo-fonctionnelles. A ce jour, des avancées méthodologiques et théoriques permettent de contourner les limites des travaux existants et ouvrent la voie vers une meilleure compréhension de ces mécanismes. L'étude des dysfonctionnements du contrôle exécutif de l'action pourrait alors permettre de revisiter les troubles de l'initiation du mouvement dans la maladie de Parkinson.

# CHAPITRE 4 : L'AKINESIE ET L'IMPULSIVITE – LES DEUX FACES D'UNE MEME PIECE ?

Dans ce quatrième chapitre, nous nous appuyons sur des avancées théoriques et méthodologiques récentes pour revisiter les troubles de l'initiation du mouvement en termes de dysfonctionnements des mécanismes d'inhibition de réponse. Notre objectif est d'identifier les fonctions neuropsychologiques à l'origine de ces troubles et leurs bases neurophysiologiques et neurochimiques.

## A. REVISITER L'AKINESIE COMME UN DYSFONCTIONNEMENT EXECUTIF DE L'INHIBITION DE REPONSE

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### 1. STRATEGIE EXPERIMENTALE

Comme révélé par notre analyse systématique (Spay et al., submitted – *Chapitre 2*), l'origine de l'akinésie et ses bases neuro-fonctionnelles restent encore débattues. Plusieurs raisons concourent à la mauvaise compréhension de ce symptôme et sont détaillées dans les chapitres précédents de ce manuscrit.

Concernant les bases neuropsychologiques, l'hypothèse d'un dysfonctionnement exécutif du contrôle inhibiteur proactif à l'origine de l'akinésie dans la maladie de Parkinson a déjà été proposée (Favre et al., 2013), mais a été ignorée jusqu'à ce jour. Ces travaux mettent en évidence une lenteur globale à l'initiation des mouvements (i.e., akinésie) sans médication dopaminergique. Ils montrent également que la médication dopaminergique a un effet global

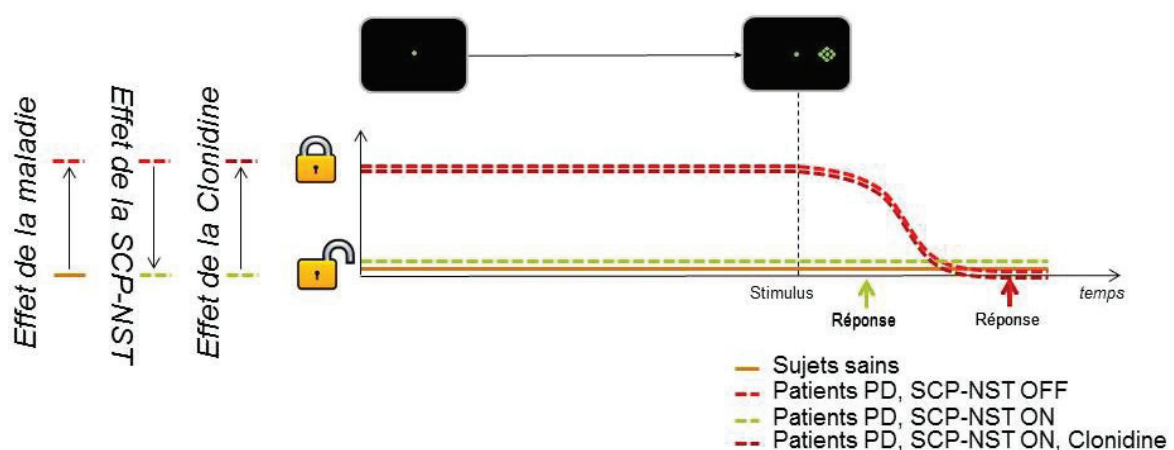
sur la composante motrice de l'akinésie en réduisant les TR des patients. Néanmoins, les patients akinétiques présentent, de façon spécifique, un déficit exécutif lié à la difficulté à déverrouiller volontairement le contrôle inhibiteur proactif dans la condition de contrôle ne requérant pourtant pas d'inhibition (Albares et al., 2015b). Alors que la médication dopaminergique n'a pas d'effet sur ce déficit exécutif observé, seule la SCP-NST permet de rétablir un pattern normal de contrôle inhibiteur. Ces résultats suggèrent que les troubles d'initiation du mouvement qui sont DA-résistants, sont dus à un dysfonctionnement exécutif du contrôle inhibiteur, et donc non-moteur. Néanmoins, aucune évidence neuro-fonctionnelle n'existe à ce jour chez l'homme pour appuyer cette hypothèse. Ces travaux suggèrent également un rôle clé du NST dans le contrôle inhibiteur proactif. Néanmoins, ils ne permettent pas de répondre aux autres questions relatives aux bases neuro-fonctionnelles et neurochimiques de la fonction.

Au regard des difficultés soulevées dans les chapitres précédents, nous proposons donc de combiner des avancées théoriques et méthodologiques afin de révisiter l'akinésie dans la maladie de Parkinson. Dans ce but, nous avons choisi : 1/ de nous baser sur une définition claire de l'akinésie en terme de lenteur à l'initiation du mouvement et de la révéler par un protocole expérimental simple de TR ; 2/ de considérer la pluralité des modèles de l'inhibition de réponse en considérant l'existence de mécanismes proactifs non sélectifs et de s'intéresser à la dynamique de ce contrôle ; 3/ d'utiliser l'EEG à haute résolution avec des méthodes avancées de traitement du signal qui nous permettront de filtrer les artéfacts de la SCP (Lio et al., 2018), de localiser les sources cérébrales (Lio & Boulinguez, 2013) et de réaliser des analyses temps-fréquence afin de sonder les mécanismes excitateurs et inhibiteurs co-occurents (Albares et al., 2015a) ; 4/ d'explorer les bases neurochimiques de l'akinésie au moyen de la manipulation pharmacologique de la NA par un agent hautement sélectif, la clonidine. Ce choix a été fait au



regard de la disponibilité de cet agent en France et de sa sélectivité, contrairement par exemple au méthylphénidate qui module à la fois la neurotransmission NA et DA (Moreau et al., 2012).

Notre démarche expérimentale repose principalement sur la manipulation croisée des neuromodulations pharmacologique et électrophysiologique. Ce choix est guidé par l'identification de données contradictoires relatives au mode d'action de la NA (*cf. Chapitre 2*). De façon consistante, les premiers résultats comportementaux de notre équipe (Albares et al., 2015b) suggèrent que l'action de la NA serait plus sélective qu'il n'est classiquement envisagé et qu'elle pourrait jouer un rôle direct dans l'activité (pathologique et restaurée) du NST chez l'homme dans la maladie de Parkinson. Ces données comportementales sont à la base de nos hypothèses (Figure 18) et suggèrent que la clonidine altère spécifiquement la capacité à lever le contrôle inhibiteur proactif dans la condition de contrôle qui requiert pourtant de laisser libre court aux automatismes sensorimoteurs. En d'autres termes, la réduction du tonus NA par la clonidine bloquerait spécifiquement l'effet positif de la SCP-NST sur l'akinésie. Néanmoins, les mécanismes neuro-fonctionnels qui sous-tendent cet effet n'ont pas encore été étudiés.



**Figure 18 : Modélisation des modulations de l'activité du contrôle inhibiteur proactif par la SCP-NST et la modulation pharmacologique noradrénergique**

La condition de contrôle dans laquelle aucune incertitude ne pèse sur la nature des stimuli potentiels (go, losange vert) autorise la levée anticipée de l'inhibition chez les sujets sains. Or,

l'akinésie DA-résistante chez le patient parkinsonien aurait une origine exécutive qui s'expliquerait par un verrouillage inapproprié des mécanismes d'initiation du mouvement dans ces situations de certitude nécessitant pourtant de laisser libre court aux automatismes sensorimoteurs (Patients PD, SCP-NST OFF ; Favre et al., 2015). Seule la stimulation du NST rétabli un pattern normal de déverrouillage du contrôle inhibiteur, i.e. restaure le déficit observé (Patients PD, SCP-NST ON ; Albares, Thobois et al., 2015). Selon les résultats comportementaux observés à savoir un rallongement pathologique du TR lors de la modulation pharmacologique, la clonidine (baisse du tonus NA) bloquerait spécifiquement l'effet positif de la SCP-NST sur le déficit exécutif en remettant les patients dans un état de verrouillage inapproprié du contrôle inhibiteur proactif (Patients PD, SCP-NST ON, Clonidine ; Albares, Thobois et al., 2015). Les analyses EEG temps-fréquence autorisent l'observation des modulations de l'activité du contrôle inhibiteur proactif dans des bandes de fréquence spécifiques.

## 2. IDENTIFICATION DES DYSFONCTIONNEMENTS DES MECANISMES INHIBITEURS A

### L'ORIGINE DE L'AKINESIE : INTERACTION DE LA MANIPULATION PHARMACOLOGIQUE


#### NORADRENERGIQUE ET DE LA STIMULATION CEREBRALE PROFONDE

Afin de révéler les bases neuro-fonctionnelles de ce verrouillage pathologique, nous avons donc utilisé l'EEG à haute résolution dans une tâche de TR simple permettant d'analyser la capacité des patients à moduler le contrôle de l'initiation de leurs mouvements au travers de l'interaction de la SCP-NST et de la neurotransmission noradrénergique (clonidine, agoniste des récepteurs alpha-2 adrénergiques).

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ORIGINAL  
ARTICLE

## Clonidine modulates the activity of the subthalamic–supplementary motor loop: evidence from a pharmacological study combining deep brain stimulation and electroencephalography recordings in Parkinsonian patients

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**Abstract**

Clonidine is an anti-hypertensive medication which acts as an alpha-adrenergic receptor agonist. As the noradrenergic system is likely to support cognitive functions including attention and executive control, other clinical uses of clonidine have recently gained popularity for the treatment of neuropsychiatric disorders like attention-deficit hyperactivity disorder or Tourette syndrome, but the mechanism of action is still unclear. Here, we test the hypothesis that the noradrenergic system regulates the activity of subthalamo-motor cortical loops, and that this influence can be modulated by clonidine. We used pharmacological manipulation of clonidine in a placebo-controlled study in combination with subthalamic nucleus-deep brain stimulation (STN-DBS) in 16 Parkinson's disease patients performing a reaction time task requiring to refrain from reacting (proactive inhibition). We recorded electroencephalographical activity of the whole cortex, and applied spectral analyses directly at the source level after advanced blind

source separation. We found only one cortical source localized to the supplementary motor area (SMA) that supported an interaction of pharmacological and subthalamic stimulation. Under placebo, STN-DBS reduced proactive alpha power in the SMA, a marker of local inhibitory activity. This effect was associated with the speeding-up of movement initiation. Clonidine substantially increased proactive alpha power from the SMA source, and canceled out the benefits of STN-DBS on movement initiation. These results provide the first direct neural evidence in humans that the tonic inhibitory activity of the subthalamocortical loops underlying the control of movement initiation is coupled to the noradrenergic system, and that this activity can be targeted by pharmacological agents acting on alpha-adrenergic receptors.

**Keywords:** clonidine, deep brain stimulation, electroencephalography, noradrenaline, Parkinson's disease, response inhibition.

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*Abbreviations used:* DBS, deep brain stimulation; NA, noradrenaline; PD, Parkinson's disease; RT, reaction time; SMA, supplementary motor area; STN, subthalamic nucleus.

Clonidine acts as an  $\alpha$ -adrenergic receptor agonist, and is commonly prescribed as an anti-hypertensive medication. As it increases noradrenergic (NA) outflow from the locus coeruleus to the prefrontal cortex and stimulates directly pre-synaptic  $\alpha$ -2A receptors in the cortex, clonidine is also likely to have effects on various functions that rely on the NA system. For instance, it has also been shown to be useful in treating some symptoms like attentional dysfunctions and impulsivity observed in attention-deficit hyperactivity disorder and Tourette syndrome (Lichter and Jackson 1996; Ming *et al.* 2011). However, the mechanisms of action of clonidine, and more generally of the whole class of pharmacological agents targeting the NA system, are still unclear. The main reason is that it is particularly challenging to investigate the functional roles of the NA system in the living human brain as there is still no satisfactory selective positron emission tomography radiotracer for *in vivo* imaging. This lack of basic knowledge about the functional networks that are modulated by the NA system impedes the potential spectrum of application of pharmacological agents acting on  $\alpha$ -adrenergic receptors. However, recent studies have given glimpses of the potential of this class of drugs by suggesting that the NA system plays a critical role in specific cognitive and motor functions, as well as in the physiopathology of other diseases like Parkinson's disease (PD) and Alzheimer's disease (Zarow *et al.* 2003; Marien *et al.* 2004; Fornai *et al.* 2007; Chamberlain and Robbins 2013; Mather and Harley 2016; Rae *et al.* 2016; Borodovitsyna *et al.* 2017; Nahimi *et al.* 2017).

Here, we focus on movement initiation disorders and, to this aim, study PD patients. The interest in PD is double. First, movement initiation disorders represent a major symptom of the disease which is both difficult to isolate (see Schilder *et al.* 2017) and difficult to treat. Second, it becomes possible, in implanted PD patients, to manipulate the activity of the subthalamic nucleus (STN), a small but critical basal ganglia nucleus whose activity cannot be easily recorded with classical neuroimaging tools. Our understanding of the neural bases of movement initiation and related disorders is still incomplete (Gauntlett-Gilbert and Brown 1998; Rodriguez-Oroz *et al.* 2009). This is partly due to the fact that there is no unified use of terminology for the range of disturbances of voluntary movement and, hence, strong potential confounds regarding the underlying dysfunctional neural mechanisms (Schilder *et al.* 2017). This is also partly due to the fact that a number of important questions about the basal ganglia (BG) circuitry remain unresolved, including the issue of the exact role of STN, one of the two input stations of the BG (Nambu 2008; Obeso and Lanciego 2011; Haynes and Haber 2013; Jin *et al.* 2014).

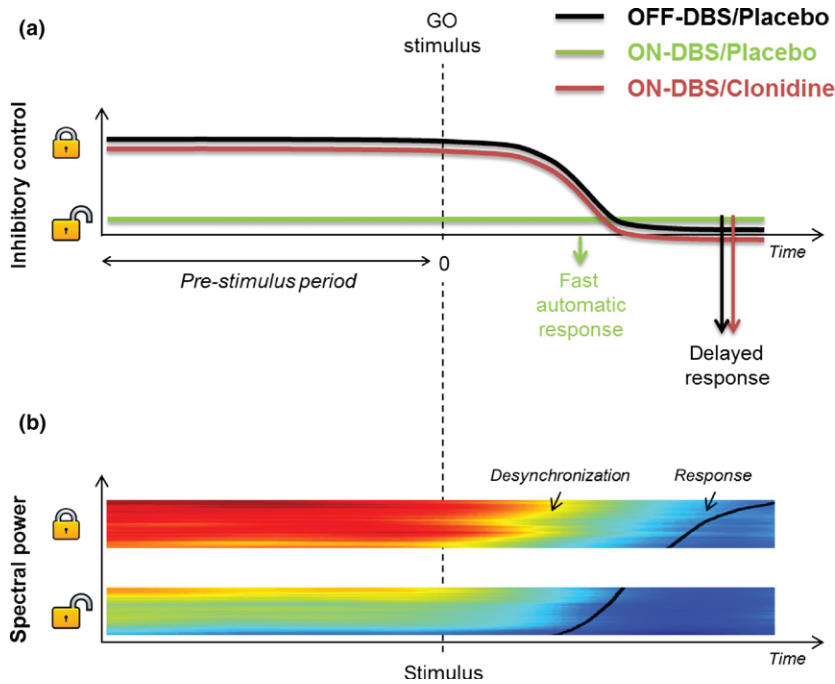
In PD, impairment of movement initiation has mostly been referred to as akinesia (e.g., Hallett 1990). It is a cardinal symptom of the disease that is not fully alleviated by dopaminergic medication (Schubert *et al.* 2002; Favre *et al.*

2013; Fox 2013). Here, we refer to slowness in movement initiation, which is not to be confounded with slowness of movement execution, that is, bradykinesia (Schilder *et al.* 2017). Slowness in movement initiation is associated with dysfunctions of movement preparation, an ensemble of sensorimotor and executive processes that build up the command to move and control its triggering before the movement is initiated (Alexander and Crutcher 1990; Kaufman *et al.* 2014). Behaviorally, it is assessed by means of reaction time (RT) measures.<sup>1</sup> Movement initiation relies on modular cortico-basal ganglia-thalamocortical loops. It involves distinct pathways of the motor circuit through which cortical inputs enter the striatum, are forwarded to the thalamus which projects back to the cerebral cortex. These different pathways exert antagonist effects on motor cortical activity. The cortico-striato-pallidal direct pathway relays activating signals from the motor cortices. These signals induce inhibition in the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr) that results in increased activation of the ventrolateral nucleus of the thalamus which, in turn, amplifies motor cortical activity. The indirect pathway has opposite effects on the GPi/SNr since it reinforces the default inhibitory outflow of the basal ganglia. Its activation leads to a reduction of activity in the motor cortices to prevent unwanted movements. The indirect pathway involves the STN in a cortico-striato-pallido (external, GPe)-STN-pallidal (GPi) circuit. Movement disorders of basal ganglia origin are thought to result from imbalanced activities between the two pathways (e.g., Albin *et al.* 1989). Importantly, another pathway, the hyperdirect pathway, also involves the STN, which receives direct cortical information that gets relayed to the GPi/SNr (Nambu *et al.* 2002; Nambu 2004). This pathway could play a role in relaying fast signals instructing to inhibit ongoing actions, or in switching from controlled to automatic sensorimotor processing by modulating the balance between facilitation and attenuation of motor cortical activity (Frank *et al.* 2007; Isoda and Hikosaka 2007; Aron 2011). Since the STN receives direct projections from both motor and non-motor cortical areas, it likely plays a pivotal role as an interface between executive and motor systems in basal ganglia-thalamocortical loops (Benarroch 2008), either via the slow indirect pathway or via the fast hyperdirect pathway. However, despite clues from subthalamic nucleus-deep brain stimulation (DBS) studies (Favre *et al.* 2013; Benis *et al.* 2014; Albares *et al.* 2015a; Faggiani *et al.* 2015) the exact role of the STN remains poorly understood.

<sup>1</sup>Although bradykinesia might also partly be due to dysfunctions of movement preparation, it mostly results from a failure of basal ganglia output to reinforce the cortical mechanisms that execute the commands to move (Berardelli *et al.* 2001). Behaviorally, bradykinesia is assessed by means of movement duration measures, but that is outside the scope of this paper.

Difficulties initiating movements in PD are generally interpreted as a motor and dopaminergic dysfunction. Distorting signals from sensorimotor, dopamine-deprived circuits would induce increased tonic inhibition from basal ganglia output, and would result in impaired automatic movements (Redgrave *et al.* 2010). According to this view, PD patients would be trapped in goal-directed control to overcome the inhibitory distortion from the malfunctioning stimulus–response control circuits in the basal ganglia. It is noteworthy that this compensatory mechanism is accompanied by increasing fatigue because this level of goal-directed input is difficult to sustain (*ibid.*). A slightly different view suggests that PD patients would be trapped in goal-directed control because of specific executive dysfunction, not just to compensate for impaired automatic movements (Ballanger

*et al.* 2009; Favre *et al.* 2013; Albares *et al.* 2015a; Criaud *et al.* 2016). This executive disorder concerns proactive inhibition, a function which is intended to inhibit movement triggering mechanisms in the absence of stimulation in uncertain environments. The goal of this function is to prevent undesired automatic responses to upcoming stimulation (Aron 2011; Criaud *et al.* 2012, 2017; Jaffard *et al.*, 2007, Jaffard *et al.* 2008; Li 2015). It involves a cortical network which is more active when subjects must refrain from reacting to external events and which deactivates to allow the response to be triggered (Fig. 1a). This network comprises notably the supplementary motor area (SMA) and the dorsomedial prefrontal/anterior cingulate cortex, which have direct connections to the STN (Benarroch 2008). PD patients would be locked into a mode of executive control



**Fig. 1** (a) Theoretical assumptions and (b) electrophysiological signature of proactive inhibitory control. The simple reaction time (RT) task probes the ability to refrain from reacting automatically to visual targets by means of proactive inhibitory control, a pivotal mechanism consisting in gating movement initiation in the pre-stimulus period when the context is uncertain. (a) When the context is uncertain, inhibitory control is implemented in the absence of stimulation. When a target is presented, inhibition must be released before a goal-directed movement can be triggered. This time consuming mechanism generates long latency responses. When the context is predictable, healthy subjects do not set proactive inhibitory control, and provide automatic short latency responses. Conversely, Parkinson’s disease patients show abnormally enhanced activity within the proactive inhibitory network leading to difficulties initiating movements (delayed responses, Criaud *et al.*

2016). As inferred from behavioral studies, the effect of STN-DBS may consist in reinstating the ability to release proactive inhibitory control in the absence of stimulation when the context does not require action restraint (Favre *et al.* 2013; Albares *et al.* 2015a). Clonidine could impede the positive action of STN-DBS on movement initiation by blocking the ability to release proactive activity within the inhibitory network (Albares *et al.* 2015a). (b) Electroencephalography (EEG) offers the possibility to track relevant spectral activity, directly at the source level after blind source separation and DBS artifacts removal. Time course of  $\alpha$  power on a trial-by-trial basis in healthy subjects. Trials are sorted according to RT (black curve) when proactive inhibition is set, an increase in tonic  $\alpha$  power is observed during the pre-stimulus period that desynchronizes when the stimulus has been identified. This proactive activity predicts RT.

which maintains inappropriate tonic, proactive inhibition over movement triggering in situations that do not require action restraint (Favre *et al.* 2013; Albares *et al.* 2015a). In accordance with this view, difficulties initiating movements are associated with pathological overactivity within the proactive inhibitory brain network (Criaud *et al.* 2016). Deep brain stimulation of the subthalamic nucleus would act by regaining control of the state of ‘self-initiated automaticity’ (ibid). However, the functional modulations accounting for the executive benefits of STN-DBS on movement initiation have not been identified.

In contrast to the acknowledged role of dopamine in motor processes, the dysfunction of proactive inhibitory control leading to delayed movement initiation in PD, and its restoration by STN-DBS, does not appear to be dopaminergic-dependent (Favre *et al.* 2013). A recent behavioral study in PD combining pharmacological manipulation using clonidine and STN-DBS suggests that the NA system plays a role in the positive action of STN-DBS on movement initiation latency (Albares *et al.* 2015a). However, there is still no direct neural evidence in humans that the NA system modulates the activity of the subthalamic-cortical loops involved in motor control. This is the first goal of this study. An associated objective is to test whether clonidine, an anti-hypertensive medication which acts as an  $\alpha$ -adrenergic receptor agonist, can regulate the activity of the cortico-basal ganglia loops underlying the executive control of movement initiation.

It is essential to assess DBS-induced modulations of brain activity to provide such neural evidence (Okun 2014; Udupa and Chen 2015). Yet, several obstacles impede the identification of the different cortico-subthalamic networks and neurotransmitter systems involved in the mechanisms of action of STN-DBS. First, it is a major technical challenge to record cortical dynamics while applying DBS. Second, controversy surrounds the interpretation of the balancing activity in these circuits due to difficulties in disentangling motor and inhibitory processes with neuroimaging data (Logothetis 2008). Here, we use electroencephalography (EEG), which offers: (i) the opportunity to assess cortical dynamics during DBS, and (ii) strong discriminative power regarding the nature of brain modulations by means of the analysis of the spectral signatures of the functions of interest.

Here, we analyzed EEG data from PD patients in a placebo-controlled experiment investigating the effects of NA attenuation by clonidine ( $\alpha$ 2-adrenergic receptor agonist) under two conditions of STN-DBS (OFF vs. ON). The behavioral results of this experiment have been described in a former publication (Albares *et al.* 2015a). Recent methodological advances from our group allowed us to remove DBS-induced electrical artifacts (Allen *et al.* 2010; Lio *et al.* 2016; revised), to separate/localize significant sources on the basis of the mixed signal recorded on the scalp (Lio and Boulinguez 2013, 2016), and to apply

advanced signal processing methods to unravel the time course of concurrent excitatory and inhibitory activity (Albares *et al.* 2015b).

