Bases neuro-fonctionnelles des troubles de l'impulsivité dans la maladie de Parkinson

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Bases neuro-fonctionnelles des troubles de l'impulsivité dans la maladie de Parkinson

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Résumé

La maladie de Parkinson (MP), deuxième maladie neurodégénérative la plus fréquente, est très invalidante. Les traitements actuels, tels que les traitements dopaminergiques et la stimulation cérébrale profonde (SCP), permettent de contrôler ses symptômes moteurs. Mais certains symptômes non-moteurs ainsi que certains effets indésirables de ces traitements restent sans solution thérapeutique satisfaisante. C'est le cas notamment de l'impulsivité, qui se manifeste sous la forme de troubles du contrôle des impulsions (TCIs ; c'est-à-dire jeu pathologique, hypersexualité, alimentation compulsive et achat compulsif) induits par la médication dopaminergique, mais aussi sous la forme de troubles du contrôle inhibiteur consécutifs à la SCP du noyau sous-thalamique (NST).

Un problème majeur limitant à ce jour les perspectives thérapeutiques est la méconnaissance de la nature et des bases neuro-fonctionnelles des multiples dysfonctionnements susceptibles d'expliquer les différents types d'impulsivité observés dans la MP. Pour tenter de le résoudre, notre approche repose sur l'utilisation combinée de modèles psychologiques des mécanismes d'intérêt, de tâches cognitives conçues pour les cibler, et de méthodes avancées de traitement du signal électroencéphalographique (EEG) permettant de caractériser l'activité spectrale directement au niveau des sources. Cette stratégie est susceptible d'augmenter substantiellement le pouvoir de discrimination fonctionnelle des mécanismes cérébraux d'intérêt.

Dans le **Chapitre 1**, nous constatons que l'impulsivité des TCIs est généralement considérée comme relevant de dysfonctionnements des mécanismes de motivation, de prise de décision et de récompense. A travers une revue systématique de la littérature en neuro-imagerie, nous montrons que les altérations de l'activité cérébrale associées aux TCIs s'étendent pourtant au-delà du réseau de traitement de la récompense. A travers deux études expérimentales, nous testons l'hypothèse jusqu'ici négligée selon laquelle un dysfonctionnement du contrôle inhibiteur est susceptible de contribuer aux TCIs. Dans la première étude, nous montrons des altérations de l'activité oscillatoire de repos liées à la présence ou à la sévérité des TCIs, qui concernent des régions et bandes de fréquence associées à l'inhibition de réponse. Dans la deuxième étude, nous montrons que les patients souffrant de TCIs sont plus impulsifs dans une tâche de Go/NoGo, et présentent une diminution de l'activité beta pré-stimulus dans des sources localisées dans l'aire motrice supplémentaire et le précuneus, en accord avec l'idée d'un déficit de contrôle inhibiteur proactif.

Dans le **Chapitre 2**, nous vérifions que les effets de la SCP-NST sur le contrôle inhibiteur contribuent à l'amélioration de l'akinésie, mais aussi à une exacerbation de l'impulsivité d'action. Dans une troisième étude expérimentale, nous explorons les mécanismes d'action sous-tendant ces effets,

en testant l'hypothèse selon laquelle ceux-ci pourraient dépendre d'une modulation directe, par activation antidromique, de l'activité du cortex moteur supplémentaire (CMS) plutôt que d'une perturbation du relai de la commande inhibitrice par le NST. En accord avec cette hypothèse, les effets de la SCP-NST sur le contrôle inhibiteur (tels que révélés par l'analyse du comportement et de l'activité du CMS) dépendent de la force de la connectivité structurelle entre la région du NST stimulée et le CMS.

En conclusion, nos résultats montrent que l'impulsivité dans la MP repose sur des bases neuro-fonctionnelles diverses. Leur identification ouvre la voie à de nouvelles pistes de recherche concernant des solutions thérapeutiques spécifiques.

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Abstract

Neuro-functional bases of impulsivity disorders in Parkinson's Disease

Parkinson's Disease (PD) is the second most common neurodegenerative disorder, and has dramatic consequences on patients' life. Nowadays, motor symptoms can be reasonably well-controlled thanks to dopaminergic medication and deep brain stimulation. But other symptoms, as well as side-effects associated with the treatments, still have no satisfactory therapeutic option. This work focuses on one of these side-effects, impulsivity, which can be manifest in the form of Impulse Control Disorders (ICDs; pathological gambling, hypersexuality, compulsive eating and compulsive shopping) induced by dopaminergic medication, or in the form of inhibitory control dysfunctions following subthalamic nucleus deep brain stimulation (STN-DBS).

A thorough assessment of the state of the art returns that the nature and neuro-functional bases of the dysfunctions contributing to these forms of impulsivity are unclear, which limits therapeutic progress. To tackle this issue, we rely on 1) the psychological modeling of the cognitive processes of interest (in particular, response inhibition mechanisms), 2) behavioral tasks designed to target precisely these processes, and 3) electroencephalography (EEG) and advanced signal processing techniques (time-frequency analyses performed directly in the source space). Indeed, combining these tools can substantially increase our discriminative power regarding the neurocognitive mechanisms involved.

In the **first Chapter**, we provide evidence against the leading hypothesis in the field, which posits that ICDs only imply dysfunctions of motivation, decision-making and reward processing. Indeed, in a systematic review of neuroimaging studies, we demonstrate various abnormalities beyond the mesocorticolimbic reward circuit. We also argue that the field needs a stronger neurocognitive footing. Then, we test the neglected hypothesis of inhibitory control dysfunctions in PD-ICDs. In a first experimental study, we show that ICDs are associated with abnormal resting-state activity within frequency bands and cortical regions supporting response inhibition. In a second study, we show that patients with ICDs are more impulsive in a Go/NoGo task, and show decreased pre-stimulus beta oscillatory activity in the precuneus and the supplementary motor area, pinpointing dysfunction of proactive inhibitory control.

In the **second Chapter**, we explore the neurophysiological mechanisms that contribute to STN-DBS effects on inhibitory control. Indeed, these effects are relevant for clinical outcome, as they can contribute to akinesia improvement, but also to increased impulsivity. The third experimental study tests the hypothesis that STN-DBS effects on inhibitory control may entail a direct modulation of the

supplementary motor cortex activity due to antidromic activation. We show that STN-DBS has a clear effect on inhibitory control, which is visible at both the level of behavior and electrophysiological activity of the supplementary motor cortex in a Go/NoGo task. Importantly, we show that this effect depends on the strength of the structural connectivity between the stimulated area of the STN and the supplementary motor cortex. We propose that STN-DBS impacts inhibitory performance by directly disrupting inhibitory control at the cortical level, rather than the relay of inhibitory signals through the STN.

In sum, this work unravels the diverse neuro-functional bases contributing to impulsivity disorders in PD. Their identification paves the way for exploring targeted therapeutic options.

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Préambule

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Abréviations

BOLD Blood-Oxygen-Level-Dependent

CMS Cortex Moteur Supplémentaire

EEG Electroencéphalographie

GPe Globus Pallidus pars externa

GPi Globus Pallidus pars interna

IFG Gyrus Frontal Inférieur

IRMf Imagerie par Résonnance Magnétique Fonctionnelle

MEG Magnétoencéphalographie

MP Maladie de Parkinson

NA Noradrénaline

NST Noyau Sous-Thalamique

Pré-SMA Aire Motrice Pré-supplémentaire

SCP Stimulation cérébrale profonde

SMA Aire Motrice Supplémentaire

SNc Substance Noire Pars compacta

SNr Substance Noire Pars reticulata

TCIs Troubles du Contrôle des Impulsions

TR Temps de Réaction

VTA Volume de Tissu Activé

Introduction

1.1 La Maladie de Parkinson

1.1.1 Enjeux sociétaux

La maladie de Parkinson (MP) est la deuxième maladie neurodégénérative la plus répandue après la maladie d'Alzheimer. En France, selon le dernier rapport de Santé publique France (Moisan et al., 2018), plus de 165 000 personnes étaient traitées pour une MP en 2015. Plus précisément, selon ce rapport, cette maladie concerne près d'une personne de plus de 60 ans sur 100, avec une prévalence de 9,25 pour 1000 pour cette catégorie d'âge. Les hommes sont 1,5 fois plus touchés que les femmes.

L'âge constitue le principal facteur de risque de la maladie : la prévalence passe ainsi d'un pour 1000 chez les personnes âgées de 50 à 59 ans à 19 pour 1000 chez celles âgées de 80 à 89 ans (Moisan et al., 2018). Ces données françaises sont proches de celles rapportées par une méta-analyse incluant 47 études réalisées partout dans le monde (Pringsheim et al., 2014). Par conséquent, il est estimé que le vieillissement de la population devrait conduire à une augmentation de 65% du nombre de personnes atteintes de MP entre 2010 et 2030 en France, pour atteindre 260 000 personnes (Wanneveich et al., 2018). Une étude portant sur 15 pays parmi les plus peuplés du monde conclut quant à elle que le nombre d'individus âgés de plus de 50 ans et atteints de MP devrait doubler entre 2005 et 2030 pour cette même raison (Dorsey et al., 2007). De plus, une augmentation de l'incidence de la maladie liée à d'autres facteurs que le vieillissement de la population est également possible (Dorsey et al., 2018; Savica et al., 2016).

Les conséquences de cette maladie sont considérables pour la personne atteinte. En effet, elle entraîne une diminution de l'espérance de vie (Hoogland et al., 2019; Macleod et al., 2014; Poortvliet et al., 2021) ainsi que de la qualité de vie des patients (Candel-Parra et al., 2021; Den Oudsten et al., 2007; Zhao et al., 2021). Elle entraîne également une invalidité importante et une diminution de l'autonomie, et donc une charge importante pour leurs proches (Mosley et al., 2017). Enfin, la MP représente un coût économique important pour la société. En France, le coût moyen pour l'assurance maladie a été estimé à 5827€ par patient et par année (Lajugie et al., 2005). Cependant, des coûts non-médicaux ou indirects (liés par exemple à une retraite anticipée ou des absences professionnelles) s'ajoutent à ces coûts médicaux. Dans une étude européenne, les coûts non-médicaux et indirects représentaient la moitié des coûts totaux, estimés à 11 153€ par patient et par année (Olesen et al., 2012).

Ainsi, du fait de sa prévalence et de ses conséquences pour la personne atteinte et la société, mieux comprendre et prendre en charge la MP est un enjeu important.

1.1.2 Etiologie et pathologie

Il existe des formes génétiques de la MP, dites monogéniques, car causées par la présence d'un seul variant génétique (Brice, 2005; Hernandez et al., 2016). Ces formes génétiques ne représentent néanmoins qu'une minorité des cas de MP, et les causes de la maladie sont inconnues dans une majorité de cas. On parle alors de MP idiopathique. Dans ces cas, la maladie est le résultat d'une combinaison ou interaction de facteurs de prédisposition génétique et de facteurs environnementaux (Simon et al., 2020). De nombreux variants génétiques liés à une augmentation du risque de MP ont été identifiés, notamment dans des études d'association pangénomique (Lill et al., 2012; Nalls et al., 2014). Cependant, l'augmentation de risque conférée par chaque variant est très faible, bien que ces effets soient cumulatifs (Nalls et al., 2014). Ainsi, il est généralement admis que la plus grande partie de la variabilité du risque de développer la maladie est liée à des facteurs environnementaux plutôt que génétiques (Goldman, 2014; Goldman et al., 2019; Hernandez et al., 2016; Simon et al., 2020). Le facteur de risque environnemental le plus connu est l'exposition à des substances toxiques telles que les pesticides (dans le cadre d'une activité professionnelle agricole ou de la vie en milieu rural), les solvants chlorés, certains métaux ou la pollution atmosphérique. Le tabagisme, la consommation de caféine, l'activité physique ou la consommation d'un régime riche en fruits et légumes seraient à l'inverse des exemples de facteurs protecteurs contre la maladie (Bellou et al., 2016; Goldman, 2014; Palacios et al., 2012; Pezzoli and Cereda, 2013; Ritz et al., 2007; Simon et al., 2020).

La caractéristique pathologique majeure de la maladie est la dégénérescence des neurones dopaminergiques de la substance noire, associée à la présence de corps de Lewy (Dickson et al., 2009). Les corps de Lewy sont des inclusions cytoplasmiques constituées en majeure partie d'agrégats insolubles d'alpha-synucléine ayant pris une mauvaise conformation. Cette protéine est normalement présente sous forme soluble à l'élément présynaptique (Wong and Krainc, 2017). Cependant, il est maintenant clair que le processus de neurodégénérescence n'est pas limité à la substance noire, ni aux neurones dopaminergiques. Un modèle très connu proposé par Braak et al. (2004) décrit une progression par stades (Figure 1). Selon ce modèle, la neurodégénérescence serait d'abord confinée au bulbe olfactif ainsi qu'à des régions du pont et de la moelle allongée. Elle progresserait ensuite vers le mésencéphale et en particulier la substance noire, marquant le début des symptômes moteurs de la maladie, avant de s'étendre au cortex paralimbique et au néocortex lors des stades les plus avancés (Braak et al., 2004). Ainsi, la maladie touche d'autres régions cérébrales (et même d'autres parties du système nerveux, notamment autonome) et d'autres systèmes de neurotransmission (Jellinger, 1991;

Langston, 2006; Lim et al., 2009), dont les systèmes sérotoninergique et noradrénergique (Delaville et al., 2011; Fornai et al., 2007; Politis and Niccolini, 2015). Ces derniers seraient même atteints avant le système dopaminergique, avec une atteinte précoce des noyaux du Raphe inférieurs et du locus coeruleus (Braak et al., 2004).

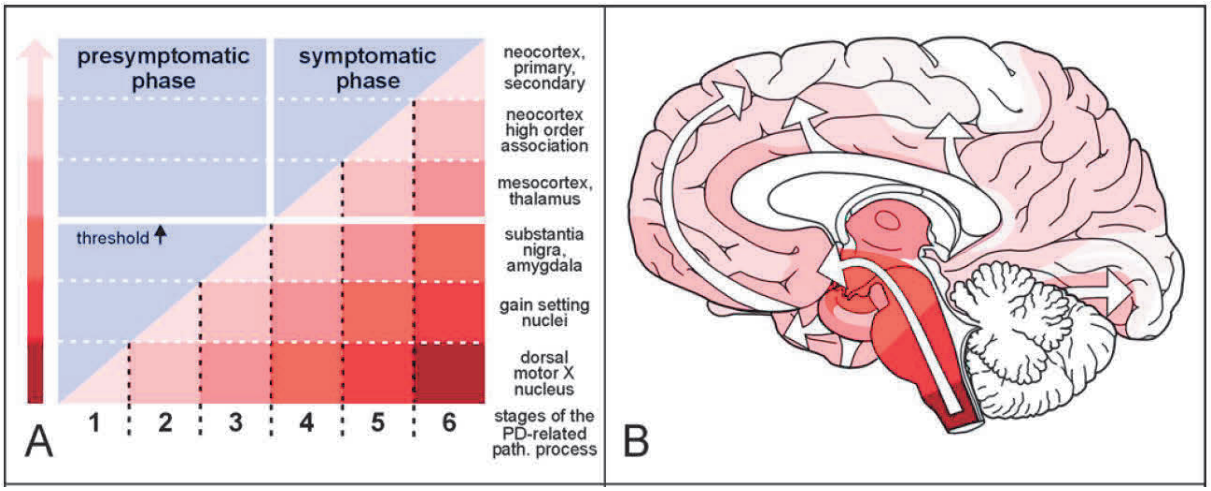

Figure 1 : **Modèle des stades de Braak.** Le processus pathologique, décrit en six stades par Braak et al. (2004), suit une progression ascendante depuis des régions du tronc cérébral jusqu'au cortex (voir le texte principal). L'atteinte de la substance noire marque le début de la phase symptomatique de la maladie. Figure tirée de Braak et al., 2004.

Les mécanismes de pathogenèse menant à cette neurodégénérescence sont multiples, complexes et interdépendants. Ils incluent le changement de conformation et l'agrégation de l'alpha-synucléine, des dysfonctions des mécanismes d'autophagie, du réticulum endoplasmique, des mitochondries, une altération de l'homéostasie calcique, et des mécanismes de neuro-inflammation (Bose and Beal, 2016; Brundin and Melki, 2017; Dias et al., 2013; Michel et al., 2016; Ransohoff, 2016; Surmeier et al., 2017; Wong and Krainc, 2017).

1.1.3 Symptômes

La MP est caractérisée par une triade de symptômes moteurs caractéristique : la bradykinésie, les tremblements, et la rigidité. L'identification de bradykinésie associée aux tremblements, à la rigidité, ou à ces deux symptômes, constitue la base du diagnostic de MP (Postuma et al., 2015). La bradykinésie est définie par une lenteur du mouvement et une diminution de l'amplitude ou de la vitesse de celui-ci au cours de son déroulement. Le tremblement caractéristique de la MP est un tremblement des membres présent au repos. Enfin, la rigidité se traduit par une résistance au mouvement passif observable au niveau des articulations des membres et du cou (Postuma et al., 2015). Il est admis que ces symptômes découlent de changements fonctionnels dans les boucles cortico-basales motrices, dus au déficit dopaminergique dans le striatum provoqué par la

dégénérescence des neurones dopaminergiques de la substance noire pars compacta (voir pour revue DeLong and Wichmann, 2009; Galvan and Wichmann, 2008; McGregor and Nelson, 2019; Rodriguez-Oroz et al., 2009; Wichmann, 2019). Plus précisément, un modèle classique explique ces symptômes (et en particulier la bradykinésie) par des changements dans les taux de décharge des neurones des différentes structures des ganglions de la base, qui causeraient un déséquilibre entre les voies directe et indirecte (Figure 2). L'influence inhibitrice des ganglions de la base sur le thalamus et le cortex serait ainsi renforcée, avec pour conséquence une suppression du mouvement (Albin et al., 1989; DeLong, 1990). Mais ce modèle reste trop simple et échoue à expliquer certaines observations cliniques (Obeso et al., 2008; Rodriguez-Oroz et al., 2009). Des modèles plus récents soulignent l'importance des altérations des patterns d'activité dans les boucles cortico-basales, plutôt que des seuls taux de décharge (Nambu et al., 2015). Ces altérations incluraient une augmentation de l'activité de type burst, ainsi que des activités oscillatoires et une synchronisation anormales, qui compromettraient le traitement normal de l'information au sein de ces boucles (Hammond et al., 2007; Little and Brown, 2014; McGregor and Nelson, 2019; Oswal et al., 2013; Stein and Bar-Gad, 2013; Wichmann, 2019).

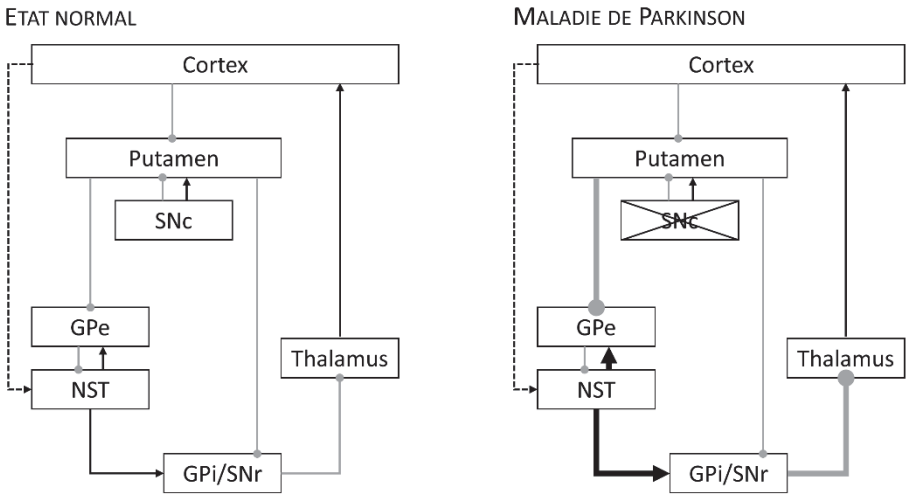

Figure 2 : Modèle classique des boucles cortico-basales motrices et leur altération dans la MP. Selon ce modèle, les aires corticales motrices projettent sur le putamen. La voie directe relie directement le putamen au globus pallidus pars interna et à la substance noire pars reticulata (GPi/SNr). La voie indirecte débute dans le putamen, puis passe par le globus pallidus pars externa (GPe), le noyau sous-thalamique (NST) et atteint enfin le GPi/SNr. La dopamine de la substance noire pars compacta (SNc) a un effet facilitateur sur les neurones du putamen appartenant à la voie directe, et un effet inhibiteur sur les neurones du putamen appartenant à la voie indirecte, en raison de la présence de récepteurs dopaminergiques de la famille D1 et D2, respectivement. Ainsi, la voie directe a un effet facilitateur du mouvement, en levant l'inhibition exercée sur le thalamus et le cortex par le GPi/SNr. A l'inverse, la voie indirecte a un effet suppresseur sur le mouvement, en augmentant cette influence inhibitrice. Dans la maladie de Parkinson, le déficit dopaminergique cause une augmentation de l'activité de la voie indirecte, et une diminution de l'activité de la voie directe. Cela entraine une augmentation de l'influence inhibitrice du GPi/SNr sur le thalamus et le cortex, ce qui entrave le mouvement et est à l'origine des symptômes moteurs (Albin et al., 1989; DeLong, 1990). Ce modèle n'inclut pas la contribution de la voie hyperdirecte (reliant le cortex au NST, représentée en pointillés) à la fonction des ganglions de la base. Celle-ci n'a été mise en avant que plus tard (Nambu et al., 2002). Les flèches noires représentent des connections excitatrices, et les flèches grises des connections inhibitrices. Figure adaptée de Rodriguez-Oroz et al., 2009.

Cependant, comme nous l'avons vu, la dégénérescence n'est pas confinée à la substance noire pars compacta, mais concerne différents systèmes. De nombreux autres symptômes de la MP, dits « non-moteurs » par opposition à la triade de symptômes moteurs caractéristique, sont associés à ces atteintes (Langston, 2006; Schapira et al., 2017; Sung and Nicholas, 2013). Ils incluent des symptômes de dysautonomie (troubles gastro-intestinaux, génito-urinaires et cardiovasculaires), des troubles du sommeil, de la fatigue, de la douleur et des troubles olfactifs, ainsi que des troubles de l'humeur (dépression et anxiété) et des troubles cognitifs pouvant aller jusqu'à la démence (Chaudhuri and Odin, 2010; Schapira et al., 2017; Weintraub and Burn, 2011). Pourtant, la prise de conscience de l'importance de ces symptômes est récente, la MP ayant longtemps été considérée comme un trouble neurologique du mouvement avant tout (Langston, 2006). Il est maintenant clair que ces symptômes sont courants (la quasi-totalité des patients rapporte au moins un symptôme non-moteur, et la plupart en rapportent plusieurs, Barone et al., 2009; Martinez-Martin et al., 2007) et qu'ils sont présents à tous les stades de la maladie, certains apparaissant même avant les symptômes moteurs caractéristiques (Lang, 2011; Pont-Sunyer et al., 2015). De plus, ces symptômes sont une source importante de diminution de la qualité de vie (Antonini et al., 2012; Barone et al., 2009, 2017; Martinez-Martin, 2011).

Enfin, il faut noter que la MP est caractérisée par une forte hétérogénéité clinique. D'abord, les patients peuvent présenter différentes combinaisons de symptômes. Par exemple, on distingue souvent les patients dont le symptôme moteur dominant est le tremblement de ceux chez qui ce sont plutôt la bradykinésie et la rigidité qui prédominent. Les symptômes non-moteurs (et en particulier la détérioration cognitive) peuvent également être plus ou moins présents. Par ailleurs, l'âge de début de la maladie ainsi que sa vitesse de progression sont également variables (Foltynie et al., 2002; Greenland et al., 2019; Marras and Lang, 2013; Merola et al., 2020).

1.1.4 Traitements et enjeux actuels de prise en charge de la MP

Les traitements proposés pour la MP sont symptomatiques. A ce jour, il n'existe pas de traitement permettant de ralentir, stopper ou inverser le cours de la maladie (Foltynie and Langston, 2018). Par ailleurs, les traitements sont dirigés contre les symptômes moteurs en priorité, tandis que la prise en charge des symptômes non-moteurs et non-dopaminergiques a longtemps été reléguée au second plan (Oertel and Schulz, 2016). Par conséquent, peu d'options thérapeutiques sont disponibles pour certains de ces symptômes, et davantage de recherches sont nécessaires (Seppi et al., 2019).

Les traitements dopaminergiques, visant l'amélioration des symptômes moteurs, constituent la base du traitement de la MP (Fox et al., 2018; Oertel and Schulz, 2016). La L-dopa, un précurseur de la dopamine, est le traitement le plus efficace et le plus utilisé. En effet, la grande majorité des patients parkinsoniens ont une réponse positive à la L-dopa ; cela constitue même un critère supportant le

diagnostic de MP (Postuma et al., 2015). Cependant, le traitement par L-dopa soulève un problème majeur. A long terme, et après une période initiale où il permet de contrôler les symptômes de façon satisfaisante, ce traitement est responsable de l'installation de complications, c'est-à-dire des fluctuations et des dyskinésies (Aquino and Fox, 2015; Fox and Lang, 2008). Les fluctuations consistent en des variations dans l'intensité des symptômes moteurs[1] au cours de la journée, avec la plupart du temps des périodes dites « On » autour des pics d'effet des doses de L-dopa, et des périodes dites « Off » entre ces pics. Les dyskinésies consistent en des mouvements involontaires et gênants, principalement des membres ou de la région cranio-cervicale, généralement présents au pic de la réponse à la L-dopa (Aquino and Fox, 2015). Ces complications motrices affectent la majorité des patients au cours de leur traitement par L-dopa (Fox and Lang, 2008): elles concerneraient déjà 40% des patients après 4 à 6 années de traitement (Ahlskog and Muenter, 2001). Les complications seraient dues à une stimulation pulsatile des récepteurs dopaminergiques du striatum, elle-même s'expliquant par la courte demi-vie de la L-dopa, et par la dégénérescence des neurones et récepteurs dopaminergiques de la voie nigro-striée. En effet, cette dégénérescence entraîne une perte de la capacité à stocker la dopamine et donc à compenser les fluctuations du niveau plasmatique de L-dopa dues à la courte demi-vie de cet agent dopaminergique (Calandrella and Antonini, 2012; Nutt et al., 2000). Ainsi, pour traiter ces complications, des stratégies visant à rendre la stimulation des récepteurs dopaminergiques du striatum plus continue vont être mises en place (Fox et al., 2018; Oertel and Schulz, 2016). Parmi celles-ci, on peut citer tout d'abord le fait de fractionner les doses de L-dopa. Une autre stratégie vise à prolonger l'action de la L-dopa, soit en utilisant des formules à libération prolongée, soit grâce à des inhibiteurs des enzymes dégradant la L-dopa ou la dopamine (inhibiteurs de la monoamine oxydase B ou de la catechol-O-methyltransférase). Il est aussi fréquent de complémenter le traitement par L-dopa par des agonistes dopaminergiques (c'est-à-dire des agents pharmacologiques activant directement les récepteurs dopaminergiques), dont la demi-vie est bien plus longue que celle de la L-dopa. Par ailleurs, l'utilisation des agonistes dopaminergiques en monothérapie en début de maladie, dans le but de retarder la prise de L-dopa et l'apparition des complications motrices, a été très populaire dans les années 1990 et 2000 (Antonini et al., 2009; Calandrella and Antonini, 2012; Olanow et al., 2000). Cependant, des travaux plus récents démontrent que cette stratégie ne modifie pas le risque de complications motrices à long terme. En effet, les agonistes dopaminergiques procurant un soulagement symptomatique moins important, l'ajout de L-dopa est nécessaire tôt ou tard chez tous les patients. De plus, le risque de complications dépendrait de la durée de la maladie et du processus de neuro-dégénérescence, ainsi que des doses de L-dopa

[1] Il faut noter que des fluctuations des symptômes non-moteurs peuvent également être observées (Franke and Storch, 2017; Witjas et al., 2002).

utilisées, plutôt que de la durée du traitement par L-dopa (Cilia et al., 2014; Fox and Lang, 2014; Oertel and Schulz, 2016). Par ailleurs, le profil d'effets indésirables des agonistes dopaminergiques est moins favorable que celui de la L-dopa, ce qui limite leur utilisation. Ces effets indésirables incluent une somnolence diurne excessive, des œdèmes, mais aussi un risque de psychose ou de troubles du contrôle des impulsions (TCIs) tels que le jeu pathologique, l'hypersexualité, l'alimentation compulsive ou l'achat compulsif (Antonini et al., 2009; Cilia and van Eimeren, 2011; Grall-Bronnec et al., 2018). Ces derniers sont particulièrement préoccupants car ils concernent un grand nombre de patients au cours de la maladie (13,5 à 28% des patients seraient concernés, Antonini et al., 2017; Weintraub et al., 2010 ; avec une prévalence cumulée sur 5 ans de l'ordre de 46%, Corvol et al., 2018). De plus, les conséquences des TCIs peuvent être dévastatrices sur le plan financier, psychologique, social et familial (voir par exemple Dodd et al., 2005). Leur occurrence est liée à la prise d'agonistes dopaminergiques plutôt qu'à la prise de L-dopa (Grall-Bronnec et al., 2018; Napier et al., 2020; Weintraub et al., 2010) probablement en raison de la haute affinité des agonistes pour les récepteurs dopaminergiques D2/D3 (Napier and Persons, 2018). En l'absence de preuves suffisantes en faveur d'autres options thérapeutiques (Tanwani et al., 2015), la seule stratégie de gestion de ces troubles consiste en l'adaptation du traitement dopaminergique, et notamment en la diminution ou la suppression des agonistes (Grassi et al., 2021; Samuel et al., 2015). Cependant, cette stratégie n'est pas satisfaisante, voire parfois même difficile à appliquer, car elle expose le patient à une recrudescence des symptômes moteurs ainsi qu'à un syndrome de sevrage (Barbosa et al., 2019; Lee et al., 2019).

La stimulation cérébrale profonde (SCP) est une autre stratégie de traitement proposée dans la MP. Elle consiste à stimuler de façon chronique le noyau sous-thalamique (NST) ou le globus pallidus pars interna (GPi)[2] via une électrode de stimulation intracérébrale, elle-même reliée à un neurostimulateur implanté sous la clavicule, dans le but de moduler l'activité pathologique des boucles cortico-sous-corticales (Okun, 2014) ; figure 3). Les mécanismes d'action de ce type de traitement ne sont cependant pas totalement élucidés. La stimulation bilatérale du NST (SCP-NST) est largement plus utilisée que celle du GPi, malgré l'absence de preuves de sa supériorité en termes d'effets sur les symptômes moteurs et la qualité de vie (Follett et al., 2010; Weaver et al., 2005).

[2] Ces cibles sont les plus courantes pour la MP, bien que d'autres cibles aient été proposées pour certains symptômes spécifiques, telles que le noyau ventral intermédiaire du thalamus pour les tremblements lorsqu'ils dominent le tableau clinique, ou le noyau pédonculopontin pour les symptômes axiaux dopa-résistants (Dallapiazza et al., 2018).

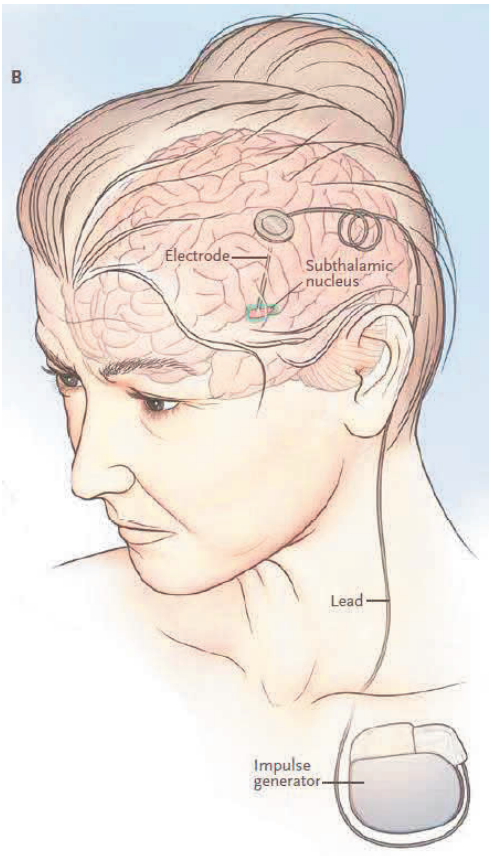

Figure 3 : Positionnement du matériel de stimulation cérébrale profonde. Figure tirée de Okun et al., 2014.

Invasif et donc non sans risques, ce traitement est proposé uniquement lorsque les symptômes moteurs ne peuvent être traités de façon satisfaisante par les traitements pharmacologiques. Plus précisément, les deux indications majeures pour la SCP sont la présence de complications motrices ou d'un tremblement qui résisteraient à un traitement dopaminergique optimisé (Defer et al., 1999; Hartmann et al., 2019). Au-delà de ces critères, tous les patients ne peuvent pas bénéficier de la SCP : d'autres critères de sélection (tels qu'une réponse suffisamment importante aux traitements dopaminergiques) ou de contre-indication (tels que la présence d'une démence) sont également pris en compte afin de réaliser une analyse du rapport risque-bénéfice (Dallapiazza et al., 2018; Defer et al., 1999; Hartmann et al., 2019). De nombreuses études ont démontré l'efficacité de la SCP-NST, qui améliore les symptômes moteurs, les complications et la qualité de vie des patients à court terme mais aussi à long terme malgré la progression naturelle de la maladie, et est supérieure au traitement médicamenteux de référence chez les patients éligibles (Bove et al., 2021; Hamani et al., 2005; Kleiner-Fisman et al., 2006; Limousin and Foltynie, 2019; Williams et al., 2010). En conséquence, alors que la SCP était traditionnellement vue comme un traitement de la dernière chance, envisageable uniquement lorsque les complications motrices sont installées depuis plusieurs années, sévères, et une fois que toutes les solutions pharmacologiques ont été envisagées, certains auteurs ont proposé d'envisager ce traitement chez des patients plus jeunes, souffrant de complications depuis moins longtemps, dans le but de préserver leur qualité de vie (Artusi et al., 2020; Schuepbach et al., 2013). Cependant, sans surprise compte tenu des nombreuses fonctions non-motrices du NST (Baunez, 2016; Baunez and Lardeux, 2011), des effets cognitifs et neuropsychiatriques négatifs consécutifs à la SCP-NST sont parfois rapportés. En particulier, elle induirait des changements subtils et spécifiques à certains domaines cognitifs, notamment la fluence verbale et les fonctions exécutives dont le contrôle inhibiteur (Cernera et al., 2019; Parsons et al., 2006; Volkmann et al., 2010; Witt et al., 2013), et favoriserait plus généralement un comportement impulsif (Jahanshahi, 2013; Lo Buono et al., 2021; Mosley et al., 2019a; Scherrer et al., 2020; Zavala et al., 2015). Les facteurs expliquant l'occurrence de ces comportements impulsifs restent largement inconnus.

En conclusion, en l'attente d'un traitement pouvant modifier la progression de la maladie, les enjeux actuels de prise en charge de la MP concernent plutôt les limites des traitements disponibles. D'une part, de nouvelles solutions thérapeutiques doivent être trouvées pour certains symptômes (notamment non-moteurs) non-remédiés par les traitements dopaminergiques. D'autre part, les complications liées au traitement par L-dopa complexifient la prise en charge, et les solutions manquent pour éviter ou supprimer certains effets indésirables des traitements proposés en réponse à ces complications. Ce travail de thèse s'intéresse à un de ces effets indésirables les plus notables, l'impulsivité, qu'elle soit caractéristique des TCIs induits par le traitement dopaminergique, ou consécutive à la SCP-NST. En effet, mieux comprendre les bases neuro-fonctionnelles de l'impulsivité dans la MP pourrait permettre de la prévenir ou de proposer de nouvelles solutions thérapeutiques.

Résumé : *La MP est une maladie relativement fréquente chez les personnes de plus de 60 ans et lourde de conséquences. Cette maladie de causes inconnues est caractérisée par la dégénérescence des neurones dopaminergiques de la substance noire pars compacta ainsi que par ses symptômes moteurs. Cependant, les altérations concernent également d'autres systèmes de neurotransmission et d'autres régions du système nerveux, donnant lieu à des symptômes non-moteurs et non-dopaminergiques, tout aussi préoccupants. Les traitements actuels sont symptomatiques et centrés en priorité sur les symptômes moteurs. A l'inverse, certains symptômes non-moteurs ou non-dopaminergiques, ainsi que certains effets indésirables liés aux traitements proposés pour les symptômes moteurs, restent sans solution thérapeutique satisfaisante. C'est le cas notamment de l'impulsivité -qu'elle soit caractéristique des TCIs induits par la médication dopaminergique ou consécutive à la SCP-NST- qui fait l'objet de ce travail de thèse. Mieux comprendre l'impulsivité dans la MP pourrait permettre de la prévenir ou de proposer de nouvelles solutions thérapeutiques.*

1.2 L'impulsivité : un concept aux multiples facettes

1.2.1 Modélisation psychologique

1.2.1.1 De la difficulté à définir l'impulsivité

Bien que chacun d'entre nous se représente ce que peut être un comportement impulsif, la question de comment définir l'impulsivité est tout sauf triviale et fait débat en psychologie et neurosciences depuis de nombreuses années (Arce and Santisteban, 2006; Evenden, 1999; Nigg, 2017). Une définition généralement acceptée propose que l'impulsivité regrouperait des actions peu réfléchies ou préparées, exprimées de façon prématurée, exagérément risquées ou inadaptées à la situation, qui induisent souvent des conséquences néfastes (« actions that appear poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences », Daruna and Barnes, 1993, p.23). Un examen attentif de cette définition générale nous permet d'observer qu'elle fait appel à différents concepts tels que la prise de risque, le manque de réflexion, l'incapacité à anticiper les conséquences de ses actions, et la désinhibition. D'autres définitions font appel à d'autres concepts, comme par exemple la recherche de sensations fortes (Whiteside and Lynam, 2001). Ainsi, l'impulsivité est un concept multidimensionnel (Arce and Santisteban, 2006; Bechara et al., 2000; Dalley and Robbins, 2017; Dalley et al., 2011; Evenden, 1999; Fineberg et al., 2014; Voon and Dalley, 2016). De nombreux travaux se sont attachés à la fractionner en différents domaines ou composantes, aussi bien dans le champ de l'étude de la personnalité en psychologie que dans celui des neurosciences. Concernant les neurosciences, une classification largement acceptée distingue l'impulsivité d'action (aussi appelée impulsivité motrice), liée aux processus d'inhibition de réponse, et l'impulsivité décisionnelle (parfois également appelée de choix ou cognitive), plutôt liée aux processus de prise de décision, de motivation et de récompense (Bari and Robbins, 2013; Bechara et al., 2000; Dalley and Robbins, 2017; Dalley et al., 2011; Hamilton et al., 2015a, 2015b; Nigg, 2017; Voon and Dalley, 2016).

1.2.1.2 L'impulsivité d'action : les processus d'inhibition de réponse

L'impulsivité d'action, aussi appelée impulsivité motrice, fait référence à une forme d'impulsivité liée à un dysfonctionnement des mécanismes d'inhibition de réponse. L'inhibition de réponse peut être définie comme la fonction cognitive permettant de supprimer une réponse motrice indésirable ou inadaptée à la situation. L'impulsivité d'action est la plupart du temps mesurée grâce aux tâches classiques de Go/NoGo ou de Signal Stop (Bari and Robbins, 2013; Dalley and Robbins, 2017; Hamilton et al., 2015b ; Figure 4). Certains auteurs placent l'impulsivité dite d'attente (« waiting impulsivity »), opérationnalisée par des réponses prématurées dans des paradigmes de temps de réaction sériels ou de performance continue, comme relevant de l'impulsivité d'action (Bari and

Robbins, 2013; Dalley and Robbins, 2017; Hamilton et al., 2015b), tandis que d'autres la considèrent comme une forme d'impulsivité à part (Voon, 2014). Il semble toutefois clair que cette forme d'impulsivité relève elle aussi d'un dysfonctionnement des mécanismes d'inhibition de réponse.

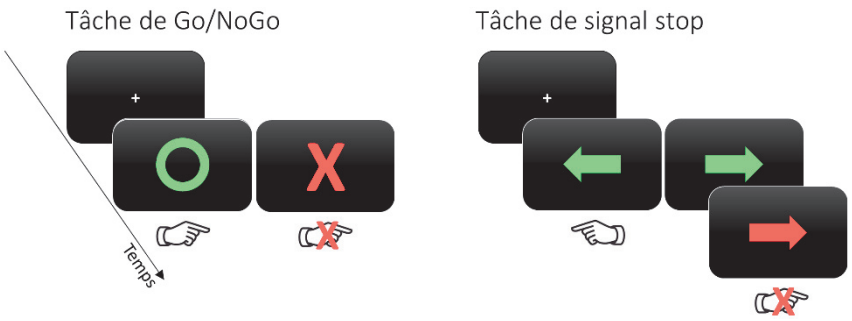

Figure 4 : Tâches classiques évaluant l'inhibition de réponse. Dans la tâche de Go/NoGo, il est demandé aux sujets de répondre le plus vite possible aux stimuli Go (ici, un cercle), tout en évitant de répondre aux stimuli NoGo (ici, une croix). La mesure principale est le taux d'erreurs de commissions, c'est-à-dire de réponses erronées au stimulus NoGo. La proportion d'essais NoGo est variable, et susceptible d'influencer la prépotence de la réponse au Go, et donc la demande placée sur l'inhibition de réponse (bien que ça ne soit pas le seul facteur, Wessel, 2018). Le nombre de stimuli associés au Go peut varier, nécessitant ou pas un choix entre plusieurs réponses motrices. Toutes ces variations placent une demande plus ou moins importante sur les processus annexes, dont la sélection de réponse, l'attention et la mémoire de travail, ce qui peut obscurcir l'interprétation du comportement ou des résultats de neuro-imagerie associés (Criaud and Boulinguez, 2013). Dans la tâche de signal stop, il est demandé au sujet de répondre le plus rapidement possible aux stimuli Go (ici, les flèches vertes), tout en évitant de répondre si un signal stop est présenté (visuel ou auditif ; ici la flèche rouge). Ce signal stop est présenté après le stimulus Go suivant un délai variable (appelé « stop signal delay », ou « SSD »), ce qui fait que la réponse au stimulus Go est alors plus ou moins initiée, et donc plus ou moins difficile à stopper. La procédure classique consiste à ajuster progressivement ce délai, de manière à arriver à un délai où le participant sera capable de stopper sa réponse dans 50% des cas. La mesure principale d'inhibition, le temps de réaction au signal stop (« SSRT »), représente le temps nécessaire pour stopper une réponse, et peut être obtenue en soustrayant le délai correspondant aux 50% de réussite au temps de réaction moyen au Go (bien qu'une méthode de calcul plus robuste soit maintenant recommandée, Verbruggen and Aron, 2019). Il est quasi-systématique dans cette tâche d'utiliser deux stimuli Go, associés à deux réponses motrices distinctes (par exemple, une réponse de l'index pour une flèche gauche, et du majeur pour une flèche droite). La proportion d'essais stop est variable. Il est généralement admis que la principale différence entre ces tâches réside dans le fait que la tâche de Go/NoGo demande de retenir une action avant son initiation, alors que la tâche de stop requiert d'arrêter une action déjà en cours.

Il existe de nombreux modèles cognitifs de l'inhibition de réponse, proposant différents types de mécanismes, dont la présentation exhaustive dépasserait le cadre de ce travail de thèse. Classiquement, on distingue les mécanismes de « stopping », permettant d'arrêter une action déjà initiée, comme il faut le faire dans la tâche de Signal Stop, et les mécanismes permettant de retenir une action avant son initiation, comme il faut le faire dans le Go/NoGo (Bari and Robbins, 2013; Eagle et al., 2008a; Schachar et al., 2007; Swick et al., 2011). Cependant, une classification plus riche des

mécanismes d'inhibition de réponse peut être établie selon les dimensions de sélectivité[3], et de temporalité (proactif versus réactif) (Aron, 2011; Meyer and Bucci, 2016). Le modèle le plus connu, le « horse race model », suggère que l'inhibition est un mécanisme réactif et sélectif. Selon ce modèle, l'inhibition serait déclenchée en réaction au stimulus auquel il ne faut pas répondre et uniquement en réaction à celui-ci (Logan et al., 1984; Verbruggen and Logan, 2008, 2009a). D'autres modèles, dont le plus connu est le modèle « hold your horses » (Frank, 2006), proposent l'existence de mécanismes d'inhibition réactifs et non-sélectifs, ou autrement dit contextuels. Ces mécanismes seraient déclenchés automatiquement en réaction à tout stimulus dès lors que le contexte est incertain, afin d'inhiber les réponses automatiques activées par la présentation des stimuli (Albares et al., 2014; Ballanger et al., 2009a; Criaud et al., 2017; Frank, 2006; Wessel et al., 2019; Wiecki and Frank, 2013). Autrement dit, selon ces modèles, si l'on prend l'exemple d'une tâche de Go/NoGo, les mécanismes d'inhibition ne seraient pas déclenchés uniquement en réaction au stimulus NoGo, mais en réaction à tout type de stimulus (Go ou NoGo) dès lors que le sujet est placé dans un contexte d'incertitude événementielle. Enfin, des mécanismes proactifs d'inhibition, c'est-à-dire implémentés en amont de la présentation de tout stimulus, ont également été proposés. Mais il n'y a pas de consensus sur la nature exacte de ces mécanismes proactifs : ils pourraient prendre la forme d'un verrouillage anticipé des mécanismes de déclenchement du mouvement (c'est-à-dire une inhibition tonique et soutenue du système moteur implémentée en amont de la présentation du stimulus ; Boulinguez et al., 2009; Criaud et al., 2012; Di Russo et al., 2016; Jaffard et al., 2007, 2008; Soh et al., 2021), d'un réglage exécutif de la sensibilité de mécanismes réactifs d'inhibition automatique (Albares et al., 2014; Chiu and Aron, 2014), ou bien d'une simple préparation à inhiber via le recrutement anticipé (« pré-activation ») des réseaux de l'inhibition réactive sélective (Chikazoe et al., 2009; Jahfari et al., 2010; Leunissen et al., 2016; Zandbelt and Vink, 2010). Ainsi, les modèles postulant l'existence de mécanismes réactifs sélectifs, réactifs non-sélectifs et proactifs ne sont pas mutuellement exclusifs. Il est même probable que des mécanismes réactifs et proactifs se complètent, voire interagissent, afin de contrôler le comportement de façon flexible et optimale (Aron, 2011; Criaud et al., 2021; Meyer and Bucci, 2016; Mirabella, 2021).

[3] Dans la littérature, la notion de sélectivité peut faire référence d'une part à une sélectivité quant au stimulus déclenchant les mécanismes d'inhibition, mais aussi à une sélectivité quant aux effets sur le système moteur. Les deux ne vont pas forcément de pair : par exemple, les mécanismes de « stopping », qui sont sélectifs du point de vue du stimulus concerné (le stimulus auquel il ne faut pas répondre, par exemple, le signal stop), seraient plutôt non-sélectifs sur le plan des effets sur le système moteur, c'est-à-dire qu'ils entraineraient une inhibition rapide et globale de celui-ci (Aron, 2011; Aron et al., 2016; Wessel and Aron, 2017). A l'inverse, des mécanismes d'inhibition sélective de certaines réponses motrices ont été proposés (Aron, 2011; Majid et al., 2013).

Au niveau cérébral, l'inhibition de réponse est supposée reposer sur un réseau constitué de l'aire motrice pré-supplémentaire (pré-SMA), du gyrus frontal inférieur (IFG) et des ganglions de la base, dont en particulier le noyau sous-thalamique (NST), qui serait principalement latéralisé à droite (voir pour revue Aron, 2011; Aron et al., 2014; Bari and Robbins, 2013; Chambers et al., 2009; Li, 2015 ; et Isherwood et al., 2021; Simmonds et al., 2008; Swick et al., 2011; Zhang et al., 2017 pour méta-analyse des études en IRMf). Plus précisément, ces régions corticales frontales (pré-SMA et IFG) enverraient une commande inhibitrice via les ganglions de la base (en particulier, via le NST), ce qui supprimerait le signal de sortie des ganglions de la base, avec par conséquent un effet inhibiteur sur le cortex moteur primaire. Cependant, les rôles respectifs de la pré-SMA et de l'IFG restent débattus. Beaucoup d'auteurs conceptualisent l'IFG comme une région critique pour l'inhibition de réponse, qui relaierait directement la commande inhibitrice via les ganglions de la base (Aron et al., 2004, 2007, 2014; Chen et al., 2020). Mais cela est fortement débattu par d'autres auteurs qui considèrent que son rôle relève plutôt de la détection de la saillance et de l'orientation de l'attention, nécessaires à la performance d'inhibition (Criaud and Boulinguez, 2013; Duann et al., 2009; Erika-Florence et al., 2014; Hampshire et al., 2010; Li, 2015; Swick and Chatham, 2014), tandis que la pré-SMA serait à l'origine de la commande inhibitrice (Duann et al., 2009; Rae et al., 2015). Par ailleurs, il faut garder à l'esprit que les réseaux de l'inhibition de réponse ont principalement été explorés sous le prisme du modèle dominant qui la considère comme un mécanisme réactif et sélectif. Or, d'autres mécanismes d'inhibition de réponse sont susceptibles de reposer sur des réseaux partiellement différents. Le fait que les corrélats cérébraux des tâches de Go/NoGo et de Signal Stop –qui sont supposées recruter des mécanismes d'inhibition au moins en partie différents– ne soient pas identiques est un premier argument en ce sens (Raud et al., 2020; Swick et al., 2011). En particulier, bien que le manque de consensus sur la nature des mécanismes proactifs ait limité l'étude de leurs bases neurales, ils pourraient reposer sur un réseau au moins partiellement différent de celui rapporté pour les mécanismes réactifs sélectifs (Aron, 2011; van Belle et al., 2014; Criaud et al., 2017; Meyer and Bucci, 2016; Zhang and Iwaki, 2019), qui impliquerait notamment des régions fronto-pariétales médiales telles que la SMA, la pré-SMA, ainsi que le précuneus (Chen et al., 2010; Criaud et al., 2017; Jaffard et al., 2008; Stuphorn and Emeric, 2012; Lio et al., en préparation). Enfin, le rôle respectif des voies hyperdirecte et indirecte des ganglions de la base n'est pas entièrement élucidé. Il est généralement proposé que la voie hyperdirecte relaie des signaux inhibiteurs rapides, ayant des effets globaux sur le système moteur, et qu'elle soit plutôt impliquée dans les mécanismes d'inhibition réactifs (Aron and Poldrack, 2006; Aron et al., 2016; Chen et al., 2020; Wessel et al., 2016, 2019). A l'inverse, la voie indirecte permettrait de relayer des signaux proactifs, ayant éventuellement des effets sélectifs à certaines réponses motrices (Aron, 2011; Dunovan et al., 2015; Leunissen et al., 2016; Majid et al., 2013; Zandbelt and Vink, 2010).

Pour finir, de nombreux travaux soulignent le rôle important du système noradrénergique pour l'inhibition de réponse (voir pour revue Chamberlain and Robbins, 2013; Chamberlain et al., 2006a; Robbins and Arnsten, 2009). Chez le rat, l'administration systémique d'atomoxetine, un inhibiteur de la recapture de la noradrénaline (NA), est associée à une amélioration de la performance d'inhibition dans une tâche de Signal Stop (Bari et al., 2009; Robinson et al., 2008). La même association est retrouvée chez l'homme, aussi bien chez le sujet sain (Chamberlain et al., 2006b, 2009) que chez des patients souffrant d'une maladie de Parkinson (Kehagia et al., 2014; O'Callaghan et al., 2021; Rae et al., 2016; Ye et al., 2015) ou encore d'un trouble déficitaire de l'attention avec ou sans hyperactivité (Chamberlain et al., 2007).

1.2.1.3 L'impulsivité décisionnelle : les processus de récompense et de prise de décision

L'impulsivité décisionnelle fait référence à une forme d'impulsivité spécifiquement liée à la prise de décision. Plusieurs formes peuvent être distinguées. D'abord, l'impulsivité de choix fait généralement référence à une préférence pour la gratification immédiate, telle qu'évaluée par les tâches dites de « delay discounting » (Dalley et al., 2011; Hamilton et al., 2015a), et peut également inclure la prise de risque (parfois assimilée à du « probability discounting »), telle qu'évaluée par l' « Iowa Gambling Task », la « Cambridge Gambling task » ou la « Balloon Analog Risk task » (Bari and Robbins, 2013; Dalley and Robbins, 2017). Un autre aspect de l'impulsivité décisionnelle est l'impulsivité de réflexion, qui fait référence à une prise de décision trop rapide, c'est-à-dire intervenant avant que suffisamment d'information soit disponible, ou sans prendre celle-ci en compte, telle qu'évaluée dans la « Beads task » ou l' « Information Sampling task » (Dalley and Robbins, 2017; Voon and Dalley, 2016). L'impulsivité décisionnelle est donc un concept encore plus large que celui d'impulsivité d'action. Elle peut refléter des dysfonctions d'une grande variété de mécanismes cognitifs sous-jacents, c'est-à-dire des mécanismes de prise de décision, de motivation et de récompense.

Différentes étapes de la prise de décision peuvent être distinguées (voir pour revues O'Doherty et al., 2017; Rangel and Hare, 2010; Rangel et al., 2008; Sugrue et al., 2005). Tout d'abord, des valeurs sont attribuées aux différentes options. Ces valeurs, subjectives, intègrent aussi bien la motivation pour la récompense (ou la punition) que des informations comme l'état interne de l'organisme (par exemple, l'état de satiété), ou encore les coûts (effort physique, cognitif), les délais, ou les probabilités associés aux différentes options (Bailey et al., 2016; Tobler and Weber, 2013). En d'autres termes, l'estimation des valeurs peut être distordue par une sensibilité accrue à la récompense ou à la punition, ou bien par une perception faussée des coûts, des délais, ou des probabilités associés aux différentes options. La deuxième étape de la prise de décision consiste en la comparaison des valeurs afin de faire un choix et de sélectionner une action. Enfin, l'évaluation des conséquences de l'action est cruciale :

la prise de décision dépend des conséquences des actions passées. En effet, les associations entre les stimuli ou actions et les valeurs sont apprises, c'est-à-dire acquises et mises à jour par l'association entre ces actions et leurs conséquences. En ce sens, l'apprentissage par renforcement joue un rôle dans la prise de décision (Schultz, 2015).

L'ensemble de ces processus implique de nombreuses régions cérébrales, en particulier des régions du cortex préfrontal, ainsi que des régions sous-corticales, dont les ganglions de la base. Brièvement, le réseau de la récompense est constitué de l'aire tegmentale ventrale, du striatum ventral, du cortex orbitofrontal et préfrontal ventromédian, du cortex cingulaire antérieur, de l'insula antérieure et de l'amygdale (Haber and Knutson, 2010; Liu et al., 2011; Sescousse et al., 2013). La dopamine, à travers les systèmes mésolimbique et mésocorticolimbique, joue un rôle clé dans les processus de motivation et de récompense (Arias-Carrión et al., 2010; Salamone and Correa, 2012; Schultz, 2015; Schultz et al., 1997). D'autre part, les valeurs semblent principalement représentées dans le cortex préfrontal ventromédian et orbitofrontal ainsi que dans le striatum, tandis que les mécanismes de comparaison de valeurs et de choix reposeraient notamment sur le cortex préfrontal latéral et sur des aires pariétales (Bartra et al., 2013; Kable and Glimcher, 2009; Levy and Glimcher, 2012; O'Doherty et al., 2017; Peters and Büchel, 2010). Enfin, on peut noter que le système sérotoninergique semble jouer un rôle dans l'impulsivité de choix telle qu'évaluée dans les tâches dites de « delay discounting » et plus largement dans la prise de décision, bien que les mécanismes impliqués soient peu clairs (voir pour revue Homberg, 2012).

1.2.1.4 Au-delà de la dichotomie entre impulsivité décisionnelle et d'action

Il apparait clairement que les différents types d'impulsivité proposés (d'action, d'attente, de choix, de réflexion) ont été articulés autour de paradigmes fréquemment utilisés. Cependant, comme nous l'avons vu, cette classification grossière ne reflète pas la complexité et la diversité des mécanismes cognitifs sous-jacents. D'une part, il semble exister différents mécanismes d'inhibition de réponse, tous susceptibles d'induire une impulsivité d'action s'ils dysfonctionnent. D'autre part, de nombreux mécanismes concourent à la prise de décision, et sont autant de sources potentielles d'une impulsivité décisionnelle. Plus important encore, la dichotomie conceptuelle entre impulsivité d'action et décisionnelle ne rend pas compte des interactions entre les différents processus cognitifs, qui fait qu'un même mécanisme peut contribuer à différentes formes ou mesures d'impulsivité. Par exemple, le modèle du « hold your horses » propose un rôle clé pour les mécanismes d'inhibition de réponse non-sélectifs dans la sélection de réponse. Selon ce modèle, en présence de conflit entre différentes réponses possibles, un signal « NoGo » rapide et global permettrait de bloquer toutes les réponses motrices afin de laisser plus de temps pour la prise en compte de l'information disponible et permettre la sélection d'une réponse appropriée (Frank, 2006; Wessel et al., 2019; Wiecki and Frank, 2013). Ainsi,

un dysfonctionnement de ce mécanisme d'inhibition de réponse pourrait entrainer une prise de décision trop rapide et impulsive (Frank et al., 2007), y compris dans une tâche utilisée pour évaluer l'impulsivité décisionnelle. Un autre exemple est celui des interactions entre motivation pour la récompense et contrôle inhibiteur. En effet, le contrôle inhibiteur est adapté selon des signaux motivationnels (Botvinick and Braver, 2015; Braver et al., 2014; Pessoa and Engelmann, 2010); en d'autres termes, il est implémenté dès lors que son application est plus avantageuse (c'est-à-dire, plus récompensée) qu'un mode de réponse rapide et automatique. Ainsi, des comportements impulsifs apparaissant comme des déficits de contrôle inhibiteur pourraient refléter une moindre *volonté* à implémenter ce contrôle, due à des dysfonctionnements des processus motivationnels, plutôt qu'une réelle *incapacité* à appliquer ce contrôle (Cools et al., 2019). En conclusion, caractériser finement l'impulsivité nécessite de s'affranchir de la simple dichotomie entre impulsivité d'action et décisionnelle pour se placer au niveau d'analyse des processus cognitifs impliqués (Figure 5).

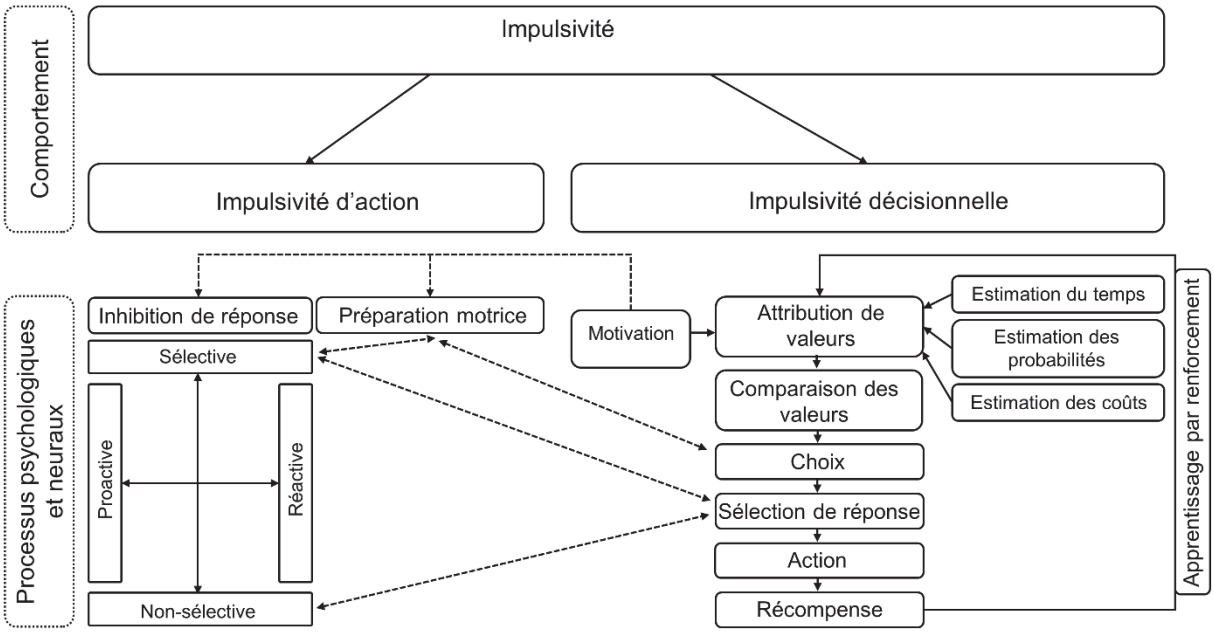

Figure 5 : L'impulsivité, un concept aux multiples facettes. En neurosciences, une distinction généralement acceptée est celle d'impulsivité d'action (liée aux processus d'inhibition de réponse) vs. impulsivité décisionnelle (liée aux processus de prise de décision, de motivation et de récompense). Cependant, cette dichotomie, articulée au niveau comportemental autour des paradigmes les plus utilisés pour mesurer l'impulsivité, ne reflète pas la complexité et la diversité des mécanismes cognitifs sous-jacents, ni les interactions entre ces différents mécanismes (flèches pointillées).

1.2.2 Implications neuropsychiatriques

Dans le domaine de la recherche en psychiatrie, les catégories diagnostiques telles que celles du Manuel diagnostique et statistique des troubles mentaux (DSM-V) sont de plus en plus critiquées. Fondées sur un consensus clinique quant à l'observation de regroupements de symptômes, plutôt que sur des connaissances relatives à la physiopathologie, elles définiraient des syndromes hétérogènes, et même se chevauchant parfois, en attestent les fréquentes comorbidités. Ces syndromes seraient ainsi très difficiles à relier à des mécanismes biologiques fondamentaux sous-jacents, ce qui freinerait également le développement de nouveaux traitements. En réponse à ces critiques, une approche différente a été proposée, selon laquelle l'identification et l'étude de dimensions neurocognitives clés d'une pathologie psychiatrique, mesurables de façon objective et moins complexe que le syndrome dans son ensemble, permettrait d'identifier les mécanismes biologiques sous-jacents -et donc potentiellement de nouvelles cibles thérapeutiques- plus aisément (voir par exemple Gottesman and Gould, 2003; Insel et al., 2010; Robbins et al., 2012). Ces dimensions neurocognitives clés pourraient par ailleurs être étudiées de façon transdiagnostique. On retrouve ces idées par exemple dans le concept d'« endophénotype neurocognitif » (Robbins et al., 2012), et dans l'initiative RDoC du National Institute for Mental Health aux Etats-Unis (Cuthbert, 2014; Cuthbert and Insel, 2013; Insel et al., 2010). Un endophénotype est en effet conceptualisé comme une caractéristique héritable, mesurable mais pas directement visible (telle qu'une mesure cognitive, ou encore anatomique, biochimique…) se situant conceptuellement entre le syndrome et son génotype. Moins complexe, il serait plus facile à relier à des gènes, permettant ainsi de faire progresser la connaissance des facteurs génétiques impliqués dans la pathologie d'intérêt (Gottesman and Gould, 2003; Walters and Owen, 2007). Mais les « endophénotypes neurocognitifs » pourraient être utilisés plus largement dans l'étude des bases biologiques de la pathologie d'intérêt, au-delà des seuls facteurs génétiques (Robbins et al., 2012). L'initiative RDoC, quant à elle, propose d'étudier différents domaines et construits cognitifs fondamentaux ainsi que les mécanismes cérébraux sous-jacents, dont le dysfonctionnement serait à l'origine des symptômes psychiatriques. Le but est d'étudier ces construits à différentes échelles, de la génétique au comportement, en passant par la physiologie, et ce à travers un continuum allant du fonctionnement normal au fonctionnement pathologique (Cuthbert, 2014; Cuthbert and Insel, 2013; Insel et al., 2010).

L'impulsivité est un concept idéal pour appliquer ce type d'approche, puisqu'elle semble être une caractéristique importante de nombreuses pathologies et troubles neuropsychiatriques tels que les troubles liés à l'abus d'alcool ou d'autres drogues, le jeu pathologique, le trouble déficitaire de l'attention avec ou sans hyperactivité, ainsi que les troubles classés comme troubles du contrôle des impulsions dans le DSM-V (Berlin and Hollander, 2014). Son utilisation comme « endophénotype

neurocognitif » présuppose cependant de distinguer ses différents sous-types (impulsivité d'action, de choix, de réflexion…), qui seraient potentiellement pertinents pour différentes pathologies (Dalley and Robbins, 2017; Fineberg et al., 2014; Robbins et al., 2012; Voon and Dalley, 2016). Par exemple, l'impulsivité décisionnelle semble particulièrement impliquée dans les troubles liés à l'abus d'alcool ou d'autres drogues, tandis que l'impulsivité d'action serait caractéristique du trouble de déficit de l'attention (Fineberg et al., 2014). Cette approche semble particulièrement prometteuse dans la mesure où des modèles animaux des principaux sous-types d'impulsivité existent et permettent d'étudier leurs bases neuropharmacologiques, et donc d'identifier des pharmacothérapies potentielles (Robbins, 2017; Winstanley, 2011). Cependant, nous avons vu que cette classification en grands types d'impulsivité ne reflète pas la complexité et la diversité des mécanismes cognitifs sous-jacents, ni leurs interactions. Ces mécanismes reposent sur des substrats neuronaux partiellement différents, qui pourraient être autant de cibles thérapeutiques potentielles. Il semble donc opportun d'aller plus loin dans le fractionnement de l'impulsivité, en identifiant précisément les mécanismes neurocognitifs impliqués dans une manifestation donnée d'impulsivité. On peut noter que ce niveau très fin d'analyse se retrouve dans le cadre proposé par l'initiative RDoC, dont plusieurs des construits ou sous-construits proposés correspondent aux processus cognitifs clés sous-tendant l'impulsivité (Brooks et al., 2017). On citera notamment dans le domaine des systèmes de valence positive, les construits et sous-construits de la sensibilité à la récompense, de l'apprentissage par renforcement, de l'évaluation des délais, du risque ou de l'effort, ou encore dans le domaine des systèmes cognitifs, le sous-construit de la sélection et de l'inhibition de réponse.

1.2.3 Considérations méthodologiques : Comment mesurer l'impulsivité ?

Si l'impulsivité est un concept multidimensionnel, il n'est pas surprenant que de nombreux instruments de mesure aient été proposés. On peut distinguer deux types d'approches, issues de traditions différentes et se plaçant à différents niveaux d'analyse : les questionnaires, issus du champ de l'étude de la personnalité, et les approches centrées sur la mesure directe du comportement, visant à évaluer des processus cognitifs précis, éventuellement en rapport avec leurs substrats neuraux grâce à l'utilisation de l'imagerie.

1.2.3.1 Les questionnaires auto-rapportés

Les questionnaires auto-rapportés constituent la première méthode de mesure de l'impulsivité. Très rapides et faciles d'utilisation, ils sont très utilisés. Parmi les nombreux questionnaires existants (Hook et al., 2021), les plus connus sont l'échelle d'impulsivité de Barratt (Patton et al., 1995), qui évalue en 30 items l'impulsivité à travers les dimensions d'impulsivité motrice, attentionnelle et de non-anticipation, et l'échelle de comportement impulsif UPPS (Whiteside and Lynam, 2001), comprenant 45 items et évaluant les dimensions de l'urgence, du manque de

préméditation, du manque de persévérance et de la recherche de sensations fortes. Ces questionnaires portent sur des comportements et attitudes de la vie quotidienne (par exemple, « j'agis sur un coup de tête » est un des items de l'échelle d'impulsivité de Barratt). De plus, les scores obtenus reflètent la perception subjective d'une personne de son propre comportement. Ainsi, il est généralement admis que ces questionnaires évaluent des traits de personnalité, et que les scores obtenus sont difficiles à relier à des processus cognitifs et substrats neuraux.

1.2.3.2 Les tâches comportementales

Les tâches cognitives constituent une mesure objective du comportement au moment du test, mesurant ainsi des états plutôt que des traits. Ainsi, il n'est pas étonnant que les scores obtenus lors de questionnaires ne corrèlent que peu ou pas avec ceux obtenus lors de tâches cognitives (Cyders and Coskunpinar, 2011; MacKillop et al., 2016; Reynolds et al., 2006). De nombreuses tâches mesurant l'impulsivité existent (voir pour revue Dalley and Robbins, 2017; Esteves et al., 2021). L'avantage de leur utilisation est que le comportement mesuré peut être lié à ses substrats neuraux grâce à l'utilisation de l'imagerie cérébrale, de l'électrophysiologie ou de manipulations pharmacologiques. Ces approches peuvent être appliquées chez l'humain ou chez un modèle animal grâce à des versions adaptées de ces tâches (Dalley and Robbins, 2017; Esteves et al., 2021; Voon, 2014).

Les tâches cognitives sont généralement conçues pour cibler et isoler des processus cognitifs particuliers. Cependant, en réalité, le comportement dans une tâche cognitive donnée est le résultat de la mise en œuvre de nombreux processus cognitifs. En d'autres termes, il reste difficile d'attribuer un comportement impulsif dans une tâche au dysfonctionnement d'un processus cognitif donné. Cette critique est souvent formulée envers les tâches les plus « écologiques », et donc complexes, telles que l'« Iowa Gambling Task » ou la « Balloon Analog Risk task » (Rochat et al., 2018), mais elle s'applique également aux tâches plus simples. Par exemple, une tâche de Go/NoGo nécessite l'implication de processus attentionnels et de mémoire de travail (Criaud and Boulinguez, 2013), mais probablement également d'une combinaison de différents mécanismes d'inhibition de réponse (Criaud et al., 2017; Meyer and Bucci, 2016). L'utilisation de tâches très simples, spécifiquement conçues pour cibler les processus cognitifs d'intérêt tout en limitant l'implication de processus cognitifs autres, est susceptible de limiter ce problème (Criaud and Boulinguez, 2013; Rochat et al., 2018). La modélisation psychologique des processus d'intérêt est cruciale pour orienter les choix méthodologiques. Par exemple, tandis que le choix entre une tâche de Signal Stop et de Go/NoGo pourrait sembler indifférent si l'on recherche une simple mesure d'impulsivité d'action, la tâche de Signal Stop fait référence pour l'évaluation des mécanismes d'inhibition réactifs tels que décrits par le « horse race model » (Verbruggen and Aron, 2019), tandis qu'une tâche de Go/NoGo permettra peut-être plus

aisément l'évaluation des mécanismes d'inhibition proactifs ou non-sélectifs, si tant est qu'une condition de contrôle appropriée est implémentée (Albares et al., 2014, 2015a; Criaud et al., 2017).

1.2.3.3 L'apport de l'imagerie cérébrale et de l'électrophysiologie

La combinaison des tâches comportementales et de l'imagerie cérébrale et ou de l'électrophysiologie permettent d'étudier les substrats neuraux des processus cognitifs d'intérêt. Cependant, l'apport de l'imagerie et de l'électrophysiologie dans l'évaluation de l'impulsivité peut aller au-delà de cela. En effet, ces outils peuvent offrir un pouvoir de discrimination supplémentaire quant aux différents mécanismes sollicités par la tâche comportementale utilisée, à condition d'exploiter le fait que ces mécanismes peuvent avoir des dynamiques temporelles différentes, reposer sur différents réseaux cérébraux ou bien avoir des signatures spectrales caractéristiques. Là encore, la modélisation psychologique sera cruciale pour orienter les choix méthodologiques : elle orientera par exemple le choix des contrastes à effectuer, ou bien de la période de temps à étudier (voir pour exemple Criaud et al., 2017). Notamment, alors qu'il est courant de se focaliser sur l'activité induite par les stimuli présentés, l'hypothèse de mécanismes proactifs nous oriente vers l'analyse de l'activité pré-stimulus.

L'imagerie par résonnance magnétique fonctionnelle (IRMf) repose sur le signal BOLD (pour blood-oxygen-level-dependent), qui est une mesure indirecte de l'activité cérébrale, basée sur la détection de changements dans le flux sanguin (Logothetis, 2008). Le décours temporel de ces changements dans le flux sanguin est bien plus lent que celui des variations d'activité cérébrale : cette méthode possède donc une très bonne résolution spatiale, mais une faible résolution temporelle. Elle est aussi complétement aveugle à la nature inhibitrice ou excitatrice de cette activité (Logothetis, 2008). Au final, le pouvoir de discrimination de l'IRMf repose majoritairement sur des indices spatiaux. Cependant, l'approche consistant à déduire l'engagement de certains processus cognitifs à partir des patterns d'activation observés, qualifiée d'inférence inverse, peut être critiquée pour son manque de spécificité, la plupart des régions cérébrales étant activées par une variété de processus (Poldrack, 2006, 2011).

A l'inverse, l'électroencéphalographie (EEG) constitue une mesure directe de l'activité neurale, le signal recueilli représentant l'activité synchronisée de larges populations de neurones corticaux de même orientation (Jackson and Bolger, 2014). Cette méthode possède une résolution temporelle de l'ordre de la milliseconde, mais sa limitation majeure est que le signal enregistré au niveau du scalp est un mélange d'activités provenant de différentes régions cérébrales, un problème exacerbé par la conduction de volume, qui a pour conséquence de propager l'activité d'une région cérébrale donnée à de larges parties du scalp (Jackson and Bolger, 2014). Les potentiels évoqués, obtenus en faisant la moyenne de l'activité à travers les essais d'une tâche, sont la méthode d'analyse la plus plébiscitée.

Mais cette méthode a plusieurs inconvénients. Pour commencer, elle n'exploite que l'activité qui est en phase d'un essai à l'autre. De plus, elle s'appuie uniquement sur la résolution temporelle de l'EEG, et échoue à résoudre le problème du mélange des différentes activités (Luck, 2014). Certaines méthodes d'analyse plus avancées s'attaquent directement à ce problème, et permettent de faire de l'EEG un outil au haut pouvoir de discrimination, en exploitant les dimensions analytiques spatiales, temporelles et spectrales (voir pour revue Bridwell et al., 2018; Meyer et al., 2021; Michel and Murray, 2012).

Résumé : *L'impulsivité est un concept aux multiples facettes. Bien que largement acceptée, la dichotomie entre impulsivité d'action et impulsivité décisionnelle ne rend compte ni de la complexité et de la diversité des mécanismes cognitifs sous-jacents, ni des interactions entre ces différents mécanismes. Pourtant, identifier l'origine précise d'un trouble de l'impulsivité en termes de mécanismes impliqués est susceptible d'être porteur de nouvelles perspectives thérapeutiques. D'un point de vue méthodologique, l'utilisation de tâches comportementales associées à l'imagerie cérébrale ou à l'électrophysiologie est idéale pour arriver à cet objectif. Il convient cependant de s'appuyer sur la modélisation psychologique des processus d'intérêt, d'utiliser des tâches adaptées ciblant spécifiquement ces processus, et d'utiliser des outils d'analyse de l'activité cérébrale offrant un pouvoir de discrimination élevé grâce à l'exploitation des dynamiques temporelles, réseaux cérébraux et signatures spectrales caractéristiques des processus d'intérêt.*

1.3 Objectifs et choix méthodologiques

Nous avons vu que différentes manifestations d'impulsivité existent dans la MP. D'une part, les agonistes dopaminergiques peuvent entraîner des TCIs. D'autre part, la SCP-NST peut entraîner des comportements impulsifs en lien avec des troubles du contrôle inhibiteur. Dans un second temps, nous avons vu que l'impulsivité est un concept multidimensionnel, et que la caractérisation précise des mécanismes neurocognitifs impliqués dans une manifestation donnée d'impulsivité, rendue possible par l'utilisation d'une méthodologie adaptée, peut être porteuse de nouvelles perspectives thérapeutiques. Ainsi, l'objectif général de ce travail de thèse est de clarifier la nature des différents troubles de l'impulsivité dans la MP, ainsi que leurs bases neuro-fonctionnelles.

Dans le premier chapitre, nous verrons que l'impulsivité des TCIs a jusqu'à présent été considérée comme relevant uniquement de dysfonctions des mécanismes de récompense et de motivation, une perspective historiquement motivée par le lien observé entre les TCIs et la prise d'agonistes dopaminergiques, qui sont connus pour leur haute affinité pour les récepteurs dopaminergiques de la famille D2, et en particulier pour les récepteurs D3, présents en nombre au sein de la voie dopaminergique mésolimbique (Cilia and van Eimeren, 2011; Voon et al., 2017). A travers *une revue systématique de la littérature* en neuro-imagerie (Meyer*, Spay* et al., 2019), nous montrons que les altérations de l'activité cérébrale associées aux TCIs s'étendent en dehors du réseau de la récompense, et qu'un ancrage plus important dans la modélisation psychologique est nécessaire afin d'envisager l'implication d'autres processus cognitifs. A l'aide de *deux études expérimentales* (Spay*, Meyer* et al, 2019 ; Meyer*, Spay* et al., 2020), nous testons l'hypothèse d'un trouble du contrôle inhibiteur chez les patients parkinsoniens souffrant de TCIs.

Dans le deuxième chapitre, nous verrons que les mécanismes et voies impliqués dans les effets de la SCP-NST sur le contrôle inhibiteur sont peu clairs. En effet, comprendre ces effets nécessite de tenir compte d'une part de la diversité des mécanismes de contrôle inhibiteur, et d'autre part de la complexité des mécanismes d'action de la stimulation (Udupa and Chen, 2015). Dans *une troisième étude expérimentale* (Meyer et al., soumis), nous explorons l'effet de la SCP sur les mécanismes de contrôle inhibiteur non-sélectifs. Plus précisément, nous testons l'hypothèse selon laquelle l'effet de la SCP sur ces mécanismes dépend de la modulation de l'activité de l'aire motrice supplémentaire. Cette hypothèse va à l'encontre de celle généralement acceptée d'effets majoritairement locaux sur l'activité du NST (Udupa and Chen, 2015), qui perturberaient donc le relai des commandes inhibitrices par le NST, plutôt que les mécanismes de contrôle inhibiteur. La connaissance des mécanismes impliqués dans les effets de la SCP-NST sur le contrôle inhibiteur pourrait informer le choix de la cible

précise et des paramètres de stimulation de la SCP dans le but d'éviter la survenue de comportements impulsifs tout en maximisant l'amélioration des signes moteurs.

Nos choix méthodologiques répondent à ces différentes considérations. Afin de tester nos processus cognitifs d'intérêt, nous utilisons une tâche de Go/NoGo très simple (Albares et al., 2014; Criaud et al., 2017). La particularité de cette tâche est qu'elle permet de sonder différents types de mécanismes d'inhibition de réponse (Figure 6), c'est-à-dire les mécanismes réactifs sélectifs, mais aussi réactifs non-sélectifs (ou contextuels) et proactifs, moins souvent étudiés. Elle est également conçue pour engager de façon la plus minimale possible les processus cognitifs annexes tels que la sélection de réponse, la mémoire de travail ou l'attention.

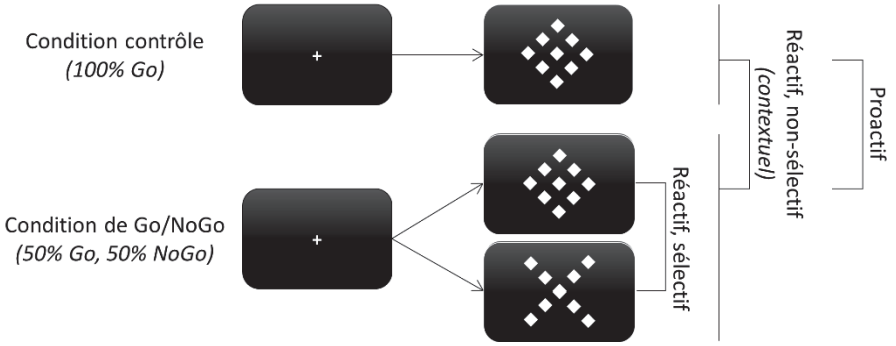

Figure 6 : Principe de la tâche de Go/NoGo. L'utilisation d'une tâche de Go/NoGo très simple, enrichie d'une condition de contrôle contenant uniquement des essais Go, permet de révéler les différents mécanismes d'inhibition de réponse. Les mécanismes d'inhibition réactifs sélectifs, censés être déclenchés uniquement en réponse au stimulus auquel il ne faut pas répondre, peuvent être révélés par la comparaison des essais Go et NoGo. Par ailleurs, la comparaison de la condition « classique » de Go/NoGo et de la condition contrôle permet de révéler les mécanismes réactifs non-sélectifs et proactifs, implémentés en fonction du contexte. En effet, dans la condition de Go/NoGo « classique », les essais Go et NoGo sont équiprobables (contexte incertain), forçant le sujet à implémenter du contrôle inhibiteur pour éviter de répondre de façon automatique à tous les stimuli présentés. A l'inverse, ce mode de réponse automatique peut être instauré dans la condition contrôle, où aucune inhibition n'est requise puisque seuls des stimuli Go sont présentés. Les mécanismes réactifs non-sélectifs et proactifs peuvent être distingués sur la base de leurs dynamiques temporelles, les premiers étant déclenchés de façon rapide, phasique, après la présentation du stimulus, tandis que les seconds sont implémentés de façon tonique en amont de la présentation de tout stimulus. Figure basée sur Criaud et al. 2017.

Nous utilisons en parallèle l'électroencéphalographie haute densité couplée à des méthodes de traitement avancées. Ces méthodes permettent, à notre sens, de remplir de façon optimale notre exigence d'un pouvoir de discrimination élevé quant aux mécanismes neurocognitifs impliqués dans notre tâche de Go/NoGo, et ce grâce à l'exploitation des dimensions analytiques temporelle, spatiale et spectrale (Figure 7). Nous utilisons tout d'abord la séparation de sources de groupe, qui permet de séparer les différentes sources d'activité cérébrale contribuant à l'activité enregistrée sur le scalp. Nous utilisons aussi des méthodes de localisation de sources, qui permettent d'identifier les générateurs anatomiques correspondant aux sources séparées. Enfin, nous appliquons des analyses temps-fréquence dans l'espace des sources séparées. L'ensemble de ces méthodes et leurs avantages sont discutés en détail –dans le contexte du traitement de la récompense– dans l'article de revue présenté en annexe (Meyer et al., 2021).