## Material and methods

### Participants

Eighteen parkinsonian patients (aged  $59.6 \pm 5.0$  years old, five females, with normal or corrected-to-normal vision) treated with bilateral STN stimulation were enrolled. The sample size was determined on the basis of the expected differences informed by former behavioral results using the same design in STN-DBS patients.<sup>2</sup> The group size was also determined in agreement with former specific recommendations regarding EEG group blind source separation analyses (Lio and Boulinguez 2016). Patient recruitment was conducted according to the following inclusion criteria: age between 40 and 70 years old, patients with idiopathic dopa-sensitive Parkinson’s disease, treated with STN-DBS for at least 3 months, under stable pharmacological anti-parkinsonian treatment for at least 2 months, and presenting no contraindication for taking clonidine (no depression, no heart disease, no lactose intolerance). Exclusion criteria were: sign of depression or other neurologic or psychiatric pathology, pharmacological treatment with cerebral or psychic impact, substance abuse according DSM-IV-TR (excluding tobacco), pregnancy or breastfeeding. The implantation of the electrodes (Model 3389; Medtronic, Minneapolis, MN, USA) was performed under local anesthesia, guided by stereotactic magnetic resonance imaging, and microelectrode recordings. The accurate placement of the electrodes was confirmed on post-operative CT scan. The electrodes were connected to a pulse generator (Kinetra or Soletta, Medtronic). The main demographic and clinical characteristics of the patients, the stimulation parameters used, the levodopa equivalent dose, and the effects of STN stimulation on the Unified Parkinson’s Disease Rating Scale (UPDRS) motor scores are presented in Table 1. All these parameters were used as covariates in order to examine potential subgroups and interactions. The patients did not exhibit major signs of tremor and were not demented (MATTIS > 130). Of note, two patients (P3, P8) presented pathological gambling and compulsive shopping tendencies while one (P14) reported dopaminergic addiction and nocturnal hyperactivity well before STN-DBS surgery (at least 3 years ago). These symptoms have been totally suppressed by stopping dopaminergic agonists. Furthermore, all patients were submitted to

<sup>2</sup>We used the RT values observed for PD patients ON STN-DBS vs. PD patients OFF STN-DBS in preliminary data (Favre *et al.* 2013), in the same conditions of interest as those described in this study (Go mixed-block vs. Go pure-block). The estimated sample size  $n$  was calculated as the solution of:

$$n = \frac{(t_{n-1, \alpha/2} + t_{n-1, \beta})^2}{d^2}$$

where  $d = \text{delta}/\text{sd} = 50 \text{ ms}/40 \text{ ms}$ ,  $\alpha = 0.05$ , power =  $1 - \beta = 0.8$ ,  $t_v$  is a Student  $t$  quantile with  $v$  degrees of freedom and probability  $p$ .  $n$  is rounded up to the closest integer. Given a desired power of 80%, and a predetermined Type I error rate  $\alpha$  of 5%, the number of patients required to evidence a RT difference of 50 ms between ON- and OFF -DBS conditions was fixed to 16.

**Table 1** Demographic and clinical characteristics of the Parkinson's disease patients treated with deep brain stimulation of the subthalamic nucleus

Patient	Sex	Age (years)	DD (years)	UPDRS III		LED (mg/day)	Stimulation parameters		TSS (months)	UPPS scores	Predominant symptoms
				ON*	OFF*		LS (plot/Hz/ $\mu$ S/V)	RS (plot/Hz/ $\mu$ S/V)			
1	H	59	10	13	33	350	1-/130/60/3,4	9-/130/60/3,5	8	50	dysarthria, dyskinesia
2	H	61	14	23	48	465,5	2-/130/60/3,2	7- and 6-/130/90/3	51	42	freezing, postural instability, hypertonia
3	H	61	7	7	23	399	3-/130/65/3,25mA	2-/130/65/3mA	6	44	freezing
4	H	50	26	6	19	160	1-/130/90/3,3	6-/130/90/3,3	35	35	dystonia
5	H	65	12	8	20	450	2-/130/60/3,5	5-/130/90/3,6	36	39	dyskinesia, mild akinesia
6	F	64	24	20	24	880	2-/130/60/3,5	5-/130/60/3	81	42	dyskinesia
7	F	64	15	12	24	660	3-/160/90/3,4	7-/160/90/2,9	34	58	bradykinesia, akinesia, postural instability
8	H	58	12	18	44	300	1-/130/60/3	5-/130/60/3,2	42	51	dystonia
9	F	61	10	10	30	0	2-/130/60/2,5	10-/130/60/2,9	8	46	facial dyskinesia, dysarthria
10	H	61	14	29	50	1160	2- and 1-/130/90/3,6	5-/130/90/3,6	61	59	mild akinesia, mild dyskinesia
11	F	65	9	12	18	150	2-/130/60/2,6	11-/130/60/2,8	6	32	dyskinesia, mild rigidity
12	H	65	12	4	23	660	2-/160/90/2,6	6-/160/90/2,4	53	34	mild tremor
13	H	55	14	10	36	560	2-/130/60/2,4	10+ and 11-/130/60/2,5	4	45	
14	H	48	12	14	38	300	11-/160/90/3,6	1- and 2+ /160/60/2,9	3	43	
15	H	56	12	2	6	1542,5	3- and 2-/130/90/2,9	11-/130/60/3,5	3	26	akinesia, rigidity
16	H	56	7	13	31	1275	3-/160/90/3,6	11-/160/60/3	5	26	mild tremor
Mean		59.3	13.1	12.5	29.2	582			27.2	41.7	
SE		5.2	5.2	7.1	11.9	433.5			25.2	9.8	

DD = disease duration; UPDRS III = motor score at the Unified Parkinson Disease Rating Scale; LED = levodopa equivalent dose; TSS = time since surgery; M=male; F=female; SE = standard error; UPPS = UPPS Impulsive behaviour state.

\*UPDRS III scores represent ON STN-DBS and OFF STN-DBS states, and were evaluated under the usual dopaminergic medication of the included patient, at the same time of the day.

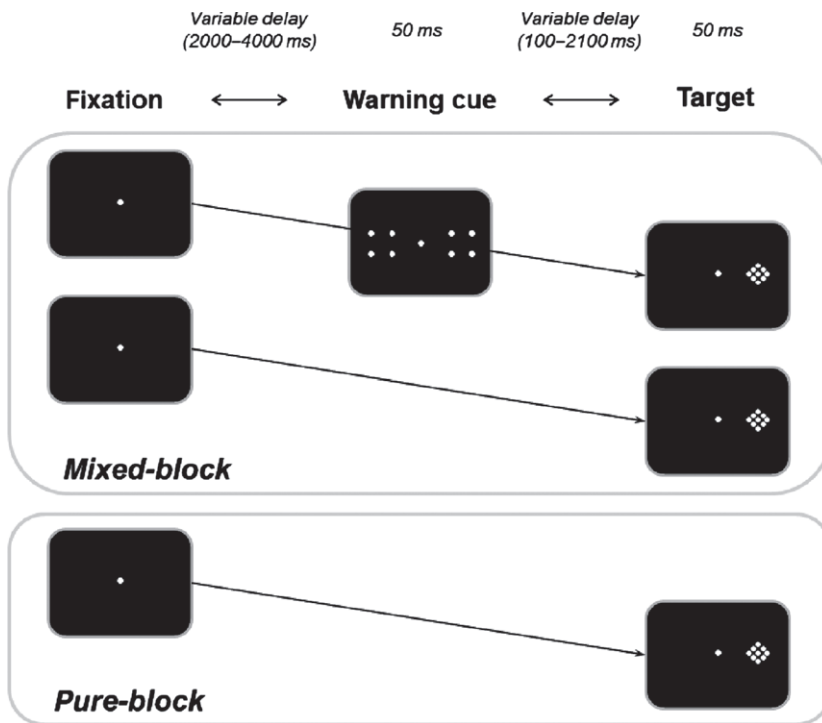
the neuropsychological Arduin scale of behavior in Parkinson's disease (Arduin *et al.* 2009), which assesses changes in usual activities, psychiatric tendencies, and evaluation of both apathic and appetitive modes. Hyperdopaminergic abnormalities were not reported in any patient. Participant consent was obtained according to the code of ethics of the World Medical Association (Declaration of Helsinki) and the experimental protocol was approved by the local Ethical Committee in Biomedical Research (Comité de Protection des Personnes sud est IV, N\_ CPP 12/039). This study was pre-registered before being conducted on the clinicaltrials.gov database under the trial record number NCT01796483.

#### Behavioral task and procedure

Patients performed a cue-target RT task fully described elsewhere (Albares *et al.* 2015a). The experiment was intended to test the ability of patients to initiate simple movements in response to visual targets while maintaining their capacity to refrain from reacting to other visual stimulations (Fig. 2). Specifically, the ability to react to

visual stimuli was assessed in separate blocks of trials in which only visual targets were presented (inducing no uncertainty about upcoming stimuli, that is, no need for subjects to refrain from reacting). In this condition (no-cue trials), short RTs are expected because subjects can react automatically to any upcoming event (Albares *et al.* 2015a; Fig. 1b). This condition represents the control condition in which healthy subjects do not implement proactive inhibitory control (Criaud *et al.* 2012). The ability to refrain from reacting to non-targets was assessed in other blocks of trials mixing targets and cues (inducing uncertainty about upcoming stimuli, i.e., requiring proactive inhibitory control). In this context, long RTs are expected when the target is not preceded by a warning cue because subjects cannot react automatically to any upcoming event. They need first to release proactive inhibition after they have identified the target stimulus. Then only, they produce delayed volitional response (Albares *et al.* 2015a; Fig. 1b).

Stimuli were projected on a screen placed 50 cm away from the participants' eyes. While keeping their gaze fixed on a central



**Fig. 2** Experimental protocol. The cue-target reaction time (RT) task is composed of two blocks of trials: A mixed-block in which cue and no-cue trials are presented randomly, and a pure-block in which only no-cue trials are presented. Since the effects of the disease (patients vs. age matched controls) and the effects of subthalamic deep brain stimulation (ON vs. OFF) have been observed only in the pure-block condition (Favre *et al.* 2013; Albares *et al.* 2015a; Criaud *et al.* 2016), the analyses of this study are restricted to this single pure-block condition.

fixation point, participants were asked to react as quickly as possible to a visual target that might or might not be preceded by a neutral warning signal by pressing a button with the right index finger (Fig. 2). In the mixed-block of trials, cue and no-cue trials were presented randomly. In the pure-block, only no-cue trials were presented. Before starting recording, two training sessions were presented: one pure-block (48 trials) and one mixed-block (96 trials). Recordings were performed in four following blocks (two pure-blocks of 48 trials each and two mixed-blocks of 96 trials each). The order of these four blocks was counterbalanced across participants and for each condition of STN-DBS and Drug. Each subject performed 288 trials for each session of stimulation and drug, equal to 1152 trials in total (four sessions).

#### Drugs procedure

NA manipulation was realized in a simple blind design, placebo-controlled study, using a 150 µg oral dose of clonidine ( $\alpha$ 2-AR agonist). Clonidine is highly selective, exerts potent agonistic effects at pre-synaptic  $\alpha$ -2 receptors, and has optimal kinetics with respect to the duration of our protocol (Delaville *et al.* 2011). Specifically, clonidine decreases NA release through pre-synaptic  $\alpha$ 2-AR activation. Each patient was tested in four experimental sessions combining all conditions of stimulation (STN-DBS ON; STN-DBS OFF) and drug (Clonidine; Placebo). The first (S1) and the second (S2) sessions were separated by 24 h. The third (S3) and fourth (S4) sessions took place 3 months later, separated by 24 h. Since the long half-life of clonidine does not allow complete withdrawal from the body from one day to the next, patients always received placebo first (at S1 and S3), and then received a clonidine (at S2 and S4, 150 mg oral dose). In this simple blind design, patients were blinded to the drug condition (Clonidine; Placebo), while clinicians were aware that placebo was always given on the

first day and clonidine on the second day. Patients were tested in the morning (at 9 am) on two consecutive days, with and without STN-DBS treatment (ON and OFF conditions) while taking their usual anti-parkinsonian drugs. Randomization blocks were used to allocate subjects to experimental groups in order to counterbalance the order of the ON and OFF conditions of STN-DBS across participants. The stimulator was switched off in the OFF condition 30 min before testing. The fact that patients were tested at the same time schedule in the ON and OFF conditions ensured that the effect of dopaminergic medication was identical in both states (see Table 1 for the demographic characteristics). The drug was administered 90 min before testing to maximize the effect. Since clonidine has well-established anti-hypertensive properties, the blood pressure was monitored every 30 min from intake time to 1 h after the experiment. Two patients were excluded from the analysis during the course of the study because the DBS battery housing was infected and removed between the S1/S2 and S3/S4 sessions. EEG analyses were conducted only on the 16 patients who have completed all experimental sessions (aged  $59.3 \pm 5.2$  years old, four females; Table 1).

#### EEG

##### EEG data acquisition procedure

The Biosemi™ ActiveTwo Mk2 system (31.25 nV resolution) (Biosemi B.V., Amsterdam, Netherlands) was used to record EEG data from 128 electrodes mounted in an elastic cap at Biosemi™ ABC system standard locations. Six additional external electrodes were added: four temporal electrodes (Biosemi spherical coordinates: Phi  $-103.5$  Theta  $-18 -36$ , and Phi  $103.5$  Theta  $18 36$ ), and two electrodes attached to the outer canthi of the left and right eyes (Phi  $103.5 -103.5$  Theta  $81 -81$ ). The Common mode sense



(CMS) active electrode and the Driven right leg (DRL) passive electrode of the ActiveTwo system were used instead of classical ground electrodes of conventional systems (these two electrodes form a feedback loop driving the average potential of the subject – the Common Mode voltage – as close as possible to the analog-to-digital reference voltage in the AD-box). All electrode offsets were kept below 20 mV. EEG data were recorded at a sampling rate of 2048 Hz. Offline, data were high-pass filtered above 1 Hz, low-pass filtered at 95 Hz, notch filtered at 50 Hz, and down-sampled to 1024 Hz. Then, data were epoched from 1500 ms before stimulus onset to 1000 ms after stimulus onset.

### EEG data pre-processing and analyses

The entire pipeline is schematized in Fig. 3. We applied recent methodological developments from our group to: (i) remove DBS artifacts (Lio *et al.* 2016), (ii) apply group Blind Source Separation (gBSS), a method that directly identifies the components that are consistently expressed in the population (Lio and Boulinguez 2013; Albares *et al.* 2015b; Huster *et al.* 2015). The other benefits of using gBSS include better sensitivity for discrimination between groups of subjects or sessions that are separated in time, which is particularly convenient for the present clinical investigation, and more efficient localization of these components (Lio and Boulinguez 2016).

First, data were filtered in order to remove the DBS-induced electrical noise that scrambles the low magnitude of the EEG signal. This step is critical since the available methods for filtering DBS artifacts are neither easy to use nor fully satisfactory. Here, we combined different techniques for optimal filtering (anti-aliasing analog and digital low-pass standard filtering, plus an optimized frequency-domain filtering technique, Hampel method) (Allen *et al.* 2010). To this aim, we used open-source toolbox DBSFILT (Lio *et al.* 2016).

Then, for each subject, corrupted epochs and artifacts (blinks, eye movements, electrical noises) were automatically detected and rejected using an Higher Order Statistics-based BSS algorithm (Infomax ICA) with EEGLAB (Delorme and Makeig 2004) and the FASTER toolbox (Nolan *et al.* 2010).

gBSS: First, we concatenated individual trials obtained from our 16 patients. Then, we applied gBSS to unmix the signals contributing to the overall electrical activity recorded on the scalp. To this end, we used a robust second-order statistics-based algorithm to optimize separation: UW-SOBI was privileged over more popular but less robust higher order statistics-based algorithms (Yeredor 2000; Lio and Boulinguez 2013). Among the 134 Independent Components (ICs) identified, we selected for further analyses only the most consistent components across subjects. To this aim, we used a standard consistency test adapted from previous studies (Congedo *et al.* 2010; Ponomarev *et al.* 2014). This method consists in separating the whole group into two subsamples of nine subjects matched for performance, and applying a test–retest strategy to select only ICs that are replicable across subjects. Among all possible combinations of two groups of nine subjects, we selected the combination with the more similar delta mean RT between the no-cue, mixed-block condition and the no-cue, pure-block condition in the Placebo condition and in the Clonidine condition. In consequence, the probability to obtain, by chance, two groups of nine subjects more similar than these two is below  $1 \times 10^{-5}$ . Then, in addition to the whole subjects gBSS (G\_all),

two supplementary gBSSs were performed, one on group 1 (G1) and one on group 2 (G2). Finally, the ICs obtained from G\_all, G1, and G2 decompositions were matched. To this aim, we used the Pearson correlation scores between the weights of the mixing matrices, with the following algorithm:

- ICs are sorted in decreasing order of explained variance.
- For  $i$ , from 1 to the number  $n$  of ICs;  $n$  triplets of matched ICs were built by searching in G1 IC\_1 ( $i$ ) and in G2 IC\_2 ( $i$ ) the components that are most similar with the component IC\_all ( $i$ ) of G\_all.
- To assess the quality of IC\_all ( $i$ ), for each triplet of components [IC\_1 ( $i$ ); IC\_2 ( $i$ ); IC\_all ( $i$ )], a quality index based on the similarity of the spatial signature of the components was used:  $Q_i = |p_{\text{pearson}}(\text{IC}_1(i), \text{IC}_2(i))| \times 100$ ,
- For each quality index  $Q_i$ , a  $p$ -value was calculated considering all possible combinations of two ICs randomly extracted from two different ICA/BSS decompositions. Only group ICs with a quality index  $Q_i > 70\%$  ( $p < 0.01$ ) were considered as reliable for further analysis.

Deconcatenation and normalization for between-subject's analyses: The consistent ICs obtained at the group level served as a filter to get back to the individual level of analysis. This step is essential because each patient was tested in four different experimental sessions separated by at least 24 h, meaning that different electrode set-ups were used for each single subject. This prevents from comparing directly the absolute potentials between the experimental conditions. This step-back to individual analyses allows individual data normalization, a prerequisite for between-subjects analyses in these circumstances. The mean relative power within each frequency band was thus calculated with respect to the total power of the EEG signal (whole spectrum) for each single source/subject.

### Statistical analyses of pre-stimulus activity

The analysis consisted in assessing STN-DBS-induced modulations and clonidine-induced modulations of the relative spectral power during the pre-stimulus period, within each frequency band of the 14 sources that are consistent across subjects. The time window used for the analysis was restricted to the [500–0 ms] pre-stimulus period. Then, the effect of STN-DBS was tested in the placebo condition by means of a non-parametric Wilcoxon signed-rank test for matched samples (ON DBS/Placebo vs. OFF DBS/Placebo). The effect of Drug was tested in the ON STN-DBS condition by means of a non-parametric Wilcoxon signed-rank test (ON DBS/Clonidine vs. ON DBS/Placebo). In accordance with our predictions based on the behavioral results, all tests were one-tailed.  $p$  values  $< 0.05$  (Bonferroni corrected) were considered significant.

### Visualization

The absolute power within each frequency band was used for visualization of the temporal dynamics of brain recordings. Initially, single-trial power modulations were estimated separately for each frequency band of the selected sources. In order to get optimal time/frequency resolution within delta/theta (1.5–7.5 Hz), alpha (7.5–13.5 Hz), beta (13.5–30.5 Hz), low gamma (30.5–44.5 Hz), and high gamma (57.5–77.5) band activities, five Elliptic Infinite Impulse Response (IIR) band pass filters were designed with the Matlab™ signal processing toolbox. Relatively large pass band

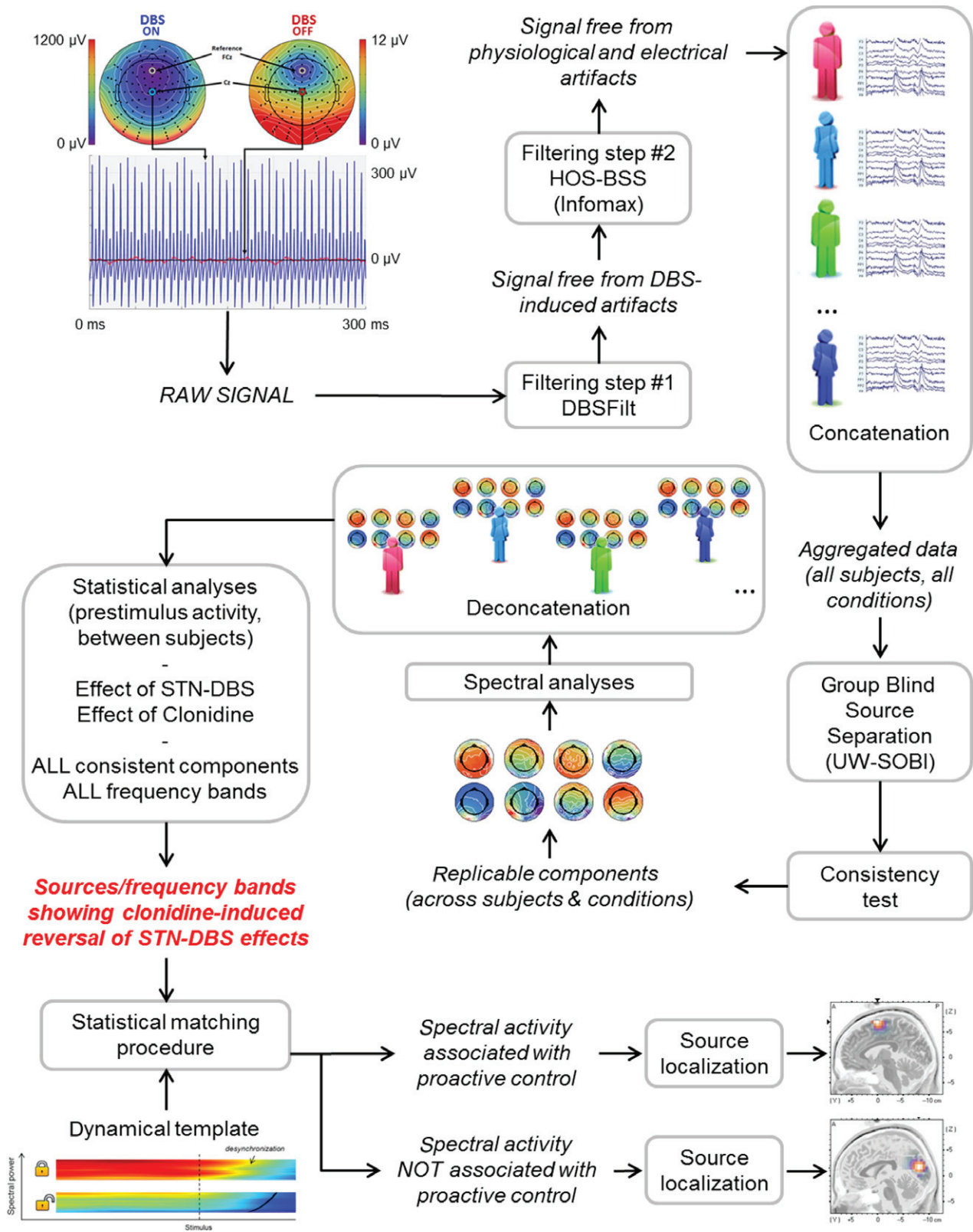


Fig. 3 Data processing pipeline configuration (see text for details).

widths were set to get optimal time resolution, that is, optimal estimation of the temporal dynamics of the band, thanks to the Hilbert transform. First, each trial was filtered with the corresponding filter in both forward and reverse directions to ensure zero-phase distortion. Second, the complex analytic signal of each filtered trial was derived by the Hilbert transform (Matlab™ Hilbert function). Third, the amplitude envelope of the signal was computed by taking the absolute magnitude of the complex waveform. The time window was restricted to the 1000 ms pre-stimulus to 800 ms post-stimulus in order to avoid edge effects/transient responses of digital filters. Finally, for visualization only, a trial moving average smoothing was applied (windows length: 300). The time course of absolute  $\alpha$  power in the SMA was displayed in a figure aggregating all subjects and all trials sorted as a function of RT (Fig. 4c).

#### Selection of the sources supporting proactive control

Importantly, in this paper, no *a priori* assumption is made about the brain regions and the frequency bands that may support the effect. Thus, rather than using a region/frequency of interest approach, preference is given to a blind strategy consisting in testing all sources that have been separated, within each frequency band.

Analyses of the temporal dynamics of the signal are required to identify the sources that desynchronize after stimulus presentation, that is, the sources that match the predictions of the theoretical model (Fig. 1b). Guidelines for assessing the cortical brain dynamics of response inhibition with EEG are summarized in Albares *et al.* (2015b). In sum, we compared the mean power of the 500 ms pre-stimulus period to the mean power of the 100 ms pre-RT period on a single-trial basis (aggregate data) by means of Kruskal–Wallis tests and post hoc testing ( $p < 0.05$  Tukey–Cramer corrected). A significant decrease is supposed to index stimulus-induced desynchronization. A lack of significant difference means that the effect (either DBS or Drug) previously observed on the pre-stimulus period is a global effect not related to proactive control.

#### IC Source localization

Finally, the 3D distribution of the selected source current densities was estimated by means of the sLoreta software (Pascual-Marqui 2002). The head model used for this analysis was obtained by applying the BEM method to the MNI152 template (Mazziotta *et al.*, 2001). The 3D solution space was restricted to cortical gray matter and was partitioned into 6239 voxels with a spatial resolution of 5 mm. Then, the sLoreta solution of the inverse problem was computed using an amount of Tikhonov regularization optimized for an estimated Signal/Noise Ratio of 100.

## Results

### Behavior (RT)

Results of interest for this study are summarized in Fig. 4(b). We previously showed that both the effect of the disease, the effect of STN-DBS, and the effect of pharmacological manipulation are restricted to the specific situation in which

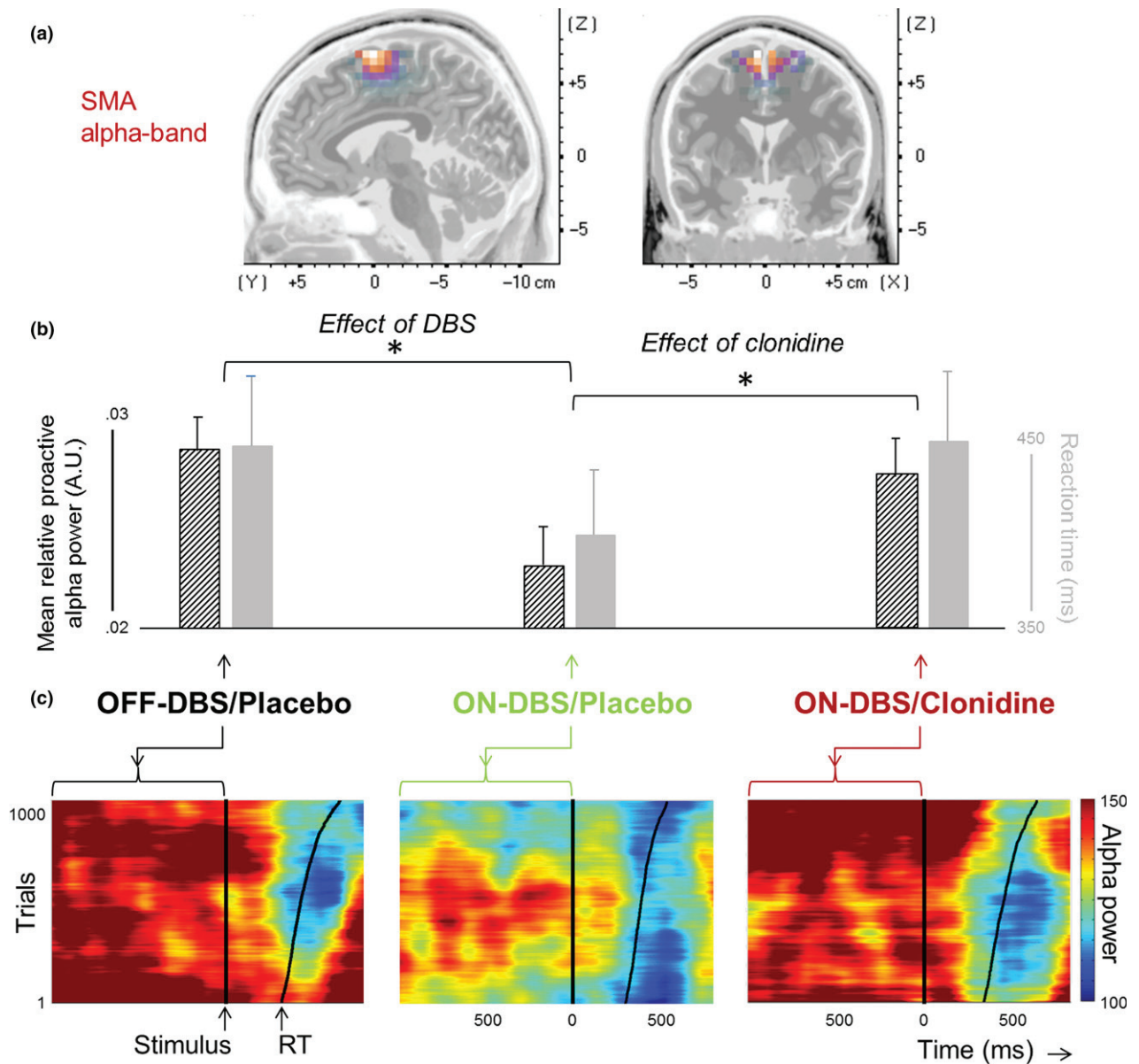
patients are supposed to provide fast automatic responses, that is, not to implement proactive inhibitory control (no-cue trials presented in separate blocks) (Albares *et al.* 2015a). In this condition, patients OFF stimulation behave exactly the same way as when they explicitly have to refrain from reacting (Fig. 1a). This suggests that slowness in movement initiation in PD is due to the fact that patients are locked into a mode of executive control maintaining inappropriate inhibition over response tendencies. STN-DBS was found to restore a normal pattern of response, that is, short RT for no-cue trials presented aside from non-target stimuli versus long RT for no-cue trials presented in blocks of trials mixing target and non-target stimuli. In other words, STN-DBS reinstates the ability to voluntarily release the default, executive control mechanism which normally refrains from reacting in uncertain contexts. Finally, clonidine was found to specifically impede the positive action of STN-DBS on movement initiation. These behavioral data clearly point out that there is only one experimental condition which is relevant to the present issue (no-cue trials in a predictable context), and we therefore focus on this condition in describing the modulations of brain activity (Fig. 1a). The reader is referred to Albares *et al.* (2015a) for a comprehensive analysis of the exhaustive behavioral data and detailed statistics. To summarize, under placebo and for the relevant condition, RT is shorter when STN-DBS is ON than when it is OFF (488 vs. 391 ms, respectively,  $p < 0.05$ ). Under Clonidine, however, RT remains at a pathological value when STN-DBS is ON, compared to Placebo (484 vs. 391 ms, respectively,  $p < 0.05$ ). Complementary analyses reveal no significant influence of the levodopa equivalent dose on this effect (Appendix S1).

### EEG

After the test-retest procedure, 14 reliable ICs were detected ( $Q_i > 70\%$ ;  $p < 0.01$ ). Only two of these sources revealed significant effects of STN-DBS and/or Drug.

The first source, centered on the SMA (Fig. 4a), showed significant modulations of pre-stimulus activity matching the pattern of desynchronization predicted by the proactive model of response inhibition in the alpha band. Mean relative alpha power was significantly attenuated when STN-DBS was switched ON with respect to the OFF state (0.0244 A.U. vs. 0.0287 A.U., respectively,  $p < 0.05$ ). Under combined clonidine and DBS, this alpha activity increased up to the level characterizing the pathological state (i.e., the OFF STN-DBS state) (0.0274 A.U. ON DBS/Clonidine vs. 0.0244 A.U. ON DBS/Placebo,  $p < 0.05$ ). (Fig. 4b and c).

The second source, centered on the cuneus, showed significant modulations of pre-stimulus activity in the beta band. Yet, this activity did not match the expected pattern of desynchronization (Appendix S2).



**Fig. 4** Effects of deep brain stimulation of subthalamic nucleus (STN-DBS) and clonidine administration on alpha band pre-stimulus power in the supplementary motor area (SMA). (a) Probability map of dipole location. (b) Reaction time (RT) and Mean relative alpha power of the pre-stimulus period (between-subjects analyses). (c) Illustration of the temporal dynamics of SMA alpha activity (absolute

power, aggregated data – all subjects, all trials – sorted as a function of RT). Under placebo, STN-DBS dampens proactive alpha power in the SMA and improves movement initiation latency. Clonidine brings alpha power back to the pathological state and cancels out the behavioral benefits of STN-DBS on movement initiation  $*:p < .05$ .

## Discussion

Animal and clinical studies have recently provided clues suggesting a NA origin of some dysfunctions of movement initiation (Delville *et al.* 2011, 2012a,b; Chamberlain and Robbins 2013; Espay *et al.* 2014; Kehagia *et al.* 2014; Albares *et al.* 2015a; Rae *et al.* 2016). Direct projections from the LC to the STN might support interactions between the NA, the motor and the executive systems (Parent and

Hazrati 1995). There is now consistent evidence that the STN receives NA innervation in rodents (Arcos *et al.* 2003; Belujon *et al.* 2007). Even more recently, NA innervation of the STN has been shown in primates, with convincing demonstration that the partial loss of NA innervation of the STN in monkeys rendered parkinsonian by chronic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) could contribute to STN dysfunctions in PD (Masilamoni *et al.* 2017). In humans, it has also been

suggested that the modulatory action of the NA system might be mediated by the STN-cortical loops (Albares *et al.* 2015a; Faggiani *et al.* 2015; Faggiani and Benazzouz 2017). This was especially inferred from the observation of interaction between pharmacological manipulation and DBS on behavior provided in the first report of the present project (Albares *et al.* 2015a). However, there was no direct neural-based evidence in humans until the analysis of the present electrophysiological data.

### Key inputs

The first original contribution of this study is that brain activity changes induced by stimulation further support the hypothesis that proactive inhibition is restored to normal function by STN-DBS. Different arguments can be put forward: First of all, modulations of electrophysiological activity during the pre-stimulus period are observed in the SMA, a key cortical region which is uniquely positioned to play a pivotal role in the loops between the basal ganglia and the motor cortex (Nambu *et al.* 1996; Nachev *et al.* 2008; Lindenbach and Bishop 2013), and which is directly involved in proactive control (Jaffard *et al.* 2008; Chen *et al.* 2010; Criaud *et al.* 2017) and related disorders in PD (Criaud *et al.* 2016). Second, these changes are observed in the critical alpha band, which indexes an active inhibitory mechanism relying on rhythmic local fluctuations of GABAergic inhibitory interneurons (Lőrincz *et al.* 2009; Jensen and Mazaheri 2010; Haegens *et al.* 2011). Third, behavioral and brain activity changes are consistent: the decrease in alpha power under STN-DBS is associated with a decrease in RT (Fig. 4).

The second original contribution of this study is that the cancelation of STN-DBS behavioral effects (as measured through movement initiation latency) by clonidine is associated with an increase in proactive alpha power in the SMA. Remarkably, this increase is observed within the source whose proactive alpha activity is precisely reduced by STN-DBS (Fig. 4b). In other words, under clonidine the abnormal proactive inhibitory activity of the SMA no longer benefits from the positive effect of STN-DBS, but returns to a pathological state. Taken together, the behavioral observations and brain activity recordings are highly consistent with the hypothesis that a single function, probably proactive inhibitory control, is differently modulated by STN-DBS and clonidine.

### Clues about the role of the NA system in inhibitory control and related disorders

Our data suggest that the NA system might have a more subtle and specific function in the control of behavior than the non-specific role it is traditionally supposed to play in cognition (e.g., arousal, Chamberlain and Robbins 2013). Nevertheless, classical non-specific effects of NA manipulation were also observed in the form of a decrease in beta

band power in the cuneus in the clonidine condition (Appendix S2). This beta modulation in the occipital cortex does not match the predictions of the proactive inhibitory control model since beta power does not desynchronize after stimulus presentation. However, this modulation is very consistent with the classical functions attributed to the NA system, such as arousal, attention, and vigilance (Chamberlain and Robbins 2013). Interestingly, a reverse effect – a significant increase in beta activity in posterior regions – was observed in another study focused on attention and the NA system but using atomoxetine, a selective NA reuptake inhibitor presenting the opposite effect of clonidine (Alegre *et al.* 2013). This attentional effect might contribute to the overall effect of clonidine on behavior in our own results, but does not interact with the effect of STN-DBS. It therefore does not challenge our interpretation of the interaction between STN-DBS and NA manipulation on movement initiation (Albares *et al.* 2015a). However, an additive effect of fatigue cannot be ruled out when the level of goal-directed input is inappropriately sustained (Redgrave *et al.* 2010).

### Clues about the functional coupling of the STN and the NA system

Although the anatomic and functional coupling of the STN to the NA system has been suggested in animal studies (Canteras *et al.* 1990; Belujon *et al.* 2007; Delaville *et al.* 2012b; Faggiani *et al.* 2015) it has not been consistently evidenced in humans yet. Only one case report of three PD patients who received an intravenous beta-blocker to reduce blood pressure during DBS surgery is available (Coenen *et al.* 2008). In this pioneer study, the bursting spiking activity of the STN was found to be temporarily dampened by the administration of a beta1-selective adrenoceptor antagonist, suggesting that NA projections may have a significant influence on STN activity. In our study, the modulation of SMA by the combined effects of clonidine and STN-DBS, a specific  $\alpha$ 2-adrenergic receptor agonist, provides further arguments that the NA system might be involved in the functioning of basal ganglia-thalamo-cortical loops (Faggiani and Benazzouz 2017). Taken together, these human data strongly suggest that the efficiency of STN-DBS on movement initiation and associated cortical activity is NA-dependent, that is, that the modulatory action of the NA system on executive control might be mediated by the STN-SMA loop. However, in this study, the executive effect is restricted to the inhibition of a simple motor response to a simple visual stimulus. This basic mechanism does not cover the wide range of executive dysfunctions that are observed in PD (Dimberger and Jahanshahi 2013), and that might be related to the NA system (Chamberlain and Robbins 2013). Future studies should examine how current findings can account for a larger range of executive dysfunctions using appropriate neuropsychological tests.

### Direct versus indirect effects of NA modulation

Importantly however, it is likely that the effect of clonidine administered by oral route does not rely exclusively on a direct effect of NA modulation of the STN through  $\alpha 2$ -adrenergic receptors (Unnerstall *et al.* 1984). Besides its high selectivity for  $\alpha 2$  autoreceptors (Starke *et al.* 1975; Starke 2001; Gilsbach and Hein 2008), clonidine also acts on heteroreceptors of non-adrenergic neurons both in the peripheral and central nervous system (Starke 1977; Schlicker and Göthert 1998). In particular, this drug is also an  $\alpha 1$ -receptor agonist (Eshel *et al.* 1990) as well as an imidazoline receptor agonist (Ernsberger *et al.* 1987; Reis and Piletz 1997). Overall, clonidine triggers a cascade of events that may lead to inhibit the release of many neurotransmitters including serotonin (Feuerstein *et al.* 1985, 1993; Jackisch *et al.* 1999), GABA (Forray *et al.* 1999; Alachkar *et al.* 2006), and dopamine (Millan *et al.* 2000; Fox *et al.* 2008). Interactions between other neurotransmitters (Gilsbach and Hein 2012) might thus also contribute to the effect of clonidine. We would point out, however, that these results apply to idiopathic PD patients, and that conclusions might be slightly different for other subtypes of PD.

### Clues about the functional role of STN in response inhibition

Our results also provide insights about the unclear anatomic and functional bases of the cortico-subthalamic system (Mathai and Smith 2011), the disputed roles of the STN in motor control and response inhibition (Cui *et al.* 2013; Benis *et al.* 2016), and the disputed mechanisms of action of STN-DBS (Udupa and Chen 2015). Classically, the STN is thought to relay a stop signal via the hyperdirect pathway when the stimulus that subjects must refrain from reacting to has been identified (Aron and Poldrack 2006; Aron *et al.* 2007). Our data clearly demonstrate that response inhibition does not only rely on this kind of reactive, fast braking signal, since our design offers no possible confound with any reactive and selective inhibitory activity (Criaud *et al.* 2017). This means that the tonic activity of the STN might play a substantial role in inhibitory control, possibly via the indirect pathway, but maybe also via the hyperdirect pathway, as suggested by the tight coupling between STN-DBS and SMA tonic activity. Recent studies using intracerebral recordings also support the idea of a substantial role of the STN in proactive inhibition (Alegre *et al.* 2013; Benis *et al.* 2014).

### Clues about the mechanisms of action of STN-DBS

STN-DBS might not act by restoring normal activity into the thalamo-cortical loops via orthodromic effects on downstream targets within the basal ganglia, as initially suggested (Benabid *et al.* 2000). Our data are consistent with the hypothesis that an antidromic stimulation of the cortico-subthalamic projections by STN-DBS induces cortical activation that directly contributes to the therapeutic effect (Li *et al.* 2007, 2014; Gradinaru *et al.* 2009; Kuriakose *et al.* 2010). Because of the numerous interconnections between

layer V neurons and local interneurons via axon collaterals, such antidromic effects would disrupt synchronized firing in the motor cortex. In PD, STN-DBS-induced antidromic action would contribute to restoring motor control by offsetting abnormal firing of the motor cortical neurons. The SMA is especially concerned with possible antidromic activation because it has direct projections to the STN (Li *et al.* 2007, 2014). The alpha band activity is especially targeted by the possible invasion of the antidromic spikes into the projection neurons because the local circuitry of the SMA involves a large proportion of inhibitory neurons (*ibid.*). Our data, showing strong effects of STN-DBS in the alpha activity of the SMA, are thus consistent with this hypothetical mechanism of action of STN-DBS. This finding might facilitate the development of other therapeutic interventions, or improve currently unsatisfactory solutions, for instance by providing an accurate target for DBS closed loop approaches (Hariz 2014) or direct cortical stimulation (Strafella *et al.* 2007).

### Conclusion

While NA has long been considered as having a minor influence on STN regulation (Parent and Hazrati 1995; Benarroch 2008, 2009), thanks to the combined use of STN-DBS and EEG recordings, our results provide evidence in humans of NA-dependent activity of the subthalamic-supplementary motor loop. The effects of clonidine assessed here are related to inhibitory control, the keystone of executive functions, and account for difficulties initiating actions. These results might open the way toward the development of non-dopaminergic therapies, an important area of research for idiopathic PD (Fox 2013; Espay *et al.* 2014; Kehagia *et al.* 2014). More generally, various clinical symptoms ranging from akinetic freezing to motor impulsivity, which probably represent the opposite ends of the same continuum of executive dysfunction, might benefit from different medications targeting NA dysfunction in various neurologic and psychiatric conditions. Obviously, this study only provides novel insight into the neurobiological mechanisms by which NA pharmacological agents might exert influence on motor and executive functions, and further clinical investigations are warranted to extend the therapeutic use of the existing drugs targeting the NA system in the different clinical populations showing similar symptoms.

### Acknowledgments and conflict of interest disclosure

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above, the authors report no financial conflict of interest and do not have to disclose any commercial considerations, such as an equity interest, patent rights, or corporate affiliation, including consultancies, for any product or process mentioned in the submission.

All experiments were conducted in compliance with the ARRIVE guidelines.

## Supporting information

Additional Supporting Information may be found online in the supporting information section at the end of the article:

**Appendix S1.** Complementary behavioral analyses.

**Appendix S2.** Complementary EEG analyses.

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## SUPPLEMENTARY MATERIAL

Spay C, Albares M, Lio G, Thobois S, Broussolle E, Lau B, Ballanger B, Boulinguez P. Clonidine modulates the activity of the subthalamic-supplementary motor loop: evidence from a pharmacological study combining DBS and EEG recordings in Parkinsonian patients. *Journal of Neurochemistry*

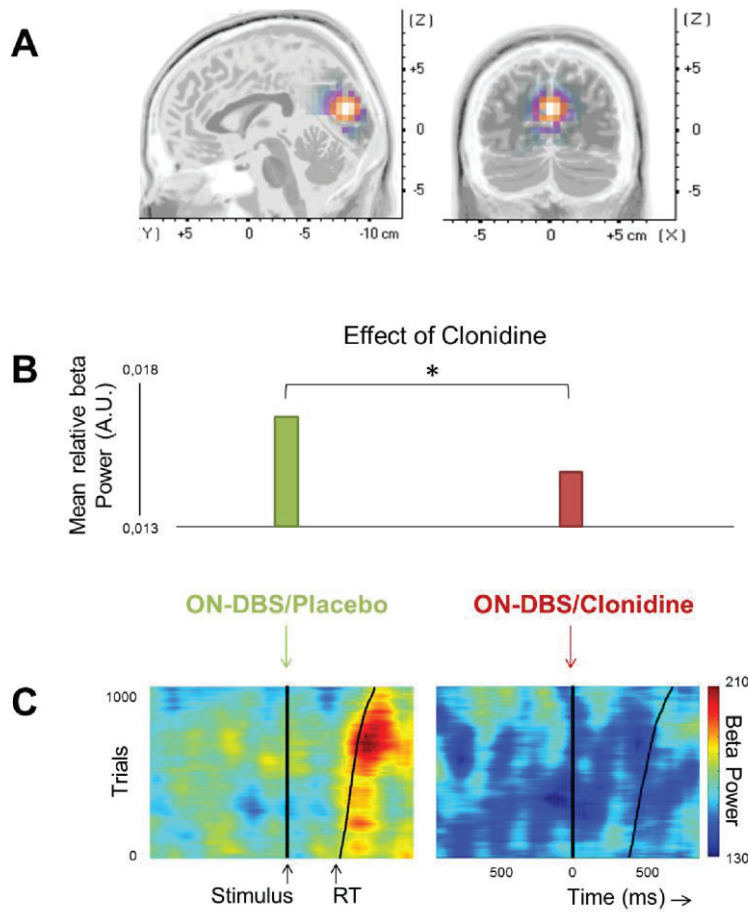
### **S1: Complementary behavioral analyses**

Complementary analyses were performed in order to test a possible interaction between the two types of medication administered to the patients. We tested the hypothesis that the behavioral effect of clonidine observed in the no-cue pure-block in the ON STN-DBS condition could be related to the levodopa equivalent dose (LED). To this aim, we exploited the inter-individual variability of LED due to variable time since surgery across subjects (Table 1). We used the mean individual difference in the no-cue pure-block RT between the ON and the OFF STN-DBS states ( $\Delta RT$ ) as a behavioral index of the drug effect. This variable was associated with the corresponding individual LED value. No significant correlation was found ( $r^2 = 0.13$ ,  $P = 0.17$ ).

### **S2: Complementary EEG analyses**

One source centered on the cuneus showed significant modulations of prestimulus activity in the beta-band. Mean relative beta power was significantly attenuated under ON DBS/Clonidine condition with respect to the OFF state (0.0148 A.U. versus 0.0167 A.U. respectively,  $p < 0.05$ ). However, this activity did not match the pattern of desynchronization predicted by the proactive model of response inhibition (Supplementary Fig. 1).

## Cuneus, Beta-band



**Figure S1** : Effects of deep brain stimulation of subthalamic nucleus (STN-DBS) and clonidine administration on beta-band prestimulus power in the visual cortex (cuneus). A) Probability map of dipole location. B) Mean relative beta power of the prestimulus period (between-subjects analyses). C) Illustration of the temporal dynamics of beta activity in the cuneus (absolute power, aggregated data –all subjects, all trials- sorted as a function of RT). Under STN-DBS, Clonidine attenuates prestimulus beta power in the cuneus. Although this pattern might be associated with a role of clonidine and basal ganglia in visual attention (Chamberlain and Robbins, 2013; van Schouwenburg et al., 2010), it does not corresponds to the dynamics predicted by the model of proactive inhibitory control, and does not predict RT.

### Supplementary References

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### 3. SYNTHÈSE & PERSPECTIVES

Cette étude apporte pour la première fois chez l'homme des évidences neurofonctionnelles directes d'un rôle du système noradrénergique dans les boucles subthalamo-corticales, jusqu'à lors suggéré par des études comportementales (Albares et al., 2015b) ou chez l'animal (Faggiani & Benazzouz, 2017; Faggiani et al., 2015). Les effets de la clonidine proposés ici sont spécifiquement liés au contrôle inhibiteur et jouent un rôle dans les difficultés d'initiation de l'action.

Concernant l'origine de l'akinésie, les résultats de cette étude permettent de revisiter ce symptôme comme un dysfonctionnement exécutif des mécanismes d'inhibition de réponse. Ils confirment que les patients parkinsoniens présentent un déficit exécutif spécifique qui se traduit par des TR anormalement longs dans des situations dans lesquelles ils sont censés réagir de façon automatique. En effet, l'akinésie est caractérisée par un verrouillage inapproprié des patients dans un état de contrôle inhibiteur, état finalement levé avec retard après l'identification de la cible. Au-delà de la contribution qu'ils apportent au débat sur la dissociation entre mécanismes internes et externes de déclenchement du mouvement (Jahanshahi et al., 1995; Thut et al., 2000), ces résultats encouragent l'utilisation de la condition de contrôle afin de révéler la pluralité des modèles de l'inhibition (*cf. Chapitre 3*).

Concernant les bases neurofonctionnelles de ce déficit exécutif, les modulations de l'activité électrophysiologique sont observées durant la période pré-stimulus dans l'AMS, une région corticale jouant un rôle clé dans les boucles entre les ganglions de la base et le cortex moteur (Lindenbach & Bishop, 2013; Nachev et al., 2008). Ce résultat renforce donc les évidences en faveur d'un rôle de l'AMS dans le contrôle proactif (Chen et al., 2010; Criaud et al., 2017; Jaffard et al., 2008) et dans la maladie de Parkinson (Criaud et al., 2016). Ces modulations électrophysiologiques sont observées dans la bande de fréquence alpha, connue pour indexer des mécanismes inhibiteurs relayés par les interneurons GABAergiques

(Haegens et al., 2011; Jensen & Mazaheri, 2010; Lorincz et al., 2009). Finalement, les modifications comportementales et de l'activité cérébrale sont consistantes : une augmentation de la puissance alpha tonique proactive liée à l'akinésie et associée à une augmentation des TR. A l'inverse, le désordre exécutif est restauré par la SCP-NST avec une diminution de la puissance alpha tonique proactif associée à une diminution des TR. Ces résultats sont donc en faveur d'un rôle pivot du NST dans le contrôle inhibiteur proactif non sélectif. Son rôle semble donc lié au passage volontaire d'un état contrôlé (i.e., inhibé) à un état de réactivité automatique (désinhibé), dysfonctionnel dans l'akinésie et restauré par la SCP. Cette conclusion est consistante avec de précédents travaux chez le singe (Isoda & Hikosaka, 2007), chez le sujet sain (Forstmann et al., 2010) et chez le patient parkinsonien (Benis et al., 2014; Wylie et al., 2010). Enfin, nous avons mis en évidence un rôle spécifique de la NA sur le contrôle inhibiteur proactif et le fonctionnement du NST. En effet, la clonidine, en réduisant la concentration de NA, bloque l'effet positif de la SCP-NST et remet les patients dans un état de verrouillage pathologique en augmentant la puissance proactive dans la bande alpha dans l'AMS. Ce travail fournit donc, pour la première fois, des preuves fonctionnelles chez l'homme d'un effet spécifique de la NA sur le fonctionnement du NST associé au contrôle inhibiteur proactif dans la maladie de Parkinson.