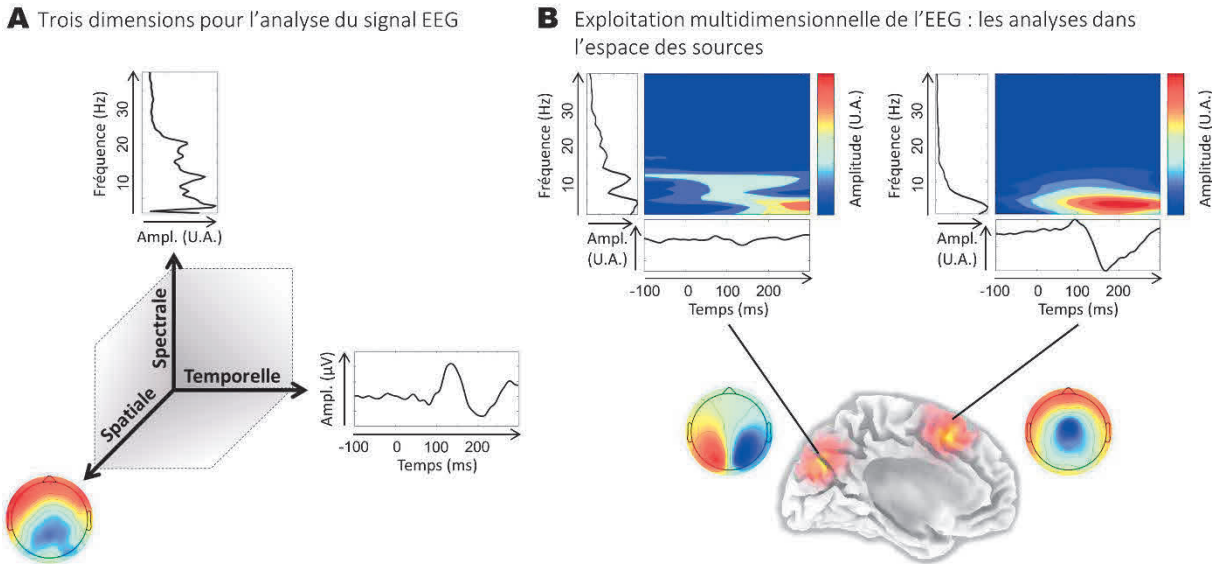

Figure 7 : Le pouvoir de discrimination de l'EEG dépend de l'exploitation de trois dimensions analytiques. (A) La haute résolution temporelle du signal enregistré permet d'examiner son évolution au cours du temps (*dimension temporelle),* mais aussi sa rythmicité oscillatoire (*dimension spectrale*). La considération de cette information spectrale est un indice important pour la distinction de différents processus ou fonctions, qui peuvent s'exprimer dans différentes bandes de fréquence. La plupart du temps, ces deux dimensions sont examinées séparément, sur la base d'analyses en potentiels évoqués (qui ignorent la dimension spectrale), ou d'analyses spectrales (qui ignorent la dimension temporelle), représentées ici à l'électrode FCz. La troisième dimension est la *dimension spatiale*. Celle-ci est souvent considérée comme le point faible de l'EEG, et donc souvent ignorée. Il est vrai que l'analyse de la topographie de l'activité de scalp (ici représentée à 210ms) n'est que peu informative, en raison notamment de la conduction de volume. Cependant, certaines solutions, dont la séparation et la localisation de sources, permettent d'exploiter au mieux l'information spatiale contenue dans l'activité de scalp. (B) Un pouvoir de discrimination optimal découle de l'exploitation combinée de ces trois dimensions (temporelle, spectrale, spatiale). Dans ce but, il est possible d'effectuer des analyses temps-fréquence directement dans l'espace des sources séparées. Nous illustrons ici, pour deux sources distinctes, le potentiel évoqué (projeté respectivement sur les électrodes B4 et FCz), la carte temps-fréquence, la topographie et la localisation obtenue via sLORETA. Adapté de Meyer et al., 2021.

Chapitre I

Les troubles du contrôle inhibiteur chez les patients parkinsoniens souffrant de troubles du contrôle des impulsions

2.1 Les bases neuro-fonctionnelles des troubles du contrôle des impulsions : Revue de la littérature

Dans la MP, les troubles du contrôle des impulsions (TCIs) sont des comportements tournés vers la récompense, excessifs et répétés, qui affectent le fonctionnement du patient (Cilia and van Eimeren, 2011; Marques et al., 2018; Weintraub and Claassen, 2017; Weintraub et al., 2015). Ils regroupent le jeu pathologique, l'hypersexualité, l'alimentation compulsive et l'achat compulsif, tels qu'évalués par exemple par la MIDI (Minnesota Impulsive Disorders Interview, Christenson et al., 1994) ou la QUIP (Screening Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, Weintraub et al., 2009 et QUIP-Rating scale, Weintraub et al., 2012 ; voir Marques et al., 2019 pour validation de la version française de la QUIP-Rating scale). D'autres comportements relevant du spectre de l'impulsivité et de la compulsivité (dits « impulsifs-compulsifs ») peuvent également se manifester dans la MP (Fusaroli et al., 2021; Weintraub et al., 2015). On observe notamment d'autres types de comportements répétitifs et excessifs, dits de « punding » lorsqu'ils relèvent de comportements très stéréotypés et sans but (par exemple, collectionner, trier ou démonter certains objets) ou de « hobbyism » lorsqu'ils relèvent de comportements plus complexes (par exemple, jardiner ou naviguer sur internet), ou encore un syndrome de dérégulation dopaminergique, c'est-à-dire la prise compulsive du traitement dopaminergique, à des doses plus importantes que celles prescrites. Les estimations de la prévalence des TCIs sont très variables (Callesen et al., 2013; Molde et al., 2018). Les deux larges études faisant référence l'ont respectivement estimée à 28% et 13,6% (Antonini et al., 2017; Weintraub et al., 2010). Une étude récente a quant à elle rapporté une prévalence cumulée sur 5 ans de 46,1% (Corvol et al., 2018). Les TCIs concernent donc un grand nombre de patients au cours de leur maladie. Par ailleurs, les TCIs ainsi que les troubles « impulsifs-compulsifs » ont parfois des conséquences désastreuses pour les patients et leur entourage. Ils peuvent notamment être responsables de difficultés sociales, en particulier de conflits intrafamiliaux, ainsi que de difficultés financières parfois importantes (Codling et al., 2015; Dodd et al., 2005; Evans et al., 2004; McKeown et al., 2020). Plus généralement, ils diminuent la qualité de vie du patient et ajoutent à la charge des aidants (Erga et al., 2020).

Les causes de l'apparition de ces troubles ne sont que partiellement connues. Le facteur le plus important est la prise d'agonistes dopaminergiques (Cao et al., 2021; Cossu et al., 2018; Eisinger et al., 2019a; Grall-Bronnec et al., 2018; Liu et al., 2019; Napier and Persons, 2018; Napier et al., 2020; Weintraub and Claassen, 2017). En effet, le risque de développer un TCI est plus de deux fois plus élevé chez les patients parkinsoniens prenant des agonistes dopaminergiques que chez les patients n'en prenant pas (Corvol et al., 2018; Weintraub et al., 2010), et un dosage plus haut semble aussi prédicteur de l'apparition de TCIs (Bastiaens et al., 2013; Callesen et al., 2014; Jesús et al., 2021; Lee et al., 2010; Perez-Lloret et al., 2012; Rodríguez-Violante et al., 2014; Valença et al., 2013; Weintraub et al., 2006), bien que certaines études aient échoué à démontrer ce type de relation (Kenangil et al., 2010; Singh et al., 2007; Voon et al., 2006). Par ailleurs, la diminution du dosage ou l'arrêt des agonistes dopaminergiques améliore les TCIs (Corvol et al., 2018; Mamikonyan et al., 2008; Sohtaoğlu et al., 2010). Enfin, des TCIs sont aussi observés chez des patients prenant des agonistes dopaminergiques dans le cadre d'un syndrome des jambes sans repos ou d'un prolactinome (Grall-Bronnec et al., 2018).

La principale stratégie de gestion des TCIs est par conséquent l'adaptation du traitement dopaminergique, et notamment la diminution ou la suppression des agonistes (Grassi et al., 2021; Samuel et al., 2015). Cependant, cette stratégie n'est pas satisfaisante, voire parfois même difficile à appliquer, car elle expose le patient à une recrudescence des symptômes moteurs ainsi qu'à un syndrome de sevrage (Barbosa et al., 2019; Lee et al., 2019). Des approches pharmacologiques alternatives ont été proposées, mais il n'existe pas suffisamment de preuves de leur efficacité (Grassi et al., 2021; Tanwani et al., 2015). Mieux comprendre les mécanismes à l'origine des TCIs pourrait aider au développement de nouvelles solutions thérapeutiques.

L'observation du fort lien entre agonistes dopaminergiques et TCIs, ainsi que de la nature de ces troubles, qui consistent en des comportements très orientés vers la récompense, a amené à l'hypothèse selon laquelle les TCIs seraient dus à des dysfonctionnements du système dopaminergique mésocorticolimbique (Aracil-Bolaños and Strafella, 2016; Béreau et al., 2019; Jiménez-Urbieta et al., 2015; Sierra et al., 2015; Voon et al., 2017; Vriend, 2018; Vriend et al., 2014a). D'abord, le profil pharmacologique des agonistes dopaminergiques serait responsable d'une suractivation de la voie mésocorticolimbique (Napier and Persons, 2018). En effet, les agonistes dopaminergiques présentent une haute affinité pour les récepteurs dopaminergiques de la famille D2 (qui comprend les récepteurs D2, D3 et D4). Mais les plus utilisés dans la MP, le pramipexole et le ropinirole, ont une affinité plus haute pour les récepteurs D3 que pour les récepteurs D2. Or, l'expression des récepteurs D3 est bien plus importante dans la voie mésolimbique que dans la voie nigrostriée (Napier and Persons, 2018). De plus, en stimulant de façon tonique les récepteurs D2 dans le striatum, les agonistes empêcheraient les pauses dans la transmission dopaminergique, qui signalent les conséquences négatives, ce qui

compromettrait l'apprentissage par renforcement négatif (Cilia, 2012; van Eimeren et al., 2009; Voon et al., 2010, 2017). Par ailleurs, la suractivation de la voie mésocorticolimbique par les agonistes dopaminergiques pourrait être amplifiée par le processus pathologique de la MP (De Micco et al., 2018; Theis et al., 2021; Voon et al., 2017; Vriend, 2018). Selon l'hypothèse de l'"overdose", les doses utilisées pour remédier aux symptômes moteurs sur-doseraient la voie mésolimbique, relativement préservée dans la MP en comparaison à la voie nigrostriée (Sparks et al., 2020; Stark et al., 2018; Voon et al., 2011). A l'inverse, selon une autre hypothèse, ce serait la dégénérescence des neurones dopaminergiques de cette voie qui augmenterait le risque de TCIs, possiblement en induisant une hypersensibilité des récepteurs D3 dans le striatum ventral, potentialisant ainsi l'effet des agonistes dopaminergiques (Hammes et al., 2019; Theis et al., 2021; Vriend et al., 2014a, 2014b). Quoiqu'il en soit, ces différentes hypothèses convergent vers l'idée d'un état hyperdopaminergique de la voie mésocorticolimbique dans les TCIs, amenant la plupart des auteurs à considérer que l'impulsivité des TCIs relèverait principalement de dysfonctionnements des processus de traitement de la récompense et de motivation (Aracil-Bolaños and Strafella, 2016; Béreau et al., 2019; Jiménez-Urbieta et al., 2015; Sierra et al., 2015; Sinha et al., 2013; Voon et al., 2017; Vriend, 2018; Vriend et al., 2014a). Autrement dit, leur impulsivité serait décisionnelle, plutôt que d'action (Voon et al., 2017).

Cependant, la prise d'agonistes dopaminergiques n'est pas une condition suffisante au développement des TCIs. Ceux-ci résulteraient plutôt d'une interaction entre ce traitement, le processus pathologique de la MP, mais aussi d'autres facteurs de susceptibilité (Cilia, 2012; Marques et al., 2018; Voon et al., 2017; Weintraub and Claassen, 2017 ; Figure 8). Certains facteurs de risques liés à des caractéristiques cliniques ou démographiques ont été rapportés, comme le fait d'être de sexe masculin, d'être plus jeune au moment du diagnostic de MP, de souffrir de dépression, ou d'avoir un historique personnel ou familial d'addiction ou de jeu pathologique (Cao et al., 2021; Cossu et al., 2018; Eisinger et al., 2019a; Fantini et al., 2020; Grall-Bronnec et al., 2018; Jaakkola et al., 2014; Liu et al., 2019; Weintraub and Claassen, 2017). Il y aurait aussi des facteurs de risque génétiques (Jesús et al., 2021; Kraemmer et al., 2016).

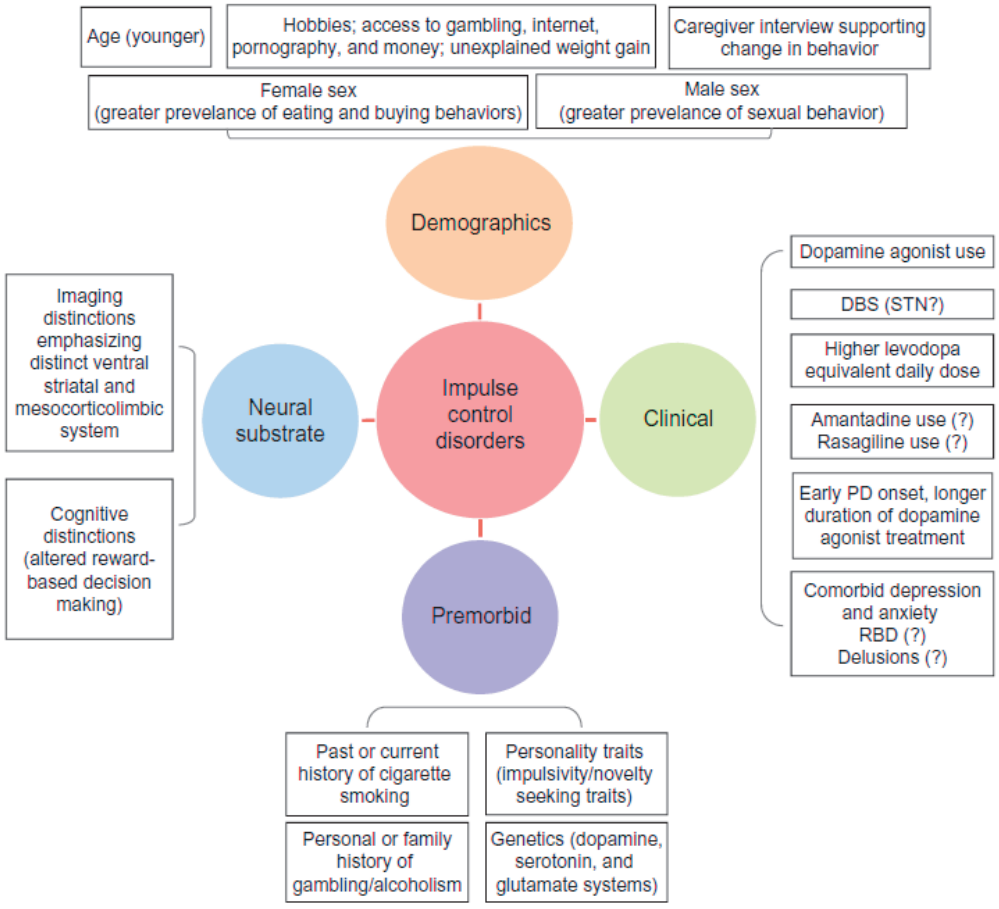

Figure 8 : Corrélats et facteurs de risques des TCIs dans la MP. Figure tirée de Weintraub & Claassen, 2017.

Si les TCIs sont multifactoriels, il semble raisonnable de penser qu'ils pourraient impliquer différentes dysfonctions sur le plan cognitif, ne reposant probablement pas toutes sur le système dopaminergique (Cilia and van Eimeren, 2011; Sinha et al., 2013; Thobois et al., 2018). Cette perspective pousse à considérer l'implication de l'ensemble des mécanismes neurocognitifs constitutifs de l'impulsivité dans ces troubles. Comme discuté dans l'introduction, l'imagerie cérébrale peut être un outil précieux pour distinguer ces différents mécanismes lorsqu'elle est combinée à des tâches cognitives ciblant spécifiquement les fonctions d'intérêt dans une démarche inférentielle. Nous avons donc réalisé une revue systématique des études en neuro-imagerie révélant les corrélats des TCIs dans la MP, dans le but d'obtenir une vue d'ensemble des mécanismes neurocognitifs contribuant à ces troubles.

Article 1: Functional imaging studies of Impulse Control Disorders in Parkinson's disease need a stronger neurocognitive footing

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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-Urbieta 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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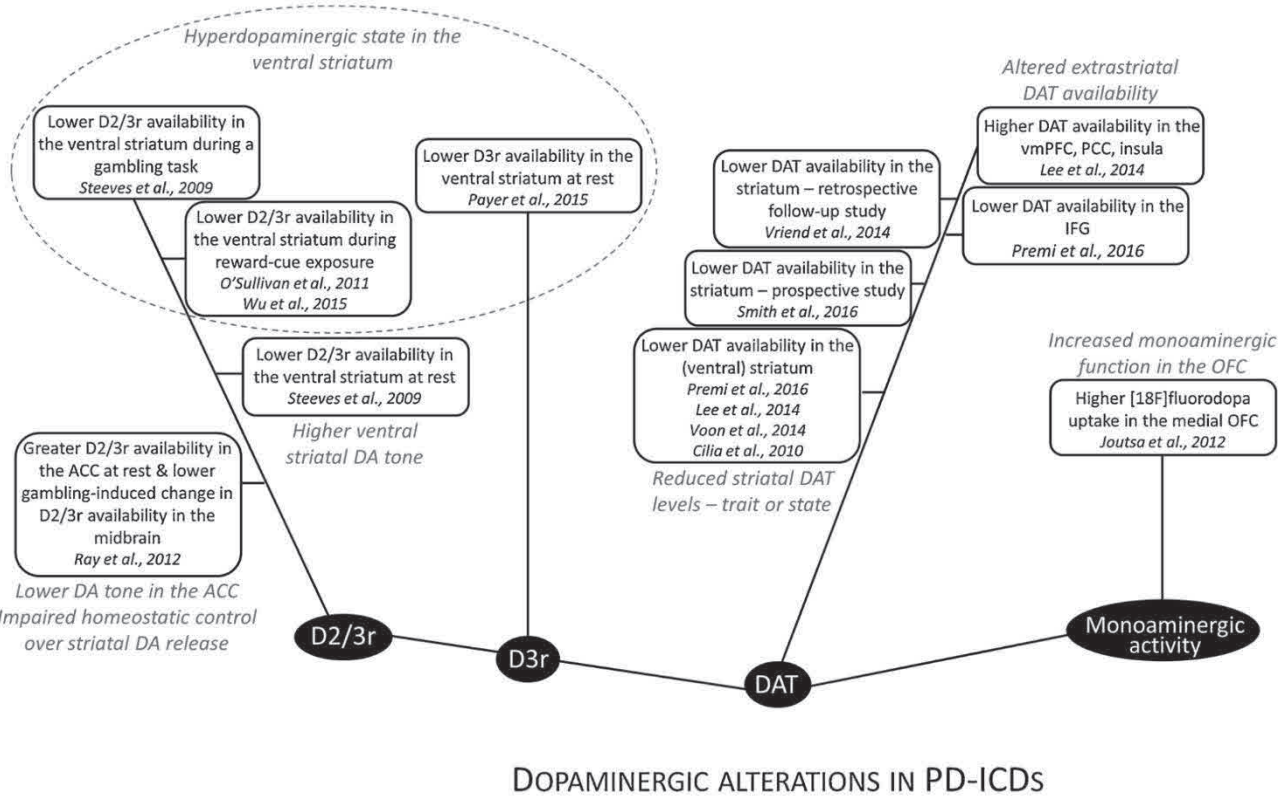

Fig. 1. Molecular imaging findings in PD-ICDs. This literature provides important insights on PD-ICDs etiology by revealing various dopaminergic alterations in ICDs + compared to ICDs- (see Aracil-Bolaños and Strafella, 2016; Vriend, 2018; Weintraub and Claassen, 2017 for extensive reviews). At the postsynaptic level, lower D2/3 dopamine receptor (D2/3 r) availability in the ventral striatum was demonstrated using [11C]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 D3 r availability in the ventral striatum in ICDs + using [11C]-(+)-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 D2/3 r density or more pronounced DA degeneration. One study using [11C]-FLB-457 found greater D2/3 r 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 D2/3 r expression. There was also a lower gambling-induced change in D2/3 r 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 [123I]-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 [11C]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 extrastriatal 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 [18 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-Urbieta 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 multidimensional (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).

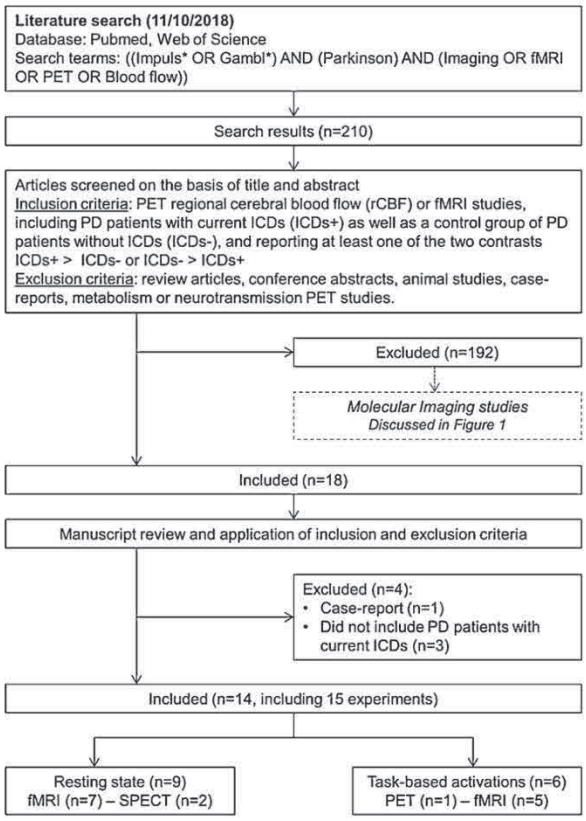

Fig. 2. Flow chart of publication selection procedure based on PRISMA guidelines (www.prisma-statement.org).

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 ± 7.3 ICDs + and 18.6 ± 12.8 ICDs-. Three studies reported QUIP-RS scores (ICDs+ = 31.5 ± 8.3; ICDs- = 19.0 ± 0.1) and one reported MIDI scores (ICDs+ = 6.8 ± 3.2, ICDs- = 0.4 ± 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 subcomponents 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

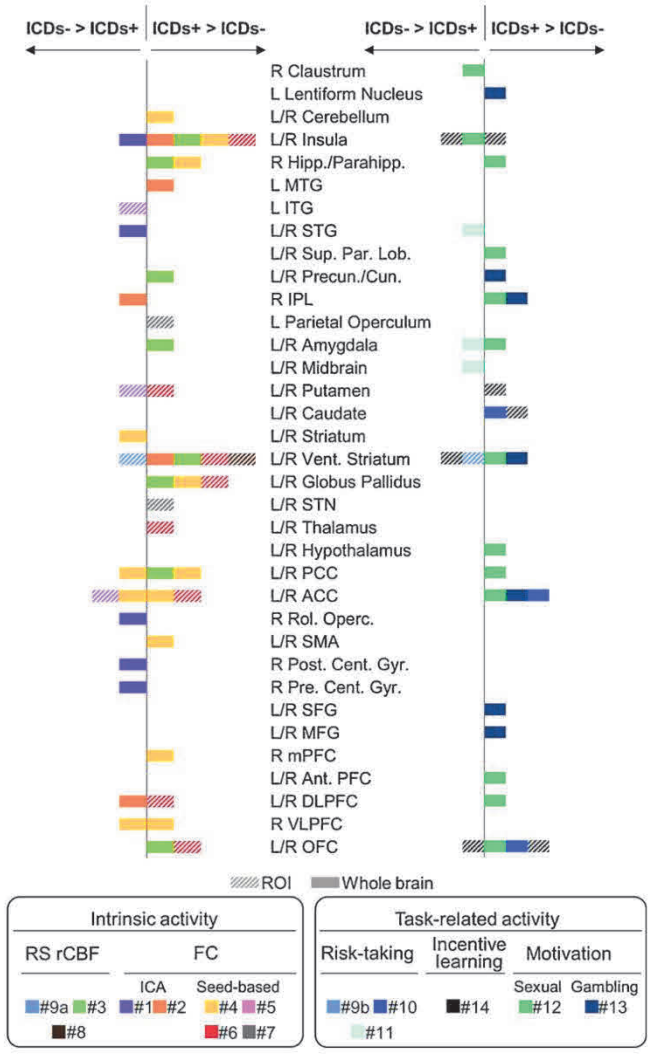

Fig. 3. Differences in functional connectivity (A) or task-related activation (B) between PD patients with (ICDs+) or without ICDs (ICDs-). For the sake of clarity, only regions involved in Group effects (and not Group x Medication effects) are reported. The heterogeneity of the methods as well as the 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 serotoninergic (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	Tool Signal	Processing methods	Authors' rationale	NOI BT	ROI		
#1	Imperiale, 2017	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 HC > ICDs+	[FC within and between RSNs] Ø [FC within Sensorimotor Network] R Precentral Gyrus - R Postcentral Gyrus - R Rolandic Operculum - R STG - L Insula [FC between RSNs] Ø [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 between RSNs] Ø [FC within and between RSNs] Ø
#2	Tessitore, 2017	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	ICDs+ > ICDs- ICDs- > ICDs+ ICDs+ > HC HC > ICDs+	[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[1] 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 HC > PG+	[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] Ø [rCBF peak/extended to] R Hippocampus/Parahippocampal Gyrus - R Insula/OFC/Striatum - R Caudate/Insula - R Putamen/Insula [rCBF] Ø
#4	Cilia, 2011	PD-PG[1] 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	PG+ > PG- PG- > PG+	[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
				Intrinsic activity Effective connectivity			Seeds: R VLPFC, R mPFC, R ACC, R PCC, L Striatum, R Insula, R Para-hippocampal Gyrus	PG+ < PG-/HC	[Main finding] Disconnection of the Striatum from ACC
								Correlation analysis	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		Populations	Neuroimaging		Behavioral tasks and targeted neurocognitive mechanisms			Results	
		ICDs + /ICDs- /HC	Tool Signal	Processing methods	Authors' rationale	NOI BT	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"	/ /	Seeds: Bilateral Dorsal Caudate, Ventral Striatum, Anterior and Posterior Putamen	ICDs- > ICDs + ICDs + > ICDs- ICDs + < > HC	[FC from L Anterior Putamen, disconnection] L Inferior Temporal Gyrus – L ACC[6] Ø [6] Ø [6]
#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" - "Because amygdala activity has also been linked with reward-motivated behaviors […], we additionally examined amygdala connectivity with reward network components."	/ /	Seeds: Bilateral Ventral Striatum, Bilateral Amygdala	ICDs + > ICDs- ICDs- > ICDs +	[Volxewise analysis - FC from ventral striatum] L and R Thalamus/Basal Ganglia/ Subgenual ACC/Lateral OFC/DLPFC Ø
							Seeds: Bilateral Ventral Striatum, Bilateral Amygdala - Connectivity to 12 target bilateral mesocorticolimbic ROIs	ICDs + > ICDs- ICDs- > ICDs + *Group x Medication*	[ROI-based analysis - FC from ventral striatum] Dorsal ACC - OFC - Insula - Putamen - Globus Pallidus - Thalamus Ø Ø
						Incentive learning Action-valence learning task			*[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 (ρ = 0.43, p < 0.01)[5]*
#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"	/	Seeds: L Putamen, Caudate, GPi, GPe, STN, Parietal	ICDs + > ICDs- ICDs- > ICDs +	[FC from STN, increased] L Parietal Operculum[6] Ø [6]
						Risk Taking Beads Task			*[Behavioral results] No group effect[5]*
#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 impulse control behaviors patients would have different CBF responses to dopamine agonist in mesocorticolimbic regions than PD patients without impulse control behaviors"	/ /	ROIs: Hippocampus, Amygdala, Pallidum, Ventral Striatum, Putamen, Caudate	ICDs + > ICDs- ICDs- > ICDs + *Correlation analysis*	[ΔCBF (ON-OFF)] Ventral Striatum Ø *Positive correlation between QUIP-RS scores and ventral striatum ΔCBF (ρ = 0.35; p = 0.043).*
#9a	Rao, 2010	PD-ICDs 9/9 Interview	fMRI rCBF	Intrinsic activity RS activation	"we hypothesized that PD patients with ICDs, compared with PD patients without an ICD, would demonstrate diminished neural activity in mesolimbic-prefrontal cortex brain regions, particularly in the ventral striatum."	/ / Risk Taking BART HRF on balloon inflation with risk level as a linear parametric modulation	Ventral Striatum	ICDs- > ICDs +	[rCBF, voxel-wise and ROI analysis] Ventral Striatum
#9b		MIDI/MGS/DSM-IV[2] ON	fMRI rCBF	Task-related activity Event-related			Ventral Striatum	ICDs- > ICDs + *Behavioral results*	[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	Tool Signal	Processing methods	Authors' rationale	NOI BT	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."	Risk Taking Gambling Task Box-car convolved with HRF on decision phase (4 s) with risk as a parametric regressor	*Whole brain*	ICDs + > ICDs- *Group effect* ICDs- > ICDs + *Group effect* *Group x Medication* *Behavioral results*[5]	[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 = 096)– No Medication x Group effect (p = 019)
#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."	Risk Taking Card selection game with probabilistic feedback, neutral and financial variant Task > Rest	*Whole brain*	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
#12	Politis, 2013	PD-HypS[1] 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"	Motivation Watching sexual cues[3] Sexual cues > Neutral cues, Sexual cues > Other cues[4]	OFC, ACC, PCC, Amygdala, Ventral Striatum, Hypothalamus	HypS + > HypS-	[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
							Whole brain	HypS + > HypS- HypS- > Hyps + *Behavioral results*	[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 < 001
#13	Frosini, 2010	PD-PG[1] 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	Motivation Watching gambling cues[3] Gambling cues > Neutral cues	*Whole brain*	PG + > PG- *Behavioral results*	[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.

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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	NOI BT	ROI		
#14 Voon, 2010	PD-PG/CB 11/11/16 DSM-IV/ McElroy criteria ON/OFF DAAs	fMRI BOLD	Task-related activity Computational modelling	"dopamine agonists would be associated with faster learning from gain outcomes along with greater ventral striatal positive δ 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)	*ROIs: Striatum, Amygdala, OFC, Insula*	ICDs + > ICDs- *Group effect*	[PO activity, gain condition] L and R OFC [Positive PE activity, gain condition] R Posterior Putamen – L OFC [Negative PE activity, gain condition] Ø [PO activity, loss condition] L Dorsolateral Striatum [Positive PE activity, loss condition] Ø [Negative PE activity, loss condition] L Anterior Insula – L Dorsomedial Caudate – L Dorsolateral Striatum
							ICDs- > ICDs + *Group effect*	[PO activity, gain condition] Ø [Positive PE activity, gain condition] Ø [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
							Group x Medication	[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] Ø [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 +

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Table 1 (*continued*)

Studies	Populations	Neuroimaging		Behavioral tasks and targeted neurocognitive mechanisms			Results
		Tool Signal	Processing methods	Authors' rationale	NOI BT	ROI	
							Behavioral results [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-[5] [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 + [5]

[1] with other ICD co-occurrence in some patients. – [2]: 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. – [3]: No responses required – [4]: Gambling, food, and dopaminergic cues – [5]: The reader is referred to the whole article for the complete results – [6]: The reader is referred to the whole article for the results of the exploratory analysis using a less stringent criteria for significance – HypS +/-: 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 – RSNs: Resting State Networks – BART: Balloon Analogue Risk Task – PE: Prediction Error – PO: Predicted Outcome – ACC: Anterior Cingulate Cortex – CEN: Central Executive Network – DLPFC: 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: Salience Network – STG: Superior Temporal Gyrus – VLPFC: Ventrolateral Prefrontal Cortex - Ø : No areas concerned by significant modification of activity/connectivity for the corresponding contrast.

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Declarations of interest

None.

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Résumé : *Les TCIs sont des troubles fréquents, parfois lourds de conséquences, et sans solution thérapeutique satisfaisante. Associés à la prise d'agonistes dopaminergiques, ils sont généralement considérés comme résultant d'un état hyperdopaminergique de la voie mésocorticolimbique, qui entrainerait des dysfonctions des processus de récompense et de motivation. Cependant, les TCIs sont des troubles multifactoriels, et d'autres mécanismes neurocognitifs pourraient être impliqués. A travers une revue systématique de la littérature en neuro-imagerie antérieure à octobre 2018 (15 expériences), nous montrons que la majorité des études (9 expériences) ont recherché de façon non spécifique des corrélats neuraux des TCIs à l'état de repos, plutôt que de cibler des mécanismes neurocognitifs précis à l'aide de tâches comportementales et d'analyses dites événementielles ». Ces études se caractérisent également par un focus récurrent sur le réseau mésocorticolimbique, se traduisant par des analyses en région d'intérêt, mais aussi par l'utilisation exclusive de tâches visant des fonctions cognitives dépendant de ce réseau (prise de risque, motivation pour la récompense, apprentissage par renforcement ; 6 expériences). Ainsi, il reste difficile d'avoir une vue exhaustive des mécanismes neurocognitifs impliqués dans les TCIs. Les résultats de ces études montrent des anomalies de la connectivité ou de l'activité dans le réseau mésocorticolimbique, néanmoins peu reproductibles, mais aussi des anomalies hors de ce réseau (notamment dans les réseaux sensorimoteurs, attentionnels, et du mode par défaut, et dans les aires préfrontales), ce qui concorde avec l'hypothèse de troubles multidimensionnels sur le plan neurocognitif.*

2.2 Les troubles du contrôle inhibiteur : une hypothèse négligée

Il semble logique d'envisager l'hypothèse d'un trouble du contrôle inhibiteur chez les patients parkinsoniens souffrant de TCIs. D'une part, comme détaillé dans l'introduction de ce travail, les mécanismes de contrôle inhibiteur peuvent jouer un rôle crucial dans l'impulsivité. D'autre part, les TCIs peuvent également être envisagés à la lueur du modèle des addictions comportementales (Béreau et al., 2019; Cilia and van Eimeren, 2011; Dawson et al., 2018; Probst and van Eimeren, 2013; Ramdave et al., 2019; Ray and Strafella, 2013), un concept en vogue depuis la reclassification du jeu pathologique dans la catégorie « troubles liés aux substances et aux addictions » du DSM-V. Or, ces modèles accordent eux aussi une place prépondérante aux mécanismes de contrôle inhibiteur (Antons et al., 2020; Goudriaan et al., 2014; Limbrick-Oldfield et al., 2013), ce qui concorde avec les données disponibles pour le jeu pathologique dans la population générale (Chowdhury et al., 2017). Enfin, notre analyse systématique des études en neuro-imagerie (Article 1) suggère aussi la possibilité de l'implication de régions cérébrales susceptibles de jouer un rôle dans le contrôle exécutif.

Pourtant, l'hypothèse d'un déficit d'inhibition de réponse chez les TCIs n'a reçu que peu d'intérêt ou de support empirique. Au vu du manque d'études issues des neurosciences cognitives (tel que discuté dans notre article de revue), la majorité de nos connaissances sur la cognition, et plus particulièrement sur les capacités d'inhibition de réponse des patients parkinsoniens souffrant de TCIs, provient d'études ayant utilisé de larges batteries de tests neuropsychologiques (voir pour revue Dawson et al., 2018; Martini et al., 2018; Santangelo et al., 2017). Or, ces tests sont conçus pour évaluer de façon rapide l'état général de la cognition chez les patients, mais pourraient passer à côté d'altérations plus fines et spécifiques de leur fonctionnement. Ces tests n'ont d'ailleurs pas permis d'identifier de déficit d'inhibition chez les patients avec TCIs comparés aux patients sans TCIs, que ce soit grâce au test de Stroop (voir pour méta-analyse Martini et al., 2018; Santangelo et al., 2017) ou au test de Go/NoGo (Bentivoglio et al., 2013; Yoo et al., 2015). Seules quelques rares études ont utilisé des tâches cognitives informatisées afin de tester les capacités de contrôle inhibiteur de ces patients. Ces études ont utilisé les tâches classiques de signal stop (Claassen et al., 2015; Leroi et al., 2013; Ricciardi et al., 2017), de Go/NoGo ou de performance continue (Hlavatá et al., 2019; Marín-Lahoz et al., 2018; Pineau et al., 2016), et de Simon (Wylie et al., 2012), et ont elles aussi échoué à identifier un déficit d'inhibition de réponse chez les patients avec TCIs comparés aux patients sans TCIs (bien qu'une étude ait montré une corrélation entre le taux d'erreurs de commissions et la sévérité des TCIs ; Marín-Lahoz et al., 2018). Cependant, ces études ont pour limite majeure de ne pas avoir considéré la multiplicité des mécanismes d'inhibition de réponse. En particulier, les designs expérimentaux utilisés ne permettent ni de tester spécifiquement les mécanismes contextuels (pourtant susceptibles de jouer un rôle plus prépondérant dans la fonction d'inhibition de réponse que les mécanismes réactifs

sélectifs ; Aron, 2011; Criaud et al., 2017), ni de distinguer les différents mécanismes d'inhibition potentiellement impliqués. En effet, comme discuté plus haut, distinguer les différents mécanismes impliqués dans une tâche cognitive reste la plupart du temps difficile sur la base du comportement seul.

Ainsi, l'hypothèse d'un potentiel déficit d'inhibition de réponse dans les TCIs gagnerait à être réévaluée à l'aide des outils des neurosciences cognitives, selon les principes méthodologiques décrits dans l'introduction de ce travail de thèse (voir partie 1.2.3), afin de tester l'ensemble des mécanismes neurocognitifs sous-jacents. Dans une première étude expérimentale, nous sondons l'intégrité fonctionnelle des réseaux corticaux de l'inhibition de réponse à l'état de repos grâce à l'électroencéphalographie, à la recherche d'une preuve de concept en faveur de cette hypothèse. Puis, dans une seconde étude expérimentale, nous la testons directement. Nous utilisons la tâche de Go/NoGo modifiée décrite plus haut (voir partie 1.3), qui nous permet de sonder l'ensemble des mécanismes d'inhibition de réponse (réactifs sélectifs, et contextuels, c'est-à-dire réactifs non-sélectifs et proactifs), tout en minimisant la demande placée sur d'autres fonctions (notamment la sélection de réponse, la mémoire de travail et l'attention), qui pourrait être un facteur confondant (Criaud and Boulinguez, 2013; Criaud et al., 2017). Comme discuté plus haut, l'usage de l'imagerie ou de l'électrophysiologie est susceptible de conférer un pouvoir de discrimination supplémentaire quant aux mécanismes impliqués. L'EEG semble être un outil particulièrement adapté, si tant est que des méthodes de traitement du signal permettant de maximiser son pouvoir de discrimination soient utilisées (Albares et al., 2015a; Meyer et al., 2021). Nous utilisons donc l'EEG afin de distinguer les différents mécanismes d'inhibition de réponse sur la base de leurs dynamiques temporelles, ainsi que de leurs signatures spatiales et spectrales.

2.2.1 Preuve de concept : analyse de l'activité oscillatoire de repos

Article 2: Resting state oscillations suggest a motor component of Parkinson's Impulse Control Disorders

Charlotte Spay*, Garance Meyer*, Guillaume Lio, Gianni Pezzoli, Bénédicte Ballanger, Roberto Cilia, Philippe Boulinguez. *Publié dans Clinical Neurophysiology, 130:2065-2075*

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Resting state oscillations suggest a motor component of Parkinson's Impulse Control Disorders

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HIGHLIGHTS

- Impulse Control Disorders (ICDs) are associated with abnormal resting state β-power.
- Beta power changes in the Supplementary Motor Area (SMA) predict ICDs severity.
- Impulsivity in ICDs patients might partly rely on motor dysfunctions.

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. Analyses were performed directly at the source level after blind source separation. Discrete differences between groups were tested by comparing patients with and without ICDs. Gradual dysfunctions were assessed by means of correlations between power changes and clinical scores reflecting ICD severity (QUIP score).

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.

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 consider, in addition to the classical interpretation based on aberrant mesocorticolimbic reward processing, the issue of motor impulsivity in PD-ICDs and its potential implications for PD therapy.

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

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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) (Avanzi et al., 2006; Grosset et al., 2006; Voon et al., 2006; Weintraub et al., 2010; Vela et al., 2016; Antonini et al., 2017; Corvol et al., 2018). ICDs in PD are associated mainly with cognitive impulsivity, also termed choice or decisional impulsivity. Cognitive impulsivity reflects dysfunctions in various aspects of decision making and motivation involving the reward system (Czernecki et al., 2002; Abler et al., 2009; Cilia and van Eimeren, 2011; Aarts et al., 2012; Antonelli et al., 2014; Piray et al., 2014; Santangelo et al., 2017; Dawson et al., 2018; Meyer et al., 2019). These dysfunctions can lead to irrational preference for immediate small rewards rather than delayed large rewards (temporal discounting), anticipated decision without enough accumulation of available evidence (reflection impulsivity), and/or biased evaluation of probabilistic gains and losses (probabilistic discounting). ICDs are considered as a side-effect of dopamine replacement therapy (Dodd et al., 2005; Weintraub et al., 2010; Leroi et al., 2013; Antonelli et al., 2014; Lopez et al., 2017; Voon et al., 2017). Thus, their management mainly involves discontinuing or decreasing dopamine agonists (Samuel et al., 2015; Cossu et al., 2018). 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; Rabinak and Nirenberg, 2010; Pondal et al., 2013; Samuel et al., 2015), and even does not guarantee symptoms remission at follow-up (Ávila et al., 2011; Cilia et al., 2016). A better understanding of these disorders is mandatory to develop more efficient therapeutic strategies (Grall-Bronnec et al., 2018).

Actually, the cognitive and neural bases of ICDs in PD have not been completely elucidated to date. Results of neuroimaging studies are largely inconsistent (see Meyer et al., 2019 for recent review). They show numerous possible abnormalities in the mesocorticolimbic circuits consistent with various dysfunctions of object and action valuation caused by biased probability estimation or reward processing, indeed. But abnormalities are also frequently observed in many other brain regions (Cilia et al., 2008, 2011; Frosini et al., 2010; Rao et al., 2010; van Eimeren et al., 2010; Voon et al., 2011; Politis et al., 2013; Carriere et al., 2015; Imperiale et al., 2017; Tessitore et al., 2017; Petersen et al., 2018). 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; Rao et al., 2010; van Eimeren et al., 2010; Kassubek et al., 2011; Voon et al., 2011; Politis et al., 2013). These studies did not test the possibility of response inhibition dysfunctions (motor impulsivity). Yet, studies of impulsivity in psychiatric conditions (Dalley and Robbins, 2017) as well as neuropsychological and behavioral investigations in PD (Nombela et al., 2014; Voon, 2014) suggest that multiple modes of impulsivity are likely to develop in ICDs. Second, neuroimaging studies mostly used fMRI or SPECT/PET, although blood flow changes 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.

Assessing resting state brain activity is essential for identifying clinically relevant brain dysfunctions (Eidelberg, 2009). This allows probing simultaneously the functional integrity of a variety of networks which specific dynamics can only be assessed separately in various functional imaging studies. Here, we analyzed resting state oscillations with high-density electroencephalography (EEG) in PD patients with and without ICDs. Indeed, EEG provides better cortical functional discrimination power than blood flow-derived measures often privileged for resting state studies since frequency-specific activity provides markers of particular cognitive functions, even at rest (e.g., Siegel et al., 2012; Cohen, 2017). This discrimination power is essential for separating multiple neural activities that might be confounded otherwise. This is especially true if spectral analyses are performed directly at the source level after blind source separation –BSS-, and might for instance be helpful for disentangling excitatory from inhibitory activity through analyses of alpha activity (Klimesch et al., 2007; Lorincz et al., 2009; Jensen and Mazaheri, 2010; Mathewson et al., 2011). In order to investigate all cortical networks potentially involved in ICDs' impulsivity, we performed whole-brain analyses without a priori about the anatomofunctional origins of the disorder.

Although we are here testing more specifically the neglected motor hypothesis, it is worth mentioning that the cognitive and motor hypotheses make distinct predictions not only about the anatomy of the circuits displaying cortical activity changes at rest, but also about the spectral signatures of these changes. The cognitive account of impulsivity predicts differences in the mesocorticolimbic system, the orbitofrontal and the lateral prefrontal cortices (e.g., Aracil-Bolaños and Strafella, 2016; Marques et al., 2018; Vriend, 2018), mainly expressed in the delta and theta bands (van Wingerden et al., 2010; Knyazev, 2012; Nacher et al., 2013; Cavanagh, 2015; Pinner and Cavanagh, 2017; Fatahi et al., 2018). The motor account 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) (Aron, 2011; Criaud and Boulinguez, 2013; Manza et al., 2016; Criaud et al., 2017), mainly expressed in the alpha and beta bands (Supplementary Table 1) (Zhang et al., 2008; Criaud and Boulinguez, 2013; Huster et al., 2013; Kilavik et al., 2013; Hwang et al., 2014; Fonken et al., 2016; Liebrand et al., 2017). Importantly, we will perform whole brain and large spectrum analyses in order not to miss the potential contribution of unpredicted 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 ≥ 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 et al., 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:

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

where d = delta/standard deviation, α = alpha (the probability of a type I error), $\beta = 1 -$ power (the probability of a type II error) 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 (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 (n) is 18. This sample size was also determined in agreement with former specific recommendations regarding EEG group blind source separation analyses (Lio and 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, cognitive impairment (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 collection due to difficulties inherent to bedside acquisition (excessive unfilterable noise, defective electrodes). In the end, two groups of 22 ICDs+ and 17 ICDs− were included in the analysis. 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 local Ethical Committee of the Parkinson Institute, Milan (Italy).

2.2. Design and procedure

Resting state activity was recorded over two continuous periods of 10 min. Subjects comfortably sat and were instructed to stay quietly with the eyes closed. The EEG signal was recorded at a sampling rate of 4096 Hz with the BioSemi™ ActiveTwo Mk2 system from 128 electrodes (BioSemi™ ABC system standard locations, electrode offsets < 20 mV). Six supplementary electrodes were used in temporal (Biosemi spherical coordinates: Phi −103.5 Theta −18 −36; Phi 103.5 Theta 18 36) and eye (Phi 103.5–103.5 Theta 81–81) regions. The CMS active electrode and the DRL passive electrode served to create a feedback loop steering the average potential of the participant in the Common Mode voltage.

2.3. Data analyses

A flowchart of methods pipeline is presented in Fig. 1 to summarize data analyses strategy.

2.3.1. Preprocessing

First, the quality of each electrode signal was checked, and spherical interpolation was used when necessary. Data were

Table 1
Patients characteristics.

	PD-ICDs+	PD-ICDs−	p-value
Demographics			
Number	22	17	–
Sex	20 M/2F	16 M/1F	–
Age	62.3 ± 7.0	59.5 ± 7.4	0.23
Disease duration	10.4 ± 4.9	7.9 ± 3.7	0.09
Clinical characteristics			
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
Neuropsychological assessment			
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.

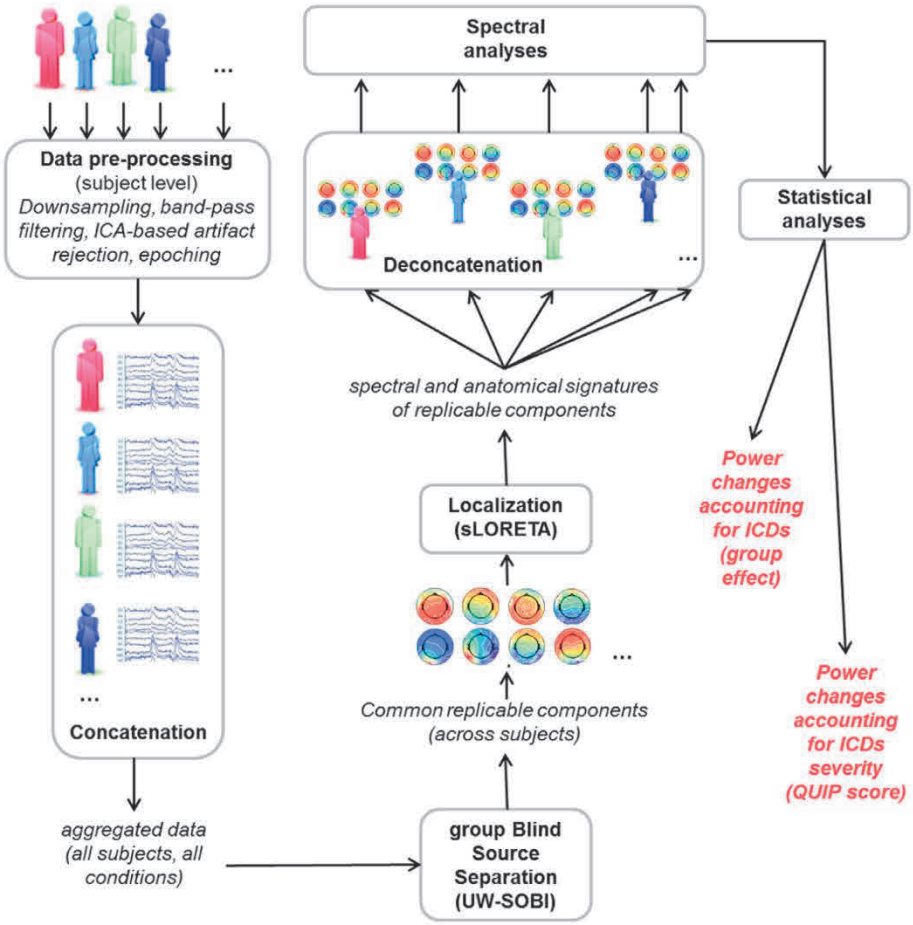

Fig. 1. Overview of data processing and analysis pipeline.

down-sampled at 2048 Hz, filtered (High-pass 0.5–1 Hz; Low-pass 46–48 Hz) and set to average reference. First, artifacts (movement-induced perturbations including especially eye movements, ballistocardiac noise, electrode displacements and other electrical noises) were rejected by means of independent component analysis (ICA)/blind source separation (BSS) (UWSOBI, 300 times delays; (Yeredor, 2000) and the EEGLAB toolbox (Delorme and 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. The Frobenius norm between the covariance matrix of each epoch and the covariance matrix of the mean dataset was calculated. 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 provides an efficient solution to the issue of multi-subject analysis by concatenating data from all subjects. A unique mixing matrix is therefore obtained for the whole group of subjects, as well as a unique demixing matrix after separation. The main advantage of the method is that gBSS reveals the independent components (ICs) that are consistently expressed across subjects (Eichele et al., 2011; Huster et al., 2015; Huster and Raud, 2018; Lio and Boulinguez, 2018). A potential benefit of this method is a better sensitivity for the identification of substantial sources that might be hidden by the most energetic ones (Sutherland and Tang, 2006). We employed UWSOBI, an algorithm relying on the approximate joint diagonalization of lagged-covariance matrices (SOS). We have recently demonstrated that this class of algorithms is especially adapted to gBSS because it is insensitive to inter-subjects differences in neuroanatomy and does not require deleterious dimension reduction before separation (Lio and Boulinguez, 2018). This method is especially adapted here because it separates the sources on the basis of time-frequency information, not on the basis of data distribution characteristics as classical higher order statistics data-based algorithms do (e.g., FASTICA or INFOMAX, see Lio and Boulinguez, 2013). This is more convenient when searching spectral signatures of cognitive processes, but this is also more convenient because SOS-based algorithms are more robust to the distortions of the mixing matrix that are inevitable in gBSS (Lio and Boulinguez, 2013, 2018). Basically, after a set of matrices of SOS between electrodes has been estimated and made symmetric – time delayed covariance is not symmetric-, a linear transformation that enhances spectral diversity between sources is searched -the mixing matrix is calculated by approximate joint diagonalization of the whole set-. Importantly, the output of the separation provides components that are statistically independent regarding the parameters used for separation (whole spectrum signature). This does not mean that independent components cannot be functionally connected and part of the same neural network, i.e., cannot provide similar or interrelated activation patterns in response to specific events or conditions within specific frequency bands.

For each epoch, 300 lagged-covariance matrices (time delays: 0/2048 s to 300/2048 s) were calculated, averaged across dataset epochs, and finally across subjects. In the end, a total of 600 lagged-covariance matrices have been approximately joint-diagonalized by means of the UWEDGE algorithm (Tichavsky and Yeredor, 2009), leading to the detection of 134 ICs. Thanks to this averaging procedure, inter-epochs and inter-subject variability

was reduced while sources with spectral modifications between ICDs+ and ICDs− were highlighted (Ramoser et al., 2000; Congedo et al., 2008). Brain regions explaining the group effect (ICDs+/ICDs−) were revealed by sorting components by percent of explained variance. Components explaining at least 1% of variance were retained for further analyses (n = 10).

2.3.3. Independent components source localization

To identify the neuronal generators of the electrical patterns recorded on the scalp, standardized low resolution electromagnetic tomography was performed with the sLoreta software (Pascual-Marqui, 2002). The cortical distribution of the electric neuronal activity generating each IC on the basis of its topography was estimated (solving the inverse problem). sLoreta uses the current density estimate obtained from the minimum norm estimate, and standardizes it by means of its variance. Here, standardized current source density was calculated at each of the 6239 voxels (resolution: 5 mm) of a head model built on the basis of the boundary element method -BEM- and the MNI152 template (Mazziotta et al., 2001). The 3D solution space was constrained to gray matter, and sLoreta solutions were calculated with an amount of Tikhonov regularization optimized for an estimated Signal/Noise Ratio of 100. The output is a map of current density power (arbitrary units) whose maximum value corresponds to the exact generating dipole location in noise-free conditions.

2.3.4. Blind spectral analysis

We performed analysis of resting state spectral activity without a priori knowledge about anatomical sources or frequency bands. The ICs obtained with group BSS were used as a filter to go back to subject level for spectral analysis (deconcatenation). For each dataset of each PD patient, and each one of the 10 ICs accounting at least for 1% of explained variance (group effect), relative power was estimated. 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:

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

2.3.5. Statistical analyses

Two analyses were performed in order to test our predictions twice: 1) by comparing ICDs+ and ICDs−, 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:

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

where b_1, b_2, b_3 represent the parameters to be estimated for the first, second and third factors, respectively, and b_4 represents the estimated intercept.

2.3.5.2. Oscillatory modulations predicting ICDs severity (QUIP score, ICDs+ only). For each IC and each frequency band, a multiple regression analysis was applied based on one factor of interest (the $QUIP_A$ – ICDs score) and two factors of no-interest (the UPDRS-III score and the LEDD):

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

where b_1, b_2, b_3 represent the parameters to be estimated for the first, second and third factors, respectively, and b_4 represents the estimated intercept. 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.

Multiple testing correction was performed when appropriate by means of false discovery rate (FDR) estimation.

3. Results

Results (controlled for motor performance -UPDRS-III score- and medication -LEDD-) are summarized in Fig. 2.

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 (Frosini et al., 2010; Rao et al., 2010; Politis et al., 2013; Aracil-Bolaños and Strafella, 2016; Voon et al., 2017; Marques et al., 2018) or rejected in behavioral studies (e.g., Rossi et al., 2009; Bentivoglio et al., 2013; Leroi et al., 2013; Yoo et al., 2015; Pineau et al., 2016; Ricciardi et al., 2017) up to date. Here, we used a resting state design and EEG to probe the functional integrity of all the cortical networks that

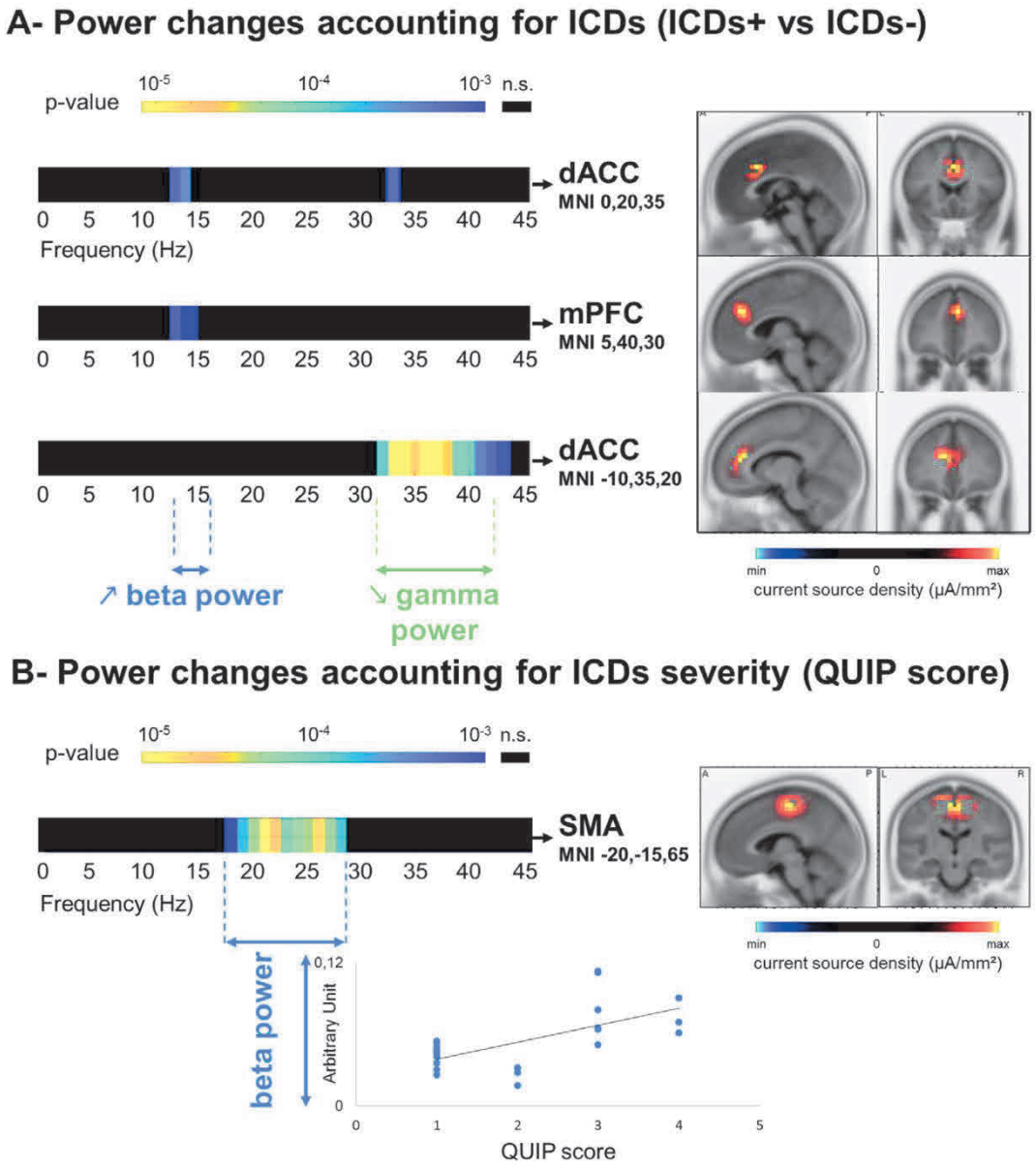

Fig. 2. Resting state cortical oscillatory activity (spectral power) predicting impulse control disorders. (A) Group effect, controlled for UPDRS-III and LEDD. The left side of the figure displays the frequency bands in which significant differences are observed for each one of the identified sources. The right side of the figure shows the location (current density map obtained with sLoreta) of the corresponding source. (B) Power changes correlating with ICDs severity (as indexed by QUIP scores), controlled for UPDRS-III and LEDD. The left side of the figure displays the frequency bands in which significant differences are observed. The right side of the figure shows the location (current density map obtained with sLoreta) of the unique source revealing power changes predicting ICD severity.

might be dysfunctional in ICDs in the hope of finding a proof of concept for the contribution of motor impulsivity to PD-ICDs. First, by contrast with blood flow imaging studies, EEG provides a direct measure of neural activity and a fair functional discrimination power. Indeed, cognitive processes have spectral signatures (Siegel et al., 2012; Keitel and Gross, 2016). Second, as it is challenging to test specifically all mechanisms involved in motor impulsivity (e.g., Criaud et al., 2017), and as brain activity during tasks (i.e., the functional architecture of cortical networks) is partly already reflected in intrinsic activity at rest (Raichle, 2015), this is an ideal starting point to probe resting state activity for the analysis of general brain function (Keitel and Gross, 2016). As illustrated in Supplementary Table 1, our original approach exploits the observation that the motor and the decisional hypotheses of impulsivity make distinct predictions regarding the cortical and spectral origins of ICDs.

4.1. Power modulation in brain regions supporting global motor inhibition

We clearly identified power modulations accounting for ICDs in a medial ensemble of areas including the mPFC, the dACC and the SMA (Fig. 2). These areas have repeatedly been found to form a functional network supporting global motor inhibition in task-based imaging studies (Jaffard et al., 2008; Criaud et al., 2017) 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 et al., 2009; Criaud et al., 2012, 2016). 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 consistent with the hypothesis according to which dysfunctions of motor inhibition account for ICDs (Rubia et al., 2001; Jaffard et al., 2008; Brevers et al., 2012; Criaud and Boulinguez, 2013; Albares et al., 2014; Manza et al., 2016).

4.2. Power modulation in frequency bands associated with motor processes and executive control

Although in some instances the ACC and the mPFC have been associated with decision making (Paus, 2001; Botvinick, 2007; Gasquoine, 2013; Shenhav et al., 2016; O'Doherty et al., 2017), 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 (Wacker et al., 2009; Park and Moghaddam, 2017). 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 et al., 1997). It is of interest to note that a broad increase in beta rhythm is a hallmark of PD (Oswal et al., 2013; Stein and Bar-Gad, 2013). In addition, some studies have also associated low gamma waves to executive and motor control (Engel and Fries, 2010; Karch et al., 2012; Gaetz et al., 2013; Stein and Bar-Gad, 2013; Iijima et al., 2015; Fonken et al., 2016) and to cortical inhibition (Jensen et al., 2012, 2014; Bonnefond and Jensen, 2013; Cheng et al., 2016). 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 and 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 et al., 2015a, 2015b; Jahanshahi and 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 et al., 2017).

4.3. Limitations and open issues

It is important to emphasize, however, that our positive results do not contradict the role of cognitive impulsivity in PD-ICDs. Indeed, although particularly useful to detect problems with self-initiation and task-set maintenance in Parkinson's disease (Ko et al., 2013; Tinaz et al., 2016), resting state oscillations can just inform incompletely about the functional integrity of neural networks. The fact that intrinsic activity at rest reflects only to some extent brain activity during tasks (Raichle, 2015) is certainly critical when considering reward-related cognitive mechanisms whose dysfunctions expected for instance in the orbitofrontal or lateral prefrontal cortex have been mainly associated with neural activity induced by cues or signals (Frosini et al., 2010; Voon et al., 2010; Politis et al., 2013). In other words, our data can provide only some clues, but a comprehensive map of dysfunctional cortical networks cannot be expected from resting state studies. In addition, EEG does not provide easy access to subcortical activity, and is therefore blind to substantial activity of the mesocorticolimbic system. Again, the lack of evidence of involvement of the reward system in the present data does not rule out the major hypothesis of mesocorticolimbic dysfunctions. Further, another issue related to patient's demographics must be acknowledged for critical appraisal: Group differences were observed for several clinical variables (Table 1). Most were expected because they are either inherent in disease management or a common comorbidity of ICDs like, respectively, medication status (e.g., Samuel et al., 2015; Cossu et al., 2018; Mamikonyan et al., 2008) and depression (Antonini et al., 2017; Martini et al., 2018). But the fact that patients with ICDs may have shorter disease duration ($p = 0.09$) represents a potential bias.

Nevertheless, our results allow relaunching the debate on the neglected hypothesis of motor inhibition dysfunctions in PD-ICDs (Antonelli et al., 2011; Kehagia et al., 2014; Nombela et al., 2014; Ye et al., 2015). Further studies are needed to provide direct causal evidence that, among the numerous neural mechanisms involved in response inhibition (Chambers et al., 2009; Verbruggen and Logan, 2009; Aron, 2011; Bari and Robbins, 2013; Criaud and Boulinguez, 2013; Li, 2015; Criaud et al., 2017), some might be dysfunctional in PD-ICDs. In this respect it is noteworthy that the valence of beta power changes observed in the present study are difficult to interpret precisely. Indeed, beta activity is known to be involved in different forms of top-down proactive control. It would directly drive, for instance, local inhibition in targeted motor structures (e.g., Hwang et al., 2014). It could also drive, however, the executive setting of local, automatic, self-inhibitory networks that gate information processing locally in the motor system[1] (Albares et al., 2014). The first mechanism predicts decreased beta power as motor impulsivity increases (see also Lee et al., 2017). The second mechanism predicts increased beta power as motor impulsivity increases (see also Threadgill and Gable, 2018). In addition, it is not possible to determine from these data if brain activity changes are a direct expression of ICDs–related dysfunctions or the manifestation of compensatory mechanisms. Another issue here is the fact that we found no difference in alpha power, a direct physiological marker of active inhibition (Klimesch et al., 2007; Jensen and Mazaheri, 2010; Haegens et al., 2011; Mathewson et al., 2011; Klimesch, 2012; Hindriks and van Putten, 2013). This does not mean that no difference in the activity of local inhibitory populations can account for dysfunctions of motor inhibition in ICDs. We just did not find significant modulations of α oscillations at rest. These issues require further investigations using specific behavioral tasks coupled with appropriate event-related brain imaging protocols (e.g., Verbruggen and Logan, 2009; Hu and Li, 2012; Swann et al., 2012; Huster et al., 2013; Zandbelt et al., 2013; Hwang et al., 2014; Lavallee et al., 2014; Albares et al., 2015; Zhang et al., 2015; Wessel et al., 2016; Bartoli et al., 2018; Wagner et al., 2018).

[1] This is a paradoxical mechanism by which voluntary control of action may be achieved. The ability to provide controlled responses in unpredictable environments would require the automatic activation of the self-inhibitory circuitry within the SMA (i.e., automatic inhibition of automatic responses). Conversely, enabling automatic behavior when the environment becomes predictable would require top-down control to deactivate anticipatorily and temporarily the default and automatic inhibitory set. For this inhibitory mechanism, more control (more β) would mean more automatic (more impulsive) behavior (Albares et al., 2014).

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., Obeso et al., 2011; Favre et al., 2013; Michely et al., 2015), and has identified the key role of the noradrenergic (NA) system (Chamberlain et al., 2006, 2009; Chamberlain and Sahakian, 2007; Robbins and Arnsten, 2009; Chamberlain and Robbins, 2013). 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 serotoninergic (5HT) system (Eagle et al., 2008; Pattij and Vanderschuren, 2008; Bari et al., 2009; Paterson et al., 2012; 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; Ye et al., 2015; Rae et al., 2016). This approach is successful in psychiatric conditions with impulsivity symptoms like Attention Deficit Hyperactivity Disorder (Pattij and Vanderschuren, 2008; Dalley and Robbins, 2017), but is still to be tested in clinical trials for PD-ICDs (Tanwani et al., 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 (Del Campo et al., 2011; Dalley and Robbins, 2017).

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Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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., G.M.; 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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2.2.2 Démonstration d'un trouble du contrôle inhibiteur dans une tâche de Go/NoGo

Article 3: Inhibitory control dysfunction in parkinsonian impulse control disorders

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Inhibitory control dysfunction in parkinsonian impulse control disorders

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Impulse control disorders (ICDs) in Parkinson's disease have been associated with dysfunctions in the control of value- or reward-based responding (choice impulsivity) and abnormalities in mesocorticolimbic circuits. The hypothesis that dysfunctions in the control of response inhibition (action impulsivity) also play a role in Parkinson's disease ICDs has recently been raised, but the underlying neural mechanisms have not been probed directly. We used high-resolution EEG recordings from 41 patients with Parkinson's disease with and without ICDs to track the spectral and dynamical signatures of different mechanisms involved in inhibitory control in a simple visuomotor task involving no selection between competing responses and no reward to avoid potential confounds with reward-based decision. Behaviourally, patients with Parkinson's disease with ICDs proved to be more impulsive than those without ICDs. This was associated with decreased beta activity in the precuneus and in a region of the medial frontal cortex centred on the supplementary motor area. The underlying dynamical patterns pinpointed dysfunction of proactive inhibitory control, an executive mechanism intended to gate motor responses in anticipation of stimulation in uncertain contexts. The alteration of the cortical drive of proactive response inhibition in Parkinson's disease ICDs pinpoints the neglected role the precuneus might play in higher order executive functions in coordination with the supplementary motor area, specifically for switching between executive settings. Clinical perspectives are discussed in the light of the non-dopaminergic basis of this function.

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Abbreviations: gBSS = group blind source separation; IC = independent component; ICDs = impulse control disorders; SMA = supplementary motor area

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Introduction

Impulse control disorders (ICDs) in Parkinson's disease, including pathological gambling, hypersexuality, compulsive eating and compulsive shopping, are a common side-effect of dopaminergic replacement therapy, which, to date, has no satisfying therapeutic strategy. ICDs have been associated with decisional—also called cognitive or choice—impulsivity (Cilia and van Eimeren, 2011; Meyer *et al.*, 2019). Decisional impulsivity refers to dysfunctions in the control of value or reward-based responding and is associated with dopamine agonist treatment and abnormalities in mesocorticolimbic circuits (Weintraub *et al.*, 2010; Cilia and van Eimeren, 2011; Aracil-Bolaños and Strafella, 2016; Hammes *et al.*, 2019; Meyer *et al.*, 2019). The hypothesis that dysfunctions in the control of motor response inhibition, i.e. motor or action impulsivity, also play a role in the aetiology of Parkinson's disease ICDs has received little interest, obtained little empirical support and has mostly been rejected (for reviews, see Cilia and van Eimeren, 2011; Meyer *et al.*, 2019). However, by reporting brain activity changes in inhibitory control regions, recent data have relaunched the hypothesis that ICDs might include a motor facet through the dysfunction of motor inhibition (van Eimeren *et al.*, 2010; Mosley *et al.*, 2019; Spay *et al.*, 2019; Paz-Alonso *et al.*, 2020). Yet, these studies only provide indirect evidence since the neural mechanisms underlying inhibitory control have not been isolated and addressed in an unconfounded manner. For instance, Spay *et al.* (2019) reported abnormal oscillatory activity in ICDs at rest in circuits supporting response inhibition [medial prefrontal cortex, rostral cingulate zone and supplementary motor area (SMA)], but did not directly test response inhibition. Mosley *et al.* (2019), too, did not directly probe response inhibition functions, but described a link between weaker structural connectivity of the response inhibition network and behavioural markers of pathological gambling. van Eimeren et al. (2010) reported dopaminergic activity changes in Parkinson's disease gamblers with PET during a card selection task in non-overlapping brain areas that have also been shown to be more or less directly involved in response inhibition (lateral orbitofrontal cortex, amygdala, external pallidum), but did not directly test response inhibition either. Paz-Alonso *et al.* (2020) used more sophisticated event-related and connectivity analyses with functional MRI in a reward-based task. They reported in patients with ICDs the involvement of various dysfunctions of a right-lateralized network of regions that are supposed to be associated with inhibitory control (subthalamic nucleus, ventral striatum, inferior frontal gyrus, insula). While there are many converging arguments in this study, there are, however, still potential confounds between reward-related and inhibitory-related activity since the slow event-related design was based on gambling-related cues. More generally, the large overlap that exists between the reward and inhibition networks as identified in the literature (e.g. ventral striatum, insula, subthalamic nucleus, anterior cingulate, inferior frontal gyrus) (Criaud and Boulinguez, 2013; Meyer *et al.*, 2019) prevents us from concluding that inhibitory dysfunctions account for impulsive behaviour when one of these regions shows reward-related activity changes (reverse inference issue) (Poldrack, 2006).

All of these observations allow for raising the hypothesis that inhibitory dysfunctions could account for abnormal activity during reward processing or at rest, but do not demonstrate inhibitory dysfunctions in Parkinson's disease with ICDs with respect to Parkinson's disease without ICDs. To this aim, it is mandatory to ensure that the neural mechanisms involved in inhibitory control are probed directly irrespective of reward processing. Here, we capitalize on recent theoretical and methodological developments that now allow testing of a range of possible mechanisms of response inhibition within a single experimental design while tracking their dynamical and spectral fingerprints directly at the EEG source level in a simple visuomotor task involving no selection between competing responses and no reward.

Material and methods

A modified version of the Go/NoGo task was used to probe different types of inhibitory mechanisms that were not all tested in previous studies using Stop-Signal Task, classical Go/NoGo Task or Continuous Performance Task (Criaud *et al.*, 2017). The present experiment is a follow-up study of Spay *et al.* (2019) using the same equipment and the same group of patients in a resting state study.

Participants

Twenty-seven patients with Parkinson's disease (23 males, four females) with ICDs (ICD+) and 22 patients with Parkinson's disease (18 males, four females) without ICDs (ICD–) were enrolled. ICD+ patients had current ICDs despite previous treatment adaptation. All the patients underwent a 30-min semistructured interview by experienced neuropsychologists to confirm the diagnosis of ICDs according to established diagnostic criteria (Siri *et al.*, 2015). Inclusion criteria were: age between 40 and 70 years old, with idiopathic Parkinson's disease according to MDS clinical diagnosis criteria (Postuma *et al.*, 2015), benefiting from a stable antiparkinsonian drug therapy for at least 2 months. Exclusion criteria were: dementia [Mini-Mental State Examination (MMSE) < 26], other neurological or psychiatric disease, pharmacological treatment with cerebral or psychic impact, substance abuse according to the criteria DSM-IV-TR (except tobacco smoking). Patients were tested in the morning in the ON state, on their usual medication. Clinical and neuropsychological assessment included the MMSE, the Frontal Assessment Battery (FAB), the Minnesota Impulsive Disorders Interview (MIDI) and the

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Table 1 Patients characteristics

	PD-ICDs+	PD-ICDs–	*P*-value
Demographics			
n	22	19	–
Sex	21M / 1F	17M / 2F	–
Age	61.2 ± 7.0	58.4 ± 7.9	0.24
Disease duration	9.6 ± 4.8	7.8 ± 3.5	0.19
Clinical characteristics			
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^{-7}
Fluctuations	15 yes / 7 no	5 yes / 14 no	
Hoehn and Yahr stage	1.8 ± 0.7	1.6 ± 0.7	0.28
Predominant type, [type]*n*	[AR]15 [TD]7	[AR]17 [TD]2	
UPDRS-III (ON)	11.8 ± 6.2	10.4 ± 7.8	0.51
Neuropsychological assessment			
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), [ICD #]*n*	[1]12; [2]7; [3]1; [4]2	0	–
QUIP (ABC), [ICD #]*n*	[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	–

Values are given as mean ± standard deviation. AR = akineto-rigid; BDI = Beck Depression Inventory; BIS = Barratt Impulsiveness Scale; DAAs = dopamine agonists; DDS = dopamine dysregulation syndrome; F = female; FAB = Frontal Assessment Battery; M = male; MMSE = Mini-Mental State Examination; QUIP = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; TD = tremor-dominant subtypes of Parkinson's disease (PD) patients; Total LEDD = total levodopa equivalent daily dose (mg/day); UPDRS-III = Unified Parkinson's Disease Rating Scale (part III).

Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease (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), the evaluation of the presence of motor fluctuations (sum of items 36 to 39 of the UPDRS part IV different from 0) and the evaluation of Hoehn and Yahr stage. Data from three participants had to be discarded following inabilities to perform the task while data from seven participants had to be discarded following technical issues during data acquisition. Ultimately, two groups of 22 ICD+ (21 male, one female) and 19 ICD– (17 male, two female) patients of similar age, disease duration, levodopa equivalent daily dose (LEDD) and UPDRS- III were included. The main demographic and clinical characteristics of the patients are displayed in Table 1.

This study was performed in agreement with the principles of the Declaration of Helsinki and the protocol was approved by the local Ethical Committee of the Parkinson Institute, Milan, Italy. Written informed consent was obtained from all the patients before the study.

Behavioural task

Principle

Patients performed a simplified Go/NoGo task developed by our group (Criaud and Boulinguez, 2013; Albares *et al.*, 2015; Criaud *et al.*, 2017) (Fig. 1A). In this task, different inhibitory mechanisms might be involved (Fig. 1B). Action restraint can first be achieved through proactive mechanisms. Proactive inhibition operates as a gating process implemented in anticipation of stimulation, which suppresses movement initiation function when the context is uncertain (Jaffard *et al.*, 2007, 2008; Criaud *et al.*, 2017). Here, context uncertainty has been manipulated in different blocks of trials mixing up or not target stimuli requiring a response (Go) and non-target stimuli requiring to refrain from reacting (NoGo). In mixed blocks, equiprobable Go and NoGo trials could be presented (uncertain context). In pure blocks (control condition), no NoGo stimuli could be presented (Go_control trials only), meaning that action restraint was no longer required since there was no uncertainty about the nature of the upcoming event [contrast 1, (Go – Go_control)]. Response inhibition can also be achieved by

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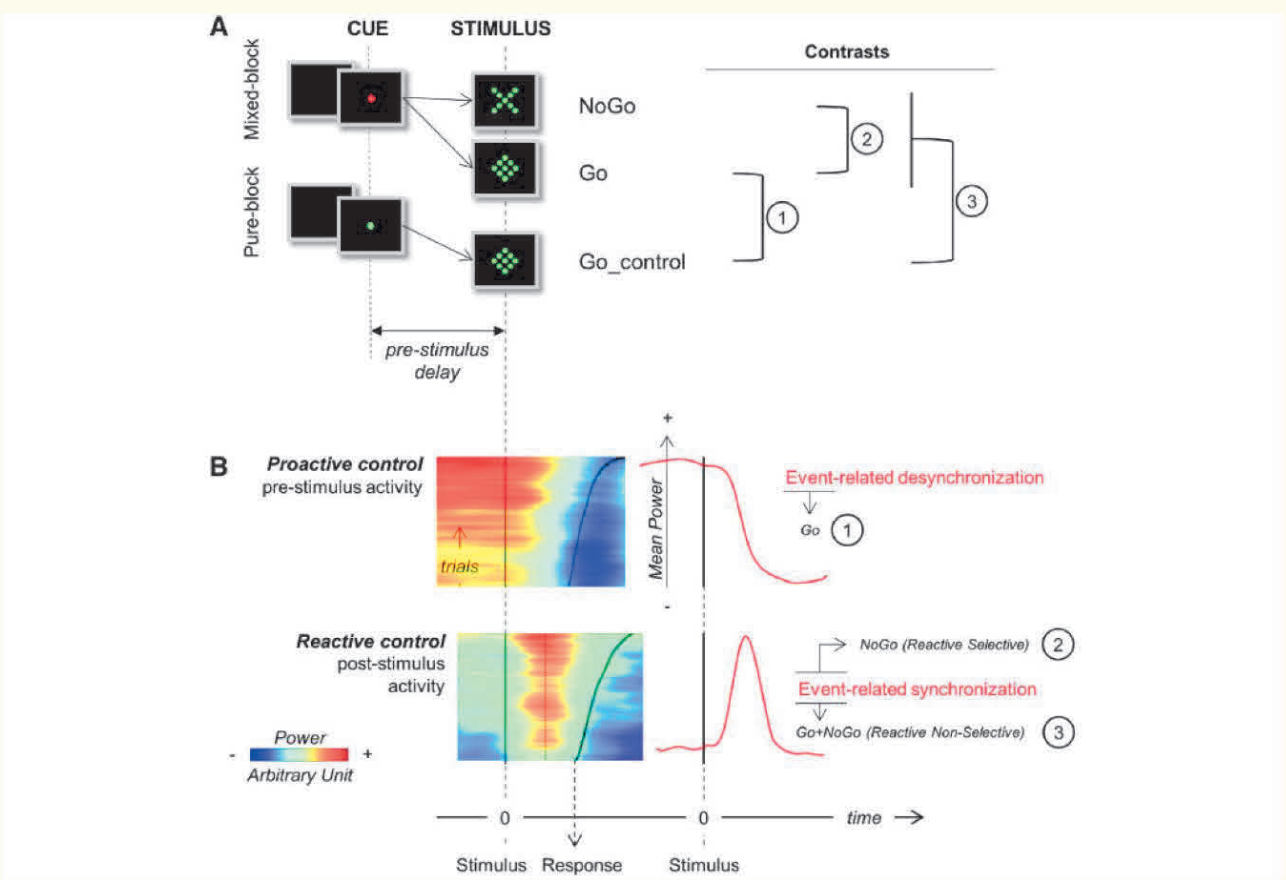

Figure 1 Design and rationale. (**A**) Illustration of the experimental design used to assess three different forms of inhibitory control with a Go/NoGo task. Participants were asked to react as fast as possible to a Go stimulus (diamond) by means of a button press, or to withhold the prepotent response to an equiprobable NoGo stimulus (X). (**B**) The different possible forms of response inhibition have distinct dynamical signatures in the brain, accessible after spectral analysis at the source level. A tonic brain activity that occurs in anticipation of stimulation and desynchronizes after the presentation of a Go or NoGo signal is typical of proactive inhibitory control (contrast 1). Spectral activity specifically induced by NoGo stimuli (event-related synchronization) might be indicative of selective reactive inhibition (contrast 2). Spectral activity induced by a stimulus, whatever the stimulus, when the context is uncertain is likely to pinpoint non-selective reactive inhibition (contrast 3). Examples of power time series in healthy participants are presented on a trial-by-trial basis [concatenated data sorted according to reaction time (black curve), *left*] and on a mean power basis (*right*). All illustrations are adapted from Criaud *et al.* (2017) and Albares *et al.* (2015).

means of late, reactive mechanisms specifically triggered by the stimulus subjects must refrain from reacting to, but not by the Go stimulus subjects must react to (Rubia *et al.*, 2001; Swick *et al.*, 2011). These selective reactive mechanisms have been assessed by contrasting NoGo and Go trials (contrast 2). Finally, response inhibition might also be achieved by means of reactive mechanisms triggered non-selectively and automatically by any stimulus (either Go or NoGo) when the context is uncertain, but not when there is no need to refrain from reacting. This form of automatic inhibition is intended to counteract automatic responses (affordances) to stimuli that have not yet been fully identified (Jasinska, 2013; Albares *et al.*, 2014) or when time is needed to settle on the decision to act or the decision to choose between actions (Frank, 2006; Wiecki and Frank, 2013). As this function is context-dependent and requires an executive setting (Chiu and Aron, 2014), it has been assessed here by means of contrast 3 [(Go + NoGo) – Go_control] (Fig. 1).

In this task, the rate of erroneous responses to NoGo stimuli (commissions) is indicative of impulsive behaviour. Since non-selective, context-dependent mechanisms of response inhibition apply to all stimuli, long latency voluntary responses are usually provided after the initial response to a Go stimulus has been suppressed. Therefore, in this task reaction time (RT) is indicative of the level of proactive inhibition and/or the involvement of non-selective reactive inhibition.

Apparatus and procedure

A panel equipped with light-emitting diodes (LEDs; 5 mm diameter, 8800 mcd) was used to present the visual stimuli. One LED was placed in the centre of the panel and set at

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the subject's eye level. It served as a fixation point for the eyes and indicated the beginning of the trial and the type of block (green: pure block or red: mixed-block). The target stimulus (Go) was composed of eight other LEDs forming a green diamond. The NoGo stimulus was composed of eight LEDs forming a green cross. A feedback stimulus was composed of four LEDs forming a square (green: correct response or red: incorrect response). Go, NoGo and feedback stimuli were centred on the fixation point and occupied 3.44° of visual angle. Stimuli were presented, and data were acquired using a real time acquisition system (ADwin Pro, Keithley Instruments) controlled by MATLAB™ software (RRID: SCR_001622).