Alors que l'akinésie est classiquement considérée comme un symptôme moteur avec une origine purement dopaminergique, ce travail apporte pour la première fois des évidences neurofonctionnelles d'un dysfonctionnement exécutif du contrôle inhibiteur proactif non-sélectif à l'origine de l'akinésie. Concernant les bases anatomo-fonctionnelles de ce contrôle, cette étude renforce le rôle de l'AMS et du NST. Ce désordre exécutif est restauré par la SCP-NST et implique spécifiquement le système noradrénergique.

## B. REVISITER LES DYSFONCTIONNEMENTS DES MECANISMES INHIBITEURS A L'ORIGINE DES TROUBLES DU CONTROLE DES IMPULSIONS

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### 1. L'ENTREMISE DES FONCTIONS EXECUTIVES A L'ORIGINE DES TCI

Comme il l'a été évoqué précédemment dans ce travail (*cf. Chapitre 2*), face à l'hétérogénéité des expressions des TCI au niveau comportemental dans la maladie de Parkinson, il est probable que des corrélats neuronaux différenciables sous-tendent les différents sous-types de TCI et les différentes formes d'impulsivité (Dalley & Robbins, 2017; Voon et al., 2017a; Meyer\*, Spay\* et al., under revision), avec des processus psychologiques, des bases anatomo-fonctionnelles et des bases pharmacologiques distinctes (Nombela et al., 2014).

Dans ce sens, il est courant de dissocier l'impulsivité cognitive de l'impulsivité motrice (*cf. Chapitre 2*). Alors que l'impulsivité cognitive est admise chez les patients parkinsoniens avec TCI et semble être un effet secondaire des DAAs, peu d'études se sont intéressées à l'impulsivité motrice chez ces patients. Des déficits d'inhibition de réponse ont été clairement observés chez des patients avec TCI non parkinsoniens (Odlaug et al., 2011; voir Chowdhury et al., 2017 pour revue). Pourtant, les quelques études qui ont testé comportementalement les déficits d'inhibition motrice ont pour la plupart échoué à observer de l'impulsivité motrice chez les patients parkinsoniens avec TCI (voir Dawson et al., 2018 pour revue). A ce jour, une seule étude apporte des évidences d'un déficit d'inhibition de réponse chez les parkinsoniens avec TCI en IRMf (Palermo et al., 2017). Cette étude de cas a révélé un dysfonctionnement des mécanismes d'inhibition de réponse et de détection des erreurs chez un patient TCI. Ce résultat est en faveur d'un rôle clé de l'impulsivité motrice chez les TCI. Néanmoins, ces résultats préliminaires nécessitent d'être confirmés sur une plus large population de patients parkinsoniens avec TCI et en contournant les limites méthodologiques évoquées précédemment

(cf. *Chapitre 3*) inhérentes aux méthodes de neuroimagerie et aux modèles standards de l'inhibition de réponse. En effet, les dysfonctionnements comportementaux de ces patients étant expérimentalement explorés au travers du prisme théorique et méthodologique du modèle standard, il est possible que les interprétations cliniques qui en découlent soient en partie biaisées. Il semble en particulier que tous les modes d'inhibition n'aient pas été testés. Pourtant, l'hypothèse selon laquelle l'impulsivité des patients parkinsoniens reposerait sur un dysfonctionnement du contrôle inhibiteur proactif a déjà été proposée (Ballanger et al., 2009). L'entremise des mécanismes exécutifs automatiques est ainsi susceptible d'apporter un éclairage nouveau dans la maladie de Parkinson.

Dans ce travail, nous faisons l'hypothèse que les TCI dans la maladie de Parkinson sont en partie expliquées par un dysfonctionnement des mécanismes d'inhibition de réponse, i.e., de l'impulsivité motrice. Nous suggérons que les TCI pourraient présenter des déficits des mécanismes neuronaux qui contribuent au verrouillage du système moteur quand le contexte requiert de se retenir de répondre (Criaud et al., 2012). Dans ce sens, les TCI pourraient avoir une origine en partie exécutive et motrice, qui aurait des conséquences larges sur de nombreux comportements, incluant ceux qui requièrent des opérations cognitives complexes faisant appel à la prise de décision.

## 2. IDENTIFICATION DES DYSFONCTIONNEMENTS DES RESEAUX NEURONAUX A L'ETAT DE REPOS A L'ORIGINE DES TCI

### a. Stratégie expérimentale

Pour tester notre hypothèse, notre raisonnement repose sur deux observations précédemment formulées : 1/ les processus impliqués dans l'impulsivité motrice et l'impulsivité cognitive reposent sur des réseaux neuronaux distincts (*cf. Chapitre 2*), et 2/ les mécanismes inhibiteurs et excitateurs impliqués dans l'impulsivité motrice et l'impulsivité cognitive présentent des empreintes spectrales distinctes qui peuvent être révélées en EEG (*cf. Chapitre 3*).

Nous avons donc choisi d'analyser les oscillations à l'état de repos afin de révéler la fonctionnalité des réseaux neuronaux associés aux TCI. Les résultats ne fourniront pas de preuves directes des mécanismes impliqués dans les dysfonctionnements associés aux TCI mais permettront d'établir une preuve de concept claire d'une différence entre patients parkinsoniens avec et sans TCI au sein des réseaux et des bandes de fréquence qui supportent notre hypothèse d'un déficit global de l'inhibition de réponse.

Dans ce sens, nous avons enregistré l'activité EEG à l'état de repos de 49 patients parkinsoniens, 27 avec TCI (PD-TCI+) vs. 22 sans TCI (PD-TCI-). Le traitement des données EEG a été réalisé en s'appuyant sur les avancées méthodologiques récentes de notre groupe (*cf. Chapitre 3* ; Albares et al., 2015a; Lio & Boulinguez, 2013; Lio et al., 2018) en combinant la séparation et la localisation des sources avec des analyses spectrales afin d'identifier les corrélats anatomiques et fonctionnels des différences cliniques observées entre patients PD-TCI+ et PD-TCI-. Ces analyses spectrales ont été réalisées en aveugle (i.e., sur l'ensemble du cortex et dans toutes les bandes de fréquence, sans à priori) et conduites au niveau des sources.



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## Resting state oscillations pinpoint a motor component of Parkinson's Impulse Control Disorders.

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## **Abbreviations**

Anterior Cingulate Cortex (ACC), Barratt Impulsiveness Scale (BIS-11), Beck Depression Inventory (BDI), blind source separation (BSS), Brodmann area (BA), Dopaminergic (DA), Electroencephalography (EEG), Frontal Assessment Battery (FAB), group Blind Source Separation (gBSS), Hoehn & Yahr scale (H&Y), Impulse Control Disorders (ICDs), independent component (IC), independent component analysis (ICA), inferior frontal gyrus (iFG), Levodopa Equivalent Daily Dose (LEDD), Minnesota Impulsive Disorders Interview (MIDI), Mini Mental State Examination (MMSE), medial Prefrontal cortex (mPFC), Noradrenergic (NA), Parkinson's Disease (PD), Serotonergic (5HT), Supplementary Motor Area (SMA), Second Order Statistics (SOS), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (QUIP), Unified Parkinson's Disease Rating Scale part III (UPDRS-III).

## **Abstract**

**Objectives:** Impulse control disorders (ICDs) in Parkinson's disease (PD) have been associated with cognitive impulsivity and dopaminergic dysfunction and treatment. The present study tests the neglected hypothesis that the neurofunctional networks involved in motor impulsivity might also be dysfunctional in PD ICDs.

**Methods:** We performed blind spectral analyses of resting state electroencephalographic (EEG) data in PD patients with and without ICDs to probe the functional integrity of all cortical networks with no a priori about anatomical sources or frequency bands. Analyses were performed directly at the source level and were controlled for motor performance (UPDRS-III) and medication (total LEDD).

**Results:** Spectral signatures of ICDs were found in the medial prefrontal cortex, the dorsal anterior cingulate and the supplementary motor area, in the beta and gamma bands. Beta power changes in the supplementary motor area were found to predict ICDs severity (QUIP score).

**Conclusion:** ICDs are associated with abnormal activity within frequency bands and cortical circuits supporting the control of motor response inhibition.

**Significance:** These results bring to the forefront the need to reconsider the issue of motor impulsivity in PD ICDs, with potential implications for PD therapy.

**Keywords:** Parkinson's disease; impulsivity; electroencephalography; resting state; beta; gamma.

## **Highlights:**

- . PD ICDs are characterized by abnormal resting-state  $\beta$  activity in the SMA, ACC and mPFC.
- . Beta power changes in the SMA predict ICDs severity
- . The impulsivity of ICDs patients might partly rely on motor dysfunctions

## 1. Introduction

Impulse control disorders (ICDs) are debilitating neuropsychiatric disorders that include hypersexuality, pathological gambling, compulsive eating and compulsive shopping, and concern up to 46% of patients with Parkinson's disease (PD) (Antonini et al., 2017; Avanzi et al., 2006; Corvol et al., 2018; Grosset et al., 2006; Vela et al., 2016; Voon et al., 2006; Weintraub et al., 2010). ICDs in PD are associated with cognitive impulsivity -also termed choice or decisional impulsivity- and considered as a side-effect of dopamine replacement therapy (Antonelli et al., 2014; Dodd et al., 2005; Leroi et al., 2013; Lopez, Weintraub, & Claassen, 2017; Voon et al., 2017; Weintraub et al., 2010). Thus, their management mainly involves discontinuing or decreasing dopamine agonists (Cossu, Rinaldi, & Colosimo, 2018; Samuel et al., 2015). But this is not a satisfactory therapeutic option since this can cause a worsening of motor symptoms or a dopamine agonist withdrawal syndrome (Evans et al., 2004; Pondal et al., 2013; Rabinak & Nirenberg, 2010; Samuel et al., 2015), and even does not guarantee symptoms remission at follow-up (Ávila, Cardona, Martín-Baranera, Bello, & Sastre, 2011; Cilia et al., 2016). A better understanding of these disorders is mandatory to develop more efficient therapeutic strategies (Grall-Bronnec et al., 2018).

To date, cognitive and neural bases of ICDs in PD have not been completely elucidated. ICDs are supposed to be due to dysfunctions of object and action valuation caused by biased probability estimation or reward processing (Aarts et al., 2012; Abler, Hahlbrock, Unrath, Grön, & Kassubek, 2009; Czernecki et al., 2002; Piray et al., 2014). However, results of neuroimaging studies are largely inconsistent, showing numerous possible abnormalities in the mesocorticolimbic circuits supporting decisional functions, indeed, but also in many other brain regions (Carriere, Lopes, Defebvre, Delmaire, & Dujardin, 2015; Cilia et al., 2011, 2008; Frosini et al., 2010; Imperiale et al., 2017; Petersen et al., 2018; Politis et al., 2013; Rao et al., 2010; Tessitore et al., 2017; van Eimeren et al., 2010; Voon et al., 2011). In addition, these studies have limitations. First, influential papers focused only on decision-making by means of tasks probing specifically risk-taking and motivation,

or by means of region of interest approaches centered on the decisional circuit (Frosini et al., 2010; Kassubek, Abler, & Pinkhardt, 2011; Politis et al., 2013; Rao et al., 2010; van Eimeren et al., 2010; Voon et al., 2011). These studies did not test the possibility of response inhibition dysfunctions (motor impulsivity). Yet, studies of impulsivity in psychiatric conditions (Dalley & Robbins, 2017) as well as neuropsychological and behavioral investigations in PD (Nombela, Rittman, Robbins, & Rowe, 2014; Voon, 2014) suggest that multiple modes of impulsivity are likely to develop in PD. Second, neuroimaging studies used fMRI or SPECT/PET, although blood flow measures are only indirect measures of neural activity. Critically, these studies cannot disentangle concurrent excitatory and inhibitory mechanisms (Logothetis, 2008), which is crucial for discriminating the neural events that contribute to the imbalance between excitatory and inhibitory activity in impulsivity.

Here, we analyzed resting state oscillations with high-density electroencephalography (EEG) in PD patients with and without ICDs in order to investigate the functional integrity of all cortical networks, without a priori about the anatomofunctional origins of the disorder. By combining source separation and localization with spectral analyses, it is possible to pinpoint the cortical and functional correlates of the clinical differences observed between PD patients with and without ICDs. The cognitive hypothesis of impulsivity predicts differences in the mesocorticolimbic system, the orbitofrontal and the lateral prefrontal cortices (e.g., Aracil-Bolaños & Strafella, 2016; Marques, Durif, & Fernagut, 2018; Vriend, 2018), expressed in the delta and theta bands (Cavanagh, 2015; Fatahi, Haghparast, Khani, & Kermani, 2018; Knyazev, 2012; Nacher, Ledberg, Deco, & Romo, 2013; Pinner & Cavanagh, 2017; van Wingerden, Vinck, Lankelma, & Pennartz, 2010). The motor hypothesis of impulsivity predicts differences in a medial network composed of the medial prefrontal cortex (mPFC), the dorsal anterior cingulate (dACC), the inferior frontal gyrus (iFG), the precuneus and the supplementary motor area (SMA) (e.g., Aron, 2011; Criaud & Boulinguez, 2013; Criaud et al., 2017; Manza et al., 2016), expressed in the alpha and beta bands (Supplementary Table 1) (Criaud & Boulinguez, 2013; Fonken et al., 2016; Huster, Enriquez-Geppert, Lavallee, Falkenstein,

& Herrmann, 2013; Hwang, Ghuman, Manoach, Jones, & Luna, 2014; Kilavik, Zaepffel, Brovelli, MacKay, & Riehle, 2013; Liebrand, Pein, Tzvi, & Kraemer, 2017; Zhang, Chen, Bressler, & Ding, 2008). Importantly, although the two hypotheses make distinct predictions, we will perform whole brain and large spectrum analyses in order to make sure not to miss the potential contribution of other brain regions/frequency bands.

## 2. Methods

### 2.1 Participants

Twenty-seven PD patients with current ICDs (ICDs+) and 22 PD without ICDs (ICDs-) were enrolled at the Parkinson Institute in February 2016. The presence of any ICDs was assessed with the Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease (QUIP score  $\geq 1$  for ICDs+, i.e., one ICD or more (Weintraub et al., 2009)). Considering that ICDs+ patients may underestimate, or even lie about and voluntarily deny any behavioral disturbance (Cilia, Siri, Colombo, & Pezzoli, 2014), caregivers were independently interviewed. For ICDs-, the absence of any behavioral disturbance during the whole disease course (i.e., QUIP score = 0) was stated and confirmed by the caregiver. The sample size was determined on the basis of the results of previous studies using EEG to assess inhibitory dysfunction in PD (e.g. (Spay et al., 2018)). The estimated sample size  $n$  was calculated as the solution of:

$$n = \frac{(t_{n-1, \alpha/2} + t_{n-1, \beta})^2}{d^2}$$

where  $d = \text{delta}/\text{sd}$ ,  $\alpha = \text{alpha}$ ,  $\beta = 1 - \text{power}$  and  $t_{v, p}$  is a Student  $t$  quantile with  $v$  degrees of freedom and probability  $p$ . Based on former EEG data assessing power modulations associated with inhibitory dysfunction in PD patients (Spay et al., 2018), the expected difference ( $\text{delta}$ ) in normalized spectral power was set at 0.2, with a standard deviation of 0.2. Setting the alpha risk at 5% and the expected power at 95%, the minimum number of patients per group to highlight the



expected difference is 18. This sample size was also determined in agreement with former specific recommendations regarding EEG group blind source separation analyses (Lio & Boulinguez, 2018). Indeed, optimal performance of source separation and subsequent source localization does not require the inclusion of large samples of subjects ( $n < 20$ ) when applying second order statistics (SOS)-based algorithms that use source spectral diversity. These algorithms can identify and gather sources that have similar functional properties despite variable location and orientation due to inter-individual neuroanatomical variability.

Inclusion criteria were: age between 40 and 70 years old, with idiopathic PD, benefiting from a stable antiparkinsonian drug therapy for at least 2 months. Exclusion criteria were: dementia (MMSE < 26), other neurologic or psychiatric disease, pharmacological treatment with cerebral or psychic impact, substance abuse according to the criteria DSM-IV-TR (except tobacco smoking). Patients remained on their usual medication during the study. Clinical and neuropsychological assessment included the Mini Mental State Examination (MMSE), the Frontal Assessment Battery (FAB), the Minnesota Impulsive Disorders Interview (MIDI) and the QUIP to assess ICDs, the Barratt Impulsiveness Scale (BIS-11), the Beck Depression Inventory (BDI), the UPDRS-III (Unified Parkinson's Disease Rating Scale part III) and the evaluation of Hoehn & Yahr (H&Y) stage. Data from 10 subjects had to be discarded following technical issues during data acquisition, leading to groups of 22 ICDs+ and 17 ICDs-. Groups were matched for age, disease duration, levodopa equivalent daily dose (LEDD) and UPDRS-III. The main demographic and clinical characteristics of the patients are displayed in Table 1. All patients gave written informed consent before the study, and the protocol was approved by the Ethical Committee.

## *2.2 Design and procedure*

Resting state activity was recorded over two continuous periods of 10min. Subjects comfortably sat and were instructed to stay quietly with the eyes closed. The BioSemi™ ActiveTwo

Mk2 system (31.25 nV resolution) was used to record the electroencephalographic signal from 128 electrodes mounted in an elastic cap at BioSemi™ ABC system standard locations. Six additional external electrodes were added: four temporal electrodes (Biosemi spherical coordinates: Phi -103.5 Theta -18 -36, and Phi 103.5 Theta 18 36), and two electrodes attached to the outer canthi of the left and right eyes (Phi 103.5-103.5 Theta 81-81). The CMS active electrode and the DRL passive electrode of the ActiveTwo system were used instead of classical ground electrodes of conventional systems (these two electrodes form a feedback loop driving the average potential of the subject in the Common Mode voltage as close as possible to the analogue-to-digital reference voltage in the AD-box). All electrode offsets were kept below 20 mV. Data was recorded at a sampling rate of 4096Hz.

### *2.3 Data analyses*

#### 2.3.1 Preprocessing.

Data were down-sampled at 2048 Hz, filtered (High-pass 0.5-1Hz; Low-pass 46-48Hz) and set to average reference. Two steps were implemented to reject artifacts. First, non-brain artifacts (eye movements, ballistocardiac noise, tremor related sensors movements and other electrical noises) were detected and rejected using subject-level independent component analysis (ICA) / blind source separation (BSS) (UWSOBI, 300 times delays ; (Yeredor, 2000)) and the EEGLAB toolbox (Delorme & Makeig, 2004). Second, data were partitioned into epochs of 2 seconds with an overlap of 50% and an automatic rejection procedure for outlier epochs was applied. For each epoch, the Frobenius norm between the epoch's covariance matrix and the dataset's mean covariance matrix was calculated and, for each dataset, the 5% of the epochs deemed as outliers according to this metric have been rejected.

#### 2.3.2 Group Blind Source Separation (gBSS).

gBSS offers a straightforward and computationally tractable solution to the problem of multi-subject analysis by creating aggregate data containing observation from all subjects. By providing a

single estimation of the mixing and the demixing matrices for the whole group, this strategy allows direct estimation of the components that are consistently expressed in the population (Eichele, Rachakonda, Brakedal, Eikeland, & Calhoun, 2011; Huster, Plis, & Calhoun, 2015; Huster & Raud, 2018; Lio & Boulinguez, 2018). A potential benefit of this method is a better sensitivity for the detection of critical sources that are often hidden by the most energetic phenomena (Sutherland & Tang, 2006). We employed UWSOBI, a Second Order Statics based gBSS algorithm based on the approximate joint diagonalization of lagged-covariance matrices. We have recently demonstrated that this method is robust with respect to anatomo-functional inter-subjects variability and can separate group specific uncorrelated sources with non-proportional power-spectra without deleterious prior dimension reduction (Lio & Boulinguez, 2018). This method is especially convenient here because it separates the sources based on their spectral signatures. Three hundred lagged-covariance matrices with time delays from 0/2048s to 300/2048s were calculated on each epoch. Then, lagged-covariance matrices were averaged across the dataset epochs first, and then across patients, resulting in 300 averaged lagged-covariance matrices for the 2 groups of PD patients (ICDs+/ICDs-). Finally, 600 lagged-covariance matrices were approximately joint-diagonalized with the UWEDGE algorithm (Tichavsky & Yeredor, 2009), leading to the identification of 134 Independent Components (ICs). Thanks to this averaging procedure, inter-epochs and inter-subject variability was reduced while sources with spectral modifications between the PD patients ICDs+ and ICDs- were highlighted (Congedo, Gouy-Pailler, & Jutten, 2008; Ramoser, Müller-Gerking, & Pfurtscheller, 2000). Brain regions explaining the group effect (ICDs+/ICDs-) were revealed by sorting components by percent of explained variance.

### 2.3.3 Independent components source localization.

The sLoreta software (Pascual-Marqui, 2002) was used with a head model obtained by applying the BEM method to the MNI152 template (Mazziotta et al., 2001). The 3D solution space was restricted to cortical gray matter and was partitioned into 6239 voxels with a spatial resolution of

5mm. Then, the sLoreta solution of the inverse problem was computed using an amount of Tikhonov regularization optimized for an estimated Signal/Noise Ratio of 100.

#### 2.3.4 Blind spectral analysis.

We performed analysis of resting state spectral activity without a priori about anatomical sources or frequency bands. The 134 ICs obtained with this group BSS were used as a filter to go back to subject level for spectral analysis. For each dataset of each PD patient, relative power was estimated for each independent component (IC). The power spectral density was calculated with the Welch's method for each epoch (with segments of 2048 samples, windowed with a Hamming window, and an overlap of 2000 samples between segments), and averaged across epochs for each dataset. This procedure generated absolute spectra with 1 Hz resolution. Relative spectra were then computed in the 1-45 Hz frequency range with respect to the total power of the component:

$$Power_{rel} = Power_{abs} / \sum_{f=1Hz}^{45Hz} Power_{abs}(f)$$

#### 2.3.5 Statistical analyses.

Two analyses were performed in order to test our predictions twice: 1) by comparing ICDs+ and ICDs- groups, assuming discrete differences between groups, and 2) by looking for correlations with a clinical score reflecting ICD severity (QUIP) within the group of PD patients with ICDs, assuming gradual dysfunctions.

2.3.5.1 Group regression analysis: We performed blind analyses and compared mean relative power differences between ICDs+ and ICDs- for all frequency bands and each component. In order to control for clinical characteristics, we performed a correlation matrix including all the dependent variables reported in Table 1. Since most of these variables were significantly correlated to each other (Supplementary Table 2), we selected the two most important variables (best model fitting F) for the subsequent group regression analyses. In other words, we controlled only for motor performance (UPDRS-III) and medication (total LEDD) to avoid collinearity issues.

For each frequency band and each IC, a multiple regression analysis was applied based on one factor of interest (ICDs: ICDs+ vs. ICDs-) and two factors of no-interest (the UPDRS-III score and the LEDD), providing one F-statistic for the quality of the model fitting, and one t-statistic for the modeled factor:

$$Power_{rel}(IC, Freq.) = b_1. ICDs\ flag + b_2. UPDRS\ III + b_3. LEDD + b_4$$

2.3.5.2 Oscillatory modulations predicting ICDs severity (QUIP score): For each IC and each frequency band, a multiple regression analysis was applied based on one factor of interest (the QUIP<sub>A</sub> - ICDs score) and two factors of no-interest (the UPDRS-III score and the LEDD):

$$Power_{rel}(IC, Freq.) = b_1. QUIP_A + b_2. UPDRS\ III + b_3. LEDD + b_4$$

The second and the third factors are constants which represent a modulation of the source spectral activity associated with the UPDRS-III motor score and the LEDD that are non-clinically relevant for the ICDs severity (QUIP score). Modeling these effects is essential because motor performance and medication-induced spectral modulations that do not account for ICDs severity are likely. The multiple regression provides an F-statistic for the quality of the model fitting, and one t-statistic for the modeled factor.

### 3. Results

Results (controlled for motor performance -UPDRS-III score- and medication -LEDD-) are summarized in Fig. 1.

#### 3.1 Power changes accounting for ICDs (group effect)

Sources localized in the dACC and the mPFC revealed power modulations of resting state activity in PD patients with ICDs+ compared with ICDs- (F=5.78; p<0.05). The first source (IC 11/BA32) showed increase in low beta (13-14 Hz) and decrease in gamma (33 Hz) mean relative power in ICDs+ compared to ICDs- (p<0.001). The second source (IC 13/BA9), showed increase in

low beta ( $p < 0.001$ ). The third source (IC 16/BA32) showed decrease in gamma (32-44 Hz) mean relative power in ICDs+ compared to ICDs- ( $p < 10^{-4}$ ).

### *3.2 Power changes accounting for ICDs severity (QUIP score)*

Only one source (IC 8/BA6) localized in the supplementary motor area (SMA proper) revealed power changes predicting QUIP scores ( $F = 11.26$ ;  $p < 0.01$ ). Within this source, a positive correlation was found between beta band power (18-28 Hz) and ICDs severity.

## **4. Discussion**

The hypothesis of a contribution of motor impulsivity to ICDs in PD (Nombela et al., 2014; Palermo et al., 2017) has mostly been ignored in neuroimaging studies (e.g., Aracil-Bolaños & Strafella, 2016; Frosini et al., 2010; Marques et al., 2018; Politis et al., 2013; Rao et al., 2010; Voon et al., 2017) or rejected in behavioral studies (e.g., Bentivoglio, Baldonero, Ricciardi, Nigris, & Daniele, 2013; Leroi et al., 2013; Pineau et al., 2016; Ricciardi et al., 2017; Rossi et al., 2009; Yoo et al., 2015) up to date. Here, we clearly identified power modulations accounting for ICDs in a medial network including the mPFC, the dACC and the SMA (Fig. 1). This network has repeatedly been found to support global motor inhibition (Criaud et al., 2017; Jaffard et al., 2008) and to be disrupted in PD-ICDs (Cilia et al., 2011). It is especially involved in proactive inhibition, an executive function that inhibits movement-triggering processes in anticipation of stimulation to prevent automatic and potentially inappropriate responses (Ballanger et al., 2009; Boulinguez, Ballanger, Granjon, & Benraiss, 2009; Criaud et al., 2016; Criaud, Wardak, Ben Hamed, Ballanger, & Boulinguez, 2012). Because this locking state is the default state of executive control (Criaud et al., 2012), it was found to be tonically active at rest (Jaffard et al., 2008). The observation that the network of brains sources whose activity at rest predicts ICDs coincides with the proactive inhibitory network is thus highly consistent with the hypothesis according to which dysfunctions of motor inhibition account for ICDs

(Albares et al., 2014; Brevers et al., 2012; Criaud & Boulinguez, 2013; Jaffard et al., 2008; Manza et al., 2016; Rubia et al., 2001).

Although in some instances the ACC and the mPFC have been associated with decision making (Botvinick, 2007; Gasquoine, 2013; O'Doherty, Cockburn, & Pauli, 2017; Paus, 2001; Shenhav, Cohen, & Botvinick, 2016), the present spectral data are more consistent with the predictions of the motor hypothesis (Supplementary Table 1). Indeed, the oscillatory activity associated with reward processing in the context of decision making in these regions involves theta and delta frequency bands (Park & Moghaddam, 2017; Wacker, Dillon, & Pizzagalli, 2009). Here, raw differences between groups of patients with and without ICDs or gradual differences indexing ICDs severity were found in beta and low gamma frequency bands (Fig. 1). The beta rhythm has been extensively studied in the sensorimotor system, and was broadly linked to motor processes and executive control (Kilavik et al., 2013; Zhang et al., 2008). Consistent with the inhibitory interpretation, beta activity over the motor cortex during movement preparation is suppressed prior to and during movement (Baker, 2007), and increases when movement is voluntarily suppressed (Zhang et al., 2008). Beta oscillations are also considered as a marker of inhibitory cortical transmission mediated by GABA (Feshchenko, Veselis, & Reinsel, 1997). It is of interest to note that a broad increase in beta rhythm is a hallmark of PD (Oswal, Brown, & Litvak, 2013; Stein & Bar-Gad, 2013). In addition, some studies have also associated low gamma waves to executive and motor control (Engel & Fries, 2010; Fonken et al., 2016; Gaetz, Liu, Zhu, Bloy, & Roberts, 2013; Iijima, Mase, Osawa, Shimizu, & Uchiyama, 2015; Stein & Bar-Gad, 2013; Swann et al., 2012) and to cortical inhibition (Bonnetfond & Jensen, 2013; Cheng et al., 2016; Jensen, Bonnetfond, & VanRullen, 2012; Jensen, Gips, Bergmann, & Bonnetfond, 2014). It is therefore likely that the power changes observed here in the dACC, mPFC and SMA are related to the control of motor inhibition.

Taken together, these anatomical and spectral data contrast with the dominant idea that ICDs in PD do not involve motor impulsivity (Voon et al., 2017; Weintraub & Claassen, 2017). They

rather suggest that inhibitory dysfunction might contribute to some of the motor and non-motor symptoms observed in various movement and psychiatric disorders (Jahanshahi, Obeso, Baunez, Alegre, & Krack, 2015; Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Jahanshahi & Rothwell, 2017). Interestingly, our observation that ICDs severity is related to motor impulsivity is reminiscent of a study on pathological gambling in non-PD patients (Brevers et al., 2012) according to which both cognitive and motor inhibition underlie the presence of ICD, but only motor impulsivity determines its severity. Motor impulsivity is indeed acknowledged in ICDs in the general population (Chowdhury, Livesey, Blaszczynski, & Harris, 2017). It is important to emphasize, however, that our results do not contradict the role of cognitive impulsivity in PD-ICDs.

Of course, although particularly useful to detect problems with self-initiation and task-set maintenance in Parkinson's disease (Ko et al., 2013; Tinaz, Lauro, Hallett, & Horovitz, 2016), resting state oscillations just inform about the functional integrity of neural networks. As a consequence, our results only allow raising the hypothesis of motor inhibition dysfunctions in PD-ICDs. Further studies are needed to provide direct causal evidence that, among the numerous neural mechanisms involved in response inhibition (e.g., Aron, 2011; Bari & Robbins, 2013; Chambers, Garavan, & Bellgrove, 2009; Criaud & Boulinguez, 2013; Criaud et al., 2017; Li, 2015; Verbruggen & Logan, 2009), some might be dysfunctional in PD ICDs. For instance, we found no clues about possible dysfunction of local, automatic, self-inhibitory networks that gate information processing locally in the motor system (e.g., Albares et al., 2014), since we found no difference in alpha power, a direct physiological marker of active inhibition (Haegens, Nacher, Luna, Romo, & Jensen, 2011; Hindriks & van Putten, 2013; Jensen & Mazaheri, 2010; Klimesch, 2012; Klimesch, Sauseng, & Hanslmayr, 2007; Mathewson et al., 2011). This does not mean that no difference in the activity of local inhibitory populations can account for dysfunctions of motor inhibition in ICDs. This issue requires further investigations using specific behavioral tasks coupled with appropriate event-related brain imaging protocols (e.g., Albares et al., 2015; Bartoli, Aron, & Tandon, 2018; Hu & Li, 2012; Huster



et al., 2013; Hwang et al., 2014; Lavallee, Meemken, Herrmann, & Huster, 2014; Swann et al., 2012; Verbruggen & Logan, 2009; Wagner, Wessel, Ghahremani, & Aron, 2018; Wessel et al., 2016; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013; Zhang et al., 2015).

## **5. Conclusions and perspectives**

Our data clearly bring to the forefront the hypothesis that PD ICDs might partly be due to motor dysfunctions leading to action impulsivity, and not only to cognitive dysfunctions leading to choice impulsivity. Potential implications for PD therapy are substantial. Indeed, recent work on the neural and neurochemical bases of response inhibition, a central function controlling the initiation of any response whatever a complex decision has to be made or not, has questioned the implication of the dopaminergic (DA) system (e.g., Favre, Ballanger, Thobois, Broussolle, & Boulinguez, 2013; Michely et al., 2015; Obeso, Wilkinson, & Jahanshahi, 2011), and has identified the key role of the noradrenergic (NA) system (Chamberlain et al., 2009, 2006; Chamberlain & Robbins, 2013; Chamberlain & Sahakian, 2007; Robbins & Arnsten, 2009). In particular, proactive response inhibition, the basic executive function supported by the circuit identified in the present results, has been linked to the NA system and movement initiation dysfunctions in PD (Albares et al., 2015; Criaud et al., 2016; Spay et al., 2018). Other clues point to the involvement of the serotonergic (5HT) system (Bari, Eagle, Mar, Robinson, & Robbins, 2009; Eagle, Bari, & Robbins, 2008; Paterson, Wetzler, Hackett, & Hanania, 2012; Pattij & Vanderschuren, 2008; Ye et al., 2016). Dysfunction of specific inhibitory processes in PD patients with ICDs might thus be treated with non-dopaminergic pharmacological agents as suggested by recent experimental data (Kehagia et al., 2014; Rae et al., 2016; Ye et al., 2015). This approach is successful in psychiatric conditions with impulsivity symptoms like Attention Deficit Hyperactivity Disorder (Dalley & Robbins, 2017; Pattij & Vanderschuren, 2008), but is still to be tested in clinical trials for PD-ICDs (Tanwani, Fernie, Nikčević, & Spada, 2015). Nonetheless, further studies are warranted to identify all possible sources

of dysfunction leading to ICDs. This should help defining subtypes of ICDs in PD differently associated with the DA, NA and 5HT systems, as inspired by former work in psychiatric conditions (Dalley & Robbins, 2017; Del Campo, Chamberlain, Sahakian, & Robbins, 2011).

## **Authors' Roles**

- 1) Research project: A. Conception: P.B., R.C., C.S., B.B.; B. Organization: P.B., R.C., G.P., C.S.; Execution: C.S., R.C.;
- 2) Statistical Analysis: A. Design: P.B., C.S., G.L.; B. Execution: C.S., G.M., G.L.; C. Review and Critique: R.C., G.P., B.B., P.B.;
- 3) Manuscript: A. Writing of the first draft: C.S., G.M.; B. Review and Critique: P.B., R.C., B.B.; C. Reading and approval of the final version of the manuscript: C.S., G.M., G.L., B.B., G.P., R.C., P.B.

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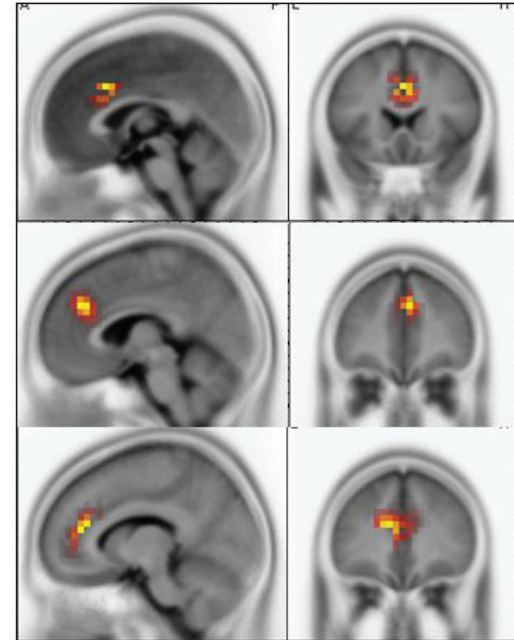
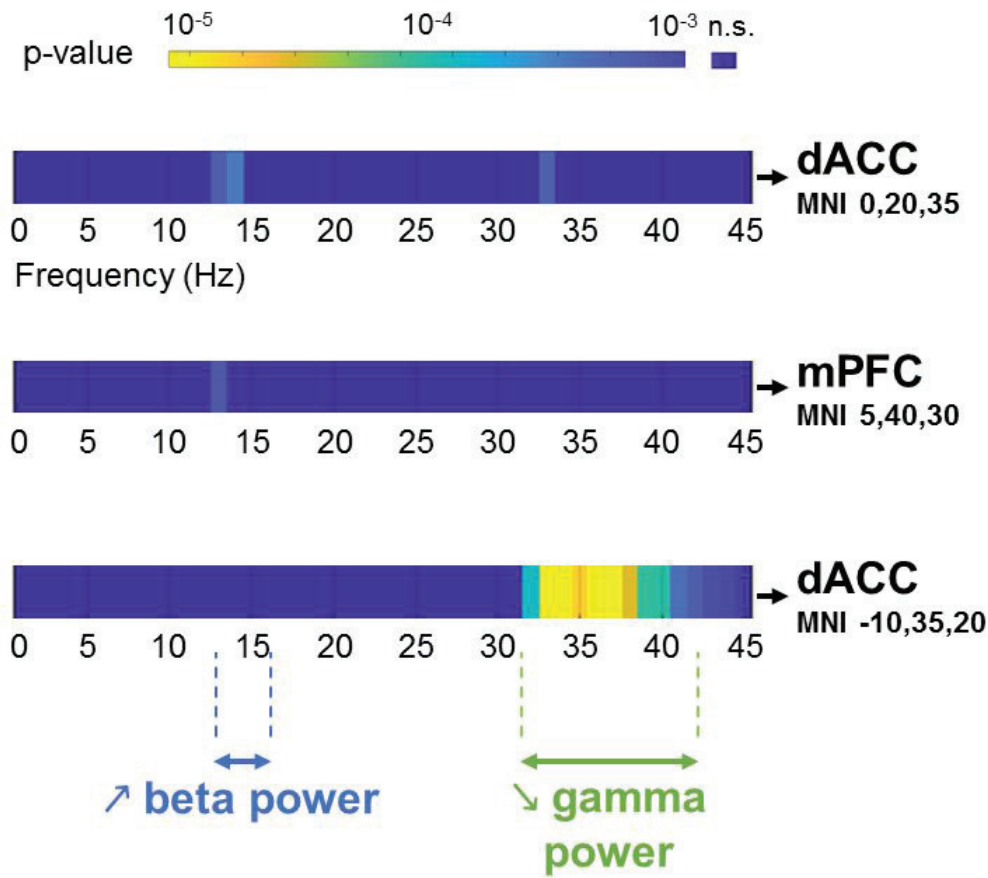
## Table legends

**Table 1:** Patients characteristics. Values are given as mean  $\pm$  SD.

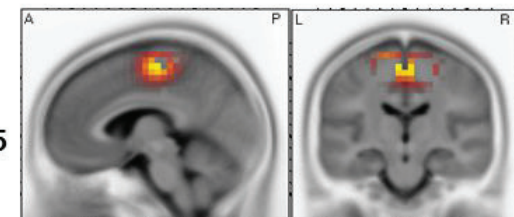
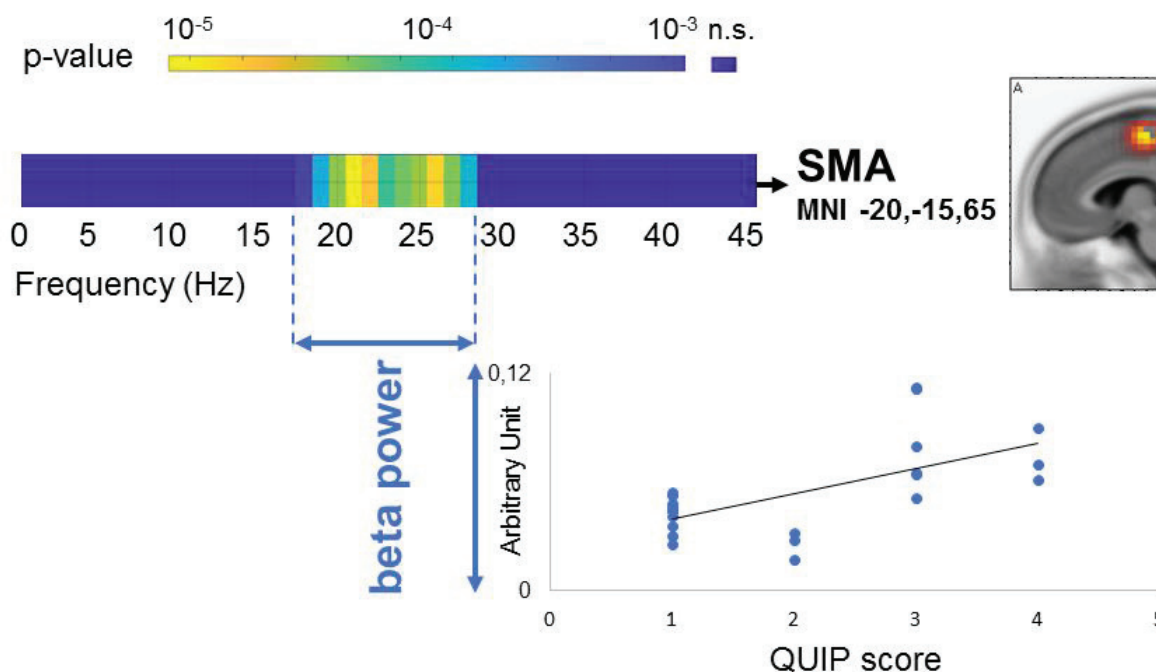
## Figure legends

**Fig. 1:** Resting state cortical oscillatory activity (spectral power) predicting impulse control disorders. (A) Group effect, controlled for UPDRS-III and LEDD. (B) Power changes correlating with ICDs severity (as indexed by QUIP scores), controlled for UPDRS-III and LEDD.

## A- Power changes accounting for ICDs (ICDs+ vs ICDs-)



## B- Power changes accounting for ICDs severity (QUIP score)



**Table 1:** Patients characteristics.

	PD-ICDs+	PD-ICDs-	p-value
<b>Demographics</b>			
Number	22	17	-
Sex	20M / 2F	16M / 1F	-
Age	62.3 ± 7.0	59.5 ± 7.4	0.23
Disease duration	10.4 ± 4.9	7.9 ± 3.7	0.09
<b>Clinical characteristics</b>			
Total LEDD	815.5 ± 285.3	761.6 ± 199.2	0.51
Levodopa dose	645.8 ± 286.4	451.5 ± 188.8	0.02
DAAs dose (LEDD)	69.4 ± 87.4	249.4 ± 94.3	3.7.10-7
Fluctuations	16 Yes / 6 No	4 Yes / 13 No	
H&Y stage	1.8 ± 0.7	1.5 ± 0.7	0.63
Predominant type, type[number of patients]	[AR]15 [TD]7	[AR]16 [TD]1	
UPDRS-III (ON)	11.7 ± 6.1	10.1 ± 7.2	0.44
<b>Neuropsychological assessment</b>			
MMSE	28.2 ± 2.1	29.6 ± 0.7	Cut-off > 26
FAB	15.4 ± 2.2	16.9 ± 1.2	Cut-off > 13.4
BDI	11.7 ± 8.7	6.9 ± 6.7	0.07
BIS-11	67.8 ± 13.7	63.8 ± 5.6	0.26
QUIP (A), ICDs #[number of patients]	[1]10; [2]3; [3]6; [4]3	0	-
QUIP (ABC), ICBs #[number of patients]	[1]8 ; [2]3 ; [3]6 ; [4]3 ; [5]2	0	-
A1 (Pathological gambling)	22	0	-
A2 (Hypersexuality)	7	0	-
A3 (Compulsive Buying)	6	0	-
A4 (Binge Eating)	7	0	-
B (Punding, Hobbyism or Walkabouts)	9	0	-
C (DDS)	2	0	-

Values are given as mean ± SD. ICDs= Impulse Control Disorders, Total LEDD= Total Levodopa Equivalent Daily Dose (mg/day), DAAs= dopamine agonists, H&Y= Hoeh & Yahr scale, AR=Akineto-rigid, TD=Tremor-dominant subtypes of PD patients, UPDRS-III= Unified Parkinson's Disease Rating Scale (part III), MMSE= Mini-Mental State Evaluation, FAB= Frontal Assessment Battery, BDI= Beck Depression Inventory, BIS= Barratt Impulsiveness Scale, QUIP= Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, ICBs=Impulsive-Compulsive Behaviors, DDS=Dopamine Dysregulation Syndrome.

## SUPPLEMENTARY FILE

Spay C, Meyer G, Ballanger B, Cilia R, Boulinguez P. Resting state oscillations pinpoint a motor component of Parkinson's Impulse Control Disorders.

**Supplementary Table 1:** Literature-based predictions

	<b>Motor impulsivity</b> Motor, executive dysfunctions	<b>Decisional impulsivity</b> Cognitive, decisional dysfunctions
<i>Processes</i>	Motor preparation, response inhibition	Motivation, valuation, decision, reward
<i>Cortical brain regions</i>	Motor executive network	Mesocorticolimbic network
	Dorsomedial Prefrontal Cortex (1–3)	Orbitofrontal Cortex - Ventromedial Prefrontal Cortex (15–19)
	Pre-supplementary Motor Area (2,4,5)	Anterior Cingulate Cortex (20–23)
	Dorsal Anterior Cingulate Cortex (6–9)	Ventrolateral Prefrontal Cortex - Dorsolateral Prefrontal cortex (18,23–25)
	Precuneus (10)	
	Right Inferior Frontal Gyrus (4,11,12) <i>but see</i> (5,13,14)	
<i>Frequency bands</i>	Alpha (8-12Hz) (3,26–35) Beta (13-30Hz)	Delta (0.5-3.5Hz) (37–43) Theta (4-7Hz) (43–52)
	Gamma (>30Hz) (30,36)	



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## SUPPLEMENTARY FILE

Spay C, Meyer G, Ballanger B, Cilia R, Boulinguez P. Resting state oscillations pinpoint a motor component of Parkinson's Impulse Control Disorders.

**Supplementary Table 2:** Correlation matrix including the main clinical dependent variables

	Age	DD	UPDRS-III	Levodopa	DA dose	LEDD	BDI	BIS-11	QUIP A	QUIP ABC
Age	1	0.26 $p < 10^{-2}$	0.012 $p = 0.92$	0.11 $p = 0.23$	-0.44 $p < 10^{-5}$	-0.018 $p = 0.86$	0.25 $p < 10^{-2}$	0.30 $p < 10^{-2}$	0.26 $p < 10^{-2}$	0.28 $p < 10^{-2}$
DD	0.26 $p < 10^{-2}$	1	0.15 $p = 0.17$	0.51 $p < 10^{-7}$	-0.31 $p < 10^{-3}$	0.45 $p < 10^{-6}$	0.12 $p = 0.31$	0.09 $p = 0.23$	0.27 $p < 10^{-2}$	0.33 $p < 10^{-3}$
UPDRS-III	0.012 $p = 0.92$	0.15 $p = 0.17$	1	0.38 $p < 10^{-4}$	-0.26 $p < 10^{-2}$	0.29 $p < 10^{-2}$	0.47 $p < 10^{-6}$	0.19 $p < 0.05$	0.30 $p < 10^{-2}$	0.32 $p < 10^{-3}$
LED	0.11 $p = 0.23$	0.51 $p < 10^{-7}$	0.38 $p < 10^{-4}$	1	-0.36 $p < 10^{-3}$	0.88 $p < 10^{-29}$	0.10 $p = 0.25$	-0.13 $p = 0.21$	0.34 $p < 10^{-3}$	0.41 $p < 10^{-4}$
DA dose	-0.44 $p < 10^{-5}$	-0.31 $p < 10^{-3}$	-0.26 $p < 10^{-2}$	-0.36 $p < 10^{-3}$	1	0.03 $p = 0.74$	-0.33 $p < 10^{-3}$	-0.04 $p = 0.67$	-0.43 $p < 10^{-5}$	-0.48 $p < 10^{-6}$
LEDD	-0.018 $p = 0.86$	0.45 $p < 10^{-6}$	0.29 $p < 10^{-2}$	0.88 $p < 10^{-29}$	0.03 $p = 0.74$	1	0.02 $p = 0.83$	-0.06 $p = 0.42$	0.22 $p < 0.05$	0.28 $p < 10^{-2}$
BDI	0.25 $p < 10^{-2}$	0.12 $p = 0.31$	0.47 $p < 10^{-6}$	0.10 $p = 0.25$	-0.33 $p < 10^{-3}$	0.02 $p = 0.83$	1	0.32 $p < 10^{-3}$	0.19 $p < 0.05$	0.22 $p < 0.05$
BIS-11	0.30 $p < 10^{-2}$	0.09 $p = 0.23$	0.19 $p < 0.05$	-0.13 $p = 0.21$	-0.04 $p = 0.67$	-0.06 $p = 0.42$	0.32 $p < 10^{-3}$	1	0.28 $p < 10^{-2}$	0.26 $p < 10^{-2}$
QUIP A	0.26 $p < 10^{-2}$	0.27 $p < 10^{-2}$	0.30 $p < 10^{-2}$	0.34 $p < 10^{-3}$	-0.43 $p < 10^{-5}$	0.22 $p < 0.05$	0.19 $p < 0.05$	0.28 $p < 10^{-2}$	1	0.96 $p < 10^{-50}$
QUIP ABC	0.28 $p < 10^{-2}$	0.33 $p < 10^{-3}$	0.32 $p < 10^{-3}$	0.41 $p < 10^{-4}$	-0.48 $p < 10^{-6}$	0.28 $p < 10^{-2}$	0.22 $p < 0.05$	0.26 $p < 10^{-2}$	0.96 $p < 10^{-50}$	1

DD: disease duration; UPDRS-III: Unified Parkinson's Disease Rating Scale – part III; Levodopa: Levodopa dose; DA dose: Dopamine-Agonists dose; Total LEDD: Total equivalent daily dose; MMSE: Mini-Mental State Evaluation; FAB: Frontal Assessment Battery; BDI: Beck Depression Inventory; BIS-11: Barratt Impulsiveness Scale; QUIP: Questionnaire for Impulsive-Compulsive disorders in Parkinson's Disease.

## b. Synthèse & Perspectives

Nos résultats fournissent deux arguments en faveur d'un dysfonctionnement des mécanismes d'inhibition de réponse chez les patients parkinsoniens avec TCI : 1/ en termes de réseaux neuronaux, les structures cérébrales impliquées dans les dysfonctionnements associés aux TCI regroupent des régions clés du contrôle inhibiteur ; 2/ en termes de signature spectrale, les modulations oscillatoires sont observées dans des bandes de fréquence associées à l'inhibition de réponse. Cette étude renforce l'intérêt de l'étude de l'impulsivité motrice chez les TCI dans la maladie de Parkinson.