The participants were seated in a darkened room in front of a screen placed 50 cm from their eyes. The appearance of the fixation point indicated the beginning of a trial and lasted until the presentation of the stimulus. Prestimulus delays (time between the beginning of a trial and stimulus presentation) varied randomly from 2 s to 4 s in steps of 500 ms. The stimuli (Go or NoGo) were presented for 50 ms. Participants were asked to react as fast as possible to target presentation by pressing a button with their right index within 1 s timing. Feedback was given to the subject to indicate if the response was correct (green square) or not (red square). The intertrial interval was up to the subject who had to press a button with the left index to go on to the next trial. This procedure allowed participants to take as many rest breaks as necessary. Participants were instructed to comply with a maximum error rate (commissions and omissions) of 20% of all trials to ensure a good understanding of the task. A block design was used to test the two conditions separately. Four blocks of trials (two mixed blocks, two pure blocks) were presented in a counterbalanced order between participants (ABBA or BAAB). Pure blocks were composed of 35 Go_control trials each, for a total of 70 Go_control trials per subject. Mixed blocks were composed of 35 Go trials and 35 NoGo trials each, randomly presented, for a total of 70 Go trials and 70 NoGo trials per subject. Participants were trained with the task before starting the experimental sessions (two pure blocks, one mixed block).

EEG recordings

Principle

We used high-density EEG for the strong functional discrimination power it provides through spectral analyses, as frequency-specific activity provides markers of cognitive-specific mechanisms. Of particular interest is the possibility to disentangle the active inhibitory mechanisms that gate information processing (active inhibition) from top-down signalling and communication between control areas (cortical drive), indexed by alpha and beta oscillations, respectively (Engel and Fries, 2010; Jensen and Mazaheri, 2010; Kilavik *et al.*, 2013; Albares *et al.*, 2015; Liebrand *et al.*, 2018). Importantly, the spectral dynamics of the different mechanisms possibly involved in inhibitory control (Fig. 1B) has been assessed directly at the source level, thanks to procedures based on group blind source separation (gBSS) issued from recent methodological developments (Lio and Boulinguez, 2013, 2018; Albares *et al.*, 2015; see Albares *et al.*, 2014 for analyses of reactive inhibition and Spay *et al.*, 2018 for analyses of proactive inhibition). To investigate all cortical networks potentially involved in impulsivity related to ICDs, we performed whole-brain/whole spectrum analyses replicated from our previous work in healthy subjects (*ibid*). Figure 2 presents an overview of the processing pipeline.

Apparatus and procedure

The BioSemi™ ActiveTwo Mk2 system (31.25 nV resolution) 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 CMS active electrode and the driven right leg 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 analogue-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 4096 Hz.

Data preprocessing

Data were downsampled at 2048 Hz, filtered (high-pass 0.5–1 Hz; low-pass 46–48 Hz; attenuation 80 dB) and set to average reference. Then, data were epoched from 1500 ms before stimulus onset to 1000 ms after stimulus onset. Two steps were implemented to reject artefacts. For each subject and each block of trials (pure block, mixed block), corrupted epochs and artefacts (blinks, eye movements, ballistocardiac noise and other electrical noises) were detected and rejected using a first independent component analysis (ICA)/blind source separation (BSS) (UWSOBI, 300 time delays; Yeredor, 2000) and the EEGLAB toolbox (Delorme and Makeig, 2004). Then, in a second step, 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 were rejected.

Group blind source separation

We applied gBSS for the detection of task-related sources. This approach offers a straightforward and computationally tractable solution to the problem of multisubject analysis by creating aggregate data containing observations from all participants. By providing a single estimation of the mixing and the demixing matrices for the whole group, gBSS allows direct estimation of the components that are consistently

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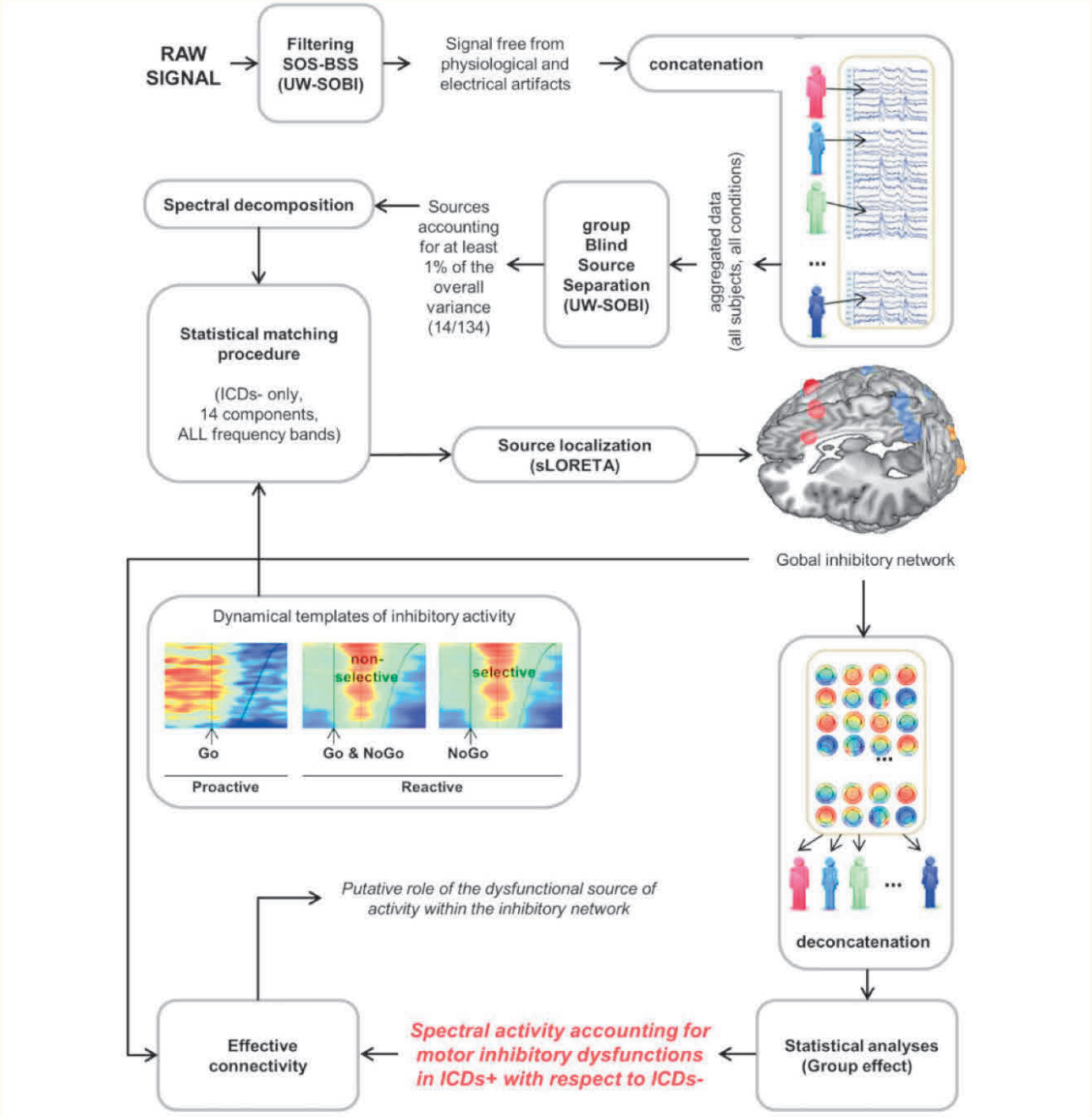

Figure 2 Data processing pipeline configuration. See text for details.

expressed in the population (Eichele *et al.*, 2011) and, hence, more efficient source separation and localization of these components (Lio and Boulinguez, 2013). A potential benefit of this method is a better sensitivity for the detection of critical sources that are often occulted by the most energetic phenomena (Sutherland and Tang, 2006). We used UWSOBI, a Second Order Statics-based gBSS algorithm based on the approximate joint diagonalization of lagged covariance matrices since this method is robust with respect to anatomo-functional intersubject variability and can separate group-specific uncorrelated sources with non-proportional power spectra without deleterious prior dimension reduction (Lio and Boulinguez, 2018). This method is especially convenient here because it separates the sources based on their spectral signatures (Albares *et al.*, 2015). Two hundred lagged covariance matrices with time delays from 0/2048 s to 200/2048 s were calculated on each epoch. Lagged covariance matrices were then averaged across the dataset epochs, and then across patients, so that 200 lagged covariance matrices were approximately joint-diagonalized

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with the UWEDGE algorithm (Tichavsky and Yeredor, 2009), leading to the identification of 134 independent components (ICs). With this averaging procedure, inter-epoch and intersubject variabilities were reduced without impeding the capacity to identify sources with spectral modifications between groups later on (Ramoser *et al.*, 2000; Congedo *et al.*, 2008). The components were sorted by per cent of explained variance. All components explaining >1% of the overall variance of the signal were selected for further analyses.

Spectral decomposition

To obtain all recordable sources underlying inhibitory control, we carried out blind spectral analyses without *a priori* anatomical sources or frequency bands. We assessed trial-by-trial modulations for all ICs explaining >1% of overall variance in the 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), and low gamma (30.5–44.5 Hz) bands. Spectral decomposition was based on six elliptic infinite impulse response (IIR) bandpass filters designed with the MATLAB signal processing toolbox to get optimal time/frequency resolution. Relatively large pass band widths were set to get optimal estimation of the temporal dynamics of the frequency bands of interest at the single trial level. Detailed specification of the filters can be found in Albares *et al.* (2014). Single trial power modulation was then estimated for each source and each frequency band thanks to the Hilbert transform. First, each trial was filtered with the corresponding filter in both forward and reverse directions to insure zero-phase distortion. Second, the complex analytical signal was derived by the Hilbert transform (MATLAB hilbert function). Third, the instantaneous amplitude envelope of the signal was computed by taking the absolute magnitude of the complex waveform. The time window under scrutiny was restricted to 500 ms prestimulus to 800 ms post-stimulus to avoid edge effects/transient responses of digital filters. Finally, for visualization only, a trial moving average smoothing was applied (windows length: 400 trials).

Statistical matching procedure

We used the following rationale to identify the sources potentially involved in inhibitory control: if the mean power of the prestimulus period [–500; 0 ms] was significantly larger than the mean power of the period preceding reaction time [RT – 100 ms; RT] for Go trials (Go-induced desynchronization), then this source/frequency band was considered as playing a possible role in proactive inhibition and was selected for further group analyses. If the mean power of the post-stimulus period [0; 300 ms] was significantly different for Go + NoGo than for Go_control trials, and if the mean power of the post-stimulus period [0; 300 ms] was significantly larger than the mean power of the prestimulus period [–500; 0 ms], then the corresponding source/frequency band was considered as playing a possible role in reactive non-selective inhibition, and was selected for further group analyses. If the mean power of the post-stimulus periods [0; 150 ms], [150; 250 ms] or [250; 350 ms] was significantly larger for NoGo than for Go trials, then the corresponding source/frequency band was considered as playing a possible role in reactive selective inhibition, and was selected for further group analyses. These testing procedures were applied to the control group data only (ICD–) and used Wilcoxon-Mann-Whitney and Wilcoxon signed-rank tests.

Group analyses

Deconcatenation for between-subject analyses has been performed to have access to interindividual variability for further statistical analyses. The consistent ICs revealed at the group level were used as filters for these analyses. This step-back to the individual level allows individual data normalization by calculating the mean relative power within each frequency band with respect to the total power of the EEG signal (whole spectrum) for each single source/subject.

Mean relative power spectral density (PSD) has been estimated for each selected source by means of short-time Fourier transforms (MATLAB signal processing toolbox spectrogram), with a window width of 800 samples and an overlap of 799 in the 1–45 Hz frequency range:

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

where SS*i* is the selected source n°*i*.

Source localization

When relevant, localization was estimated by means of the sLoreta software (Pascual-Marqui, 2002) and 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 grey 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.

Statistical analyses

Behavioural variables

Commissions (erroneous responses to NoGo stimuli) are usually considered as the main behavioural marker of impulsivity and inhibitory dysfunction in Parkinson's disease (Ballanger *et al.*, 2009). The rate of commissions was assessed only in the mixed block condition where erroneous responses to NoGo stimuli are possible. Normality and homoscedasticity were controlled using Lillefors test and Fisher's test, respectively. Between subjects' analyses of mean percentage of commissions were performed after ArcSine transforms. The group effect (ICD + versus ICD–) was tested by means of a one-sided *t*-test for independent samples. Reaction time is known to pinpoint the level of action restraint (Chiu and Aron, 2014). In the Go_control condition, when no inhibition is required, automatic motor activations usually give rise to fast responses. Conversely, when action

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restraint is required in uncertain contexts, proactive inhibition and/or reactive non-selective inhibition prevent fast automatic responses. Volitional responses can be provided only after the Go stimulus has been identified and the executive inhibitory set has been released. This generates long latency responses (Jaffard *et al.*, 2007, 2008; Boulinguez *et al.*, 2008; Criaud *et al.*, 2012, 2017). Accordingly, we assessed the difference in reaction time between Go and Go_control conditions (ΔRT), which is known to index the level of non-selective inhibition (the context-dependent inhibitory set) (Chiu and Aron, 2014). Normality and homoscedasticity were controlled using the Lillefors test and Fisher's test, respectively. The group effect (ICD + versus ICD–) was tested by means of a one-sided *t*-test for independent samples.

EEG variables

For each selected source/frequency band showing relevant proactive activity, mean relative power spectral density during the prestimulus period [–500; 0 ms] was assessed by means of a two groups (ICD + versus ICD–) × two conditions (Go + NoGo versus Go_control) ANOVA. These analyses were performed with R (R Core Team, 2018). *Post hoc* tests used the R package emmeans. *P*-values <0.05 were considered significant. No similar analyses have been applied to reactive non-selective or reactive selective activities as the statistical matching procedure returned no ICs/frequency bands showing significant modulation (see 'Results' section).

Complementary analyses

To understand the role of the dysfunctional components within the global sensorimotor network identified in the previous step, we performed complementary analyses to estimate the directionality and lag between the respective brain activities. Since the spectral dynamics of the dysfunctional neural sources identified in the previous step present patterns consistent with proactive inhibition, we tested the directionality of the relationship between the desynchronizations that occur just before the motor onset. Specifically, we used cross-correlation of instantaneous amplitudes estimated via the Hilbert transform to measure lagged consistency between the desynchronization patterns of the different sources and infer the direction of functional connectivity. This method was privileged over algorithms relying on the concept of Granger causality (which is the standard method to assess this kind of relationships between time series) (Astolfi *et al.*, 2007) because it circumvents the bias related to differences in signal-to-noise ratios between sources (Adhikari *et al.*, 2010). Indeed, when such differences are observed (as it was expected to be the case in this study), the algorithms based on Granger causality interpret the related asymmetries as directions of information flow, leading to false estimations of the directional connectivity (Nolte *et al.*, 2008; Adhikari *et al.*, 2010; Haufe *et al.*, 2013; Bastos and Schoffelen, 2015).

The technique was adapted to focus on task-related changes in cross-correlations, and avoid potential confounds with volume conduction effects leading to spurious false positives (Schoffelen and Gross, 2009; Bastos and Schoffelen, 2015). More precisely, each connection was evaluated with the following procedure: first, the instantaneous amplitude time course of each trial was split in one prestimulus baseline epoch (from 1000 ms to 100 ms before the stimulation onset) and one post-stimulus epoch of interest (–100 ms; 800 ms). Second, for each subject, all epochs were averaged and the resulting average time-course was *Z*-transformed to reduce the non-stationarity of the signal. Then, cross-correlation limited by 200 ms between each pair of components was estimated on an individual basis. Third, each lag was tested using the Wilcoxon-Mann-Whitney test, tracking significant increases in cross-correlations in the post-stimulus period relative to spontaneous cross-correlations in the baseline. Connections showing a lagged correlation with a *P*-value <0.05 (Bonferroni corrected for all tested connections) were deemed significant. For each pair of source/frequency band combinations of interest, the most significant cross-correlation was considered as the most probable connection. If the same minimal *P*-value was observed for two or more different lags, the smallest lag was selected.

Data availability

The data will be made available upon request to the corresponding author.

Results

Behavioural variables

More commission errors were observed for ICD + than for ICD– patients [17.1% versus 7.0%, $t(39) = 3.28$, $P = 0.007$]. Shorter ΔRT was observed for ICD + than for ICD– patients [165.47 versus 193.54, $t(39) = -1.69$, $P = 0.048$]. Control analyses indicated that experiencing motor fluctuations or not (157.63 versus 181.12, $W = 40$, $P = 0.41$) as well as having single ICD or multiple ICDs (163.94 versus 166.50, $W = 66$, $P = 0.72$) did not significantly influence the behaviour (ΔRT) of ICD + patients.

EEG variables

Detailed EEG results are displayed in Supplementary Table 1.

Network involved in inhibitory control as assessed in ICD– patients

The gBSS revealed a network comprising visual, frontal and parietal areas (14 ICs explaining >1% of overall variance) (Fig. 3 and Supplementary Table 1). The statistical matching procedure revealed 47 IC/frequency band combinations with dynamics consistent with proactive inhibition (i.e. Go-induced desynchronization) (Supplementary Table 1).

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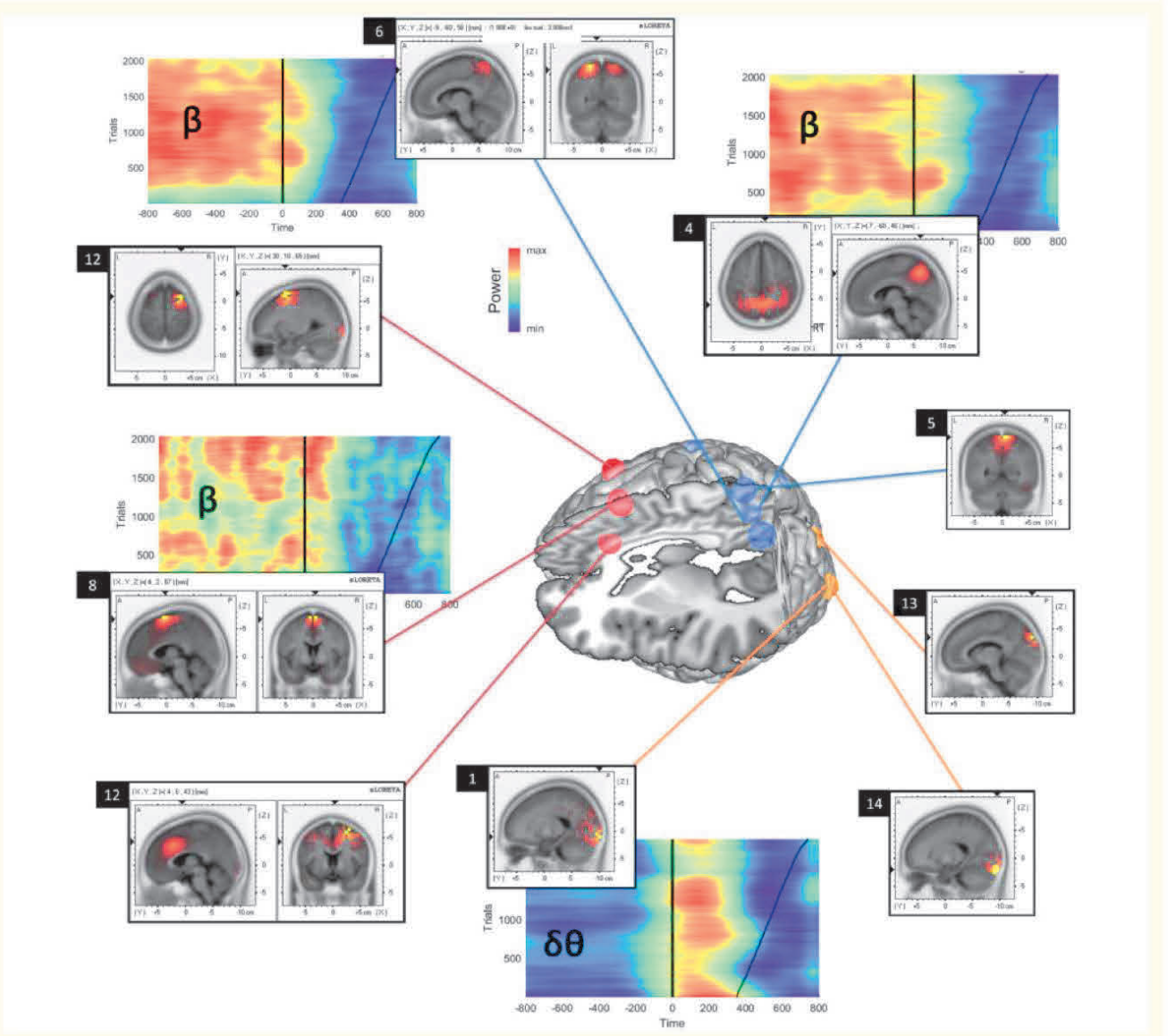

Figure 3 Global network involved in the inhibitory task. Illustration of various independent components (separated with gBSS and localized with sLoreta) and dynamical patterns (predicted by inhibitory models) within different frequency bands (β = beta; δ = delta; θ = theta). IC number is indicated in the black squares. An exhaustive list is presented in Supplementary Table 1.

Fourteen ICs/frequency bands showed stimulus-induced synchronization patterns. However, none revealed significant differences between NoGo + Go and Go_control trials consistent with reactive non-selective inhibition, nor significant differences between NoGo and Go trials consistent with reactive selective inhibition.

Dysfunctional sources in ICD + patients

Among the 47 IC/frequency band combinations showing activity consistent with proactive inhibition, seven showed significant Group × Condition interaction (Supplementary Table 1). Planned *post hoc* comparisons were applied to track the impact of belonging to one or the other group on the ability to modulate as expected proactive activity according to the context (i.e. more power for NoGo + Go trials than for Go_Control trials). Only three IC/frequency band combinations reported a consistent pattern in ICD– patients but a different one in ICD + patients: ICs 4 and 6 centred on the precuneus (beta 1–2 activity) and IC 8 in the medial frontal cortex (centred on the SMA; beta 3 activity) (Supplementary Table 1). For these three ICs, ICD + patients showed either no significant difference between conditions (ICs 4 and 6), or an opposite pattern (IC 8) (Fig. 4 and Supplementary Table 1).

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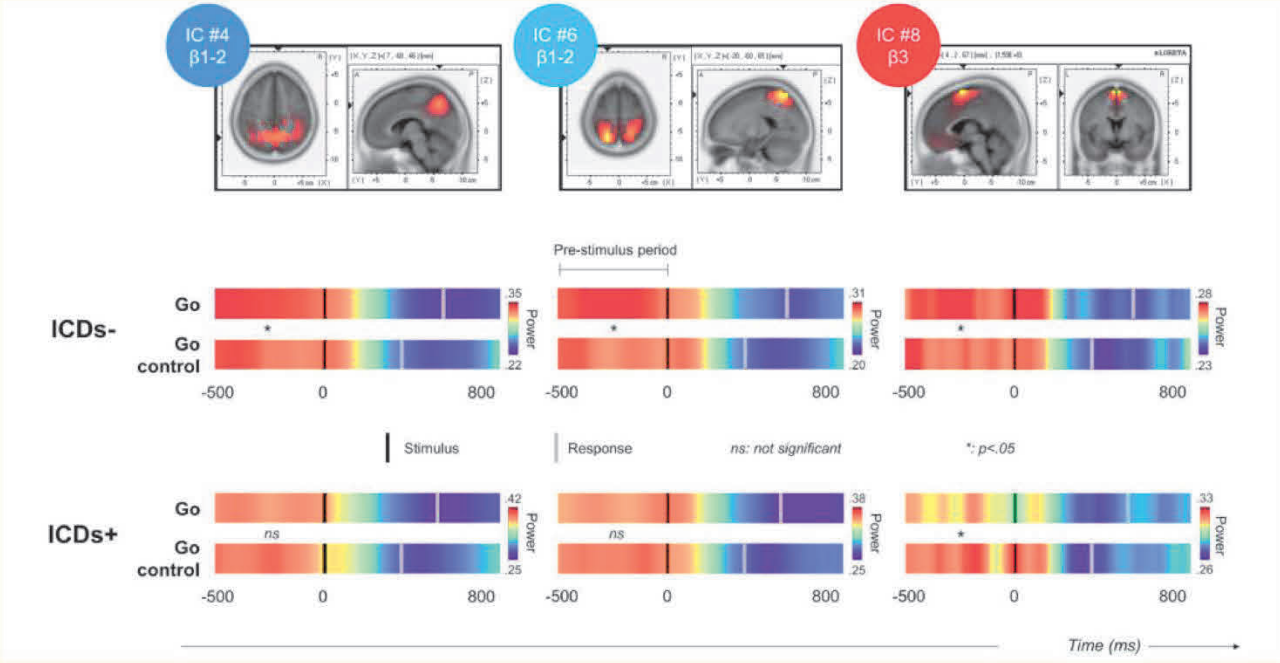

Figure 4 Neural correlates of motor impulsivity in patients with Parkinson's disease with ICDs (ICD+) with respect to patients with Parkinson's disease without ICDs (ICD–). Precuneus (ICs 4 and 6) and SMA (IC 8) beta activity (absolute power data averaged across subjects) is abnormal in ICD+ patients. While ICD– patients show a pattern of prestimulus activity suggesting increased proactive inhibitory control when action restraint is required (increased power in Go trials) with respect to the control condition (Go_control trials), ICD+ patients do not show similar activation. This dysfunction is associated with more commission errors and shorter reaction time in ICD+ patients with respect to ICD– patients.

Position of the dysfunctional sources within the functional fronto-parietal network

Directionality analyses reported that desynchronization of parietal IC 6 precedes stimulus-induced modulations of parietal IC 4 by 8 ms ($P < 0.0001$) and frontal IC 8 by 17 ms ($P < 0.0001$). Desynchronization of IC 8 was also found to precede stimulus-induced modulations of parietal IC 4 by 58 ms ($P < 0.0001$). A detailed report of lag statistics between these three dysfunctional sources and all other frontal and parietal sources of the network involved in inhibitory control as assessed in ICD– patients (see above) is available in Supplementary Table 2. The most notable result is that frontal IC 8 leads all other frontal sources. Figure 5 presents a synthesis of this connectivity analysis.

Discussion

In a simple task involving no selection between multiple competing responses, no reward, and no delay discounting, the increased commission error rate in patients with Parkinson's disease with ICDs provides global evidence for impaired motor response inhibition. The decrease in ΔRT to Go stimuli also suggests that less motor inhibition is implemented in uncertain contexts (Wardak *et al.*, 2012; Chiu and Aron, 2014; Criaud *et al.*, 2017). In other words, ICDs in Parkinson's disease might partly be due to action impulsivity, not just choice impulsivity. This outcome provides empirical support to former isolated hypotheses (van Eimeren *et al.*, 2010; Cilia and van Eimeren, 2011; Brevers *et al.*, 2012; Mosley *et al.*, 2019; Spay *et al.*, 2019; Paz-Alonso *et al.*, 2020).

Consistent with behavioural results, electrophysiological analyses pinpoint dysfunctions of proactive response inhibition as seen in reduced prestimulus beta activity in the SMA and the precuneus when action restraint is required (Fig. 4). The abnormal activity observed in the SMA in Parkinson's disease ICDs is highly consistent with its well known role in executive control and response inhibition (Rubia *et al.*, 2001; Isoda and Hikosaka, 2007; Sumner *et al.*, 2007; Nachev *et al.*, 2008; Swick *et al.*, 2011). It is also reminiscent of a former connectivity study emphasizing the implication of SMA abnormalities in ICDs through structural disconnections with motor and associative regions of the basal ganglia (Mosley *et al.*, 2019). By contrast, the identification of the precuneus as a source of dysfunction of motor inhibition may, at a first glance, come as a surprise regarding the minor role the precuneus is usually supposed to play in higher-order cognitive functions (but see Cavanna and Trimble, 2006 for a review of some contradictory evidence). However, the present result is in line with the observation

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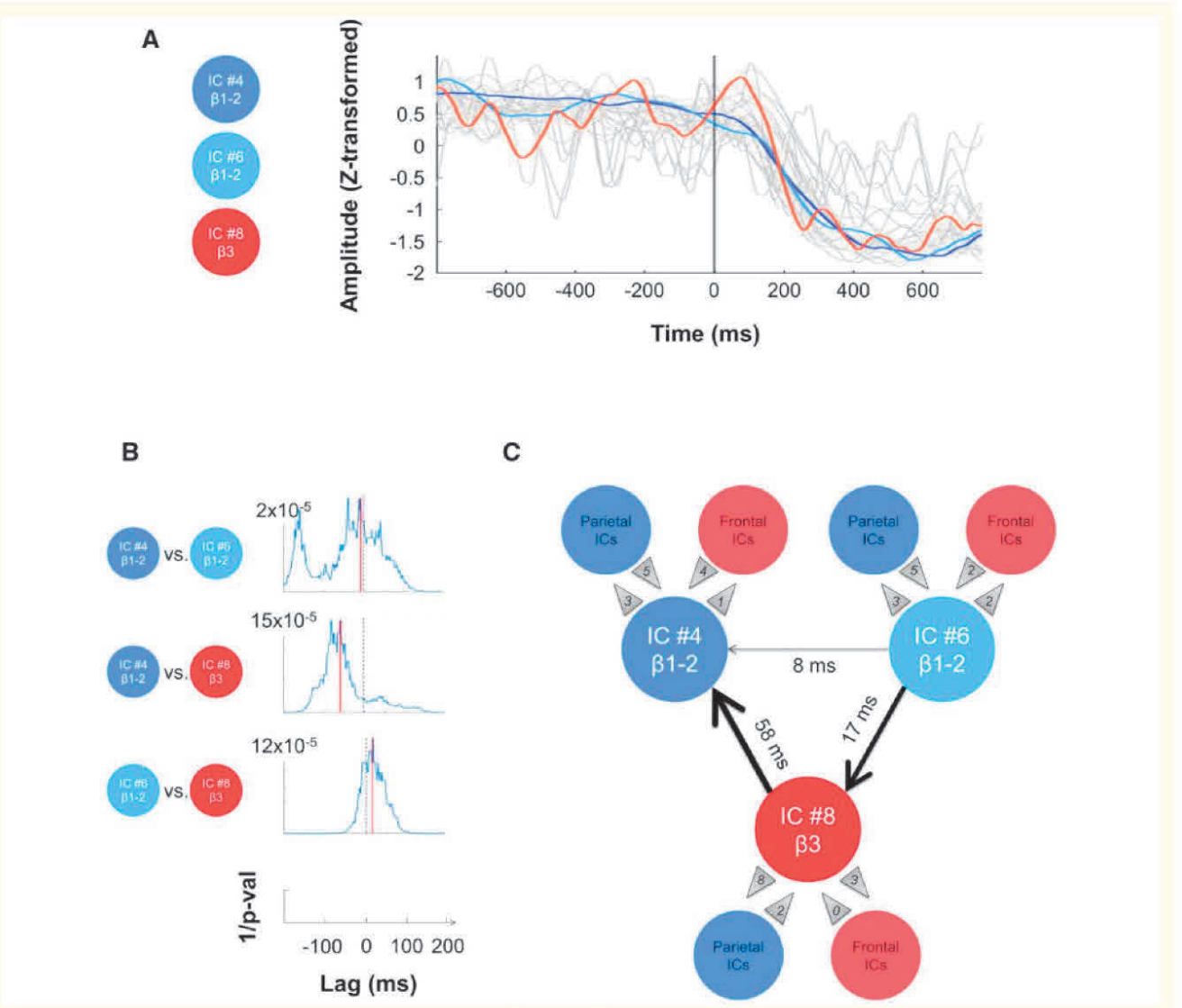

Figure 5 Position of the dysfunctional sources within the functional fronto-parietal network. (**A**) Stimulus-induced desynchronization of proactive activity [mean amplitude (Z-transformed) for each IC/frequency band revealing consistent dynamics]. Sources accounting for ICDs are highlighted in colour. (**B**) Lag statistics. The direction of functional connectivity was assessed by cross-correlation of instantaneous amplitudes. The directionality and delay between two sources were estimated by tracking significant increases of the lagged correlations in the post-stimulus period relative to spontaneous lagged correlations in the baseline. Only the significant results between the three sources accounting for differences between ICD + and ICD– patients are displayed for illustrative purpose. (**C**) Synthetic pattern of effective connectivity. The directionality, significance and delay between the three sources accounting for ICDs are indicated by arrows. The position of these major sources within the functional fronto-parietal network can be estimated by calculating the number of precedencies and subsequences (indicated by grey triangles) with respect to all other sources within the network.

that the precuneus is involved, although in a very unclear way, in the preparation and execution of spatially guided behaviours in association with the sensorimotor fronto-parietal network (Zhang and Li, 2012), and in the control of response inhibition (Barber and Carter, 2005; Criaud *et al.*, 2017; Lemire-Rodger *et al.*, 2019) in healthy subjects. It is also consistent with former observations that impaired activity in the precuneus is associated with response control disorders. More specifically, abnormally high proactive activity in the precuneus has been related to exaggerated inhibitory control in Parkinson's disease (Criaud *et al.*, 2016) while, conversely, decreased activity in the precuneus has been related to impulsivity in patients with Parkinson's disease (Ballanger *et al.*, 2009).

The fact that neural correlates of ICDs are observed in the precuneus and in the SMA in the beta band suggests that the origin of the problem is not purely motor. Indeed, in the context of the present study, beta oscillations are likely to

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index top-down signalling between sensorimotor and non-sensorimotor areas (Engel and Fries, 2010; Albares *et al.*, 2015). As such, the alteration of the cortical drive of proactive motor inhibition observed in ICDs at the level of the SMA and the precuneus might rather index an impairment of the executive control of motor inhibitory networks, and more particularly in the ability to switch between executive sets for which both are known to play a major role (Lemire-Rodger *et al.*, 2019).

Although the exact role played by the SMA and precuneus cannot be precisely identified in the present study, connectivity analyses reveal a prominent position within the fronto-parietal network involved in response control (Figs 3 and 5). In particular, one of the two dysfunctional beta sources in the precuneus desynchronizes early within the cascade of events induced by stimulus presentation in the overall sensorimotor network. This source is likely to lead to the subsequent desynchronization of the beta SMA dysfunctional source (Fig. 5A), which itself has a leading role in the cascade of event-related desynchronizations observed in the frontal areas of the network (Fig. 5C). In other words, according to the hypothetical role of beta activity in top-down signalling (Engel and Fries, 2010; Albares *et al.*, 2015), the precuneus may act as a trigger in the frontal control processes, and its dysfunction may result in an impaired capacity to implement inhibitory control in the motor system in anticipation of stimulation. This observation is reminiscent of previous reports of abnormal connectivity between the precuneus and the motor system in patients with Parkinson's disease (Thibes *et al.*, 2017). However, the complex pattern of interactions between the dysfunctional sources in ICDs and the rest of the sensorimotor system can still not be fully inferred from the present results.

In conclusion, our findings support the hypothesis that the specific impairment of patients with Parkinson's disease with ICDs with respect to patients with Parkinson's disease without ICDs would stem in the weaker ability of the former to sustain and switch between executive settings. However, there remain important caveats that must be borne in mind when interpreting these results. First, it cannot be concluded that the frontal mechanisms that directly suppress motor activation are more impaired in patients with Parkinson's disease with ICDs than in patients with Parkinson's disease without ICDs. Second, the present data do not mean that there are no other specific frontal dysfunctions in Parkinson's disease ICDs with respect to Parkinson's disease without ICDs (Mosley *et al.*, 2019). In the present experiment, which does not confound reward processing and inhibitory control, this would rather mean that the frontal dysfunctions often observed in Parkinson's disease ICDs (in particular in cingulate and orbitofrontal cortices) (van Eimeren *et al.*, 2010; Santangelo *et al.*, 2019) might not be directly related to motor response inhibition *per se*. This does not mean, either, that no other brain region can account for the behavioural differences observed between ICD + and ICD– patients. Given the limited capacity of EEG to identify deep sources, and the acknowledged role of the basal ganglia in both proactive and reactive control inferred from direct electrophysiological recordings (Benis *et al.*, 2014), it is most likely that abnormal beta activity in the precuneus and in the SMA are not the unique sources of inhibitory dysfunction in Parkinson's disease ICDs. In addition, the task used in this study certainly makes fewer demands on reactive mechanisms of inhibition (Criaud and Boulinguez, 2013) and likely ignores other cortical sources of inhibitory dysfunction in Parkinson's disease ICDs.

Notwithstanding these limitations, the evidence that dysfunctions of action control play a role in ICDs might open the door to new research avenues and support possible treatment strategies including complementary non-dopaminergic medication. Indeed, dopamine medication would mainly influence the neural network underlying impulsive choices but not the neural network underlying impulsive action (Antonelli *et al.*, 2014). Importantly, previous work on the neural and neurochemical bases of inhibitory control has identified the key role of both the noradrenergic (NA) and the serotoninergic (5HT) systems (Eagle *et al.*, 2008; Robbins and Arnsten, 2009; Ye *et al.*, 2014). In light of former studies in Parkinson's disease (Kehagia *et al.*, 2014; Rae *et al.*, 2016; Spay *et al.*, 2018), greater emphasis might especially be placed on noradrenergic therapies in future clinical trials for the treatment of ICDs. However, the present results suggest that the diverse forms of response inhibition might be differently affected in ICDs. Thus, as inspired by former psychiatry research (Eagle *et al.*, 2008; Dalley and Robbins, 2017), fractionating impulsivity into distinct neural mechanisms might prove necessary to identify and treat specifically various possible forms of impulsive behaviour in Parkinson's disease ICDs that remain to be elucidated (Meyer *et al.*, 2019).

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Competing interests

The authors report no competing interests.

Supplementary material

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Résumé : *En dépit des modèles des addictions comportementales et de l'impulsivité, l'hypothèse d'un déficit de contrôle inhibiteur chez les patients parkinsoniens avec TCIs n'a reçu que peu d'intérêt et de support empirique. Il semble néanmoins opportun de la réévaluer grâce aux méthodes des neurosciences cognitives. Dans une première étude, nous avons utilisé l'électroencéphalographie pour sonder l'intégrité des réseaux corticaux de l'inhibition de réponse à l'état de repos. Nous avons analysé l'activité oscillatoire des sources séparées dans toutes les bandes de fréquence jusqu'au bas gamma. Nous démontrons des altérations de l'activité oscillatoire de repos associées à la présence ou à la sévérité des TCIs, qui concernent des régions (cortex cingulaire antérieur dorsal, cortex préfrontal médian, aire motrice supplémentaire) et des bandes de fréquence (beta, gamma) précédemment associées à l'inhibition de réponse. Nous interprétons ces résultats comme une preuve de concept, justifiant d'évaluer directement l'hypothèse d'un déficit de contrôle inhibiteur chez les TCIs. Dans une deuxième étude, nous avons testé cette hypothèse à l'aide d'une tâche de Go/NoGo, en recherchant des marqueurs EEG spécifiques afin d'identifier précisément les mécanismes neurocognitifs impliqués. Nous montrons que les patients parkinsoniens avec TCIs se montrent plus impulsifs que les patients sans TCIs dans la tâche de Go/NoGo, avec un taux d'erreur de commission plus élevé et une moindre adaptation du temps de réaction au contexte. Parmi les sources dont le pattern d'activité pouvait correspondre à une activité de contrôle inhibiteur, nous identifions trois sources ayant un pattern d'activité anormal chez les patients avec TCIs. Plus précisément, chez ces patients, l'activité beta pré-stimulus de ces sources localisées dans le précunéus et l'aire motrice supplémentaire était réduite lorsque l'inhibition était requise. L'analyse de connectivité révèle le rôle directeur de ces sources au sein du réseau fronto-pariétal de contrôle de l'action identifié. Nous concluons que les patients parkinsoniens avec TCIs souffrent d'un déficit de contrôle inhibiteur proactif comparé aux patients sans TCIs. L'impulsivité de ces patients ne serait donc pas uniquement une impulsivité décisionnelle, mais également une impulsivité d'action.*

2.3 Conclusions et perspectives

A travers une revue systématique, nous avons démontré que la littérature en neuro-imagerie sur les TCI s'est focalisée sur le réseau mésocorticolimbique et ne s'est pas suffisamment appuyée sur l'utilisation de tâches comportementales et d'analyses événementielles permettant d'identifier les mécanismes neuraux sous-jacents. Ainsi, cette littérature n'a pas permis d'évaluer toutes les sources de dysfonctions contribuant potentiellement aux TCIs. Parmi ces sources de dysfonction potentielles, l'hypothèse d'un trouble du contrôle inhibiteur n'a reçu qu'étonnamment peu d'intérêt ou de support. Nous avons apporté plusieurs arguments en faveur de cette hypothèse : dans une première étude, la présence et la sévérité des TCIs étaient associées à des altérations de l'activité oscillatoire de repos dans des régions et des bandes de fréquence liées à l'inhibition de réponse. Dans une deuxième étude, les patients avec TCIs étaient plus impulsifs dans une tâche de Go/NoGo, ce qui était accompagné d'une réduction de certaines activités liées au contrôle inhibiteur proactif.

Depuis la réalisation de ces travaux, différentes études ont contribué à avancer notre connaissance des mécanismes neurocognitifs impliqués dans les TCIs dans la MP, en combinant des tâches cognitives évaluant différents aspects de l'impulsivité et différentes mesures d'activité ou de connectivité cérébrale (Esteban-Peñalba et al., 2021; Girard et al., 2019; Haagensen et al., 2020; Mosley et al., 2019b; Paz-Alonso et al., 2020; Ruitenberg et al., 2018). En particulier, plusieurs études ont contribué au débat sur l'existence ou non de déficits d'inhibition de réponse chez ces patients. Deux études ont mis en évidence des altérations de l'activité et de la connectivité fonctionnelle des réseaux du contrôle inhibiteur, mais dans des tâches n'évaluant pas directement l'inhibition de réponse (« Iowa Gambling Task », Paz-Alonso et al., 2020 ; et tâche de jeu de dés, Haagensen et al., 2020), et en absence d'un effet du groupe sur le comportement dans la tâche. Une étude utilisant une tâche de signal stop conditionnelle a montré une activité accrue liée au contrôle inhibiteur proactif dans le réseau du contrôle inhibiteur chez les patients avec TCIs. En l'absence de différences dans le comportement, cela a été interprété comme une activité compensatoire (Esteban-Peñalba et al., 2021). Une autre étude a démontré des altérations de la connectivité fonctionnelle au repos des réseaux sensorimoteurs et limbiques des ganglions de la base chez les patients avec TCIs. La connectivité de ces réseaux corrélait également avec l'impulsivité dans la « Beads task » à travers l'ensemble du groupe, mais les patients avec TCIs n'étaient pas plus impulsifs que les patients sans TCIs dans cette tâche, mettant en doute le caractère causal des altérations de la connectivité identifiées (Ruitenberg et al., 2018). Enfin, Mosley et al. (2019b) ont montré une association entre connectivité structurelle dans les réseaux du contrôle inhibiteur et de la récompense et comportement de jeu dans un casino virtuel. Cette association permettait de distinguer les patients souffrant de TCIs de ceux n'en souffrant pas.