Nous suggérons que l'impulsivité cognitive et l'impulsivité motrice ne sont pas indépendantes, mais au contraire interagissent fortement chez les PD-TCI+. Les résultats de cette étude en termes de fonctionnalité des réseaux neuronaux appellent à revisiter les bases neurofonctionnelles des TCI dans la maladie de Parkinson. Néanmoins, l'étude de l'activité au repos ne permet pas d'aller étudier les processus neurocognitifs spécifiques déficitaires chez les TCI. Appuyé par notre récente analyse systématique de la littérature (Meyer\*, Spay\* et al., under revision), nous défendons l'intérêt de cibler des mécanismes neurocognitifs plus spécifiques afin d'accéder aux bases neurales des TCI. L'intérêt est donc d'utiliser des tâches comportementales adaptées pour révéler la complexité de l'impulsivité chez les patients parkinsoniens avec TCI.

**Alors que les TCI sont classiquement considérés comme purement sous-tendus par de l'impulsivité cognitive et associés à un dysfonctionnement du système méso-cortico- limbique dopaminergique, cette étude est en faveur d'un rôle de l'impulsivité motrice dans le développement des TCI.**

### 3. IDENTIFICATION DES DYSFONCTIONNEMENTS DES MECANISMES INHIBITEURS A L'ORIGINE DES TCI DANS LA MALADIE DE PARKINSON

#### a. Stratégie expérimentale

Nous faisons l'hypothèse selon laquelle que les TCI reflètent à la fois de l'impulsivité de choix et un déficit de l'inhibition de réponse conduisant à de l'impulsivité d'action (Jahanshahi et al., 2015a). Pour tester notre hypothèse, notre raisonnement repose sur deux observations formulées dans le *Chapitre 3* : 1/ les protocoles expérimentaux classiques ne permettent pas de tester en même temps les différents modèles d'inhibition et se sont cantonnés à l'analyse des mécanismes réactifs, et 2/ les méthodes d'imagerie n'ont pas permis de dissocier les mécanismes inhibiteurs et excitateurs co-occurents et n'offrent pas la résolution temporelle suffisante pour dissocier les mécanismes inhibiteurs dans les périodes pré et post-stimulus.

Nous avons donc choisi d'utiliser : 1/ un protocole expérimental adapté d'une tâche de Go/NoGo avec une réelle condition de contrôle, afin de tester les différents modèles d'inhibition, 2/ l'EEG à haute résolution offrant la résolution temporelle nécessaire pour s'intéresser aux activités pré et post-stimulus, et 3/ des méthodes avancées de traitement du signal permettant de démêler les différentes activités en procédant à des analyses temps/fréquence et de localiser les sources cérébrales responsables de l'activité d'intérêt.

Dans ce sens, nous avons enregistré l'activité EEG lors d'une tâche adaptée de Go/NoGo de 49 patients parkinsoniens, 27 avec TCI (PD-TCI+) vs. 22 sans TCI (PD-TCI-). Le traitement des données EEG a été réalisé en s'appuyant sur les avancées méthodologiques récentes de notre groupe (*cf. Chapitre 3*) en combinant la séparation et la localisation des sources avec des analyses spectrales afin d'identifier les corrélats anatomiques et fonctionnels des différences cliniques observées entre patients PD-TCI+ et PD-TCI- en termes d'impulsivité motrice. Ces analyses spectrales ont été réalisées en aveugle (i.e., sur l'ensemble du cortex et

dans toutes les bandes de fréquence, et en testant les différents modèles d'inhibition, sans à priori) et conduites au niveau des sources.

**Article 5 :** Spay, C., Gaugain, G., Ballanger, B., Pezzoli, G., Boulinguez, P., Cilia, R. (submitted). Abnormal beta activity in the precuneus is associated with inhibitory control dysfunction in Parkinsonian Impulse Control Disorders. *Journal of Neuroscience*.



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Abnormal beta activity in the precuneus is associated with inhibitory control dysfunction in Parkinsonian Impulse Control Disorders

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Commercial Interest:

1 Abnormal beta activity in the precuneus is associated with inhibitory control  
2 dysfunction in Parkinsonian Impulse Control Disorders

3  
4  
5 Running title: Precuneus dysfunction in PD-ICDs

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45

46

47 **Abstract**

48           Impulse control disorders (ICDs) in Parkinson’s disease (PD) have been associated  
49 with dysfunctions in the control of value- or reward-based responding -choice impulsivity-  
50 and abnormalities in mesocorticolimbic circuits. To date, the hypothesis that dysfunctions in  
51 the control of response inhibition -action impulsivity- also play a role in PD-ICDs has been  
52 rejected, but all neural mechanisms have not been probed in previous studies. Here, we used  
53 high resolution EEG recordings in Parkinson’s disease patients of both genders with and  
54 without ICDs to track the spectral and dynamical signatures of different mechanisms involved  
55 in inhibitory control. Behaviorally, PD patients with ICDs proved more impulsive than PD  
56 patients without ICDs in a simple visuomotor reaction time task. This was associated with  
57 decreased beta activity in the precuneus. The underlying dynamical pattern indicated  
58 dysfunction of proactive inhibitory control, a mechanism intended to gate movement initiation  
59 by suppressing associated motor activity in anticipation of stimulation in uncertain contexts.  
60 These results indicate that action impulsivity plays a part in PD-ICDs. This might be due to  
61 the alteration of the cortical drive of proactive inhibition by the precuneus.

62

63

64 **Significance Statement**

65           Impulse Control Disorders (ICDs) are debilitating side-effects of antiparkinsonian  
66 dopaminergic drugs leading to pathological gambling, hypersexuality, compulsive eating and  
67 shopping. There is no satisfying therapeutic option because reducing dopaminergic drugs  
68 reinstates motor symptoms, or induces dopamine agonist withdrawal syndrome. Here, we take  
69 advantage of the temporal and spectral discrimination power of electroencephalographic  
70 recordings to identify unknown dysfunctions of motor inhibition in ICDs. Results suggest an  
71 impairment of the cortical drive of proactive inhibition, a function locking the motor system  
72 when time is needed before responding to stimulation. This opens new therapeutic  
73 perspectives because this function is already known to involve the noradrenergic system. This  
74 also sheds light on the obscure but pivotal role the precuneus plays in processing states.

75

76

## 77 **Introduction**

78           Impulse control disorders (ICDs) include pathological gambling, hypersexuality,  
79 compulsive eating and compulsive shopping (Cilia and van Eimeren, 2011; Weintraub et al.,  
80 2015). ICDs are very debilitating (Evans et al., 2004; Dodd et al., 2005) and can affect up to  
81 46% of Parkinson's disease (PD) patients (Weintraub et al., 2010; Vela et al., 2016; Antonini  
82 et al., 2017; Corvol et al., 2018). Since ICDs are associated with dopaminergic dysfunction  
83 and treatment (Weintraub et al., 2010; Cilia and van Eimeren, 2011; Aracil-Bolaños and  
84 Strafella, 2016; Voon et al., 2017b; Marques et al., 2018; Vriend, 2018), their management  
85 involves decrement or discontinuation of dopamine agonists. This is, however, at the expense  
86 of other clinical signs including a worsening of motor symptoms or the development of  
87 dopamine agonist withdrawal syndrome (Connolly and Fox, 2014; Samuel et al., 2015).  
88 Advancing our understanding of the neurocognitive substrates of ICDs is key for developing  
89 more efficient therapeutic strategies (Cilia and van Eimeren, 2011).

90           PD-ICDs have been associated with decisional impulsivity, also called cognitive or  
91 choice impulsivity (van Eimeren et al., 2009; Rao et al., 2010; Voon et al., 2010; Claassen et  
92 al., 2011; Ray et al., 2012). Decisional impulsivity refers to dysfunctions in the control of  
93 value- or reward-based responding (Dalley and Robbins, 2017). It can be due to irrational  
94 preference for small, immediate rewards versus larger but delayed rewards -temporal  
95 discounting-, irrational estimation of probabilistic gains -probabilistic discounting-, or  
96 irrational ill-timed decision without adequate accumulation and consideration of available  
97 evidence -reflection impulsivity- (ibid). Such disorders are consistent with numerous  
98 observations of abnormalities in mesocorticolimbic circuits in PD-ICDs (Cilia et al., 2008,  
99 2011; van Eimeren et al., 2009; Frosini et al., 2010; Rao et al., 2010; Voon et al., 2011,  
100 2017a; Politis et al., 2013; Carriere et al., 2015; Aracil-Bolaños and Strafella, 2016; Tessitore  
101 et al., 2017; Imperiale et al., 2018; Petersen et al., 2018; Vriend, 2018). But impulsivity is a

102 multidimensional construct that also includes a motor facet through the dysfunction of motor  
103 inhibition (Jahanshahi et al., 2015a, 2015b). The fact that motor –or action- impulsivity plays  
104 a role in the etiology of ICDs has been widely documented for various psychiatric conditions  
105 (Brevers et al., 2012; Bari and Robbins, 2013; Chowdhury et al., 2017; Dalley and Robbins,  
106 2017). The hypothesis, however, has received little interest for PD-ICDs (but see Jahanshahi  
107 et al., 2015a, 2015b), little empirical support (with the exception of one recent case report  
108 from Palermo et al., 2017), or has even been rejected (Rossi et al., 2010; Bentivoglio et al.,  
109 2013; Leroi et al., 2013; Claassen et al., 2015; Yoo et al., 2015; Pineau et al., 2016; Ricciardi  
110 et al., 2017). This contradiction could arise from the difficulty to model the response  
111 inhibition function, which is itself multidimensional, and the difficulty to test all its  
112 components with standard neuroimaging tools (Criaud and Boulinguez, 2013; Criaud et al.,  
113 2017).

114 To test the hypothesis that action impulsivity plays a role in ICDs, we capitalized on  
115 recent theoretical and methodological developments that now allow testing proactive,  
116 reactive, selective and non-selective mechanisms of response inhibition within a single  
117 experimental design (Figure 1), in PD patients with and without ICDs. Since standard  
118 neuroimaging methods based on blood flow measurements cannot disentangle the time-course  
119 of concurrent excitatory and inhibitory mechanisms (Logothetis, 2008), a central issue here,  
120 we used high-resolution EEG recordings. Provided that advanced source separation has been  
121 applied, EEG offers the opportunity: *i*) to assess brain dynamics with the appropriate temporal  
122 resolution for our purpose, *ii*) to localize relevant cortical sources with good spatial resolution,  
123 and *iii*) to provide spectral fingerprints of concurrent excitatory and inhibitory processes  
124 (Albares et al., 2015). Results reveal that PD-ICDs patients respond more impulsively than  
125 PD patients in a simple visuomotor task. This impulsive behavior is associated with abnormal

126 beta activity in the precuneus, a central node of the network supporting proactive motor  
127 inhibition. This indicates that action impulsivity plays a part in PD-ICDs.

128

## 129 **Material and Methods**

### 130 *Participants*

131 Twenty-seven PD patients (23 men, 4 women) with current ICDs (ICDs+) and 22 PD  
132 patients (18 men, 4 women) without ICDs (ICDs-) were enrolled at the Parkinson Institute in  
133 Milan. The presence of any ICDs was assessed with the Questionnaire for Impulsive-  
134 Compulsive Disorders in Parkinson Disease (QUIP score  $\geq 1$  for ICDs+, i.e., one ICD or  
135 more, (Weintraub et al., 2009)). Considering that ICDs+ patients may underestimate, or even  
136 lie about and voluntarily deny any behavioral disturbance (Cilia et al., 2014), caregivers were  
137 independently interviewed. For ICDs-, the absence of any behavioral disturbance during the  
138 whole disease course (i.e., QUIP score = 0) was stated and confirmed by the caregiver. The  
139 sample size was determined on the basis of the results of previous studies using commission  
140 errors to assess impulsivity and inhibitory dysfunction in PD (e.g., Ballanger et al., 2009).  
141 Accordingly, we expected an increase about 10% of the commission errors for ICDs+. The  
142 estimated sample size  $n$  was calculated as the solution of:

$$143 \quad n = \frac{(z_{\alpha/2} - z_{1-\beta})^2}{2(\text{Arc sin } \sqrt{P1} - \text{Arc sin } \sqrt{P2})^2}$$

144 where  $P1 = 1\%$  for ICDs-; and  $P2 = 11\%$  for ICDs+. Given a desired power of 90%, and a  
145 predetermined Type I error rate  $\alpha$  of 5%, the number of patients required to evidence a  
146 difference of 10% of commission errors between ICDs+ and ICDs- is 18 per group. This  
147 sample size was also determined in agreement with former specific recommendations  
148 regarding EEG group blind source separation analyses (Lio and Boulinguez, 2018). Indeed,



149 optimal performance of source separation and subsequent source localization does not require  
150 the inclusion of large samples of subjects ( $n < 20$ ) when applying second order statistics  
151 (SOS)-based algorithms that use source spectral diversity. These algorithms can identify and  
152 gather sources that have similar functional properties despite variable location and orientation  
153 due to inter-individual neuroanatomical variability.

154 Inclusion criteria were: age between 40 and 70 years old, with idiopathic PD,  
155 benefiting from a stable antiparkinsonian drug therapy for at least 2 months. Exclusion criteria  
156 were: dementia (MMSE  $< 26$ ), other neurologic or psychiatric disease, pharmacological  
157 treatment with cerebral or psychic impact, substance abuse according to the criteria DSM-IV-  
158 TR (except tobacco smoking). Patients remained on their usual medication during the study.  
159 Clinical and neuropsychological assessment included the Mini Mental State Examination  
160 (MMSE), the Frontal Assessment Battery (FAB), the Minnesota Impulsive Disorders  
161 Interview (MIDI) and the QUIP to assess ICDs, the Barratt Impulsiveness Scale (BIS-11), the  
162 Beck Depression Inventory (BDI), the UPDRS-III (Unified Parkinson's Disease Rating Scale  
163 part III) and the evaluation of Hoehn & Yahr (H&Y) stage. Data from 3 subjects had to be  
164 discarded following inabilities to perform the task while data from 7 subjects had to be  
165 discarded following technical issues during data acquisition, leading to groups of 22 ICDs+  
166 and 19 ICDs-. Groups were matched for age, disease duration, levodopa equivalent daily dose  
167 (LEDD) and UPDRS-III. The main demographic and clinical characteristics of the patients  
168 are displayed in Table 1. All patients gave written informed consent before the study, and the  
169 protocol was approved by the local Ethical Committee.

170

### 171 *Behavioral task*

172 The experimental task was reproduced from previous studies with healthy subjects and  
173 PD patients (e.g., Criaud et al., 2016, 2017). Patients performed a simplified Go/NoGo task

174 based on former methodological recommendations (Criaud and Boulinguez, 2013). In brief,  
175 subjects were asked to react as fast as possible to Go stimuli (a green diamond) by pressing a  
176 button with the right index (prepotent response) while refraining from reacting to NoGo  
177 stimuli (a green cross) (Figure 1). A block design was used to test two conditions separately.  
178 In mixed-blocks, both Go or NoGo stimuli could be presented with equal probability. In pure-  
179 blocks, only Go stimuli (Go\_control trials) could be presented. In mixed-blocks, the high  
180 level of uncertainty required action restraint and/or reactive inhibition. In pure-blocks, no  
181 inhibition was required at all, and subjects could react automatically to any upcoming event.  
182 Four blocks of trials (two of each type) were presented in a counterbalanced order between  
183 subjects (ABBA or BAAB).

184

#### 185 *Apparatus*

186 A panel equipped with light-emitting diodes (LEDs – Ø5mm, 8800mcd) was used to  
187 present the visual stimuli. One LED was placed in the center of the panel and set at the  
188 subject's eye level. It served as a fixation point for the eyes and indicated the beginning of the  
189 trial and the type of block (green –pure-block- or red –mixed-block-). The target stimulus  
190 (Go) was composed of eight other LEDs surrounding the central fixation point and forming a  
191 green diamond (3.44° of visual angle, 50 ms duration). The NoGo stimulus was composed of  
192 eight LEDs forming a green cross of 3.44° of visual angle centered on the fixation point (50  
193 ms duration). A feedback stimulus was composed of four LEDs forming a square of 3.44° of  
194 visual angle centered on the fixation point (green –correct response- or red –incorrect  
195 response-). Stimuli were presented, and data were acquired using a real time acquisition  
196 system (ADwin Pro, Keithley Instruments, Cleveland, OH) controlled by Matlab<sup>TM</sup> software  
197 (MATLAB, RRID:SCR\_001622).

198

199 *Procedure*

200           The subjects were seated in a darkened room in front of a screen placed 50cm from  
201 their eyes. The appearance of the fixation point indicated the beginning of a trial and lasted  
202 until the presentation of the stimulus. Pre-stimulus delays (time between the beginning of a  
203 trial and stimulus presentation) varied randomly from two to four seconds in steps of 500 ms.  
204 The stimuli (Go or NoGo) were presented for 50 ms. Subjects were asked to react as fast as  
205 possible to target presentation by pressing a button with their right index within one second  
206 timing. A feedback was given to the subject to indicate if the response was correct (green  
207 square) or not (red square). The inter-trial interval was up to the subject who had to press a  
208 button with the left index to go on the next trial. This procedure allowed subjects to take as  
209 many rest-breaks as necessary. Subjects were instructed to comply with a maximum error rate  
210 (commissions and omissions) of 20% of all trials to ensure a good understanding of the task.  
211 Pure-blocks were composed of 35 Go\_control trials each, for a total of 70 Go\_control trials  
212 per subject. Mixed-blocks were composed of 35 Go trials and 35 NoGo trials each, randomly  
213 presented, for a total of 70 Go trials and 70 NoGo trials per subject. Subjects were trained  
214 with the task before starting the experimental sessions (2 pure-blocks, 1 mixed-block).

215

216 *Electroencephalographic recordings*

217           The EEG methods used here are issued from methodological developments from our  
218 group (Lio and Boulinguez, 2013, 2018; Albares et al., 2015) and were reproduced from  
219 previous works (e.g., see Spay et al., 2018 for analyses of proactive inhibition and Albares et  
220 al., 2014 for analyses of reactive inhibition). Data processing pipeline is summarized in  
221 Figure 2.

222

223 *Apparatus*

224           The Biosemi™ ActiveTwo Mk2 system (31.25nV resolution) was used to record EEG  
225 data from 128 electrodes mounted in an elastic cap at Biosemi™ ABC system standard  
226 locations. Six additional external electrodes were added: four temporal electrodes (Biosemi  
227 spherical coordinates: Phi -103.5 Theta -18 -36, and Phi 103.5 Theta 18 36), and two  
228 electrodes attached to the outer canthi of the left and right eyes (Phi 103.5 -103.5 Theta 81 -  
229 81). The CMS active electrode and the DRL passive electrode of the ActiveTwo system were  
230 used instead of classical ground electrodes of conventional systems (these two electrodes  
231 form a feedback loop driving the average potential of the subject - the Common Mode voltage  
232 - as close as possible to the analogue-to-digital reference voltage in the AD-box). All  
233 electrode offsets were kept below 20mV. EEG data were recorded at a sampling rate of  
234 4096Hz.

235

236 *Data preprocessing*

237           Data were down-sampled at 2048 Hz, filtered (High-pass 0.5-1 Hz; Low-pass 46-48  
238 Hz; Attenuation 80 dB) and set to average reference. Then, data were epoched from 1500 ms  
239 before stimulus onset to 1000 ms after stimulus onset. Two steps were implemented to reject  
240 artifacts. For each subject and each block of trials (pure-block, mixed-block), corrupted  
241 epochs and artifacts (blinks, eye movements, ballistocardiac noise and other electrical noises)  
242 were detected and rejected using a first independent component analysis (ICA) / blind source  
243 separation (BSS) (UWSOBI, 300 times delays; (Yeredor, 2000) and the EEGLAB toolbox  
244 (Delorme and Makeig, 2004). Then, in a second step, an automatic rejection procedure for  
245 outlier epochs has been applied. For each epoch, the Frobenius norm between the epoch's

246 covariance matrix and the dataset's mean covariance matrix was calculated and, for each  
247 dataset, the 5% of the epochs deemed as outliers according to this metrics have been rejected.

248

#### 249 *Group Blind Source Separation (gBSS)*

250 We applied gBSS for the detection of task related sources. This approach offers a  
251 straightforward and computationally tractable solution to the problem of multi-subject  
252 analysis by creating aggregate data containing observations from all subjects. By providing a  
253 single estimation of the mixing and the demixing matrices for the whole group, gICA allows  
254 direct estimation of the components that are consistently expressed in the population (Eichele  
255 et al., 2011) and, hence, more efficient source separation and localization of these components  
256 (Lio and Boulinguez, 2013). A potential benefit of this method is a better sensitivity for the  
257 detection of critical sources that are often occulted by the most energetic phenomena  
258 (Sutherland and Tang, 2006). We employed UWSOBI, a Second Order Statics based group-  
259 BSS algorithm based on the approximate joint diagonalization of lagged-covariance matrices.  
260 We have recently demonstrated that this method is robust with respect to anatomo-functional  
261 inter-subjects variability and can separate group specific uncorrelated sources with non-  
262 proportional power-spectra without deleterious prior dimension reduction (Lio and  
263 Boulinguez, 2018). This method is especially convenient here because it separates the sources  
264 based on their spectral signatures (Albares et al., 2015). Three hundred lagged-covariance  
265 matrices with time delays from 0/2048s to 300/2048s were calculated on each epoch. Then,  
266 lagged-covariance matrices were concatenated across the dataset epochs, and then across  
267 patients, resulting in 200 averaged lagged-covariance matrices for the 2 groups of PD patients  
268 (ICDs+/ICDs-). Finally, 400 lagged-covariance matrices were approximately joint-  
269 diagonalized with the UWEDGE algorithm (Tichavsky and Yeredor, 2009), leading to the  
270 identification of 134 Independent Components (ICs). Thanks to this averaging procedure,

271 inter-epochs and inter-subjects variability was reduced. Conversely, sources with spectral  
272 modifications between groups of patients were highlighted (e.g., Ramoser et al., 2000;  
273 Congedo et al., 2008). The components accounting for most of the group effect (ICDs+ vs.  
274 ICDs-) were sorted by percent of explained variance. All components explaining more than  
275 1% of between-group variance were selected for further analyses (between group test).

276

### 277 *Blind spectral analyses*

278 To get all recordable sources underlying inhibitory control, we performed spectral  
279 analysis without a priori about anatomical sources or frequency bands. We assessed trial-by-  
280 trial modulations for all ICs explaining between-group variance in all frequency bands:  
281 delta/theta (1.5-7.5 Hz), alpha (7.5- 13.5 Hz), beta 1-2 (13.5-19.5 Hz), beta 3 (19.5-30.5 Hz),  
282 low gamma (30.5-44.5 Hz) and high gamma (57.5-77.5) band activities. In order to get  
283 optimal time/frequency resolution, six Elliptic Infinite Impulse Response (IIR) bandpass  
284 filters were designed with the Matlab™ signal processing toolbox. Relatively large pass  
285 band widths were set to get optimal time resolution, i.e., optimal estimation of the temporal  
286 dynamics of the frequency bands of interest at the single trial level. Detailed specification of  
287 the filters can be found in (Albares et al., 2014). Single trial power modulation was then  
288 estimated for each source and each frequency band thanks to the Hilbert transform: First, each  
289 trial was filtered with the corresponding filter in both forward and reverse directions to insure  
290 zero-phase distortion. Second, the complex analytic signal was derived by the Hilbert  
291 transform (Matlab™ hilbert function). Third, the instantaneous amplitude envelope of the  
292 signal was computed by taking the absolute magnitude of the complex waveform. The time  
293 window under scrutiny was restricted to 500 ms pre-stimulus to 800 ms post-stimulus in order  
294 to avoid edge effects/transient responses of digital filters. Finally, for visualization only, a  
295 trial moving average smoothing was applied (windows length: 400).

296

297 *Selection of the sources involved in inhibitory control*

298         A statistical matching procedure was performed on the basis of the control group data  
299 (ICDs-) in order to identify the sources revealing patterns of activity consistent with any  
300 template pattern of proactive inhibition, reactive selective inhibition, or reactive non-selective  
301 inhibition (Figure 1, Figure 2). The statistical matching procedure used Kruskal-Wallis tests,  
302 and was applied to each frequency band of each selected source. The rationale was as follows.  
303 If the mean power of the pre-stimulus period [-500: 0 ms] was significantly larger for Go than  
304 for Go\_control trials (contextual proactive activity), and if the mean power of the pre-stimulus  
305 period was significantly larger than the mean power of the post-stimulus period [0: 500 ms]  
306 (Go-induced desynchronization), then this source was considered as playing a substantial role  
307 in proactive inhibition and was selected for further group analyses. If the mean power of the  
308 post-stimulus period [0; 500 ms] was significantly larger for Go and NoGo than for  
309 Go\_control trials (event-related synchronization), then the corresponding source/frequency  
310 band was considered as playing a substantial role in reactive non-selective inhibition, and was  
311 selected for further group analyses. If the mean power of the post-stimulus period [0; 500 ms]  
312 was significantly larger for NoGo than for Go trials, then the corresponding source/frequency  
313 band was considered as playing a substantial role in reactive selective inhibition, and was  
314 selected for further group analyses. Data were then deconcatenated in order to have access to  
315 inter-individual variability for further statistical analyses.

316

317 *Power spectral analysis*

318         Mean relative power spectral density (PSD) differences were assessed between ICDs+  
319 and ICDs-. PSD has been estimated for each selected source by means of short-time Fourier

320 transforms (Matlab™ signal processing toolbox spectrogram), with a window width of 800  
321 samples and an overlap of 799 in the 1-45 Hz frequency range:

$$\forall f \in [1,45], PSD_{rel}(SS_i, f) = \frac{PSD_{abs}(SS_i, f)}{\sum_{f_k=1}^{45} PSD_{abs}(SS_i, f_k)}$$

322 Where  $SS_i$  is the selected source n°i.

323

### 324 *Source localization*

325 When relevant, localization was estimated by means of the sLoreta software (Pascual-  
326 Marqui, 2002) and a head model obtained by applying the BEM method to the MNI152  
327 template (Mazziotta et al., 2001). The 3D solution space was restricted to cortical gray matter  
328 and was partitioned into 6239 voxels with a spatial resolution of 5mm. Then, the sLoreta  
329 solution of the inverse problem was computed using an amount of Tikhonov regularization  
330 optimized for an estimated Signal/Noise Ratio of 100.

331

### 332 *Statistical analyses*

#### 333 *Behavioral variables*

334 Commissions: Commissions (erroneous responses to NoGo stimuli) are usually  
335 considered as the main behavioral marker of impulsivity and inhibitory dysfunction in PD  
336 (e.g., (Ballanger et al., 2009). The rate of commissions was assessed only in the mixed-block  
337 condition where erroneous responses to NoGo stimuli are possible. Normality and  
338 homoscedasticity were controlled using respectively Lilliefors test and Fisher test. Between  
339 subjects' analyses of mean percentage of commissions were performed after ArcSine  
340 transforms. The group effect (ICDs+ vs. ICDs-) was tested by means of a one-sided t test for  
341 independent samples.

342 Reaction time (RT): RT is known to pinpoint the level of action restraint (e.g.,(Chiu  
343 and Aron, 2014). In the Go\_control condition, when no inhibition is required, automatic



344 motor activations usually give rise to fast responses. Conversely, when action restraint is  
345 required in uncertain contexts, proactive inhibition and/or reactive non-selective inhibition  
346 prevent fast automatic responses. Volitional responses can be provided only after the Go  
347 stimulus has been identified and the executive inhibitory set has been released. This generates  
348 long latency responses (e.g., Boulinguez et al., 2008; Criaud et al., 2012, 2017; Jaffard et al.,  
349 2007, 2008). Accordingly, we assessed the difference in RT between Go and Go\_control  
350 conditions (delta RT), which is known to index the level of non-selective inhibition (the  
351 context-dependent inhibitory set, (Chiu and Aron, 2014). Normality and homoscedasticity  
352 were controlled using respectively Lillefors test and Fisher test. The group effect (ICDs+ vs.  
353 ICDs-) was tested by means by means of a one-sided t test for independent samples.

354

#### 355 *EEG variables*

356 Different tests were applied to probe brain activity accounting for proactive inhibition,  
357 brain activity accounting for reactive non-selective inhibition, and brain activity accounting  
358 for reactive selective inhibition (between-subjects analyses).

359 Proactive inhibition: For each selected source/frequency band showing relevant  
360 proactive activity, mean relative PSD during the pre-stimulus period [-500; 0 ms] was  
361 assessed by means of a 2 groups (ICDs+ vs. ICDs-) x 2 conditions (Go+NoGo vs.  
362 Go\_control) ANOVA. Tukey-Cramer tests were used for Post-hoc comparisons. P  
363 values<0.05 (corrected) were considered significant.

364 Reactive non-selective inhibition: For each selected source/frequency band showing  
365 relevant reactive activity, Mean relative PSD during the post-stimulus period [0; 500 ms] was  
366 assessed by means of a 2 groups (ICDs+ vs. ICDs-) x 2 conditions (Go+NoGo vs.  
367 Go\_control) ANOVA. Tukey-Cramer tests were used for Post-hoc comparisons. P  
368 values<0.05 (corrected) were considered significant.

369           Reactive selective inhibition: For each selected source/frequency band showing  
370 relevant reactive activity, mean relative PSD during the post-stimulus period [0; 500 ms] was  
371 assessed by means of a 2 groups (ICDs+ vs. ICDs-) x 2 conditions (NoGo vs. Go) ANOVA.  
372 Tukey-Cramer tests were used for Post-hoc comparisons. P values<0.05 (corrected) were  
373 considered significant.

374

375

## 376 **Results**

### 377 Behavioral variables

378           Behavioral results are summarized in Figure 3A.

379           *Commissions*: More commission errors are observed for ICDs+ than for ICDs- (17.1%  
380 vs 7.0%,  $T(39)=3.28$ ,  $p=0.007$ ).

381           *Delta RT*: Shorter delta RT is observed for ICDs+ than for ICDs- (165.47 vs 193.54,  
382  $T(39)=-1.69$ ,  $p=0.048$ ).

383

### 384 EEG variables

385           EEG results are summarized in Figure 3B/C.

386           Spectral modifications accounting for broad differences between ICDs+ and ICDs-  
387 (between group variance test) were observed in 20 sources/frequency bands: the precuneus  
388 (delta, alpha, beta 1-2, beta 3), the supplementary motor area -SMA- (delta, alpha, beta 1-2,  
389 beta 3), the posterior cingulate cortex -PCC- (delta, alpha, beta 1-2, beta 3), the lingual gyrus  
390 (delta, alpha, beta 1-2, beta 3), the fusiform gyrus (delta, beta 1-2) and the primary visual  
391 cortex (delta, alpha). Among these sources/frequency bands, the statistical matching  
392 procedure identified eight dynamical patterns consistent with proactive control, twelve  
393 dynamical patterns consistent with reactive non-selective control, and eleven dynamical

394 patterns consistent with reactive selective control in the control population (ICDs-). However,  
395 only one of these sources/frequency bands exhibited significant differences between ICDs+  
396 and ICDs -. This source lies in the precuneus (BA7) and is involved in proactive inhibition  
397 (Figure 3B). Power changes were found in the beta band (13-20Hz), as revealed by the Group  
398 by Condition interaction ( $F(1,1)=3.0$ ,  $p=0.037$ ). While an increase in relative beta power  
399 during the pre-stimulus period of Go and NoGo trials with respect to Go control trials was  
400 found for ICDs- (0.0239 vs. 0.0187 AI,  $p=0.0015$ ), no significant difference was found for  
401 ICDs+ (0.0216 vs. 0.0229 AI,  $p=0.18$ ) (Figure 3C).

402

403

## 404 **Discussion**

405 The present study is the first controlled experiment to report behavioral and  
406 neurofunctional markers of action impulsivity in PD-ICDs patients. As compared to ICDs-,  
407 ICDs+ show higher commission error rate and shorter RT in a simple stimulus-response task  
408 when uncertainty requires to refrain from reacting. This difficulty in maintaining proactive  
409 response inhibition is associated with decreased proactive beta activity in the precuneus.

410

### 411 *Behavioral and neural correlates of motor impulsivity in PD-ICDs*

412 A modified version of the Go/NoGo task was used to probe different possible types of  
413 inhibitory mechanisms that were not all tested in previous studies using Stop-Signal Task  
414 (SST), classical Go/NoGo Task or Continuous Performance Task: *i*) selective reactive  
415 inhibition (response inhibition is selectively triggered by the NoGo stimulus), *ii*) non-selective  
416 reactive inhibition (automatic response inhibition is triggered by any stimulus in uncertain  
417 contexts, and eventually followed by a long latency volitional response to Go stimulus), and  
418 *iii*) non-selective proactive inhibition (response inhibition is implemented before any stimulus

419 is presented in uncertain contexts, released after a Go stimulus has been identified, and  
420 eventually followed by a long latency volitional response) (Figure 1). The increase in  
421 commission error rate in ICD+ (erroneous responses to NoGo stimuli) provides global  
422 evidence for impaired motor response inhibition in a simple reaction time task involving no  
423 choice, no reward, and no delay discounting. The decrease in delta RT to Go stimuli in ICD+  
424 (the RT difference induced by the need for action restraint) suggests that less inhibition is  
425 implemented in uncertain contexts, as predicted by both proactive and reactive non-selective  
426 models (Figure 1). Finally, spectral analyses provide consistent neural correlates only for  
427 proactive response inhibition. Indeed, group differences were observed only for sustained pre-  
428 stimulus activity matching the dynamical pattern of proactive inhibition (Figure 1, Figure 3).  
429 Therefore, we conclude that ICDs in PD might partly be due to action impulsivity, not just  
430 choice impulsivity, and that the origin of the disorder likely comes from dysfunctional  
431 proactive response inhibition. This outcome provides empirical support to former hypotheses  
432 (Jahanshahi et al., 2015a, 2015b). Yet, it does not contradict former behavioral studies  
433 revealing no reactive inhibition dysfunction in ICDs+ (Leroi et al., 2013; Ricciardi et al.,  
434 2017).

435 At a first glance, the identification of the precuneus as the source of dysfunction of  
436 motor inhibition may come as a surprise regarding the major role of the prefrontal and motor  
437 cortices in this function (Bari and Robbins, 2013; Wang et al., 2016b; Dalley and Robbins,  
438 2017; Xu et al., 2017) and the fact that the behavioural functions subserved by the precuneus  
439 are still uncertain (Cavanna and Trimble, 2006; Utevsky et al., 2014). Yet, it is consistent with  
440 numerous observations in healthy subjects involving the precuneus in response inhibition  
441 (Menon et al., 2001; Albrecht et al., 2014; Popov et al., 2018), and more specifically in  
442 proactive inhibition (Jaffard et al., 2008; Chikazoe et al., 2009; Zhang and Li, 2012; Criaud et  
443 al., 2017; Pretto et al., 2017). It is also consistent with numerous observations that movement

444 initiation disorders are associated with precuneus dysfunctions in PD (Cilia et al., 2008;  
445 Frosini et al., 2010; Zhang et al., 2015; Criaud et al., 2016; Hou et al., 2017). Interestingly,  
446 difficulties initiating movements in PD have been associated to abnormally high activity in  
447 the precuneus during the prestimulus period of similar tasks (Criaud et al., 2016) while,  
448 conversely, impulsivity in PD patients stimulated in the subthalamic nucleus has been  
449 associated with decreased activity in the precuneus (Ballanger et al., 2009). However, the  
450 exact role of the precuneus in inhibitory control is still uncertain and has rarely been discussed  
451 thoroughly in the above-mentioned papers. Broadly, since the precuneus displays strong  
452 interconnections with the striatum, the anterior cingulate cortex, and the supplementary motor  
453 cortex (Zhang and Li, 2012; Thibes et al., 2017), it is in a unique position to play a pivotal  
454 role in executive control through its engagement under a variety of processing states (Utevsky  
455 et al., 2014). Proactive inhibitory control, which is known to be the ‘default mode’ of  
456 executive function (Criaud et al., 2012) is certainly one of these states (Jaffard et al., 2008).

457 Proactive inhibitory control is known to be supported by interactions between  $\alpha$  and  $\beta$   
458 rhythms (Bengson et al., 2012; Hwang et al., 2014). Alpha oscillations would index an active  
459 inhibitory mechanism that gates information processing (Thut et al., 2006; Klimesch et al.,  
460 2007; van Dijk et al., 2008; Mathewson et al., 2009; Mazaheri et al., 2009; Jensen and  
461 Mazaheri, 2010; Mathewson et al., 2011; Hamm et al., 2012; Klimesch, 2012; Hindriks and  
462 van Putten, 2013; Zumer et al., 2014; Liu et al., 2016; Wang et al., 2016a). Beta oscillations  
463 would index top-down signaling and communication between sensorimotor and non-  
464 sensorimotor areas (Zhang et al., 2008; Swann et al., 2009; Engel and Fries, 2010; Kilavik et  
465 al., 2013). Here, blind analyses of all sources/frequency bands were performed, but behavioral  
466 and clinical differences between ICDs+ and ICDs- were associated only with changes in  $\beta$   
467 activity. It is noteworthy that this spectral signature is highly consistent with the dynamical  
468 signature described above. Both are predicted by the proactive inhibition model: sustained  $\beta$

469 power in the prestimulus period as proactive inhibition must be maintained,  
470 desynchronization induced by the Go stimulus to release proactive inhibition, and response  
471 initiation after complete desynchronization (Figure 3). This  $\beta$  signature is also consistent with  
472 recent data showing a link between STN  $\beta$  activity and broad motor suppressive effects during  
473 response inhibition (Bastin et al., 2014; Wessel et al., 2016), especially during proactive  
474 inhibitory control (Benis et al., 2014). This supports the fMRI-based view that the precuneus  
475 is a node of the cortico-basal ganglia network supporting inhibitory control (Jaffard et al.,  
476 2008; Chikazoe et al., 2009; Zhang and Li, 2012; Criaud et al., 2017; Pretto et al., 2017). As  
477 such, it can be suggested that an alteration of the cortical drive or relay of proactive motor  
478 inhibition at the level of the precuneus likely plays a role in the development of ICDs.

479

#### 480 *Implications for managing ICDs*

481 ICDs are associated with dopaminergic dysfunction and treatment (Cilia et al., 2011;  
482 Weintraub et al., 2015; Aracil-Bolaños and Strafella, 2016; Marques et al., 2018; Vriend,  
483 2018), but simply discontinuing or decreasing dopamine agonists is not a fully satisfying  
484 option of management (Samuel et al., 2015). The evidence that action inhibition dysfunctions  
485 play a role in ICDs might open the door to new research avenues and possible treatment  
486 strategies including complementary non-dopaminergic medication, a critical issue in PD (Fox,  
487 2013; Freitas and Fox, 2016). Indeed, the different subcomponents of impulsivity in ICDs+  
488 are differentially sensitive to DA treatment. DA medication would mainly influence the neural  
489 network underlying impulsive choices, but not the neural network underlying impulsive  
490 action (Antonelli et al., 2014). Importantly, previous work on the neural and neurochemical  
491 bases of motor inhibition has identified the key role of both the noradrenergic (NA)  
492 (Chamberlain et al., 2009; Robbins and Arnsten, 2009; Ye et al., 2015; Borchert et al., 2016;  
493 Spay et al., 2018) and the serotonergic (5HT) (Eagle et al., 2008; Ye et al., 2014, 2016)

494 systems. Fractionating impulsivity into distinct, yet interdependent, neural mechanisms whose  
495 chemical bases are known has proven useful in psychiatry to identify and treat specifically  
496 various forms of impulsive behavior (Robbins et al., 2012; Chamberlain and Robbins, 2013;  
497 Cuthbert and Insel, 2013; Dalley and Robbins, 2017). This approach is promising in PD  
498 research as well (Antonelli et al., 2014; Kehagia et al., 2014; Nombela et al., 2014), and the  
499 present results could contribute to better identification, classification and treatment of PD-  
500 ICDs.

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847

848

849 **Table legends**

850

851 **Table 1:** Patients characteristics. Values are given as mean  $\pm$  SD.

852

853

854 **Figure legends**

855

856 **Figure 1:** Illustration of the experimental design used to assess three different forms of  
857 inhibitory control. **A)** The Go/NoGo task. In mixed-blocks, participants were asked to react as  
858 fast as possible to a Go stimulus (diamond) by means of a button press, or to withhold  
859 response to an equiprobable NoGo stimulus (X). The rate of erroneous responses to NoGo  
860 stimuli (commissions) is indicative of impulsive behavior. The contrast [NoGo - Go] (1) is  
861 likely to highlight the brain activity which is selectively triggered by the NoGo signal in order  
862 to inhibit the associated motor response (reactive selective inhibition). In mixed-blocks,  
863 participants were asked to react as fast as possible to the same Go stimulus (diamond) by  
864 means of the same button press. In this condition no NoGo stimuli could be presented,  
865 meaning that action restraint was no longer required in Go\_control trials. The contrast  
866 [(Go+NoGo) - Go\_control] (2) is likely to highlight the brain activity which is non-selectively  
867 triggered by any stimulus when the context is uncertain in order to inhibit any automatic  
868 motor response (reactive non-selective inhibition). This contrast is also likely to highlight the  
869 brain activity which occurs in anticipation of stimulation in order to gate movement initiation  
870 by suppressing associated motor activity when the context is uncertain (proactive inhibition).  
871 Reaction time (RT) is indicative of the level of proactive inhibition. Indeed, RTs are usually

872 shorter in Go\_control trials than Go trials (delta RT) because in uncertain contexts proactive  
873 inhibition can only be released after Go stimulus identification, which requires a substantial  
874 amount of time. **B)** Electrophysiological signatures of different possible forms of inhibitory  
875 control. Electroencephalography (EEG) offers the possibility to track relevant spectral activity  
876 directly at the source level. Previous studies in healthy subjects and PD patients have  
877 identified typical dynamical patterns of reactive and proactive inhibition (Albares et al., 2014,  
878 2015; Spay et al., 2018). Power changes induced specifically by NoGo signals pinpoint  
879 reactive selective inhibition. Power changes induced by NoGo and Go signals but not by  
880 Go\_control signals pinpoint reactive non-selective inhibition. A power increase during the  
881 pre-stimulus period of NoGo and Go trials with respect to Go\_control trials which is followed  
882 by stimulus induced desynchronization pinpoints proactive inhibition. Examples of power  
883 time-series in healthy subjects are presented on a trial-by-trial basis (concatenated data sorted  
884 according to RT -black curve-, left side) and on a mean power basis (right side). *Data taken*  
885 *from Albares et al., (2014).*

886

887 **Figure 2:** Data processing pipeline configuration (see text for details).

888

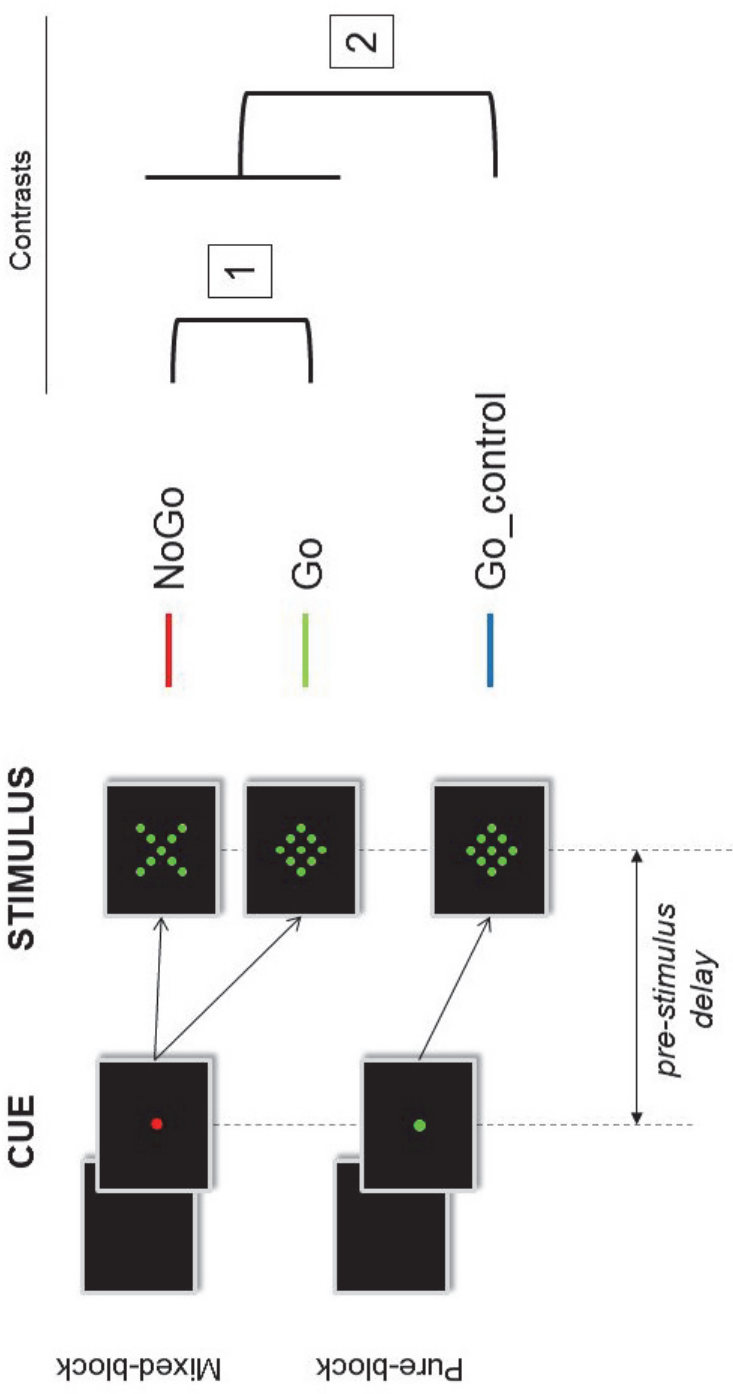
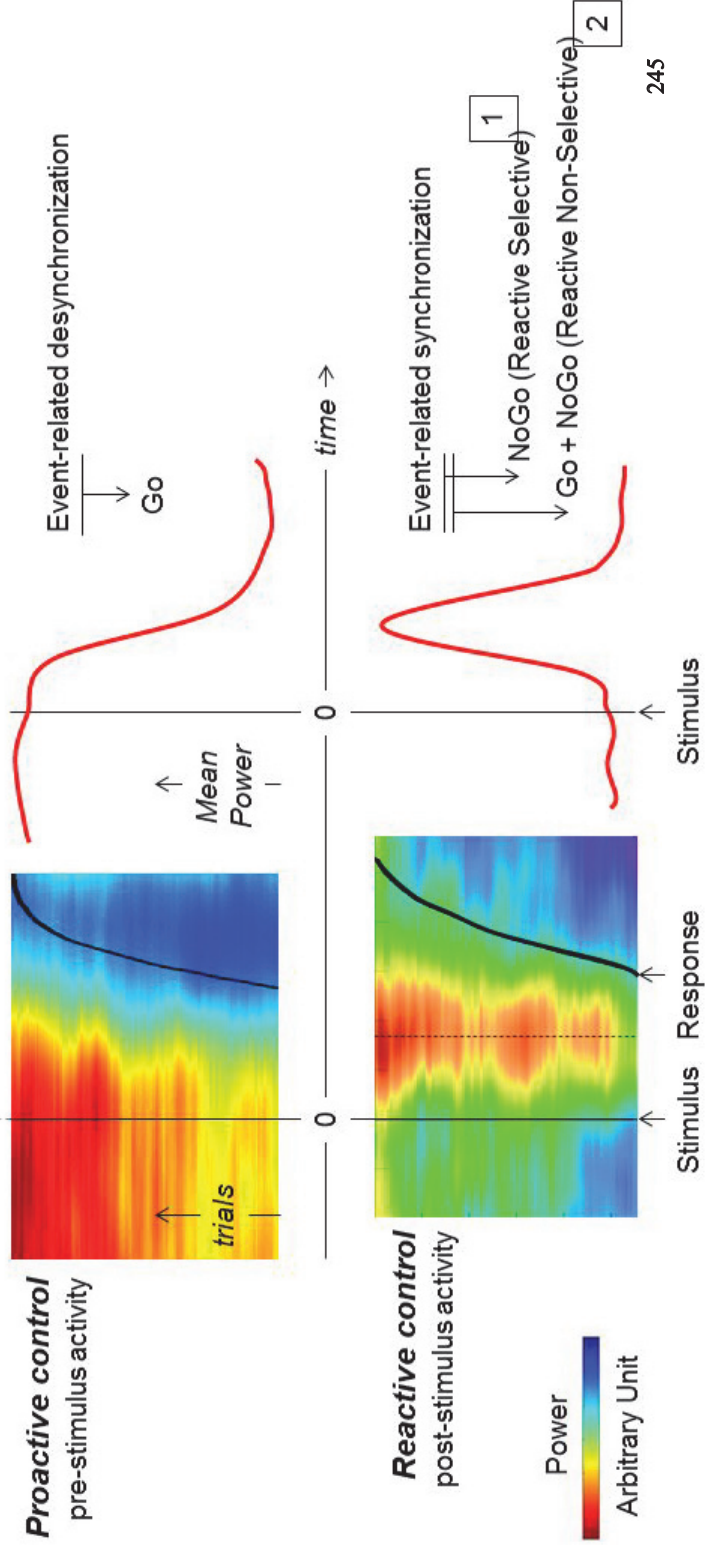
889 **Figure 3:** Behavioral and neural correlates of motor impulsivity in PD patients with ICDs  
890 (ICDs+). **A)** Behavioral results. ICDs+ make more commission errors (erroneous responses to  
891 NoGo stimuli). The RT difference between Go and Go\_control trials (delta RT), indicative of  
892 the level of proactive inhibition, is shorter for ICDs+. **B)** Probability map of dipole location  
893 for the single source accounting for motor inhibition-related brain activity differences  
894 between ICDs+ and ICDs- (Precuneus). **C)** Illustration of the temporal dynamics of precuneus  
895 beta activity for each condition of interest (Go vs Go\_control) and each group (ICDs+ vs.