Malgré un faisceau d'indices intéressants, ces études n'apportent pas de preuves directes d'un déficit d'inhibition de réponse chez les patients parkinsoniens avec TCIs comparés aux patients sans TCIs. D'abord, il reste problématique d'interpréter des différences d'activité ou de connectivité fonctionnelle en absence de différences dans le comportement. Plus généralement, le problème de l'inférence inverse se pose : étant donné que la plupart des régions cérébrales concernées supportent différentes fonctions cognitives, il reste délicat d'inférer l'engagement ou l'état de certains processus cognitifs sur la seule base de variations dans l'activité ou la connectivité de ces régions (Poldrack, 2011). Notre étude reste, à notre connaissance, la seule présentant des arguments concordants basés sur le comportement (impulsivité dans une tâche de Go/NoGo) et l'activité cérébrale (diminution de l'activité beta pré-stimulus dans la SMA et le précuneus, interprétée comme une activité de contrôle inhibiteur proactif) en faveur de l'hypothèse d'un déficit d'inhibition de réponse chez les patients parkinsoniens avec TCIs comparés aux patients sans TCIs.

Nous pouvons spéculer qu'un déficit du contrôle inhibiteur pourrait être un facteur de prédisposition aux TCI, plutôt qu'une conséquence du traitement dopaminergique et de l'état hyper-dopaminergique consécutif à celui-ci. En effet, les mécanismes de contrôle inhibiteur –y compris les mécanismes de contrôle proactif identifiés comme dysfonctionnels dans notre étude– semblent être plutôt sous influence noradrénergique que dopaminergique (Albares et al., 2015b; Chamberlain and Robbins, 2013; Chamberlain et al., 2006a; Robbins and Arnsten, 2009; Spay et al., 2018). Dans le même ordre d'idée, un déficit de contrôle inhibiteur pourrait conditionner la sévérité de ces troubles, plutôt que leur déclenchement (Brevers et al., 2012; Marín-Lahoz et al., 2018). Quoiqu'il en soit, si l'impulsivité des TCIs repose au moins en partie sur un déficit de contrôle inhibiteur, des traitements visant le système noradrénergique pourraient être envisagés. En effet, il a déjà été montré que l'atomoxetine, un inhibiteur de la recapture de la noradrénaline, peut améliorer la performance d'inhibition de patients parkinsoniens dans une tâche de signal stop, ainsi que restaurer l'activité des réseaux sous-jacents (Kehagia et al., 2014; O'Callaghan et al., 2021; Rae et al., 2016; Ye et al., 2015). Un essai clinique en cours aux Hospices Civils de Lyon teste l'efficacité d'un autre agent noradrénergique, la clonidine, pour l'amélioration des TCIs (https://clinicaltrials.gov/ct2/show/NCT03552068).

Pour finir, il semble important d'envisager les interactions entre motivation pour la récompense et contrôle inhibiteur dans cette population de patients. En effet, des travaux récents chez le sujet sain ont souligné que les fonctions de motivation et de contrôle inhibiteur ne sont pas indépendantes. Plus généralement, les signaux motivationnels influencent le contrôle cognitif de façon spécifique, comme démontré dans un large ensemble d'études ayant introduit et manipulé des récompenses dans des tâches classiques de contrôle cognitif (voir pour revue Botvinick and Braver,

2015; Braver et al., 2014; Pessoa and Engelmann, 2010; Yee and Braver, 2018). Dans des tâches d'inhibition de réponse, la performance de contrôle inhibiteur est améliorée lorsqu'elle est récompensée de façon extrinsèque, souvent en associant des récompenses monétaires aux essais NoGo ou Stop réussis. Récompenser les réponses rapides aux stimuli Go produit l'effet inverse (Boehler et al., 2012, 2014; Greenhouse and Wessel, 2013; Leotti and Wager, 2010; Padmala and Pessoa, 2010). Ainsi, il semble que l'application du contrôle inhibiteur soit modulée selon le contexte motivationnel : les sujets s'engageraient dans un processus de prise de décision basé sur les valeurs associées aux différents modes de réponse (c'est-à-dire, répondre vite au Go vs. éviter les erreurs au NoGo/Stop) afin d'adapter les niveaux de contrôle appliqués en fonction (Dixon and Christoff, 2012; Leotti and Wager, 2010; Shenoy and Yu, 2011). Ce cadre théorique prévoit qu'une motivation exagérée pour la récompense puisse fausser ce processus de prise de décision et conduire à une diminution des niveaux de contrôle appliqués. Autrement dit, des comportements semblant refléter une *incapacité* à implémenter le contrôle pourraient refléter en réalité une moindre *volonté* d'implémenter ce contrôle (Cools et al., 2019).

Cette hypothèse semble particulièrement prometteuse dans le cas des patients parkinsoniens souffrant de TCIs. D'une part, les mécanismes de contrôle proactif, montrés comme dysfonctionnels chez ces patients dans notre étude, sont particulièrement susceptibles de supporter ce type d'influences motivationnelles, en comparaison aux mécanismes réactifs (Botvinick and Braver, 2015; Braver, 2012; Braver et al., 2014; Verbruggen and McLaren, 2018). D'autre part, les processus de prise de décision basés sur la valeur du contrôle seraient sous influence de la transmission dopaminergique dans le striatum (Cools et al., 2019; Froböse and Cools, 2018). Ce cadre théorique prévoit ainsi qu'un état hyperdopaminergique au niveau striatal –comme observé dans les TCIs– puisse être responsable d'une diminution de la valeur du contrôle. Il semble d'ailleurs intéressant d'envisager certains résultats récents à la lueur de cette hypothèse : une réduction de l'inhibition proactive a été observée chez des sujets sains lors de la prise de ropinirole, un agoniste dopaminergique ayant une haute affinité pour les récepteurs D3 (Rawji et al., 2020). Enfin, plus largement, les interactions entre motivation et contrôle inhibiteur reposent sur des interactions entre les réseaux de la récompense et du contrôle inhibiteur (Botvinick and Braver, 2015; Pessoa and Engelmann, 2010; Yee and Braver, 2018). Or, une étude récente a souligné une altération de la connectivité fonctionnelle entre ces réseaux chez les TCIs dans une tâche de jeu de dés (Haagensen et al., 2020). Par ailleurs, le cortex antérieur cingulaire dorsal, une région considérée comme un « hub » important pour ces interactions, a souvent été reporté comme ayant une activité altérée chez les patients avec TCIs (Meyer et al., 2019; Santangelo et al., 2019).

D’un point de vue expérimental, nous prévoyions initialement de réaliser un travail collaboratif avec le Dr Roberto Cilia de Milan (Italie) visant précisément à déterminer si le manque de contrôle inhibiteur des patients parkinsoniens avec TCIs relevait d’un dysfonctionnement réel des mécanismes de contrôle, ou bien d’une moindre implémentation de ce contrôle due aux dysfonctions présentes sur le plan motivationnel. Cette distinction semble cruciale, car seule la première hypothèse prédit une amélioration possible des TCIs par des agents noradrénergiques. La réalisation de ce projet a finalement été compromise par la crise sanitaire liée à la Covid-19. Par conséquent, seul le travail préalable visant à caractériser ces interactions chez le sujet sain a pu être réalisé, mais n’est pas finalisé au moment de l’écriture de ces lignes. Ce travail est néanmoins présenté de façon succincte dans la partie « Conclusion et perspectives » de ce manuscrit.

Chapitre II

Les troubles du contrôle inhibiteur induits par la stimulation cérébrale profonde du noyau sous-thalamique

3.1 Revue de la littérature

3.1.1 Effets de la SCP-NST sur le contrôle inhibiteur

3.1.1.1 Pertinence clinique

La stimulation cérébrale profonde du noyau sous-thalamique (SCP-NST) est un traitement très efficace contre les symptômes moteurs de la MP (Bove et al., 2021; Hamani et al., 2005; Kleiner-Fisman et al., 2006; Limousin and Foltynie, 2019). Cependant, des effets secondaires neuropsychiatriques sont parfois rapportés. Sur le plan cognitif, la SCP-NST n'induit pas de détérioration du fonctionnement global, mais semble provoquer des changements subtils et spécifiques à certains domaines cognitifs, dont les fonctions exécutives et en particulier le contrôle inhibiteur (Cernera et al., 2019; Jahanshahi, 2013; Jahanshahi et al., 2015a; Parsons et al., 2006; Volkmann et al., 2010). Comprendre les effets de la SCP-NST sur le contrôle inhibiteur est important, car ces effets sont susceptibles d'avoir des répercussions sur le plan clinique. En effet, l'akinésie (définie comme la difficulté à initier les mouvements, Schilder et al., 2017) et l'impulsivité d'action pourraient représenter les deux extrémités d'un continuum lié à la capacité d'inhibition de réponse (Ballanger et al., 2009a; Jahanshahi and Rothwell, 2017). La SCP-NST, en agissant sur le contrôle inhibiteur, pourrait donc améliorer l'akinésie, mais également exacerber l'impulsivité des patients.

Plus précisément, il a été proposé que l'akinésie des patients parkinsoniens (évaluée grâce au temps de réaction, qui indexe directement le temps nécessaire à l'initiation du mouvement) soit due au moins en partie à un niveau de contrôle inhibiteur proactif anormalement élevé (Criaud et al., 2016)[4], et plus particulièrement à une incapacité à relâcher ce contrôle dans les contextes où répondre de façon automatique serait pourtant approprié (Albares et al., 2015b; Favre et al., 2013; Spay et al., 2018). Ce déficit serait spécifiquement amélioré par la SCP-NST (Albares et al., 2015b; Favre et al., 2013; Spay et al., 2018). Par ailleurs, nous avons réalisé une revue systématique de la littérature en neuro-imagerie sur l'akinésie dans la MP (Spay*, Meyer* et al., 2018 ; présentée en annexe), dont les

[4] Ce contrôle inhibiteur proactif anormal pourrait d'ailleurs aussi jouer un rôle dans le trouble d'initiation de la marche également présent dans la MP (« freezing of gait », Ziri et al., 2019).

résultats sont aussi en faveur de la présence de dysfonctionnements autres que purement moteurs. En effet, nous avons notamment relevé, en plus des anomalies d'activité ou de connectivité dans les circuits moteurs, des anomalies dans des régions plutôt liées au contrôle exécutif de l'action (Spay*, Meyer* et al., 2018).

Concernant l'autre côté du continuum, il n'existe pas de preuve concrète liant les effets de la SCP-NST sur le contrôle inhibiteur tels qu'observés en laboratoire à une exacerbation de l'impulsivité des patients dans la vie de tous les jours (Jahanshahi, 2013; Jahanshahi et al., 2015a). En réalité, la SCP-NST ne semble induire que très rarement des TCIs *de novo* (Abbes et al., 2018; Amstutz et al., 2020; Merola et al., 2017; Santin et al., 2020 ; les TCIs préexistants étant souvent améliorés grâce à la réduction du traitement dopaminergique qui accompagne la chirurgie, Lhommée et al., 2012). Cependant, une forme d'impulsivité se traduisant par d'autres types de changements dans le comportement et la personnalité du patient pourrait être présente (par exemple, de l'irritabilité et de l'impatience, ou un comportement donnant au patient le sentiment d'avoir retrouvé la personnalité de sa jeunesse ; Mosley et al., 2019a). Cela dit, on notera -tout en gardant les limites de ces méthodes en tête (voir partie 1.2.3.1)- que la plupart des études ayant comparé l'impulsivité des patients avant et après la chirurgie grâce à des échelles d'impulsivité auto-rapportées n'ont pas trouvé de différences significatives (Scherrer et al., 2020, mais voir Kardous et al., 2021).

3.1.1.2 Démarche générale

Le NST joue un rôle important dans l'inhibition de réponse (voir pour revue Aron et al., 2016; Jahanshahi et al., 2015a; Zavala et al., 2015). Différents types de travaux ont apporté des arguments en ce sens, notamment des travaux basés sur la modélisation computationnelle (modèle « hold your horses » ; Frank, 2006; Wiecki and Frank, 2013), l'imagerie fonctionnelle (Aron and Poldrack, 2006; Aron et al., 2007; Li et al., 2008; Rae et al., 2015), les enregistrements électrophysiologiques intra-crâniaux réalisés chez des patients lors des chirurgies de SCP (Alegre et al., 2013; Bastin et al., 2014; Benis et al., 2014, 2016; Chen et al., 2020; Kühn et al., 2004; Mosher et al., 2021; Ray et al., 2009; Wessel et al., 2016, 2019), ou l'observation des effets de lésions et de la stimulation de ce noyau chez le rat (Baunez and Robbins, 1997; Baunez et al., 1995, 2007; Eagle and Baunez, 2010; Eagle et al., 2008b).

Ainsi, il n'est pas étonnant que les effets de la SCP-NST sur les performances d'inhibition de réponse aient fait l'objet de nombreux travaux. Ces effets ont été évalués à l'aide de différentes tâches cognitives, la plupart du temps en comparant la performance des patients sous stimulation à celle stimulateur éteint (« ON » et « OFF »). L'avantage de ce type de design expérimental, comparé à des designs comparant la performance pré- et post-opératoire, est qu'il permet de révéler les effets de la

stimulation, sans confusion avec les effets imputables aux microlésions dues à la chirurgie ou à la modification post-opératoire du traitement dopaminergique.

3.1.1.3 Mécanismes d'inhibition de réponse affectés

De façon générale, la littérature suggère que la SCP-NST diminue les performances d'inhibition de réponse (voir pour revues Jahanshahi, 2013; Jahanshahi et al., 2015a; Lo Buono et al., 2021; Scherrer et al., 2020; Zavala et al., 2015). Mais il reste difficile de déduire de cet ensemble de travaux quels mécanismes d'inhibition de réponse sont précisément affectés par la SCP-NST. Certaines études ont utilisé des tâches qui ne permettent pas d'isoler spécifiquement les processus d'inhibition de réponse, telles les tâches de Stroop, de production aléatoire de chiffres, ou d'anti-saccades (voir pour revue Jahanshahi, 2013; Jahanshahi et al., 2015a). Le modèle « hold your horses » (Frank, 2006)[5] a aussi inspiré une large série d'études utilisant des tâches testant la prise de décision en présence de conflit (Cavanagh et al., 2011; Frank et al., 2007; Green et al., 2013; Hell et al., 2018; Herz et al., 2018; Pote et al., 2016). Par ailleurs, même les études ayant utilisé des tâches ciblant l'inhibition de réponse de façon plus spécifique (présentées dans la Table 1, pages suivantes) ne permettent pas tout à fait de trancher cette question. Concernant la tâche de signal stop, l'indice comportemental mesuré, le temps de réaction au signal stop (SSRT), est généralement considéré une mesure robuste des mécanismes d'inhibition réactifs et sélectifs (« stopping »). Cependant, il est bien connu que la performance à cette tâche repose aussi sur des mécanismes de contrôle proactif (voir par exemple Verbruggen and Logan, 2009b). Quoiqu'il en soit, les effets rapportés de la SCP-NST sur la performance à ce type de tâches sont variables : amélioration (Mirabella et al., 2012; Swann et al., 2011; van den Wildenberg et al., 2006, 2021; van Wouwe et al., 2020), détérioration (Lofredi et al., 2021; Obeso et al., 2013; Ray et al., 2009), ou absence d'effet significatif (Mancini et al., 2018) ; Table 1). Concernant la tâche de Go/NoGo, la plupart des études ont conclu à un effet négatif de la SCP-NST sur la performance dans cette tâche (Ballanger et al., 2009a; Georgiev et al., 2016; Hershey et al., 2004, 2010, mais voir Campbell et al., 2008; van den Wildenberg et al., 2006). Mais les mécanismes impliqués sont, là encore, peu clairs. D'abord, la performance à la tâche de Go/NoGo dépend probablement d'une combinaison de mécanismes d'inhibition de réponse réactifs et proactifs (voir par exemple Criaud et al., 2017). De plus, certaines études n'ont analysé que l'index de discriminabilité, calculé en soustrayant le taux d'erreurs de commission au taux de réussite au Go, renforçant encore l'incertitude quant aux processus cognitifs

[5] Ce modèle computationnel influent propose que le rôle du NST soit de relayer un signal « NoGo » global empêchant temporairement l'exécution de toute réponse motrice dès lors qu'il y a conflit entre plusieurs réponses possibles, ce qui laisserait plus de temps pour sélectionner la plus appropriée (Frank, 2006; Wiecki and Frank, 2013). Certains auteurs ont par la suite suggéré que ce rôle ne soit pas spécifique des situations complexes de conflit explicitement lié à la sélection d'une réponse parmi plusieurs possibles, mais qu'il s'applique à toute situation d'incertitude événementielle (Aron et al., 2016; Ballanger et al., 2009a; Brass and Haggard, 2008; Wessel and Aron, 2017).

affectés (Campbell et al., 2008; Gourisankar et al., 2018; Hershey et al., 2004). Une augmentation du taux d'erreurs de commissions, une mesure plus pure de la performance d'inhibition, a néanmoins été démontrée (Ballanger et al., 2009a; Hershey et al., 2010, mais voir Campbell et al., 2008; Georgiev et al., 2016).

Les modèles proposant d'autres types de mécanismes d'inhibition que les mécanismes classiques réactifs sélectifs (« stopping », Logan et al., 1984), c'est-à-dire des mécanismes d'inhibition contextuels, qu'ils soient proactifs (Boulinguez et al., 2009; Jaffard et al., 2007, 2008) ou bien réactifs non-sélectifs (Albares et al., 2014; Ballanger et al., 2009a; Criaud et al., 2017; Frank, 2006; Wessel et al., 2019; Wiecki and Frank, 2013 ; voir partie 1.2.1.2.), ont eu une influence importante sur cette littérature. En effet, plusieurs études ont tenté de mettre en évidence des effets spécifiques de la SCP-NST sur ce type de mécanismes, qui sont susceptibles de jouer un rôle plus prépondérant dans la fonction d'inhibition de réponse que les mécanismes réactifs sélectifs (Aron, 2011; Criaud et al., 2017). Dans une tâche de temps de réaction (TR) simple indicé[6], il a été montré que la SCP-NST restaurait la capacité à relâcher le contrôle inhibiteur proactif dans les contextes où répondre de façon automatique serait pourtant approprié. En d'autres termes, l'effet net consisterait en une réduction du niveau de contrôle inhibiteur appliqué dans ces conditions (Albares et al., 2015b; Favre et al., 2013; Spay et al., 2018). Cependant, d'autres études ont conclu à une absence d'effet de la SCP-NST sur le contrôle proactif, une conclusion basée sur l'absence d'effet de la stimulation sur l'adaptation du TR Go au contexte, et plus précisément à la présence de stimuli Stop ou NoGo ou à leur probabilité (c'est-à-dire, en termes statistiques, une absence d'effet d'interaction SCP x contexte sur le TR, De Pretto et al., 2021; Mancini et al., 2018; Mirabella et al., 2012). Pourtant, ce pattern pourrait s'expliquer par un effet global de la SCP-NST sur les niveaux de contrôle appliqués, produisant une réduction globale des TR. Autrement dit, la réduction du TR observée sous SCP-NST pourrait refléter un mélange d'effets moteurs et exécutifs, difficiles à distinguer sur la seule base du comportement (Albares et al., 2015b; Favre et al., 2013; Neumann et al., 2018).

[6] Cette tâche est directement inspirée des paradigmes classiques d'attention. Elle est composée d'une condition comprenant uniquement des stimuli Go (TR simple), et d'une condition dans laquelle les stimuli Go sont parfois précédés par des signaux d'alertes (TR simple indicé). L'idée est que la condition indicée nécessiterait d'implémenter des mécanismes de contrôle inhibiteur contextuels afin d'éviter de répondre aux signaux d'alerte, tandis qu'un mode de réponse automatique à tous les stimuli présentés serait approprié dans la condition de TR simple (Boulinguez et al., 2008, 2009; Jaffard et al., 2007, 2008).

3.1.1.4 Effets sur l'activité cérébrale associée

L'utilisation de l'imagerie ou de l'électrophysiologie, selon les principes méthodologiques proposés dans l'introduction de ce travail de thèse, est susceptible de compléter cet ensemble de travaux majoritairement comportementaux, en aidant d'une part à identifier les mécanismes d'inhibition de réponse précisément affectés, et d'autre part à distinguer ces effets exécutifs d'effets moteurs. Mais les possibilités d'enregistrement et d'analyse de l'activité cérébrale sous SCP sont limitées, en raison de préoccupations pour la sécurité des patients qui limitent fortement l'utilisation de l'IRMf, et de la présence d'artefacts liés aux électrodes de stimulation et/ou à la stimulation en elle-même, qui entrave l'exploitation du signal EEG ou MEG (Carmichael et al., 2007; Litvak et al., 2021). Ces dernières années, différentes méthodes ont néanmoins été proposées afin de supprimer correctement ces artefacts (voir pour revue Lio et al., 2018; Litvak et al., 2021).

Deux études ont tout de même utilisé ces outils, apportant des arguments en faveur d'effets de la SCP-NST sur les mécanismes d'inhibition contextuels (voir Table 1). La première étude, utilisant la TEP, a utilisé une démarche d'inférence inverse : des modulations de l'activité de régions des réseaux sous-tendant les mécanismes d'inhibition de type « hold your horse » et proactifs ont été interprétées comme des arguments en faveur d'un effet sur ces mécanismes (Ballanger et al., 2009a), avec la limitation néanmois de l'incapacité à accéder à la dynamique temporelle des mécanismes sondés avec cette méthode. Une étude utilisant l'EEG a montré une réduction de la puissance de l'activité alpha pré-stimulus dans l'aire motrice supplémentaire (SMA), interprétée comme une activité d'inhibition proactive sur la base cette fois de ses caractéristiques temporelles, spatiales et spectrales (Spay et al., 2018). Enfin, on notera qu'une étude récente a également tenté de révéler des effets de la SCP-NST sur l'inhibition proactive, cette fois en analysant les potentiels évoqués par l'indice indiquant la probabilité d'apparition d'un stimulus NoGo. Bien que cette étude ait montré des effets de la stimulation sur cette activité évoquée, localisés par la suite dans des régions habituellement associées à l'inhibition de réponse, la méthode des potentiels évoqués semble particulièrement peu adaptée pour révéler des corrélats neuraux de l'inhibition proactive, qui serait un mécanisme implémenté de façon tonique et soutenue, plutôt que de façon phasique en réponse à un stimulus (Criaud et al., 2012).

Table 1 : Etudes de l'effet de la SCP-NST sur le contrôle inhibiteur dans la MP, ayant utilisé des tâches d'inhibition de réponse et un design de type « ON vs. OFF » stimulation. Seules les études ayant utilisé une tâche ciblant directement l'inhibition de réponse sont rapportées (voir le texte principal). Le mécanisme d'inhibition de réponse testé est rapporté selon les termes des auteurs. Seuls les résultats principaux sont rapportés. Sauf mention contraire, les patients étaient implantés dans les deux hémisphères et recevaient la stimulation selon les paramètres choisis cliniquement. *ON/OFF méd. : patients testés sous / après le retrait de leur traitement dopaminergique habituel – ctl : sujets sains – MP-ctl : patients parkinsoniens non implantés – SST : Tâche de signal stop – GNG : Tâche de Go/NoGo – SSRT : temps de réaction au signal stop – TR : temps de réaction – ↓ : détérioration de la performance d'inhibition – ↑ : amélioration de la performance d'inhibition – = : pas d'effet sur la performance d'inhibition.*

Etude	Patients, traitement DA	Tâche	Mécanisme testé	Variable mesurée	Effet de la SCP-NST
Tâches de signal stop					
Van den Wildenberg et al., 2021	16 SCP-NST (3 unilat.) ON méd. *16 ctl*	SST (30% « stop-change »)	« Stopping » Annulation et remplacement d'une réponse planifiée	SSRT TR « Stop-change »	Diminué (↑) Diminué (↑ au niveau des ctl)
Lofredi et al., 2021	17 SCP-NST ON méd.	Initiation et arrêt de mouvements continus	« Stopping »	Temps requis pour stopper *Analyse des patterns de connectivité structurelle des contacts actifs*	Augmenté (↓) *Corrélation entre augmentation du temps requis pour stopper et connectivité à la pré-SMA et au gyrus inférieur frontal droits*
Mancini et al., 2018	10 SCP-NST unilat. D. 10 SCP-NST unilat. G. ON méd. *22 ctl*	SST (0 et 33% stop)	Inhibition réactive Inhibition proactive	SSRT Ralentissement des TR Go en présence de signaux stops	Pas d'effet significatif (=) de la stimulation unilatérale droite ou gauche Pas d'effet significatif (=) de la stimulation unilatérale droite ou gauche
Van Wouwe et al., 2020	24 SCP-NST (12 ON, 12 OFF) OFF méd.	SST (0 et 25% stop)	« Stopping »	SSRT	Diminué (↑) par la stimulation des contacts ventraux, mais pas dorsaux
Obeso et al., 2013	15 SCP-NST ON méd. *29 ctl*	SST (conditionnelle, 12,5% stop et 12,5% stop non-critique)	Inhibition réactive Inhibition proactive Résolution de conflit	SSRT Ralentissement des TR Go dans la direction critique vs. non-critique Ralentissement des TR au stop non-critique vs. au Go non-critique	Augmenté (↓) Augmenté (↑ au niveau des ctl) Pas d'effet significatif (=)

Mirabella et al., 2012	10 SCP-NST OFF méd. *13 ctl*	SST (33% stop)	« Stopping »	SSRT	Diminué (↑ au niveau des ctl) sous stimulation bilatérale mais pas unilatérale Pas de différence significative (=) entre stimulation des contacts ventraux vs. dorsaux
			Contrôle proactif	Ralentissement des TR Go en présence de signaux stops	Pas d'effet significatif (=)
				Ralentissement des TR Go après un essai stop	Pas d'effet significatif (=)
Greenhouse et al., 2011	20 SCP-NST ON méd.	SST (33% stop)	« Stopping »	SSRT	Pas de différence significative (=) entre stimulation des contacts ventraux vs. dorsaux (pas de condition OFF)
Swann et al., 2011	13 SCP-NST ON méd. *14 ctl*	SST (33% stop)	« Stopping »	SSRT *EEG : Activité oscillatoire beta frontale droite au moment du « stopping »*	Diminué (↑ au niveau des ctl) *Augmentée*
Ray et al., 2009	16 SCP-NST ON méd. *10 ctl*	SST (34% stop)	« Stopping »	SSRT	Augmenté (↓) par la stimulation unilatérale uniquement chez les patients ayant une performance normale OFF
Van den Wildenberg et al., 2006	17 SCP-NST (2 unilat.) ON méd. *15 SCP-Vim*	SST (30% stop)	« Stopping »	SSRT	Diminué (↑)
Tâches de Go/NoGo					
De Pretto et al., 2021	14 SCP-NST ON méd. *7 SCP-GPi* *7 MP-ctl*	GNG (0, 25 et 75% NoGo)	Inhibition proactive	Adaptation du TR aux probabilités de NoGo	Pas d'effet significatif (=)
				Commissions (%)	Non analysé (**?**)
				EEG : Activité évoquée par l'indice indiquant la probabilité de NoGo	*Pas d'effet significatif d'interaction SCP x condition*
Gourisankar et al., 2018	74 SCP-NST OFF méd.	GNG (17% NoGo)	Inhibition de réponse	Index de discriminabilité	Pas d'effet significatif (=) de la stimulation unilatérale des contacts ventraux ou dorsaux
				Commissions (%)	Non analysé (**?**)
				Cartographie statistique des effets	*Pas de relation entre position du contact actif et effet sur le comportement*
Georgiev et al., 2016	20 SCP-NST ON méd. *10 MP-ctl* *10 ctl*	GNG (0, 20, 50 et 80% NoGo)	« Action restraint »	Index de discriminabilité	Diminué (↓) seulement dans la condition avec 20% de NoGo
				Commissions (%)	Pas d'effet significatif (=)

Hershey et al., 2010	10 SCP-NST OFF méd.	GNG (17% NoGo)	Inhibition de réponse	Index de discriminabilité Commissions (%)	Diminué (↓) par la stimulation unilatérale des contacts ventraux, mais pas dorsaux Augmenté (↓) par la stimulation des contacts ventraux
Ballanger et al., 2009	7 SCP-NST OFF méd.	GNG (40% NoGo)	Inhibition proactive et de type "hold your horses"	Commissions (%) *TEP : Flux sanguin (rCBF) dans les réseaux associés à ces mécanismes*	Augmenté (↓) *Modulation du flux sanguin dans les réseaux de l'inhibition de réponse proactive et de type « hold your horses »*
Campbell et al., 2008	24 SCP-NST OFF méd.	GNG (17 et 50% NoGo)	Inhibition de réponse	Index de discriminabilité Commissions (%) *TEP : Flux sanguin (rCBF) dans les régions frontales liées à l'inhibition de réponse*	Pas d'effet significatif (=) Non analysé (?) *Corrélation négative entre le changement dans le flux sanguin dans l'ACC et le changement dans la performance d'inhibition*
Van den Wildenberg et al., 2006	17 SCP-NST (2 unilat.) ON méd. *15 SCP-Vim*	GNG (50% NoGo)	Inhibition de réponse	Commissions (%)	Pas d'effet significatif (=)
Hershey et al., 2004	21 SCP-NST OFF méd.	GNG (17 et 50% NoGo)	Inhibition de réponse	Index de discriminabilité Commissions (%)	Diminué (↓ seulement dans la condition avec 17% de NoGo) Non analysé (?)
Tâches de Simon et similaires					
Fluchère et al., 2018	16 SCP-NST ON/OFF méd.	Tâche de Simon	Expression des impulsions Suppression des impulsions	*EMG : Nombre d'activations motrices incorrectes* *EMG : Taux de correction*	Augmentée (↓) Diminué (↓)
Van Wouwe et al., 2017	23 SCP-NST (12 ON vs. OFF, 11 ON) OFF méd. *22 ctl*	Tâche de Simon	Contrôle proactif (force de l'impulsion de réponse initiale) Contrôle réactif (suppression des impulsions)	Erreurs impulsives rapides (analyse des « conditional accuracy functions ») Réduction de l'interférence (analyse de la pente des « delta plots »)	Pas d'effet significatif (=) de la stimulation aux contacts choisis cliniquement, pas de différence significative entre stimulation des contacts ventraux vs. dorsaux Augmentée (↑) par la stimulation aux contacts choisis cliniquement, et par la stimulation aux contacts dorsaux vs. ventraux
Plessow et al., 2014	13 SCP-NST OFF méd. *26 ctl*	Tâche de compatibilité spatiale	Force de l'interférence (Force des impulsions motrices et contrôle inhibiteur)	Effet de compatibilité spatiale sur les TR et erreurs	Augmenté (↓)

Wylie et al., 2010	17 SCP-NST ON méd. *17 ctl*	Tâche de Simon	Force de l'impulsion de réponse initiale	Erreurs impulsives rapides (analyse des « conditional accuracy functions »)	Augmentées (↓ y compris comparé aux ctl)
			Contrôle inhibiteur (suppression des impulsions)	Réduction de l'interférence (analyse de la pente des « delta plots »)	Améliorée (↑ au niveau des ctl)
Autres tâches					
Spay et al., 2018	16 SCP-NST ON méd. x placebo vs. clonidine	Tâche de TR simple, avec et sans signal d'alerte	Contrôle inhibiteur proactif	*EEG : Activité oscillatoire pré-stimulus*	*Puissance réduite d'une l'activité interprétée comme une activité inhibitrice tonique (alpha pré-stimulus dans la SMA ; sous placebo et non sous clonidine)*
Albares et al., 2015	16 SCP-NST ON méd. x placebo vs. clonidine	Tâche de TR simple, avec et sans signal d'alerte	Contrôle inhibiteur proactif	TR dans la condition sans signal d'alerte	Diminué - Restauration de la capacité à relâcher le contrôle inhibiteur proactif quand approprié (sous placebo et non sous clonidine)
Favre et al., 2013	11 SCP-NST ON méd. *11 MP-ctl* *14 ctl*	Tâche de TR simple, avec et sans signal d'alerte	Contrôle inhibiteur proactif	TR dans la condition sans signal d'alerte	Diminué - Restauration de la capacité à relâcher le contrôle inhibiteur proactif quand approprié (vs. déficit résiduel sous méd. DA)

3.1.2 *Mécanismes d'action de la SCP-NST et pertinence pour ses effets sur le contrôle inhibiteur*

Le NST est composé de trois domaines fonctionnels, moteur, associatif et limbique, définis selon leurs connections aux boucles cortico-basales (Figure 9). Il semble néanmoins que ces domaines se chevauchent, et correspondent plutôt à un gradient fonctionnel qu'à des domaines séparés qui auraient des limites anatomiques bien définies (Alkemade and Forstmann, 2014; Ewert et al., 2018; Haynes and Haber, 2013; Lambert et al., 2012, 2015 ; voir pour revue Emmi et al., 2020). Dans la MP, la partie dorso-latérale, correspondant au domaine moteur, est ciblée pour l'implantation de l'électrode de SCP, bien que certains centres préfèrent une cible légèrement plus centrale (Hamel et al., 2017). Les variations dans la position des contacts actifs, ainsi que dans les paramètres de stimulation, font que la région d'influence de la stimulation est variable d'un patient à l'autre, et donc plus ou moins restreinte au domaine moteur. Ainsi, des effets plus ou moins importants de la SCP sur les boucles motrice, associative, voire limbique, sont attendus. Pour cette raison, la localisation précise du contact actif et de la région d'influence de la stimulation est susceptible d'influencer grandement les effets de la SCP. On notera qu'il est généralement admis que la propagation du courant jusqu'au domaine limbique puisse être à l'origine d'effets neuropsychiatriques délétères (Castrioto et al., 2014; Mosley et al., 2018; Volkmann et al., 2010; Witt et al., 2013).

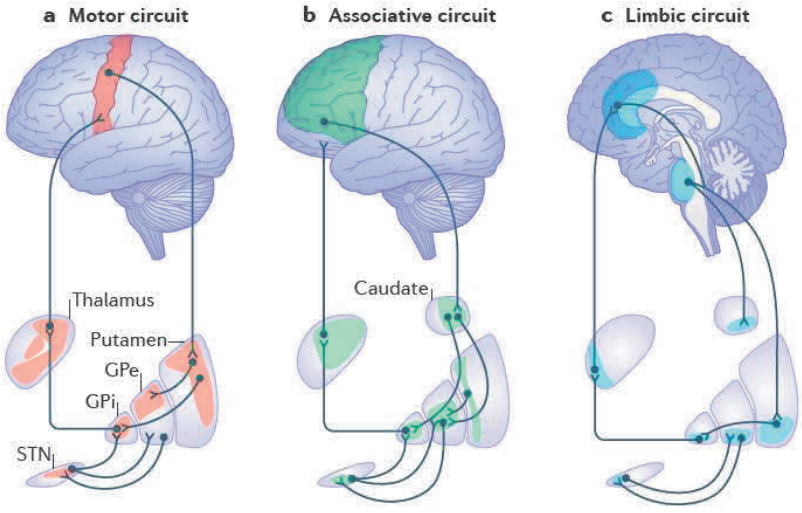

Figure 9 : Boucles cortico-basales motrice, associative et limbique. Seules les projections corticales vers le striatum, et non vers le NST, sont représentées. Tous les noyaux des ganglions de la base sont topographiquement organisés selon des territoires moteurs, associatifs et limbiques. Pour le NST, le territoire moteur est situé dans la partie dorso-latérale, tandis que le territoire limbique se situe dans la partie ventro-médiale, le territoire associatif se situant dans la partie intermédiaire. STN : Noyau sous-thalamique ; GPe : Globus Pallidus pars externa ; GPi : Globus Pallidus pars interna. Figure tirée de Jahanshahi et al., 2015b.

Au niveau neurophysiologique, les effets thérapeutiques de la SCP-NST ont été initialement envisagés comme résultant principalement d'effets locaux sur l'activité du NST (Chiken and Nambu, 2016; Deniau et al., 2010). L'observation d'effets sur les symptômes similaires à ceux des lésions a forgé l'idée initiale selon laquelle la SCP à haute fréquence agirait comme une lésion fonctionnelle (Benabid et al., 1996), diminuant ou supprimant l'activité des neurones au point de stimulation (Filali et al., 2004; Meissner et al., 2005; Welter et al., 2004). Cette hypothèse concordait par ailleurs avec le modèle dominant de la MP (« rate model » ; Albin et al., 1989; DeLong, 1990), selon lequel les symptômes moteurs de la MP résulteraient d'un déséquilibre entre les voies indirecte et directe, qui serait alors contrebalancé par la lésion ou la stimulation du NST ou du GPi. Mais il est apparu rapidement que l'effet de la SCP ne peut être limité à une simple inhibition ou activation des neurones au point de stimulation, et que des mécanismes bien plus complexes sont mis en jeu (Deniau et al., 2010). Un modèle influent propose qu'elle découple l'activité des corps cellulaires et des axones (McIntyre et al., 2004a). L'activité des corps cellulaires serait inhibée, tandis que les axones présents au point de stimulation, qu'ils soient afférents, efférents ou de passage, seraient activés (McIntyre et al., 2004a). Cette activation génèrerait des potentiels d'action se propageant de façon orthodromique, mais aussi antidromique, et serait un mécanisme clé pour les effets thérapeutiques de la SCP (Butson et al., 2007; Henderson, 2012; McIntyre et al., 2004b).

Ces nouvelles connaissances sur les effets neurophysiologiques de la SCP ont eu pour conséquence un changement de paradigme total : l'effet thérapeutique de la stimulation n'est plus considéré comme résultant d'effets principalement locaux sur l'activité de la cible, et de leurs conséquences sur l'activité du réseau en aval, mais comme résultant d'une combinaison d'effets locaux et distaux via l'activation des axones, ayant pour conséquence des effets à large échelle sur des réseaux cérébraux spécifiques (Ashkan et al., 2017; Deniau et al., 2010; Eisinger et al., 2019b; Henderson, 2012; Jakobs et al., 2019; Lozano and Lipsman, 2013; McIntyre and Hahn, 2010; Middlebrooks et al., 2020; Udupa and Chen, 2015). En accord avec cette perspective, des études en TEP, EEG et MEG ont permis de caractériser des modulations de l'activité corticale dans de larges réseaux (voir pour revue Ballanger et al., 2009b; Gonzalez-Escamilla et al., 2020; Harmsen et al., 2018; Litvak et al., 2021; Udupa and Chen, 2015). Plus précisément, il semble que la SCP opère en altérant l'activité pathologique de réseaux responsables de l'expression des symptômes (Chiken and Nambu, 2014, 2016; Jakobs et al., 2019; Lozano and Lipsman, 2013; McIntyre and Hahn, 2010; Udupa and Chen, 2015), et notamment les patterns d'activité oscillatoire anormale (Blumenfeld and Brontë-Stewart, 2015; Eusebio et al., 2012; Muthuraman et al., 2018). Dans le cas de la SCP-NST, la stimulation modulerait notamment l'activité beta oscillatoire anormale considérée comme causale pour la bradykinésie et la rigidité dans la MP (Feldmann et al., 2021; de Hemptinne et al., 2015; Kehnemouyi et al., 2020; Kühn et al., 2008;

Muthuraman et al., 2021; Oswal et al., 2016; Rosa et al., 2011; Whitmer et al., 2012 ; voir pour revue Eusebio et al., 2012; Muthuraman et al., 2018). Enfin, à ces effets électrophysiologiques à court terme s'ajoutent des effets à plus long terme, liés par exemple à des phénomènes de plasticité (Ashkan et al., 2017; Jakobs et al., 2019). Ces effets semblent cependant plus susceptibles d'expliquer des effets thérapeutiques au long cours que des effets quasi-immédiats de la SCP tels que ceux observés sur les symptômes moteurs dans la MP.

Parmi tous les effets neurophysiologiques attribués à la SCP, l'activation antidromique de la voie hyperdirecte, qui relie les aires frontales au NST, a émergé ces dernières années comme un mécanisme potentiellement clé de la SCP-NST (Li et al., 2014). Différentes études ont démontré qu'une activation du cortex moteur pouvait se produire en réponse à la stimulation de ses afférences au NST, aussi bien chez l'animal (Dejean et al., 2009; Li et al., 2012, 2007), que chez des patients parkinsoniens implantés, grâce à l'enregistrement de potentiels évoqués par la stimulation (Baker et al., 2002; Devergnas and Wichmann, 2011; Hartmann et al., 2018; Kuriakose et al., 2010; Miocinovic et al., 2018; Walker et al., 2012). De façon intéressante, une étude récente réalisée chez des patients parkinsoniens a montré que ces potentiels évoqués corticaux de courte latence peuvent être enregistrés dans d'autres régions frontales également connectées au NST via la voie hyperdirecte, en l'occurrence le gyrus frontal inférieur (Chen et al., 2020). Cette activation antidromique corticale aurait pour conséquence de modifier l'activité corticale, et potentiellement de désynchroniser l'activité oscillatoire pathologique liée aux symptômes moteurs de la MP (Li et al., 2014), comme montré dans des études chez l'animal (Dejean et al., 2009; Li et al., 2012, 2007) ou utilisant la modélisation computationnelle (Anderson et al., 2018; Kang and Lowery, 2014). Pour finir, un argument fort en faveur de l'importance de ce mécanisme d'activation antidromique corticale provient d'études utilisant l'optogénétique chez la souris, qui ont montré que l'activation sélective des projections du cortex moteur vers le NST était suffisante pour reproduire l'effet thérapeutique de la SCP-NST (Gradinaru et al., 2009; Sanders and Jaeger, 2016). Dans la seconde étude, cette activation rétablissait également un pattern d'activité oscillatoire proche de celui observé à l'état normal (Sanders and Jaeger, 2016). A l'heure actuelle, il n'existe cependant pas de preuve directe de l'implication de ce mécanisme chez l'humain.