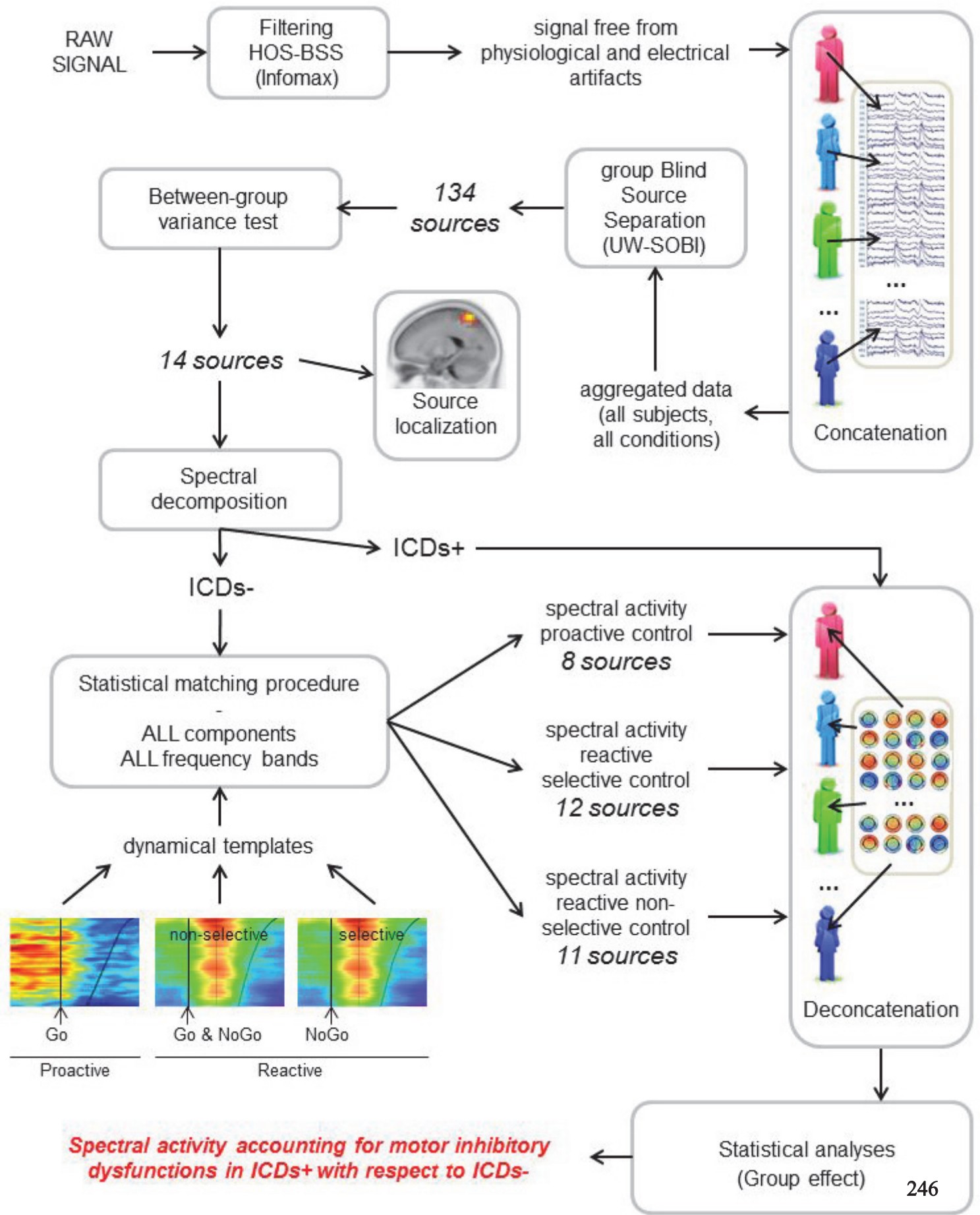
896 ICDs-). Absolute power data are presented, aggregated across subjects and sorted as a  
897 function of RT. Only PD patients without ICDs (ICDs-) show a pattern of pre-stimulus  
898 activity suggesting increased proactive inhibitory control when action restraint is required (Go  
899 trials) with respect to the control condition requiring no action restraint (Go\_control trials).

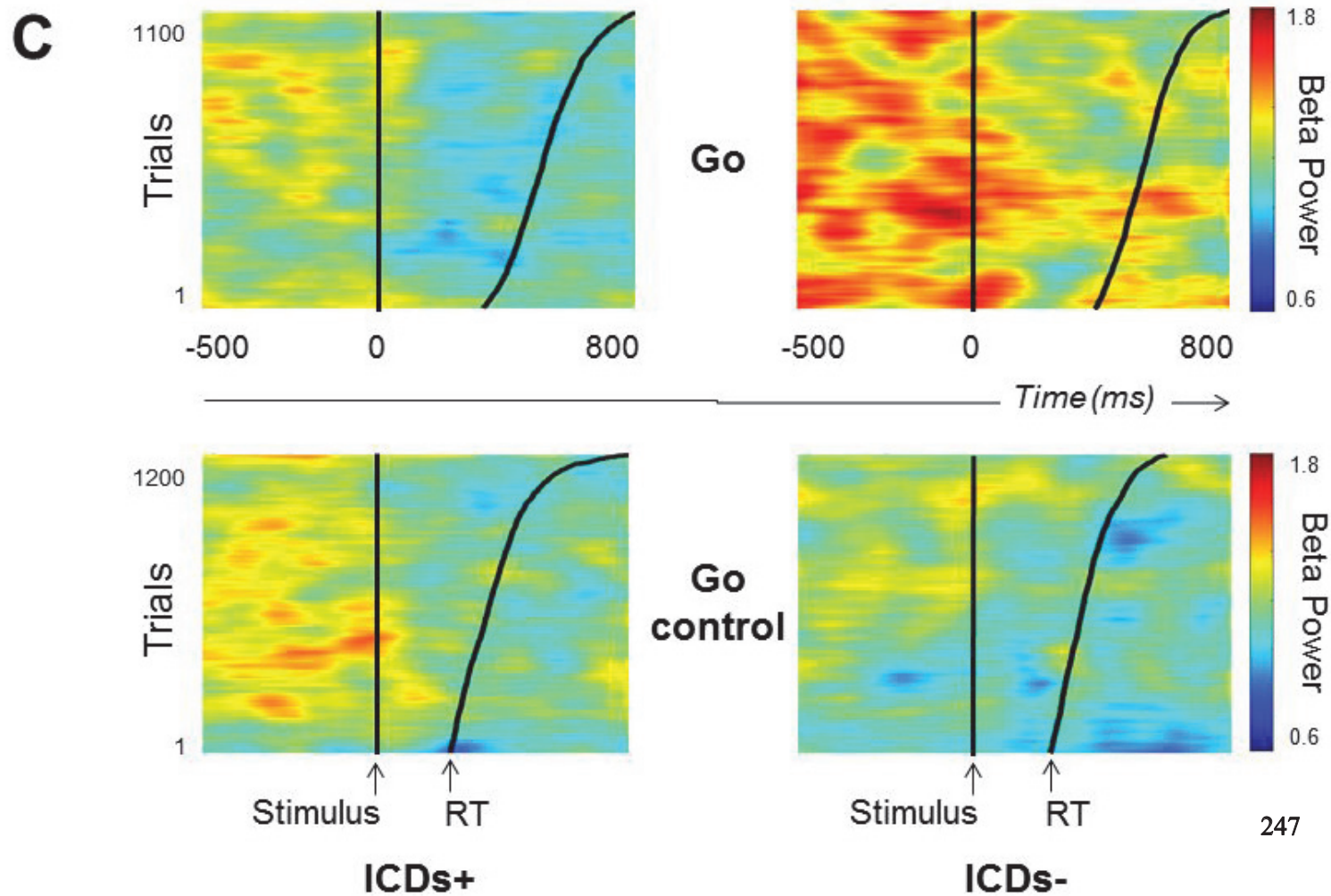
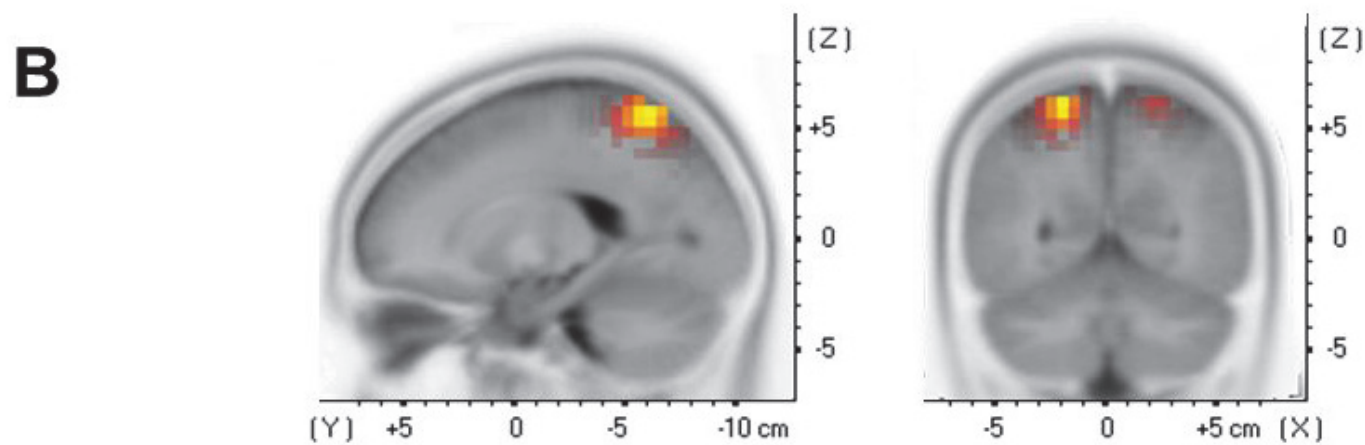
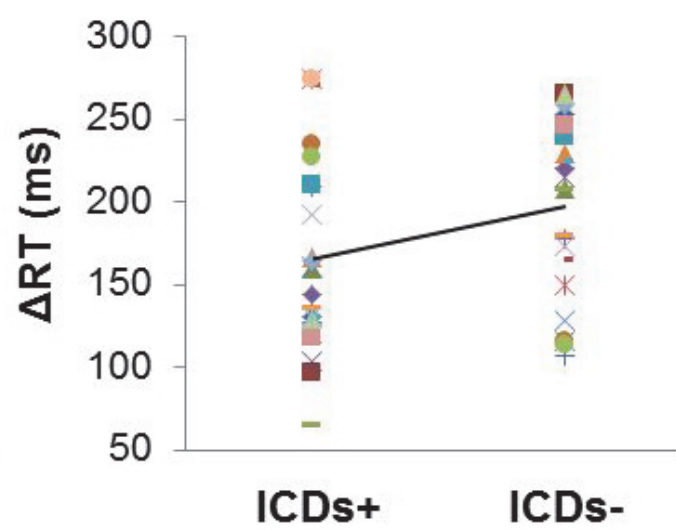
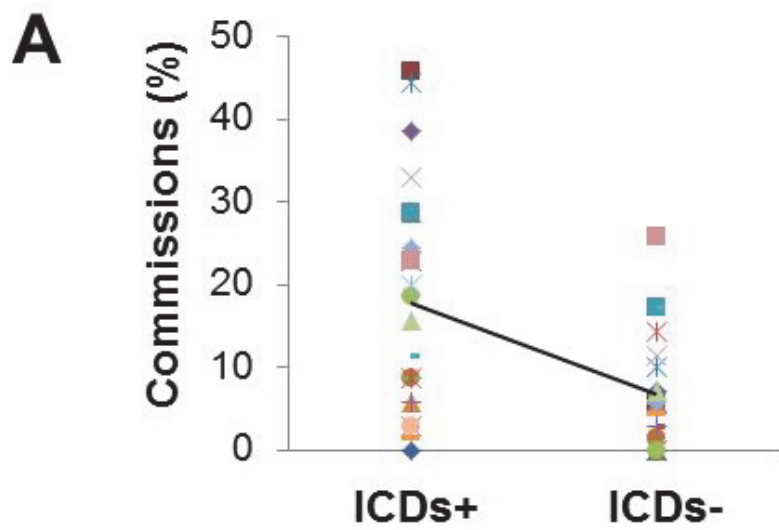
**Table 1:** Patients characteristics.

	PD-ICDs+	PD-ICDs-	p-value
<b>Demographics</b>			
Number	22	19	-
Sex	21M / 1F	18M / 1F	-
Age	61.2 ± 7.0	58.4 ± 7.9	0.24
Disease duration	9.6 ± 4.8	7.8 ± 3.5	0.19
<b>Clinical characteristics</b>			
Total LEDD	791.6 ± 290.2	745.0 ± 205.8	0.56
Levodopa dose	621.7 ± 296.8	418.4 ± 208.8	0.016
DAAs dose (LEDD)	75.3 ± 87.4	254.4 ± 92.5	1.1.10 <sup>-7</sup>
Fluctuations	15 Yes / 7 No	5 Yes / 14 No	
H&Y stage	1.8 ± 0.7	1.6 ± 0.7	0.28
Predominant type, type[number of patients]	[AR]15 [TD]7	[AR]17 [TD]2	
UPDRS-III (ON)	11.8 ± 6.2	10.4 ± 7.8	0.51
<b>Neuropsychological assessment</b>			
MMSE	28.5 ± 1.3	29.4 ± 1.1	Cut-off > 26
FAB	15.5 ± 2.1	16.8 ± 1.2	Cut-off > 13.4
BDI	12.1 ± 8.4	7.5 ± 7.3	0.07
BIS-11	67.7 ± 13.6	63.8 ± 6.1	0.13
QUIP (A), ICDs #[number of patients]	[1]12; [2]7; [3]1; [4]2	0	-
QUIP (ABC), ICDs #[number of patients]	[1]9 ; [2]5 ; [3]6 ; [4]1 ; [5]1	0	-
A1 (Pathological gambling)	22	0	-
A2 (Hypersexuality)	7	0	-
A3 (Compulsive Buying)	3	0	-
A4 (Binge Eating)	5	0	-
B (Punding, Hobbyism or Walkabouts)	9	0	-
C (DDS)	0	0	-

ICDs= Impulse Control Disorders, Total LEDD= Total Levodopa Equivalent Daily Dose (mg/day), DAAs= dopamine agonists, H&Y= Hoeh & Yahr scale, AR=Akineto-rigid, TD=Tremor-dominant subtypes of PD patients, UPDRS-III= Unified Parkinson's Disease Rating Scale (part III), MMSE= Mini-Mental State Evaluation, FAB= Frontal Assessment Battery, BDI= Beck Depression Inventory, BIS= Barratt Impulsiveness Scale, QUIP= Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, ICBs= Impulsive-Compulsive Behaviors, DDS= Dopamine Dysregulation Syndrome.

**A****B**







## b. Synthèse & Perspectives

Pour la première fois, cette étude s'est intéressée aux marqueurs comportementaux et fonctionnels de l'impulsivité motrice chez des patients parkinsoniens avec TCI. Au niveau comportemental, les patients PD-TCI+ présentent plus d'erreurs de commissions et des TR plus courts dans une tâche simple. Cette difficulté à maintenir un contrôle inhibiteur en situation d'incertitude est associée à une diminution de l'activité bêta (13-20 Hz) dans le précuneus. Alors que ce lien avait précédemment été rejeté (Dawson et al., 2018), ce travail suggère que les TCI sont caractérisés à la fois par de l'impulsivité cognitive et de l'impulsivité motrice.

Plus précisément, en utilisant une tâche adaptée de Go/NoGo et des analyses EEG sans a priori (i.e., ni sur les sources ni sur les bandes de fréquence), nous avons testé pour la première fois la pluralité des modèles de l'inhibition de réponse : réactif sélectif, réactif non sélectif et proactif non-sélectif. Ils s'avèrent, en cohérence avec les précédentes études ayant uniquement testé les mécanismes réactifs au niveau comportemental (Leroi et al., 2013; Ricciardi et al., 2017), que les patients parkinsoniens avec TCI ne présentent aucun dysfonctionnement en termes de mécanismes réactifs, qu'il soit sélectifs ou non-sélectifs. Un effet du groupe TCI+ a seulement été observé sur l'activité proactive non-sélective dans une seule source, le précuneus et dans la bande de fréquence beta.

Cette étude apporte des évidences en faveur d'un rôle du précuneus dans le contrôle inhibiteur. Ce rôle est supporté par plusieurs observations chez les sujets sains (Albrecht et al., 2014; Menon et al., 2001; Popov et al., 2018), et plus précisément dans le contrôle inhibiteur proactif (Chikazoe et al., 2009; Criaud et al., 2017; Jaffard et al., 2008; Pretto et al., 2017; Zhang & Li, 2012). Ce résultat est également consistant avec les dysfonctionnements déjà observés au sein du précuneus dans les troubles de l'initiation du mouvement chez les patients parkinsoniens (Cilia et al., 2008; Criaud et al., 2016; Frosini et al., 2010b; Hou et al., 2017; Zhang et al., 2015). De même, les résultats de l'analyse spectrale sont cohérents avec cette

hypothèse et impliquent la bande de fréquence beta qui indexerait des mécanismes top-down du contrôle inhibiteur (Engel & Fries, 2010; Kilavik et al., 2013; Swann et al., 2009; Zhang et al., 2008). Cette étude est donc en faveur d'une altération de la commande du contrôle inhibiteur proactif non-sélectif chez les patients PD-TCI au niveau du précuneus.

Comme proposé par Brever et collaborateurs (2012), alors que l'impulsivité cognitive pourrait être un facteur de risque de développer des TCI, un déficit d'inhibition de réponse, i.e., de l'impulsivité motrice, pourrait constituer un facteur de prédisposition à la progression et la sévérité des TCI (Brevers et al., 2012; Palermo et al., 2017). Ces deux déficits semblent en effet co-existants dans d'autres pathologies (Sonuga-Barke, 2002). En nous appuyant sur les travaux issus des troubles de l'attention avec hyperactivité (TDAH), nous pourrions proposer un modèle avec deux voies distinctes à l'origine des TCI : la première liée à une dérégulation de la prise de décision et une autre liée à un déficit de contrôle inhibiteur (Sonuga-Barke, 2003). Alors que la prise de décision a été fortement associée au système méso-limbique et aux circuits de la récompense sous-tendus par le système dopaminergique, il a récemment été montré que le contrôle inhibiteur pourrait avoir une origine noradrénergique (Kehagia et al., 2014; Spay et al., 2018). Cette étude ouvre donc de nouvelles perspectives thérapeutiques en termes de médication non-dopaminergique (Fox, 2013; Nombela et al., 2014).

**Cette étude apporte, pour la première fois, des évidences neurofonctionnelles d'un rôle clé de l'impulsivité motrice associée à l'impulsivité cognitive dans le développement des TCI. Plus précisément, un dysfonctionnement du contrôle inhibiteur proactif non-sélectif observé dans le précuneus serait impliqué.**

## CONCLUSION GENERALE

Comme le révèle le **Chapitre 1**, les troubles de l'initiation de l'action (lenteur pour initier, i.e., akinésie, ou difficulté à réprimer un mouvement, i.e., impulsivité) dans la maladie de Parkinson sont très invalidants et sans solution thérapeutique satisfaisante. Bien que constituant un symptôme cardinal de la maladie, l'akinésie, actuellement considérée comme un trouble purement moteur, n'est pourtant pas entièrement restaurée par la médication dopaminergique (Favre et al., 2013). A l'opposé, les TCI sont fréquemment observés chez les patients traités pharmacologiquement (avec des DAAs) ou par stimulation cérébrale profonde (le plus souvent du NST) (Ballanger et al., 2009; Callesen et al., 2013; Ray & Strafella, 2013; Rodriguez-Oroz et al., 2011; Thobois et al., 2007). Leur prise en charge actuelle repose sur la diminution de la médication dopaminergique (DAAs), au risque de voir s'aggraver la symptomatologie motrice (Samuel et al., 2015; Schreiber et al., 2011). A ce jour, les bases neuropsychologiques mais également neuro-fonctionnelles et neurochimiques de ces troubles sont encore mal comprises (Spay et al., submitted - *Chapitre 2* ; Meyer\*, Spay\* et al., under revision).

Nous avons identifié, dans le **Chapitre 2**, différents obstacles à une meilleure compréhension de ces troubles. Alors que les bases neuropsychologiques nécessitent d'être revisitées, il semble que la physiopathologie de la maladie de Parkinson soit plus complexe que la dégénérescence dopaminergique nigro-striée communément admise (Braak & Del Tredici, 2008). De même, l'effet des traitements, qu'ils soient dopaminergiques ou de stimulation, nécessite d'être investigué. Le **Chapitre 3** révèle l'entremise des mécanismes exécutifs automatiques qui est susceptible d'apporter un éclairage nouveau sur ces symptômes cliniques dans la maladie de Parkinson. En effet, le modèle proactif prédit, à la différence des modèles réactifs standards, deux effets possibles du dysfonctionnement du contrôle inhibiteur :

l'impulsivité, possiblement engendrée par des troubles d'implémentation du contrôle proactif (e.g., Ballanger et al., 2009), et les difficultés d'initiation du mouvement –e.g., akinésie, freezing-, possiblement engendrées par des troubles de levée du contrôle inhibiteur (e.g., Favre et al., 2013). Mais l'étude de ces mécanismes inhibiteurs a nécessité différents amendements théoriques et méthodologiques avant de pouvoir tester leurs dysfonctionnements dans la maladie de Parkinson.

Dans le **Chapitre 4**, nous avons montré que le contrôle inhibiteur proactif non sélectif (i.e., contexte-dépendant) joue un rôle clef à la fois dans l'akinésie et dans les TCI. L'akinésie peut en partie s'expliquer par un dysfonctionnement exécutif, non restauré par la médication dopaminergique, et donc non moteur (Favre et al., 2013). En effet, l'akinésie est caractérisée par une difficulté à relâcher volontairement ce contrôle proactif non sélectif dans des conditions où les patients sont pourtant censés laisser libre court aux automatismes sensorimoteurs (Spay et al., 2018). A l'opposé, les TCI reflètent à la fois de l'impulsivité de choix et un déficit de l'inhibition de réponse conduisant à de l'impulsivité motrice (Jahanshahi et al., 2015a ; Spay et al., submitted – *Chapitre 4-2* ; Spay et al., submitted – *Chapitre 4-3*). En effet, les patients avec TCI présentent un défaut d'implémentation de ce contrôle inhibiteur proactif non sélectif dans des conditions d'incertitude qui nécessitent pourtant de se retenir de répondre.

Pour la première fois, ce travail de thèse apporte des évidences anatomo-fonctionnelles de ces dysfonctionnements du contrôle inhibiteur proactif à l'origine des troubles de l'initiation du mouvement. De façon intéressante, l'akinésie a été associée avec une augmentation anormale de l'activité dans le précuneus dans la période pré-stimulus (Criaud et al., 2016 ; Spay et al., submitted – *Chapitre 2*) ; alors qu'à l'inverse, l'impulsivité motrice chez des patients parkinsoniens avec TCI a été associée avec une diminution de l'activité dans le précuneus (Ballanger et al., 2009 ; Spay et al., submitted – *Chapitre 4-3*). Il semble ainsi que le précuneus soit impliqué dans le déclenchement du contrôle proactif non-sélectif (Jaffard et al., 2008 ;

Criaud et al., 2017 ; Spay et al., submitted – *Chapitre 4-3*) et que ce contrôle soit médié par la voie subthalamo-corticale impliquant l'AMS (Spay et al., 2018). En effet, le désordre exécutif pathologique observé chez les patients akinétiques est restauré par la SCP-NST. Ce travail fournit donc des arguments en faveur d'un rôle pivot du NST dans le contrôle inhibiteur proactif non sélectif lié au passage volontaire d'un état contrôlé (i.e., inhibé) à un état de réactivité automatique (désinhibé). Enfin, ce travail apporte pour la première fois chez l'homme des évidences neuro-fonctionnelles directes d'un rôle du système noradrénergique dans les boucles subthalamo-corticales liées au contrôle de l'action. En effet, nous avons mis en évidence que le fait d'abaisser artificiellement la concentration de NA via l'administration de clonidine a des effets parfaitement contraires à ceux de la SCP-NST sur l'akinésie.

Nos résultats sont en faveur d'un rôle spécifique du système NA dans le contrôle inhibiteur et ouvrent la voie d'un développement des thérapies non-dopaminergiques. Tout d'abord, ce travail invite à envisager un traitement médicamenteux possédant le même mode d'action que la clonidine (agoniste  $\alpha_2$  adrénergique) pour atténuer l'impulsivité induite par la SCP-NST et réduire l'impulsivité motrice observée chez les patients avec TCI. En effet, comme proposé pour les TCI chez des patients non parkinsoniens, un déficit d'inhibition de réponse (i.e., impulsivité motrice) pourrait constituer un facteur de prédisposition à la progression et la sévérité des TCI (Brevers et al., 2012; Palermo et al., 2017). La seconde perspective invite au contraire à envisager un traitement médicamenteux aux propriétés antagonistes des récepteurs adrénergiques  $\alpha_2$  pour pallier l'akinésie. La lenteur à l'initiation motrice pourrait être remédiée par le biais de la restauration de la fonction exécutive de déverrouillage « volontaire » du NST.

En conclusion, à la lumière du contrôle inhibiteur proactif mettant en avant les processus inhibiteurs automatiques non sélectifs, il convient de revisiter la signification des troubles du contrôle de l'action dans la maladie de Parkinson. Ce travail propose de revisiter l'akinésie et

les TCI comme des symptômes et effets secondaires antagonistes présentant une origine exécutive commune. Il apporte, pour la première fois, des évidences neuro-fonctionnelles directes d'un rôle du système noradrénergique à l'origine des dysfonctionnements exécutifs observés dans la maladie de Parkinson. Ces conclusions ouvrent donc de nouvelles perspectives thérapeutiques en termes de médication non-dopaminergique.

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