Au final, il semble important d'intégrer l'ensemble de ces connaissances neurophysiologiques sur les mécanismes d'action de la SCP lorsqu'on considère ses effets sur l'inhibition de réponse, ce qui n'a pas été fait jusqu'alors. En effet, une limite importante des études existantes est qu'elles n'ont que peu considéré l'influence de la localisation du contact actif, et donc de la région du NST précisément soumise à l'influence de la stimulation. Quelques études ont abordé cette question, le plus souvent en comparant les effets de la stimulation appliquée à des contacts dorsaux vs. ventraux (Gourisankar et

al., 2018; Greenhouse et al., 2011; Hershey et al., 2010; Mirabella et al., 2012; van Wouwe et al., 2017, 2020 ; Table 1). Mais cette méthode est imparfaite, car la position ventrale ou dorsale du contact n'est que peu prédictive de sa position exacte dans le NST et de la zone précise concernée par les effets de la stimulation. Il existe maintenant des méthodes et outils permettant de localiser précisément le contact actif dans le NST, et ce dans un espace commun à l'ensemble du groupe de patients (Ewert et al., 2018; Horn et al., 2019; Lauro et al., 2016), ainsi que de modéliser le volume de tissu activé -une estimation mathématique de la région d'influence de la stimulation- sur la base des paramètres appliqués (voir pour revue Duffley et al., 2019). Les variations interindividuelles dans la position du contact actif ou du volume de tissu activé peuvent ensuite être reliées aux variations interindividuelles dans les effets de la stimulation, par exemple sur la performance à une tâche ou sur les scores cliniques (Dembek et al., 2021; Elias et al., 2021; Treu et al., 2020).

Résumé : *Dans la MP, la SCP-NST diminue la performance d'inhibition de réponse. Ces effets sont susceptibles d'avoir des retombées sur le plan clinique, en contribuant à l'amélioration de l'akinésie mais aussi à l'exacerbation de l'impulsivité. Parmi les différents mécanismes existants, les mécanismes d'inhibition contextuels semblent particulièrement affectés, mais des controverses subsistent en raison de la difficulté à distinguer sur la base du comportement les différents mécanismes exécutifs et moteurs potentiellement affectés par la stimulation. L'usage de l'imagerie et de l'électrophysiologie est susceptible d'aider à distinguer ces mécanismes. Les rares travaux utilisant ces méthodes soutiennent l'hypothèse d'un impact de la SCP-NST sur les mécanismes d'inhibition contextuels. Par ailleurs, les principales questions en suspens concernent les mécanismes d'action de la SCP-NST. D'une part, la relation entre la position de l'électrode et de la région du NST effectivement concernée par la stimulation et ses effets sur le contrôle inhibiteur reste à explorer sur la base des nouveaux outils et méthodes disponibles. D'autre part, les mécanismes neurophysiologiques contribuant à l'effet de la SCP-NST sur le contrôle inhibiteur restent à déterminer.*

3.2 Etude expérimentale

Il semble nécessaire de caractériser les mécanismes d'action contribuant à l'effet de la SCP-NST sur le contrôle inhibiteur, afin de mieux en maîtriser les retombées cliniques (c'est-à-dire, favoriser l'amélioration de l'akinésie, tout en évitant l'impulsivité).

Inspirés par les dernières connaissances sur les mécanismes neurophysiologiques sous-tendant les effets thérapeutiques de la SCP-NST, nous faisons l'hypothèse selon laquelle les effets de la SCP sur le contrôle inhibiteur pourraient dépendre d'une modulation de l'activité du cortex moteur supplémentaire (SMA et pré-SMA), via l'activation antidromique de la voie hyperdirecte. Cette hypothèse prévoit 1) une modulation par la stimulation de l'activité liée au contrôle inhibiteur dans le cortex moteur supplémentaire, et 2) que les effets de la SCP sur le contrôle inhibiteur soient plus importants lorsque la région soumise à l'influence de la stimulation correspond à la région du NST connectée au cortex moteur supplémentaire.

Concernant la première prédiction, nous tirons avantage de travaux récents visant à optimiser la suppression dans le signal EEG des artefacts liés à la stimulation (Lio et al., 2018), et recherchons des modulations d'un marqueur électrophysiologique déjà connu de l'activité de contrôle inhibiteur dans le cortex moteur supplémentaire (Albares et al., 2014). Ce marqueur est spécifique des mécanismes d'inhibition contextuels (Albares et al., 2014), et nous permet ainsi de distinguer les effets de la SCP-NST sur ces mécanismes exécutifs d'effets sur d'autres mécanismes, y compris moteurs.

Nous nous appuyons sur des outils et méthodes récemment rendus accessibles publiquement (Horn et al., 2019) pour tester directement la deuxième prédiction. Nous recherchons des corrélations entre, d'une part, les effets de la SCP sur la performance d'inhibition et, d'autre part, la force de la connectivité entre les volumes de tissu activés et le cortex moteur supplémentaire.

Article 4: Subthalamic stimulation facilitates movement initiation by modulating automatic response inhibition

Manuscrit en révision. Le matériel supplémentaire est disponible à la suite du texte principal.

Subthalamic stimulation facilitates movement initiation by modulating automatic response inhibition

Running title: Subthalamic stimulation modulates inhibition

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Abstract

As an input station of the basal ganglia, the subthalamic nucleus is a key component of the different cortico-basal networks involved in movement control. Subthalamic deep brain stimulation in Parkinson's disease is an efficient therapy for the management of motor symptoms including movement initiation, but it can have adverse effects like impulsivity since it also modulates executive networks supporting inhibitory control. However, the relationship between the beneficial effects of stimulation on movement initiation and its adverse effects on the ability to inhibit movements is still obscure. Here, we test automatic inhibition, a function intended to suppress any kind of response when the context is uncertain, whose modulation might account for both the improvement of movement initiation and the greater difficulties in refraining from reacting.

We assessed the effects of subthalamic deep brain stimulation in 19 Parkinson's disease patients with regard to I) behavioral changes in a motor inhibitory task (Go/NoGo), II) electroencephalographic changes analyzed at the source level, and III) structural connectivity between the stimulated area of the subthalamic nucleus and the supplementary motor complex.

Stimulation decreased reaction times and increased commission errors. These behavioral changes were associated with a modulation of an electrophysiological marker of automatic response inhibition in the supplementary motor complex, and were correlated with the number of fibers connecting the stimulated area of the subthalamic nucleus and the upstream supplementary motor complex.

Our study shows that subthalamic stimulation, by modulating automatic inhibition within a functional network that does not fully overlap with the stopping network, reduces action restraint and facilitates movement initiation.

Keywords

Parkinson's Disease, Deep Brain Stimulation, Subthalamic Nucleus, Response inhibition, Impulsivity

Abbreviations

DBS: Deep Brain Stimulation; ERP: Event Related Potential; gBSS: Group Blind Source Separation; PD: Parkinson's Disease; ROI: Region of Interest; RT: Reaction Time; SMA: Supplementary Motor Area; SMC: Supplementary Motor Cortex; STN: Subthalamic Nucleus; VTA: Volume of Tissue Activated.

1. Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an established treatment for advanced Parkinson's disease (PD). STN-DBS is very efficient in relieving motor symptoms and complications. This includes the improvement of movement initiation difficulties (akinesia) that resist dopaminergic medication.[1,2] However, STN-DBS can also induce side-effects such as inhibitory dysfunctions (impulsivity), which are still poorly understood.[3–5]

Several limitations impede our understanding of STN-DBS effects. Indeed, it is unclear whether, how and which cognitive/motor mechanisms and associated networks are modulated by STN-DBS.[3,4,6] First, movement initiation undoubtedly benefits from the direct modulation of motor activity [7], but might also benefit from the modulation of executive functions through a reduction of abnormal response inhibition.[2,8] Second, predicting the extent of the affected networks is difficult because it requires precise estimates of the STN area affected by stimulation, which depend on electrode position and stimulation parameters. Indeed, the organization of the STN follows a gradient between dorsolateral motor, intermediate associative, and ventromedial limbic territories, which are embedded into distinct functional networks.[9–11] Third, our ability to assess these network effects is limited by the difficulty in performing whole brain activity recordings under DBS using fMRI, MEG or EEG because of safety concerns or artifacts related to the presence of the electrodes or to the stimulation itself.

Impulsivity and disinhibition as side-effects of STN-DBS have mostly been associated with the impairment of the ability to stop ongoing movements.[12,13] The process, which relies on a triangulated network composed of the inferior frontal gyrus (iFG), the pre-supplementary motor area (pre-SMA) and the STN, consists in identifying the stimulus that explicitly instructs stopping the action, and then generating an online inhibitory command intended to cancel the movement before it has been completed.[14,15] However, the impaired ability to suppress ongoing actions in response to a stop signal has not been found to correlate with the beneficial effects of stimulation on movement initiation.[12,16] Still, inhibitory control includes other possible mechanisms that have been far less investigated.[14] We refer here to mechanisms that automatically and non-selectively inhibit any kind of fast motor response before its initiation

as soon as the context is uncertain.[7;17,19,23] The modulation of this function, which is supported by the supplementary motor complex (SMC)[19,20] and likely relies on the STN, might be clinically relevant. Indeed, by setting action restraint, it is likely to play a major role both in movement initiation dysfunctions at the pathological state, and in the beneficial as well as in the adverse effects of STN-DBS.[2,8,23–25] Difficulties in setting an appropriate level of automatic inhibition sensitivity according to the context might lead to difficulties in initiating movements (akinesia; too much automatic inhibition)[8] or, conversely, to difficulties in refraining from reacting to external stimuli (impulsivity; too little automatic inhibition). In this study, we test the hypothesis that both the improvement of movement initiation and the appearance of impulsivity under STN-DBS relate to the modulation of automatic inhibition and of the associated brain network.

We used high density EEG in PD patients with STN-DBS during a simple Go/NoGo task eliciting automatic inhibition,[19,20] in both the ON- and OFF-DBS states. The protocol included a control condition (only Go trials), which allowed us to probe movement initiation prolongation in PD and abnormal inhibition even when the context does not require action restraint.[2,8,24] We characterized the effects of DBS on SMC activity by combining recent developments allowing removal of DBS artifacts[27] and source-space analyses.[28,29] Based on current advances in DBS imaging and electrode reconstruction[12,13,30,31], we calculated the volume of activated tissue (VTA) and assessed the relationship between its structural connectivity with the SMC -calculated on the basis of a normative connectome-[32] and changes in task performance.

[7] The concept is inspired by the pioneering work of Frank and colleagues positing that the STN dynamically modulates decision thresholds to adjust action restraint during high-conflict situations.[17,18] By extension, it was later shown in healthy subjects that, when the environment is unpredictable (even when low-conflict decisions are involved), response inhibition is triggered automatically, non-selectively (by any stimulus, whether relevant or not), within very short delays to prevent automatic motor activations from triggering premature -and potentially erroneous- responses.[19–21] This automatic inhibition of automatic responses is followed by the production of a long latency controlled response (dual process model[22]). This executive mechanism is context-dependent, meaning that it can be modulated as a function of the likelihood of the expected events, from maximum restraint up to full switch-off enabling automatic behavior when the environment is fully predictable.
[8] It has been suggested that exaggerated non-selective inhibition over voluntary movements, even when the situation does not require action restraint, would be a hallmark of PD.[24] In other words, PD patients would be locked into an inhibitory control mode that STN-DBS could contribute to release.[2,8,23,26]

2. Materials and methods

2.1. Patients

Nineteen patients with idiopathic PD and bilateral STN-DBS were included in the study (59.7±7.2 years; five females). Detailed patients' characteristics and inclusion criteria are available as Supplementary material 1 and 2. Patients were tested while taking their regular antiparkinsonian medication, in the morning, on two consecutive days in the ON- and OFF-DBS states, in a randomized order. Testing included the UPDRS-III and the behavioral experiment. For the OFF state, stimulation was turned off 35min before starting. For the ON state, clinical stimulation settings were used. All patients provided written informed consent following the code of ethics of the World Medical Association (Declaration of Helsinki). The research was approved by the local ethics committee (CPP sud-est IV, N°11/097).

2.2. VTA calculation and structural connectivity

We used the publicly available Lead-DBS toolbox[32] (v2.5, www.lead-dbs.org) to localize the DBS electrodes (model 3389, Medtronic). For this analysis, four patients were excluded because preoperative and postoperative images were not available (N=3) or because of extended atrophy precluding accurate normalization (N=1), leading to a sample size of N=15 (all the 19 patients were included in the other analyses). The Lead-DBS analysis pipeline has been fully described elsewhere.[32] Briefly, this includes linear coregistration of the pre- and postoperative images, normalization into the MNI-ICBM152-NLIN-2009b template space using the ANTs-SYN approach, brain shift correction, and electrode reconstruction in the MNI space. VTAs were modeled based on the stimulation parameters (i.e., active contact and voltage) using the "Simbio/Fieldtrip" method implemented in Lead-DBS. The validated default presets of the toolbox[32] were applied for all steps (Supplementary material 2).

Then, the strength of the structural connectivity between the VTAs and the SMC was computed for each patient based on a structural normative connectome ("PPMI-85", derived from PD patients data) available in the Lead-DBS "Connectome Mapper" toolbox.[32] The bilateral SMC regions of interest (ROI) were built on the basis of the AAL3 atlas.[33] Pre-SMA was defined as $y>0$.[34] For each patient, the number of fibers connecting the right and left VTA to the ROIs was extracted as an index of structural connectivity strength.

2.3. Behavioral experiment and EEG recordings

We used a Go/NoGo task assessing automatic response inhibition (Fig. 1A; Supplementary material 2).[19,20] Following previous recommendations,[35] this simple task minimizes stimulus identification difficulty as well as working memory load, and uses equiprobable Go and NoGo stimuli, in order to minimize confounds between inhibitory and auxiliary processes (i.e., working memory, attentional processes). Patients were asked to respond as fast as possible with a right thumb button press to Go signals (green diamonds), while refraining from responding to NoGo signals (green crosses). Two conditions were presented in separate blocks, with equiprobable Go and NoGo trials in the mixed condition (uncertain context, requiring action restraint), and only Go trials in the control condition (fully predictable context, allowing automatic responses). The color of the fixation point was used as a simple reminder of the ongoing condition (red for mixed, green for control). Patients performed 70 trials of each type.

EEG signal was recorded throughout the task using the Biosemi ActiveTwo Mk2 system with 128+6 (four temporal, two at the outer canthi of the eyes) electrodes. Offline, data were band-pass filtered (0.75-45Hz), down-sampled to 1024Hz and set to average reference.

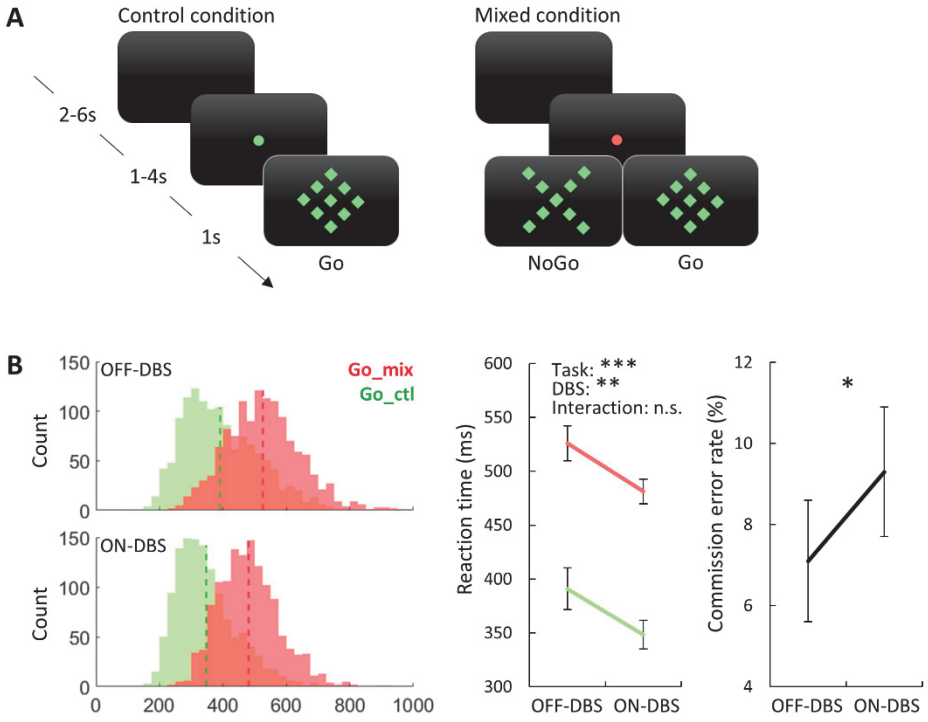

Figure 1: Behavioral task and results. **(A)** Go/NoGo task assessing automatic response inhibition. Patients were asked to respond as fast as possible to Go signals, while refraining from responding to NoGo signals. In the control condition, a green fixation point indicated that only a Go could be presented. This fully predictable context invited participants to respond automatically to any upcoming stimulus. In the mixed condition, a red fixation point indicated that either a Go (green diamond) or a NoGo (green cross) could be presented (50% probability for each). This uncertain context invited participants to refrain from reacting automatically to any stimulus by setting automatic response inhibition mechanisms in order to avoid responding to NoGo signals (automatic responses to any stimulus are automatically inhibited when the context is uncertain, allowing more time to settle on the best decision before eventually providing long latency responses). In this task, commission errors (NoGo responses) directly pinpoint impulsive responding. A lengthening in reaction time (RT) indirectly reflects the implementation of automatic response inhibition by identifying associated long latency volitional responses.[19,20] **(B)** PD is characterized by exaggerated inhibition over voluntary movements even when the situation does not require action restraint.[24] This can be seen in the Go_ctl RT distribution in the OFF state, where the distribution tail is abnormally extended (for a large number of control trials, patients behave as in the mixed condition, where inhibition is required). This is interpreted as a specific difficulty in switching from controlled to automatic sensorimotor processing in PD.[24] As shown in distribution analyses, DBS attenuates this pattern (Supplementary material 3) and, as expected, reduces RT in both conditions. Concomitantly, DBS increases commission errors (impulsive responding).

2.4. EEG data processing

We used group blind source separation (gBSS)[28,29] to track a known neural marker of automatic response inhibition: the DMF170, a source-space event-related potential (ERP).[19] At the scalp level, this early marker is obscured by powerful visual activity and hence can only be revealed through source separation (Supplementary Material 2).[19] This marker reflects automatic, non-selective inhibition of response, a mechanism supported by the SMC that would allow deliberate, longer latency responses when the context is uncertain.[19]

The entire analysis pipeline is based on published methods, and is described in more detail in the Supplementary material 2. Briefly, we used the open-source toolbox DBSFILT[27] (https://github.com/guillaumelio/DBSFILT) to filter out the DBS artifacts. Automatic epoch rejection and individual source separation with the FASTER and EEGlab toolboxes were used for rejection of other artifacts. Extraction of the DMF170 was based on previous work.[19] First, we performed gBSS with the UWSOBI algorithm using aggregated data from all trials and patients,[28,29] leading to the identification of 134 components. Components with a medial frontal topography and a localization consistent with a SMC source (performed using sLORETA) were selected among the 19 components explaining more than 1% of variance. The time-courses of these two medial frontal components were filtered (<30Hz), baseline-corrected (baseline: [-200, 0ms]), and the grand average waveforms were inspected to select the component showing the DMF170. For this component, mean ERP amplitude was extracted for each patient, task condition (Go_mix, Go_ctl) and DBS state (ON, OFF).

Since PD is characterized by exaggerated inhibition over voluntary movements even when the situation does not require action restraint,[24] DBS effects on inhibitory control are also expected in the control condition. This means that DBS effects on inhibitory control vs. motor processes cannot be revealed by simply contrasting DBS effects in the mixed vs. the control condition. Hence, to test to what extent automatic inhibition accounts for response initiation latency, we assessed the correlations between Go reaction time (RT) and DMF170 amplitude.[19] To this aim, for each trial, we extracted the amplitude of the component's activity at the DMF170 peak latency. For visualization only, Go trials (Go_mix and Go_ctl) from all subjects were pooled together and partitioned in nine bins according to RT distribution percentiles, and mean DMF170 amplitude and mean RT were computed for each bin and plotted against each other.

2.5. Statistical analyses

RT were analyzed using a 2 DBS states (ON, OFF) by 2 task conditions (mixed, control) repeated measure ANOVA. A two-tailed Wilcoxon signed-rank test was used for UPDRS-III scores (ON vs OFF-DBS). Commission errors were analyzed using a generalized linear mixed model (GLMM, which accounted for the underlying Bernoulli distribution), with subject entered as a random factor and DBS state as a fixed factor (R package lme4). Omission errors being very variable, a mixed model would not converge; a simpler, slightly less powerful GLM was fitted, which also included task condition as a fixed factor. Supplementary analyses were performed to assess more subtle effects of DBS on response initiation. We compared group RT distributions across DBS states using Kolmogorov-Smirnov tests. We then fitted ex-Gaussians to these distributions to determine which distribution parameters changed (Supplementary material 3).

DMF170 amplitude was analyzed using a 2 DBS states (ON, OFF) by 2 task conditions (mixed, control) repeated measures ANOVA. The relationship between RT and DMF170 amplitude was evaluated using a linear mixed model (R package lme4). DMF170 amplitude was used as the variable to be explained. Subject was entered as a random effect, while log-transformed RT as well as DBS state and task condition were entered as fixed effects. The model did not include interaction effects.

Finally, the relationship between structural connectivity strength between the simulated area and the bilateral SMA and pre-SMA (number of fibers) and change in behavior (commission error rate ON-OFF; Go RT OFF-ON, Go_Mix and Go_ctl pooled, see Behavioral results) as well as in clinical scores (UPDRS-III total and bradykinesia subscore) was evaluated using the Pearson correlation coefficient (r). Although its assumptions were verified (Shapiro bivariate normality test), we chose to additionally report Spearman coefficients (ρ) due to our relatively low sample size.

Statistical analyses used an alpha level of .05.

2.6. Data availability

Data is available from the corresponding author.

3. Results

3.1. Behavioral results

DBS improved UPDRS-III scores (ON- vs OFF-DBS, W=190, p<.001; mean improvement: 60±15.7%, range: 17-83%). RT was shorter in the ON- than in the OFF-DBS state (main effect of DBS, F=11.7, p=.003), and shorter in the Go_ctl than in the Go_mix condition (main effect of task condition, F=385.6, p<.001; Fig. 1B). No significant interaction effect was found (F=.08, p=.78). Patients made more commission errors under DBS (9.3 ± 6.9 vs 7.1 ± 6.6 %, β=0.31, Z=2.17, p=.030; Fig. 1B). Patients made less omission errors in the mixed than in the control condition in the ON-DBS state only, as revealed by a DBS state by Task condition interaction (β=-1.22, z=-3.41, p<0.001; with the main effects being non-significant, DBS state: p=.14, Task condition: p=.26).

3.2. EEG results

The DMF170, a stimulus-locked rather than a movement-locked activity (see Supplementary material 4) was found to peak at 165ms, and the corresponding component was localized in the dorsomedial frontal cortex, consistent with previous work[19] (Supplementary fig. 2). DMF170 amplitude was higher in the ON- than in the OFF-DBS state (main effect of DBS, F=5.0, p=.039). There was no significant effect of task condition (F=.50, p=.49) nor interaction (F=.03, p=.86; Fig. 2A).

Moreover, the linear mixed model showed that log-transformed RT was significantly correlated to DMF170 amplitude (β=-.10, t=-4.87, p<.001; Table 1). The largest DMF170 were found for the fastest trials belonging mostly to the Go_ctl condition, while the smallest or no potential at all were found for the slowest trials belonging mostly to the Go_mix condition (Fig. 2B).

Table 1: Linear mixed model for DMF170 amplitude

	β	**t**	**p-value**
Intercept	.049	4.33	<.001
RT (log-transformed)	-.10	-4.87	<.001
DBS state	.004	1.52	.13
Task condition	.011	3.94	<.001

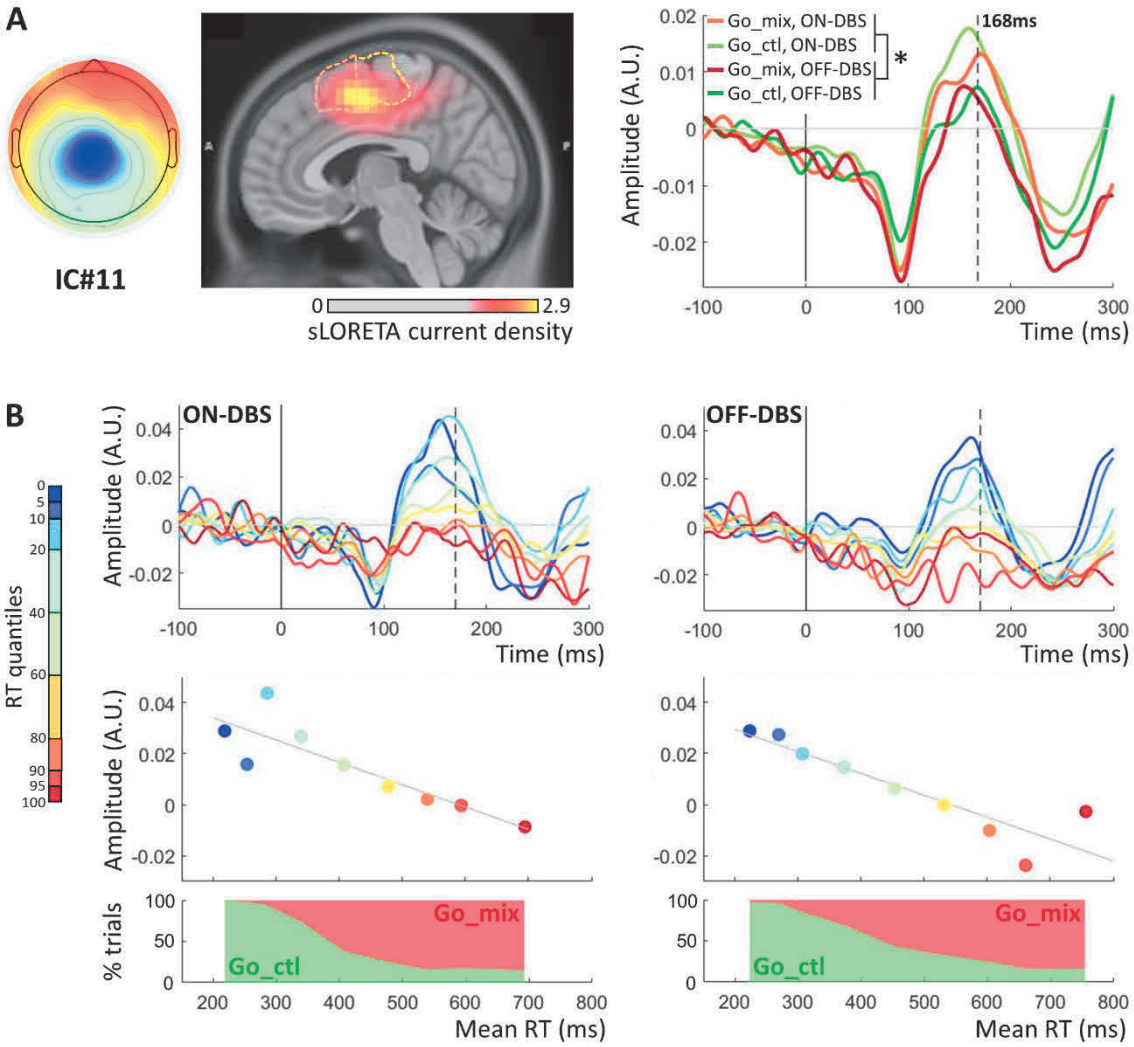

Figure 2: STN-DBS modulates the DMF170, a psychophysiological marker of automatic response inhibition. Large DMF170 amplitudes are associated with fast uninhibited responses and are mostly observed when the context does not require action restraint. The attenuation of this motor potential, which may go as far as its complete suppression, is a direct outcome of inhibition.[19] **(A)** Consistent with previous work,[19] the DMF170 potential was expressed by a dorsomedial frontal component whose current density map encompassed the pre-SMA and SMA (ROIs used for structural connectivity analysis are outlined in orange and yellow, respectively). Broadly, the amplitude of the DMF170 was significantly modulated by STN-DBS. **(B)** A significant linear correlation was found between RT and DMF170 amplitude using a linear mixed model ($p<.001$), meaning that the larger the DMF170, the shorter the RT. Here, for easier visualization, we represent this relationship separately for the ON and OFF-DBS conditions, after partitioning all the trials in nine bins according to RT. In accordance with the interpretation suggesting that inhibition attenuates the motor activity giving rise to the DMF170 potential the RT reduction observed under DBS (Fig. 1) can be associated with a decrease in automatic inhibition of response.

3.3. Structural connectivity

The structural connectivity strength between the VTA and the SMC was significantly correlated to the DBS-induced change in commission error rate (pre-SMA: r=.58, p=.023, ρ=.44, p=.099; SMA: r=.52, p=.048, ρ=.49, p=.065). The correlation between connectivity strength and change in RT was also significant for the pre-SMA (r=.67, p=.007, ρ=.57, p=.029), and approached significance for the SMA-proper (r=.49, p=.061, ρ=.48, p=.073; Fig. 3). The specificity of these relationships was substantiated by the absence of significant correlation between changes in behavior and connectivity to the primary motor cortex, the inferior frontal gyrus, or total VTA volume (Supplementary material 5). Furthermore, the correlations between the strength of the connectivity to the pre-SMA and SMA-proper and motor scores improvement (UPDRS-III, total and bradykinesia subscore) were not significant (all ps>.1, Supplementary material 5).

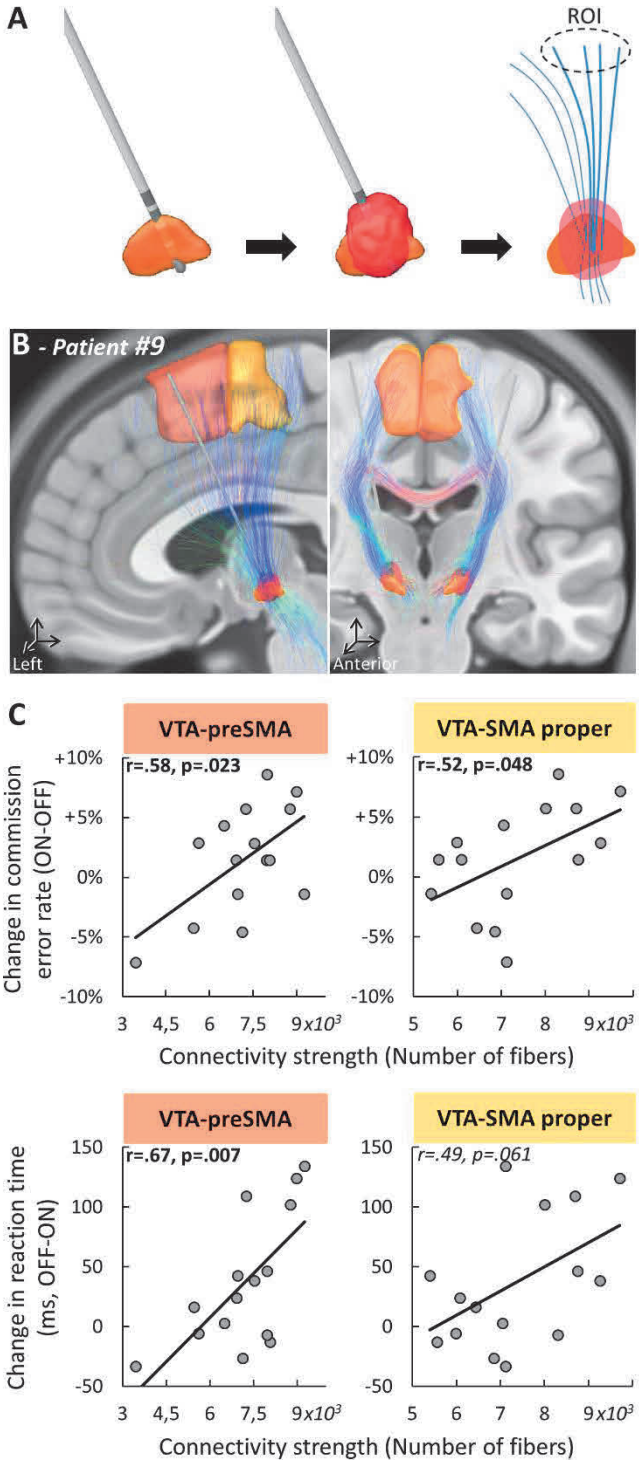

Figure 3: The effects of DBS depend on the strength of the connectivity between the VTA and the supplementary motor complex. **(A)** The connectivity strength was assessed as the number of fibers linking the VTAs to the ROIs, based on a normative connectome.[21] **(B)** An example of a structural connectivity pattern from the VTA (red) is shown (left and anterior views). **(C)** The change in commission error rate under DBS was significantly correlated with the strength of the structural connectivity between the VTA and the pre-SMA (orange) and between the VTA and the SMA-proper (yellow). A similar correlation was also observed between the change in RT and connectivity to the pre-SMA -while the correlation between the change in RT and connectivity to the SMA proper approached significance-, meaning that stronger connectivity with the SMC was associated with faster movement initiation at the expense of higher impulsive responding under DBS.

4. Discussion

It is established that STN-DBS improves movement initiation at the expense of impaired response control,[2–5,13,23] but previous studies failed to demonstrate a correlation between the beneficial effects of stimulation on movement initiation and its adverse effects on the ability to stop ongoing movements.[12,16] This has been interpreted as evidence that these effects depend on the modulation of different networks.[12,13] Here, we focus on another inhibitory function, automatic inhibition, which is intended to automatically suppress any motor impulse when the situation requires action restraint. We show that subthalamic stimulation conjointly reduces action restraint and facilitates movement initiation by modulating automatic inhibition within a functional network linking the STN and the SMC.

4.1. STN-DBS modulates automatic response inhibition

Here, we show that STN-DBS broadly reduces reaction time, both in situations in which patients must refrain from reacting (the mixed condition, in which Go and Nogo trials are unpredictably mixed within the same block) and situations in which they are encouraged to react automatically (the control condition, in which only Go trials are presented). Theoretically, this effect could just be accounted for by motor improvements.[6,7] However, the increase in commission errors (impulsive responding, a variable that was not analyzed in a previous contradictory study[6]) that goes along with RT reduction also suggests a weakening of response inhibition. It is therefore likely that RT reduction is partly due to reduced inhibitory control, including when subjects are free to react automatically. Accordingly, the effect of STN-DBS can be interpreted as a partial release of the inhibitory control state into which patients are locked in the pathological state, and which substantially affects movement initiation delays even when the situation does not require restraint.[2,8,24] This interpretation is strongly supported by the fact that the DMF170, an electrophysiological potential whose amplitude is directly modulated by inhibitory mechanisms,[19] directly accounts for RT both in the ON- and OFF-DBS states (Fig. 2).

Evidence is still sparse about the network supporting automatic inhibition[9]. Neuroimaging studies in healthy subjects have identified various cortical areas whose exact roles in Go/NoGo

[9] It must be noticed that this network does not appear to fully overlap the stopping network, supporting the idea of distinct functional entities

tasks remain unclear, although they likely contribute to monitoring the environment or the internal state[20,35]. In contrast, the SMC is thought to play the pivotal role, either by setting-up a self-inhibitory circuitry that gates information within the SMC itself[19] or by relaying the braking signal to the STN via the hyperdirect pathway[20,35]. However, direct evidence is still missing because of technical difficulties in acquiring reliable signal due to the small size, deep location and anatomical complexity of the STN.[36] In particular, a recent functional connectivity study did not produce evidence for coupling between the SMC and the STN during automatic inhibition in healthy subjects,[21] leaving both hypotheses equally plausible. The present results cannot distinguish between these two hypotheses. Still, they support the involvement of a STN-SMC network in the modulation of automatic inhibition by STN-DBS. Indeed, greater connectivity between the subthalamic VTA and the SMC was associated with greater disruption of inhibitory control (as observed on commission errors) and greater improvement of the capacity to initiate movements (as observed on reaction time, Fig. 3).

It is difficult to know whether the SMC region involved in automatic inhibition is the same hub as for the other, more documented, forms of inhibition. The source of the DMF170 potential seems to originate from the pre-SMA rather than the SMA-proper (Fig. 2 and[19]), but the method lacks spatial resolution to identify the exact site in the cortex that plays this critical role, i.e. to allow direct comparison with stopping studies. Nevertheless, the present study supports the idea that stopping of ongoing movements and automatic inhibition of prepared movements rely on partly separate networks. Of particular interest is the fact that the iFG does not seem to be part of the network supporting automatic inhibition while it is a key component of the stopping network.[20] Indeed, no source explaining at least 1% of variance was found in the iFG (Supplementary fig. 1), and the structural connectivity strength between the STN and the iFG did not account for the changes in behavior (Supplementary material 5).

4.2. Mechanisms of action

While the mechanisms of action of STN-DBS on the motor side of the disease are documented (DBS likely exerts motor benefit by suppressing the propagation of beta band activity from the cortex to the STN in part via the hyperdirect pathway[37–40]), the mechanisms by which it would affect the functional networks supporting executive functions, including automatic inhibition, are still obscure.

We propose that STN-DBS effects on movement initiation relate to the disruption of the exaggerated automatic inhibition observed in the SMC at the pathological state, which locks PD patients into a default mode of inhibitory control over movement triggering[2,8,24]. This disruption would be the net, observable result of the modulation of a functional network linking the STN and the SMC. Indeed, the structural connectivity strength between the subthalamic VTA and the SMC correlated with the changes in behavior under DBS (i.e., increased commissions and decreased RT), and DBS modulated the SMC activity associated with automatic inhibition (i.e., increased DMF170 amplitude). However, the associated neurophysiological mechanisms of action are unknown and cannot be firmly established from the present dataset. Indeed, STN-DBS is known to induce complex modulations of the surrounding cellular elements, including the cell bodies but also the axons,[41,42] which can be activated both in the orthodromic and antidromic directions.[43–47]. In particular, the antidromic activation of the hyperdirect pathway has emerged as a potential major determinant of STN-DBS effects.[12,30,31,45,48,49] Thus, it is tempting to interpret our results as reflecting the antidromic activation of the hyperdirect pathway linking the SMC and the STN. Indeed, the SMC is a major node of motor control networks through its connection to the STN via the hyperdirect pathway,[14,34,50] and hence is a good candidate for supporting antidromic activation and associated effects. However, this interpretation remains speculative. Our connectivity results may also reflect downstream, orthodromic effects on the STN-SMC loops, or a disruption of afferent information transfer from the hyperdirect pathway without antidromic activation, although this last hypothesis does not easily account for the observed modulation of the SMC activity (i.e., increased DMF170 amplitude).

Whatever the mechanisms of action of STN-DBS and the circuitry of automatic inhibition, the increased DMF170 amplitude pinpointing reduced automatic inhibition in the SMC is the net observable effect upon the cortex. It would not be surprising that the cortical activity modulated by STN-DBS is inhibitory in nature, since the local circuitry of the SMC is known to involve a large proportion of inhibitory neurons that play a crucial role in response inhibition and action control.[34,51] Recent electroencephalographic evidence in stimulated patients[26] supports this interpretation as DBS was found to decrease the “baseline” tonic alpha inhibitory activity of the SMC. Such modulation might proactively set the level of sensitivity of the local population of inhibitory neurons and give rise to the observed changes in the event-related

activity (i.e., DMF170). Yet, it remains unclear how the modulation induced by high frequency stimulation (around 130 Hz), whether ortho- or antidromic, can reduce synchronized activity patterns in the much lower frequency bands (below 40 Hz) supporting the motor and executive functions of the SMC.[45,52]

4.3. Clinical implications

From a clinical point of view, these findings mean that stimulation settings that maximize the improvement of movement initiation may also promote impulsive behavior.[3–5,13,23] However, our data suggest that the development of impulsive behavior that goes along with the improvement in motor symptoms is more specific to the effects of STN-DBS on the network supporting automatic inhibition. Indeed, only the markers of impulsive behavior under DBS were found to correlate with the connectivity strength between the stimulated volume of the STN and the SMC, but not the clinical markers of motor improvement (i.e., UPDRS-III total or bradykinesia subscore). Although at variance with previous reports,[30,48] this is consistent with the idea that the multiple effects of DBS might rely on various action mechanisms and networks, which is a major current issue.[13,53] Together with other recent evidence (e.g.[12]), such dissociation might offer opportunities to better balance between the therapeutic benefits and the adverse effects of stimulation as a function of fiber-specific neuromodulatory effects[53,54].

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Competing interests

The authors report no competing interests.

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Supplementary material

Meyer et al. – Subthalamic stimulation facilitates movement initiation by modulating automatic response inhibition

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Supplementary material 1: Patients characteristics

	Age	Sex	Laterality	LEDD	DD	TS	UPDRS-III ON	UPDRS-III OFF	Right stimulation parameters	Left stimulation parameters
1	58	M	0,83	475	8	4	10	37	7-/3,6V/60µs/130Hz	3-/2,7V/60µs/130Hz
2	49	M	0,83	160	15	25	6	18	6-/3,3V/90µs/130Hz	1-/3,3V/90µs/130Hz
3	64	F	0,83	770	23	77	20	24	5-/ 2,8V/60µs/130Hz	2-/ 3,3V/60µs/130Hz
4	67	M	0,50	560	10	41	4	23	6-/ 2,4V/90µs/160Hz	2-/ 2,6V/90µs/160Hz
5	43	M	0,67	600	8	23	23	35	6-/ 2,9V/60µs/130Hz	3-/ 3,7V/60µs/130Hz
6	64	F	1,00	610	26	24	11	24	7-/ 2,9V/90µs/160Hz	3-/ 3,4V/90µs/160Hz
7	61	M	1,00	450	23	45	23	48	6-,7-/ 3V/90µs/130Hz	2-/ 3,2V/60µs/130Hz
8	50	F	0,83	750	10	3	4	19	6-/ 2,8V/60µs/130Hz	3-/ 3V/60µs/130Hz
9	64	F	0,92	262,5	24	48	26	60	5-/3,3V/90µs/130Hz	1-/3,4V/60µs/130Hz
10	68	F	0,91	575	7	18	5	16	6-/2,6V/60µs/130Hz	2-/2,7V/60µs/130Hz
11	69	M	0,75	450	13	59	12	38	7-/2,6V/60µs/160Hz	3-/3,4V/60µs/160Hz
12	59	M	0,83	200	9	3	13	33	9-/ 3V/60µs/130Hz	1-/ 2,8V/60µs/130Hz
13	70	M	0,83	710	13	63	25	55	6-/ 3,2V/60µs/130Hz	2-/ 3,1V/60µs/130Hz
15	60	M	0,58	940	12	51	4	11	6-/ 3,4V/60µs/130Hz	2-/ 3,9V/60µs/130Hz
16	55	M	1,00	0	13	21	16	48	6-/ 3V/60µs/160Hz	2-/ 3,3V/60µs/160Hz
17	65	M	1,00	800	11	29	8	19	5-/ 4,2V/60µs/70Hz	2-/ 4V/60µs/70Hz
18	51	M	0,83	1030	8	43	6	30	6-/ 3,7V/90µs/130Hz	2-/ 2V/60µs/130Hz
19	58	M	1,00	225	11	35	18	44	5-/ 3,2V/60µs/130Hz	1-/ 3V/60µs/130Hz
20	59	M	0,70	825	10	54	29	59	5-/ 3,5V/60µs/130Hz	1-/ 3,4V/60µs/130Hz
	59,7	***5F***		***547,0***	***13,4***	***35,1***	***13,8***	***33,7***		
	7,2			***274,6***	***5,9***	***20,5***	***8,2***	***14,8***		

Supplementary table 1: Patients' characteristics. Laterality score; LEDD: Levodopa equivalent daily dose; DD: Disease duration, years; TS: Time since surgery, months; UPDRS-III ON and OFF-DBS assessed at the time of the experiment.

Supplementary material 2: Detailed methods

1. Patient selection

Patients were included if they benefited from STN-DBS for at least three months and had stable dopaminergic treatment for at least two months. Exclusion criteria were dementia (MATTIS <130), presence of another neurologic or psychiatric disease (excepted depression), substance use or dependence according to the DSM-IV-TR criteria (excepted tobacco smoking), being treated for another medical condition with a medication that would have psychological or neurological effects. Patients took part in the experiment during their regular follow up visits and were compensated 120€ for their participation in the entire study, which included two other experimental sessions.

2. Task selection

In standard inhibitory tasks using complex designs, most of the activity typically elicited by stimuli that require response inhibition is actually driven by the engagement of high attentional or working memory resources, not by inhibitory processes per se (see[1] for meta-analysis and methodological suggestions). A recent study following the recommendation to refine behavioral designs in order to limit confounds between response inhibition and parallel cognitive processes revealed that non-selective inhibition of response (the automatic inhibition of automatic responses to any stimulus when the context is uncertain, which allows more time to settle on the best decision before eventually providing long latency responses) accounts much more for behavior than the mechanisms of selective inhibition of response inferred from classical designs[2]. We thus used a similar unbiased Go/NoGo design in the present study and focused on the behavioral and electrophysiological markers of contextual response inhibition.

3. Task procedure

Participants completed two blocks of each type (mixed and control) in a counterbalanced order, for a total of 70 trials of each type. All stimuli were presented on a light-emitting diode panel (LED, Ø5 mm, 8800mcd). A central LED served as a fixation point. Go (green diamonds) and NoGo (green crosses) stimuli were composed of eight LEDs centered on it (3.44° of visual angle, stimulus duration: 50ms).

4. Parameters for VTA calculation and structural connectivity

Images available for localization of the electrodes with the LeadDBS toolbox were preoperative T1 and post-operative CT, N=7; preoperative T1 and T2 and post-operative CT, N=4; or preoperative and postoperative T1, N=5. At each step of the LeadDBS analysis pipeline, results were carefully checked by visual inspection using the built-in tools. In particular, the accuracy of the normalization is critical for correct electrode localization, and was verified with special attention to the correspondence of template and patient images at published subcortical anatomical fiducials (anterior commissure, posterior commissure, ponto-mesencephalic junction, left and right mesencephalic sulci)[3]. When necessary, manual corrections of the normalization and electrode reconstruction were applied using the dedicated tools in Lead-DBS v2.5.

For calculation of the volume of tissue activated (VTA), the "Simbio/Fieldtrip" method implemented in Lead-DBS was used.[4,5] It estimates the E-field in a four compartment tetrahedral mesh (electrode material, contacts, and white and grey matter as defined based on the DISTAL atlas[6]) based on a finite element model. Preset values of 0.14 S/m and 0.33 S/m were used for the conductivity of white and grey matter, respectively. Finally, the binary VTA was obtained by thresholding the electric field strength at a heuristic value of 0.2 V/mm. All the patients concerned by this analysis (N=15) had monopolar stimulation, which is important because VTA estimated with E-field methods may differ from those obtained from more realistic computational axon models in the case of bipolar stimulation[7].

The procedure used to build the structural normative connectome available in Lead-DBS has been fully described elsewhere[5]. It is derived from global fibersets based on high quality diffusion-weighted imaging data from 85 PD patients of the Parkinson's Disease Progression Marker Initiative database.

5. EEG data processing

5.1. Pre-processing

When recording ON-DBS, EEG signal is corrupted by DBS artifacts, that may not be completely eliminated by standard low-pass filtering.[8,9] Thus, we used the dedicated open-source toolbox DBSFILT (https://github.com/guillaumelio/DBSFILT/releases) to filter out the DBS artifacts present in the ON-DBS data. The toolbox combines analog and digital low-pass filtering with frequency-domain filtering based on artifact identification procedures.[8] Then, epoching and automatic epoch rejection were performed using the FASTER toolbox.[10] Epochs were cut from 1500ms before to 1000ms after stimulus onset, for both Go and NoGo stimuli. Finally, individual source separation (SOBI algorithm[11]) was performed using the EEGlab toolbox[12] to reject the artifactual components (e.g., eyes movements, blinks, muscle activity). For defective channels, spherical interpolation was privileged over rejection of the corresponding artifactual components.

5.2. Group blind source separation (gBSS) and selection of components of interest

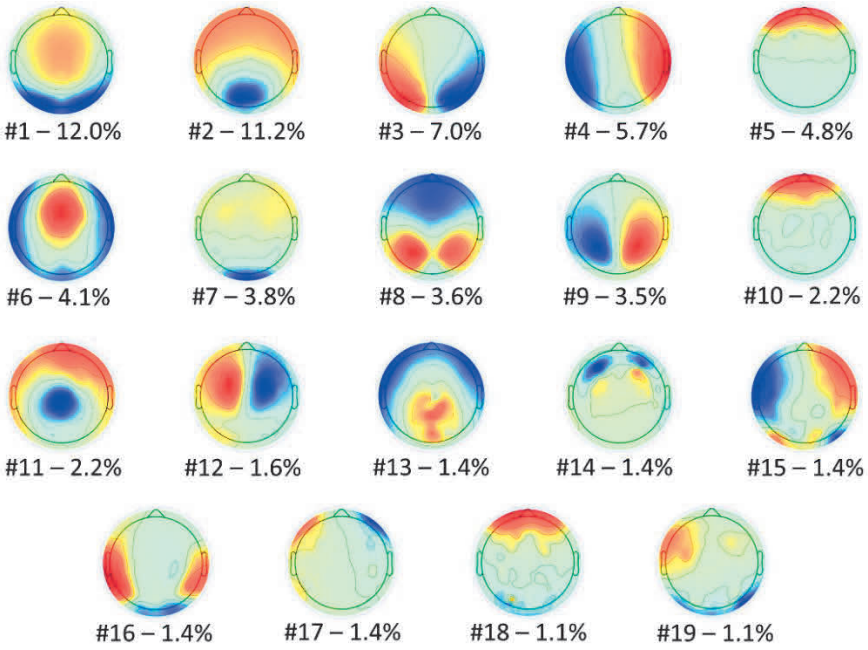
A major limitation of EEG is that the recorded signal reflects a mixture of ongoing brain activities coming from different brain regions and spreading across the scalp. Blind source separation allows to "unmix" the constituent overlapping brain activities as components (i.e., sources), without the need of any a priori information about the sources or the mixing process. Group blind source separation (gBSS) can further extract components that are uniformly expressed at the group level.[13–15]

Group Blind Source Separation (gBSS) was applied on the aggregated data, including all the trials obtained from the patients (all types of trials were used, including NoGo trials). The UWSOBI algorithm was used. Indeed, such algorithms based on second order statistics have been shown to be more robust than those based on higher order statistics with regard to anatomo-functional inter-individual variability, and are thus more suitable for gBSS.[14,15] Two hundred lagged-covariance matrices with time delays ranging from 0/1024s to 200/1024s were calculated on each epoch. The lagged-covariance matrices were averaged across the patient's epochs, and then across all patients and conditions, so that 200 lagged covariance

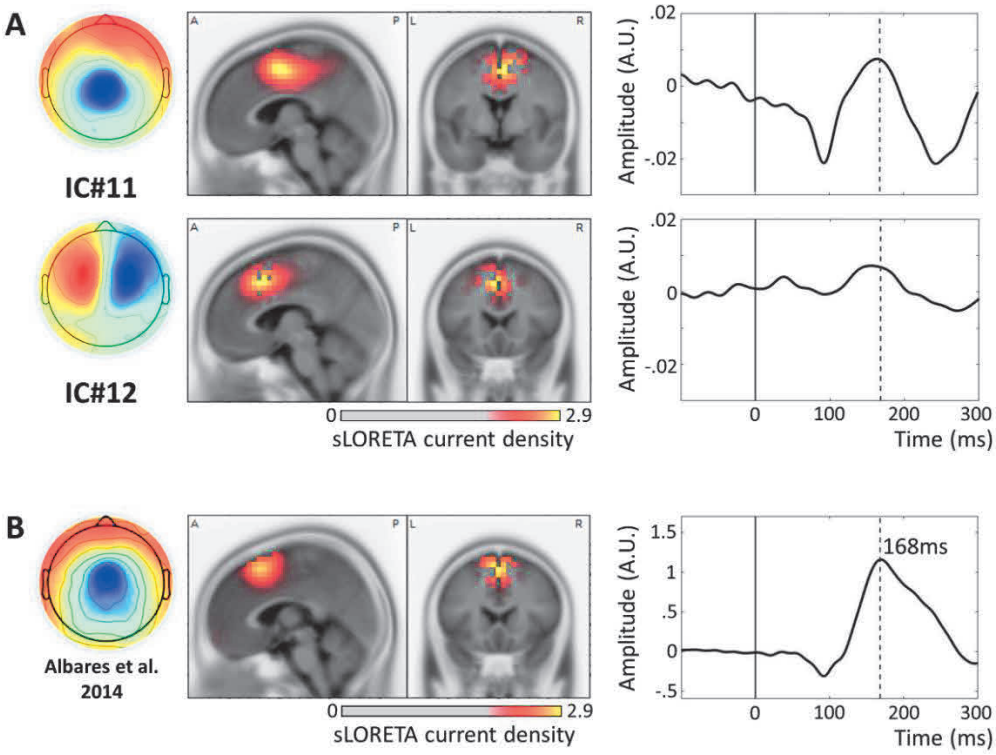
matrices were approximately joint-diagonalized with the UWEDGE algorithm.[16] This led to the identification of 134 components (ICs).

Then, components were sorted by percent of variance explained, and those explaining more than 1% of the variance were retained for further consideration (19 components, see Supplementary Figure 1). The sLORETA software[17] was used to localize the components based on a head model obtained by applying the boundary element method to the MNI152 template (solution space restricted to cortical grey matter, 6239 voxels at 5mm resolution, Tikhonov regularization optimized for a signal/noise ratio of 100).[18] Components characterized by a topography consistent with a medial frontal source and a sLORETA localization probability map encompassing the SMC were retained (two components, IC#11 and #12).

To ensure that these components are reasonably replicable across subjects, we applied a consistency test.[19] This test consists in separating the cohort in two subgroups that are the most similar regarding their clinical characteristics and behavior (here we used age, LEDD, disease duration, UPDRS-III ON and OFF, RTs ON and OFF and commission error rates ON and OFF), and then computing a quality index Q_i based on the spatial correlations within triplets of ICs that are deemed the most similar among the entire group and the subgroups. A complete description of the test implementation is available elsewhere.[20] According to this test, the two medial frontal components were reasonably replicable across subjects (IC#11: Q_i=61%, p=.004; IC#12: Q_i=90%, p<.001). The components' activity time-courses were reconstructed by applying the group BSS filter (i.e., weights) to individual subjects' data, filtered under 30Hz, and baseline-corrected (baseline: [-200, 0ms]). Visual inspection of the grand average waveforms revealed that activity consistent with the DMF170 was present in IC#11, but not IC#12 (Supplementary figure 2). Thus, mean DMF170 amplitude was extracted for IC#11. Mean amplitude was extracted at 168ms, (i.e. the peak latency of the DMF as previously identified[21]).



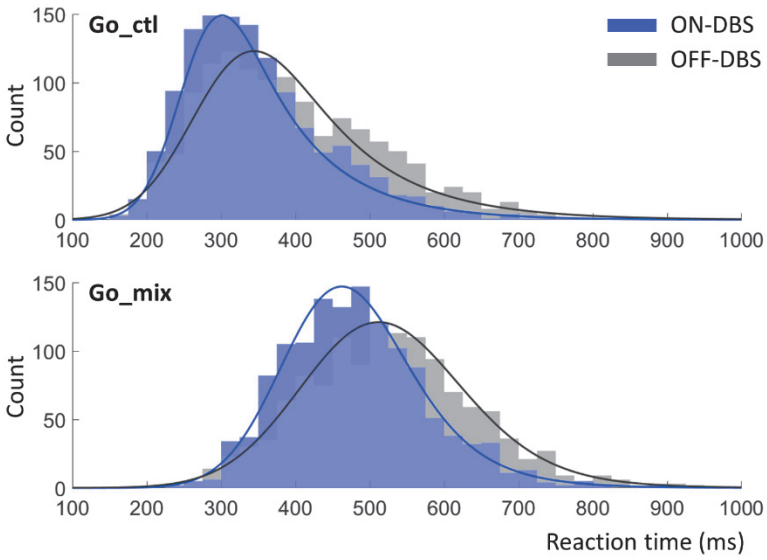
Supplementary Figure 1: Topographies of the gBSS components explaining more than 1% of variance.



Supplementary figure 2: Identification of the DMF170. (A) Characteristics of the two medial frontal components (IC#11 and IC#12) identified in the present study. Topography, localization and ERP of IC#11 resembled those of the DMF170 component identified in healthy subjects21. (B). Illustrations for panel B are adapted from21. Note that in the original paper21, and unlike in the present figure, the DMF170 ERP was shown as back-projected on the scalp, and thus appeared as a negative-going deflection.

Supplementary material 3: Distribution analyses

Distribution analyses showed that DBS significantly modified both Go_mix and Go_ctl distributions (Kolmogorov-Smirnov tests; Go_mix: D=.21, p<.001; Go_ctl: D=.18, p<.001). We then used the DISTRIB toolbox[22] to fit ex-gaussians to these distributions. This showed that the significant changes in RT distributions were most likely attributable to changes in μ (Go_mix: 459.8 vs. 415.2; Go_ctl: 283.7 vs. 256.1) and σ (Go_mix: 95.2 vs. 71.2; Go_ctl: 65.5 vs. 43.5) in both conditions, as well as to a change in τ (Go_mix: 65.8 vs. 65.5; Go_ctl: 107.4 vs. 43.5) in the control condition (Supplementary figure 3).



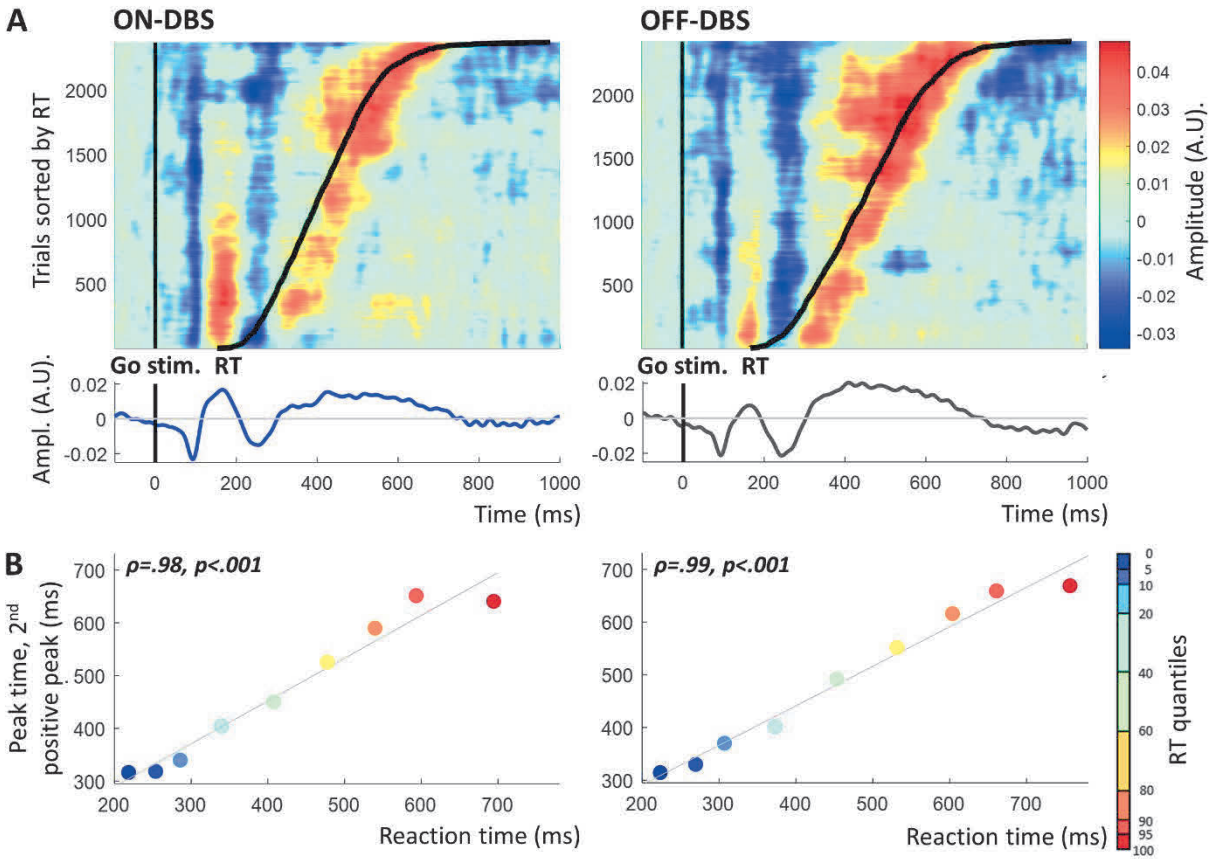
Supplementary figure 3: Fitted ex-gaussian distributions.

Supplementary material 4: Relationship between EEG activity and movement onset

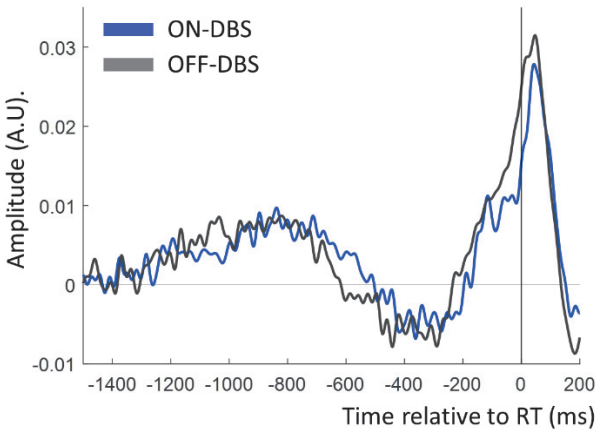
The control of movement-related changes is an inherent problem when testing for correlations with RT in neurophysiology. Indeed, the correlation between RT and DMF170 amplitude may be explained by a relationship of the DM170 with movement onset instead of stimulus occurrence (i.e., the DF170 may be a movement-locked rather than a stimulus-locked activity). The stronger variability would hence explain the lower amplitude of this ERP with longer RTs. To investigate this, we plotted IC#11 activity across trials, pooling Go trials from all subjects. For visualization, a trial moving average smoothing has been applied (window length: 200 trials). We then tested the correlation between ERP peak latency and RT (see below). To this aim, Go trials (Go_mix and Go_ctl) from all subjects were pooled together and partitioned in nine bins according to RT distribution percentiles. ERP peak latency and mean RT were computed for each bin, and the correlation was evaluated using the Spearman correlation coefficient. Finally, we extracted the response-locked activity of IC#11 (epoch limits: [-1500, 200ms] relative to RT, baseline: [-1500, -1300ms]). Note that for this control response-locked analysis, 30 trials OFF-DBS (out of 2423) and 11 trials ON-DBS (out of 2367) with RTs above 800ms were excluded, to allow the re-epoching to be done on the existing epochs ([-1500, 1000ms] relative to stimulus occurrence) rather than on the continuous data.

When plotting IC#11 activity across trials, the first ERP observable component locked to stimulus presentation is the DMF170. A second ERP component peaking close to RT was observed (Supplementary figure 4A). Its latency was significantly correlated with RT (ON: ρ=.98, p<.001; OFF: ρ=.99, p<.001; Supplementary figure 4B). Aligning the data on movement onset (RT) clearly revealed this response-locked activity (Supplementary figure 5).

Overall, these results support the original interpretation of the DMF170 component (Albares et al 2014) as a marker of automatic motor activation consecutive to stimulus presentation, whose attenuation is a direct outcome of inhibition. On the other hand, we suggest that the second ERP component locked to the motor response reflects the motor activity related to the execution of voluntary long latency responses.



Supplementary figure 4: Relationship between IC#11 activity and RT. (A) Event-related activity of IC#11 displayed across all Go trials (Go_mix and Go_ctl) sorted by RT. (B) The second ERP component's peak time significantly correlates with RT at the group level, both in the ON- and in the OFF-DBS conditions.



Supplementary figure 5: Response-locked activity for IC#11.

Supplementary material 5: Supplementary structural connectivity analyses

	Change in commission error rate (%)	Change in mean reaction time (OFF-ON)
Structural connectivity strength, VTA-bilateral M1	- *ρ*=.35, p=.20	*r*=-.03, p=.91 *ρ*=.06, p=.84
Structural connectivity strength, VTA-bilateral IFG	*r*=.41, p=.13 *ρ*=.40, p=.14	*r*=.35, p=.20 *ρ*=.49, p=.06
Total VTA volume	*r*=.22, p=.42 *ρ*=.27, p=.33	*r*=.37, p=.17 *ρ*=.21, p=.45

Supplementary table 2: Correlations with connectivity to M1, IFG, and total VTA volume. Pearson coefficients are reported only when assumptions are met.

Structural connectivity strength	Change in commission error rate (%)	Change in reaction time (ms)
VTA-Left pre-SMA	*r*=.48, p=.069 *ρ*=.24, p=.38	*r*=.45, p=.089 *ρ*=.47, p=.076
VTA-Right pre-SMA	*r*=.57, p=.025 *ρ*=.44, p=.10	*r*=.72, p=.002 *ρ*=.63, p=.014
VTA-Left SMA	*r*=.52, p=.045 *ρ*=.55, p=.032	*r*=.41, p=.13 *ρ*=.31, p=.25
VTA-Right SMA	*r*=.33, p=.23 *ρ*=.31, p=.26	*r*=.40, p=.13 *ρ*=.47, p=.081

Supplementary table 3: Lateralization effects in the correlation between change in behavior and strength of structural connectivity between the VTA and SMC.

Structural connectivity strength	Improvement of UPDRS-III (%)	Improvement of UPDRS-III bradykinesia subscore (ms)
VTA-bilateral pre-SMA	- *ρ*=-.12, p=.66	- *ρ*=-.02, p=.93
VTA-bilateral SMA	*r*=.20, p=.47 *ρ*=.08, p=.77	- *ρ*=.10, p=.72

Supplementary table 4: Correlation between change in clinical scores and strength of structural connectivity between the VTA and SMC.

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3.3 Conclusions et perspectives

Dans notre étude, nous montrons, en accord avec de précédents travaux (Albares et al., 2015b; Ballanger et al., 2009b; Favre et al., 2013; Spay et al., 2018), que la SCP-NST affecte les mécanismes contextuels d'inhibition de réponse. Cela est attesté par une diminution du TR, une augmentation du taux d'erreurs de commission, et la modulation de l'amplitude de la DMF170, un marqueur électrophysiologique de ces mécanismes dans le cortex moteur supplémentaire (CMS ; c'est-à-dire les aires motrices supplémentaire et pré-supplémentaire). Surtout, nos résultats supportent, chez l'homme, l'hypothèse selon laquelle ces effets seraient dépendants de l'activation antidromique de la voie hyperdirecte liant le CMS au NST. En effet, nous avons observé que les effets de la SCP sur le comportement dans notre tâche de Go/NoGo sont plus importants lorsque la connectivité structurelle entre le VTA et le CMS est plus forte.

Certains points méritent d'être soulignés et discutés plus en détail que ce que permet l'espace restreint correspondant au format choisi pour la publication de notre article. Tout d'abord, nos résultats sont en accord avec l'idée avancée plus haut selon laquelle la diminution du TR sous SCP-NST reflèterait au moins en partie des effets exécutifs, c'est-à-dire des effets sur le contrôle inhibiteur, et pas seulement des effets strictement moteurs (Albares et al., 2015b; Favre et al., 2013; Neumann et al., 2018). En effet, nous observons en parallèle de la diminution du TR une augmentation du taux de commissions, mais surtout une modulation de la DMF170, dont l'amplitude corrèle par ailleurs directement avec le TR au niveau du groupe. Pour rappel, une diminution du TR sous l'effet de la stimulation dans des tâches d'inhibition était également rapportée dans de précédentes études, mais interprétée comme relevant d'effets purement moteurs. Ces études avaient conclu à une absence d'effet de la SCP-NST sur les mécanismes d'inhibition de réponse contextuels (De Pretto et al., 2021; Mancini et al., 2018; Mirabella et al., 2012).

Il convient également de souligner que les résultats des analyses de connectivité structurelle ne constituent en aucun cas une preuve directe de l'implication d'une activation antidromique de la voie hyperdirecte (voir pour discussion Horn and Fox, 2020). Ces résultats signifient simplement que les effets de la SCP sur le contrôle inhibiteur sont plus importants lorsque la région stimulée correspond à la région du NST connectée au CMS. Cela pourrait tout à fait s'expliquer par d'autres mécanismes neurophysiologiques qu'une modulation de l'activité corticale résultant d'une activation antidromique de la voie hyperdirecte, telle que la suppression par la SCP de l'action modulatrice des projections hyperdirectes du CMS sur le NST, ou bien encore la suppression de l'activité en sortie de la région concernée du NST (Lofredi et al., 2021; Neumann et al., 2018). Ces hypothèses alternatives sont

néanmoins plus difficiles à réconcilier avec la modulation de l'activité du CMS observée dans notre étude, c'est pourquoi nous privilégions l'hypothèse de l'activation antidromique.

Par ailleurs, les corrélations entre l'effet de la SCP sur l'amplitude de la DMF170 et la force de la connectivité structurelle n'ont pas pu être explorées en raison de limitations méthodologiques. Un des avantages de la méthode de séparation de sources de groupe que nous avons utilisée est de permettre d'extraire des sources d'activité communes à l'ensemble du groupe, gommant de ce fait la variabilité interindividuelle neuro-anatomique et fonctionnelle (Lio and Boulinguez, 2013, 2018). Ainsi, bien que les filtres spatiaux obtenus puissent ensuite être appliqués au niveau individuel pour extraire le pattern d'activité des sources identifiées au niveau du groupe pour chaque sujet, cette stratégie n'est pas forcément la plus adaptée à l'extraction de marqueurs électrophysiologiques très robustes à l'échelle individuelle. En d'autres termes, cette méthode est très adaptée pour révéler l'effet moyen de la SCP sur l'amplitude de notre marqueur, la DMF170, à l'échelle du groupe (ce qui était notre objectif principal), mais elle l'est moins s'il s'agit d'obtenir une estimation précise de la taille de cet effet pour chaque patient.

Sur le plan théorique, l'hypothèse selon laquelle les effets de la SCP-NT sur le contrôle inhibiteur dépendent d'une modulation de l'activité corticale du CMS liée à l'activation de la voie hyperdirecte va à l'encontre de l'idée jusqu'alors généralement acceptée selon laquelle ces effets seraient dus à une influence de la stimulation sur l'activité locale du NST. Nous pouvons alors proposer, de façon certes spéculative, que la SCP-NST n'impacte pas la performance d'inhibition de réponse en perturbant le relai de *la commande d'inhibition* via le NST, mais en perturbant directement l'activité corticale liée au *contrôle inhibiteur.*

Nos résultats sont par ailleurs en accord avec ceux d'études récentes ayant réalisé le même type d'analyses de connectivité structurelle. Il a en effet été montré que la force de la connectivité structurelle du VTA au réseau de l'inhibition de réponse (SMA, gyrus frontal inférieur droit) pouvait expliquer la détérioration de la performance d'inhibition dans une tâche de type signal stop sous SCP-NST (Lofredi et al., 2021), ou encore l'impulsivité post-opératoire des patients stimulés dans le NST (Mosley et al., 2020). Une étude a également retrouvé une corrélation entre les effets de la SCP-NST sur le contrôle exécutif de l'action dans une tâche visuo-motrice et la proportion de fibres de la voie hyperdirecte (définie comme reliant les aires motrices et pré-motrices au NST) passant dans la sphère d'influence des contacts actifs (Neumann et al., 2018). Sur le plan clinique, il semble également qu'une forte connectivité entre le VTA (ou le contact actif) et la SMA soit prédictive d'une amélioration plus

importante du sous-score clinique (UPDRS-III) de bradykinésie[10] (Akram et al., 2017; Avecillas-Chasin et al., 2019), ou même du score total d'UPDRS-III (Elias et al., 2021; Horn et al., 2017), une relation que nous ne retrouvons cependant pas dans notre étude. Une étude ayant inclus 262 patients atteints de MP a également montré que les contacts actifs plus antérieurs, c'est-à-dire placés plutôt dans le domaine associatif du NST, sont associés à une meilleure amélioration de la bradykinésie (Welter et al., 2014).

Du point de vue clinique, ces connaissances sur les relations entre la position ou la connectivité des contacts actifs et les effets de la SCP sont précieuses, car elles pourraient informer le choix des paramètres de stimulation, voire même de la position précise de l'électrode visée au sein de la structure cible. Fondé sur l'idée que la SCP agit en influençant les réseaux cérébraux spécifiques de la pathologie ou du symptôme visé (Fox et al., 2014; Siddiqi et al., 2021), le nouveau champ d'étude de la neuromodulation connectomique vise en effet à identifier lesdits réseaux -ce qui contribue en retour à améliorer nos connaissances sur le plan pathophysiologique-, et à incorporer ces connaissances dans la pratique clinique (Horn and Fox, 2020; Horn et al., 2022a). L'objectif proposé est, à long terme, d'aller vers une « médecine personnalisée », où la position cible des contacts actifs, ainsi que les paramètres de stimulation, seraient déterminés de façon à moduler le plus précisément possible les réseaux liés à l'amélioration des symptômes spécifiquement présentés par le patient, tout en évitant de moduler les réseaux liés à l'apparition d'effets secondaires de la stimulation (Hollunder et al., 2021; Rajamani et al., 2022). Cette approche s'appuierait sur les progrès en cours dans les méthodes d'imagerie (Horn, 2019; Horn et al., 2022b), et sur les évolutions du matériel de stimulation (Krauss et al., 2021), notamment l'apparition des électrodes directionnelles, qui permettent de diriger plus précisément le champ électrique dans la structure cible. De nombreux travaux ont déjà identifié des réseaux dont la modulation est liée à l'amélioration de symptômes spécifiques, ou à l'apparition d'effets secondaires (voir pour revue Georgiev et al., 2021; Horn, 2019; Middlebrooks et al., 2020). Il semble par exemple dans la MP que différents réseaux soient liés à l'amélioration de la rigidité, de la bradykinésie, et des tremblements sous SCP-NST (Akram et al., 2017; Strotzer et al., 2019), tandis que des réseaux liés à l'aggravation post-opératoire de la dépression ou à des effets secondaires de la stimulation tels que les paresthésies ou la dysarthrie ont pu être identifiés (Irmen et al., 2020; Strotzer et al., 2021). Cette perspective contraste avec -et pourrait se substituer à- celle visant à rechercher une cible optimale et universelle, souvent appelée « sweetspot », susceptible de d'améliorer de façon maximale l'ensemble des symptômes visés de la pathologie (par exemple, les tremblements, la rigidité

[10] On notera que ces évaluations cliniques de la bradykinésie évaluent des aspects plus larges de la capacité motrice du patient, notamment la vitesse et l'amplitude du mouvement, ainsi que leur diminution progressive au cours de mouvements séquentiels, et pas seulement la difficulté et la lenteur d'initiation du mouvement, qui constituent spécifiquement l'akinésie (voir Schilder et al., 2017 pour une discussion de cette terminologie).

et la bradykinésie pour la MP), et ce chez une grande majorité de patients (Dembek et al., 2019; Elias et al., 2021, voir pour revue de Roquemaurel et al., 2021). Il reste que cette stratégie de ciblage de réseaux pourrait être plus difficile à appliquer dans le cas où la modulation d'un même réseau serait liée aussi bien à l'amélioration d'un symptôme qu'à l'apparition d'effets secondaires. Cela pourrait être le cas avec le réseau de l'inhibition de réponse, et plus particulièrement les connections au CMS, puisque nos résultats, couplés à ceux cités plus haut, laissent à penser que sa modulation pourrait être responsable aussi bien d'une amélioration de l'akinésie que d'une exacerbation de l'impulsivité.

Résumé : *La SCP-NST, bien que très efficace contre les symptômes moteurs de la MP, est connue pour affecter le contrôle inhibiteur. Il est important de mieux comprendre ces effets, car ils sont susceptibles d'être liés, sur le plan clinique, à une amélioration de l'akinésie, mais aussi à une exacerbation de l'impulsivité. Une question importante, mais peu explorée, est celle de la dépendance entre les effets de la SCP sur le contrôle inhibiteur et la position des contacts actifs, et donc de la région du NST concernée par la stimulation. En effet, le NST est fonctionnellement hétérogène, de par la participation respective de ses différents territoires aux boucles cortico-basales motrice, associative et limbique. Inspirés par les dernières connaissances sur les mécanismes neurophysiologiques sous-tendant les effets thérapeutiques de la SCP-NST, nous testons l'hypothèse selon laquelle les effets de la SCP sur le contrôle inhibiteur pourraient dépendre d'une modulation de l'activité du cortex moteur supplémentaire, via l'activation antidromique de la voie hyperdirecte. Nos résultats sont en accord avec cette hypothèse : une forte connectivité structurelle entre le VTA et le cortex moteur supplémentaire correspond à des effets plus importants de la SCP sur le comportement dans notre tâche de Go/NoGo. Nos résultats suggèrent aussi que la SCP-NST impacte directement l'activité corticale liée au contrôle inhibiteur, contrastant avec l'idée selon laquelle ses effets délétères sur la performance d'inhibition seraient liés à la perturbation du relai de la commande inhibitrice par le NST.*

Conclusion et perspectives

4.1 Bilan du projet doctoral

La MP est une maladie connue pour ses altérations dopaminergiques et ses symptômes moteurs, mais elle entraîne également des altérations non-dopaminergiques et des symptômes non-moteurs. Les traitements proposés sont symptomatiques et visent principalement les symptômes moteurs. Mieux gérer leurs effets indésirables potentiels constitue un enjeu actuel important. Ce travail de thèse s'est intéressé à l'impulsivité, qu'elle soit caractéristique des TCIs induits par la médication dopaminergique ou consécutive à la SCP-NST, dans le but d'en caractériser les bases neuro-fonctionnelles. Pour cela, nous sommes allés au-delà de la conception classique d'impulsivité d'action vs. décisionnelle, en adoptant une approche visant à identifier précisément certains des mécanismes neurocognitifs impliqués. Cette approche est basée sur la modélisation psychologique des processus d'intérêt, et leur ciblage grâce à la combinaison de tâches adaptées et du pouvoir de discrimination fonctionnelle élevé procuré par l'EEG lorsqu'elle est couplée à des méthodes de traitement du signal avancées. Les résultats obtenus permettent de replacer les différentes manifestations d'impulsivité présentes dans la MP à travers différents niveaux de dysfonctionnement (Figure 10).

Dans le **Chapitre 1** (Figure 10, encarts orange), nous avons mis en évidence, à travers une revue systématique de la littérature (Meyer*, Spay* et al., 2019 ; Article 1), les altérations d'activité et de connectivité dans les réseaux mésocorticolimbiques présentes chez les patients parkinsoniens souffrant de TCIs, en accord avec la conceptualisation courante de ces troubles comme résultant d'un état hyperdopaminergique et de dysfonctionnements des processus de récompense et de motivation. Cependant, nous avons également mis en lumière des altérations hors de ces réseaux, soulignant le caractère multidimensionnel des TCIs. Par ailleurs, nous soutenons que ces travaux de neuro-imagerie ne se sont pas suffisamment appuyés sur l'utilisation de tâches et d'analyses de type événementiel, et ont échoué à tester l'ensemble des mécanismes contribuant potentiellement à l'impulsivité des patients souffrant de TCIs. Nous avons contribué à remédier à cette limite des travaux existants en testant l'hypothèse jusque-là négligée d'un trouble du contrôle inhibiteur. Dans une première étude expérimentale (Spay*, Meyer* et al., 2019 ; Article 2), nous avons utilisé l'EEG pour sonder l'intégrité des réseaux corticaux de l'inhibition de réponse à l'état de repos, apportant ainsi de premiers éléments en faveur de cette hypothèse. En effet, nous avons mis en évidence des altérations de l'activité oscillatoire de repos associées à la présence ou à la sévérité des TCIs, au sein de régions et de bandes de fréquence liées à l'inhibition de réponse. Dans une deuxième étude expérimentale (Meyer*, Spay*

et al., 2020 ; Article 3), nous avons testé plus directement notre hypothèse. Nous avons sondé les différents mécanismes d'inhibition de réponse en recherchant leurs marqueurs EEG spécifiques dans une tâche de Go/NoGo. Les patients parkinsoniens avec TCIs se sont montrés plus impulsifs que les patients sans TCIs dans cette tâche, tout en présentant une diminution de l'activité beta pré-stimulus dans la SMA et le précuneus, interprétée comme une activité de contrôle inhibiteur. Ces résultats suggèrent une altération des mécanismes de contrôle inhibiteur proactif au niveau cortical chez ces patients, c'est-à-dire un dysfonctionnement exécutif. Au final, ces travaux contribuent à remettre sur le devant de la scène l'hypothèse de troubles du contrôle inhibiteur chez les patients parkinsoniens atteints de TCIs, remettant en question l'hypothèse de troubles relevant uniquement du spectre de l'impulsivité décisionnelle.

Dans le **Chapitre 2** (Figure 10, encarts bleu), nous avons exploré les mécanismes et voies impliquées dans les effets de la SCP-NST sur le contrôle inhibiteur. Ces effets sont bien connus, et pourraient contribuer à l'amélioration de l'akinésie, possiblement au prix d'une exacerbation de l'impulsivité. Mais la littérature existante n'a pas suffisamment pris en compte l'impact de la position du contact actif au sein du NST, et n'a que peu intégré les dernières connaissances concernant les mécanismes neurophysiologiques sous-tendant les effets de la SCP. Dans une troisième étude expérimentale (Meyer et al., soumis ; Article 4), nous avons fait l'hypothèse selon laquelle les effets de la SCP sur le contrôle inhibiteur pourraient dépendre d'une modulation de l'activité du cortex moteur supplémentaire (SMA et pré-SMA), via l'activation antidromique de la voie hyperdirecte. Si tel est le cas, la stimulation de la région du NST la plus fortement connectée au cortex moteur supplémentaire devrait entraîner des effets plus importants sur le contrôle inhibiteur. Pour tester cette prédiction, nous avons analysé le comportement et l'activité du cortex moteur supplémentaire lors de la tâche de Go/NoGo, et nous sommes appuyés sur des avancées méthodologiques récentes pour modéliser les volumes de tissu activé et extraire leurs patterns de connectivité structurelle. Les changements observés dans le comportement et l'activité du le cortex moteur supplémentaire confirment que la SCP-NST impacte les mécanismes de contrôle inhibiteur contextuels. De plus, la corrélation observée entre les effets comportementaux de la SCP-NST d'une part, et la connectivité structurelle entre les volumes de tissu activé et le cortex moteur supplémentaire d'autre part, ainsi que la modulation observée de l'activité du cortex moteur supplémentaire, supportent notre hypothèse d'activation antidromique. Nos résultats suggèrent que les effets de la SCP-NST sur la performance d'inhibition pourraient être liés à un impact direct de la stimulation sur l'activité corticale liée au contrôle inhibiteur, plutôt qu'à la perturbation du relai de la commande inhibitrice par le NST.

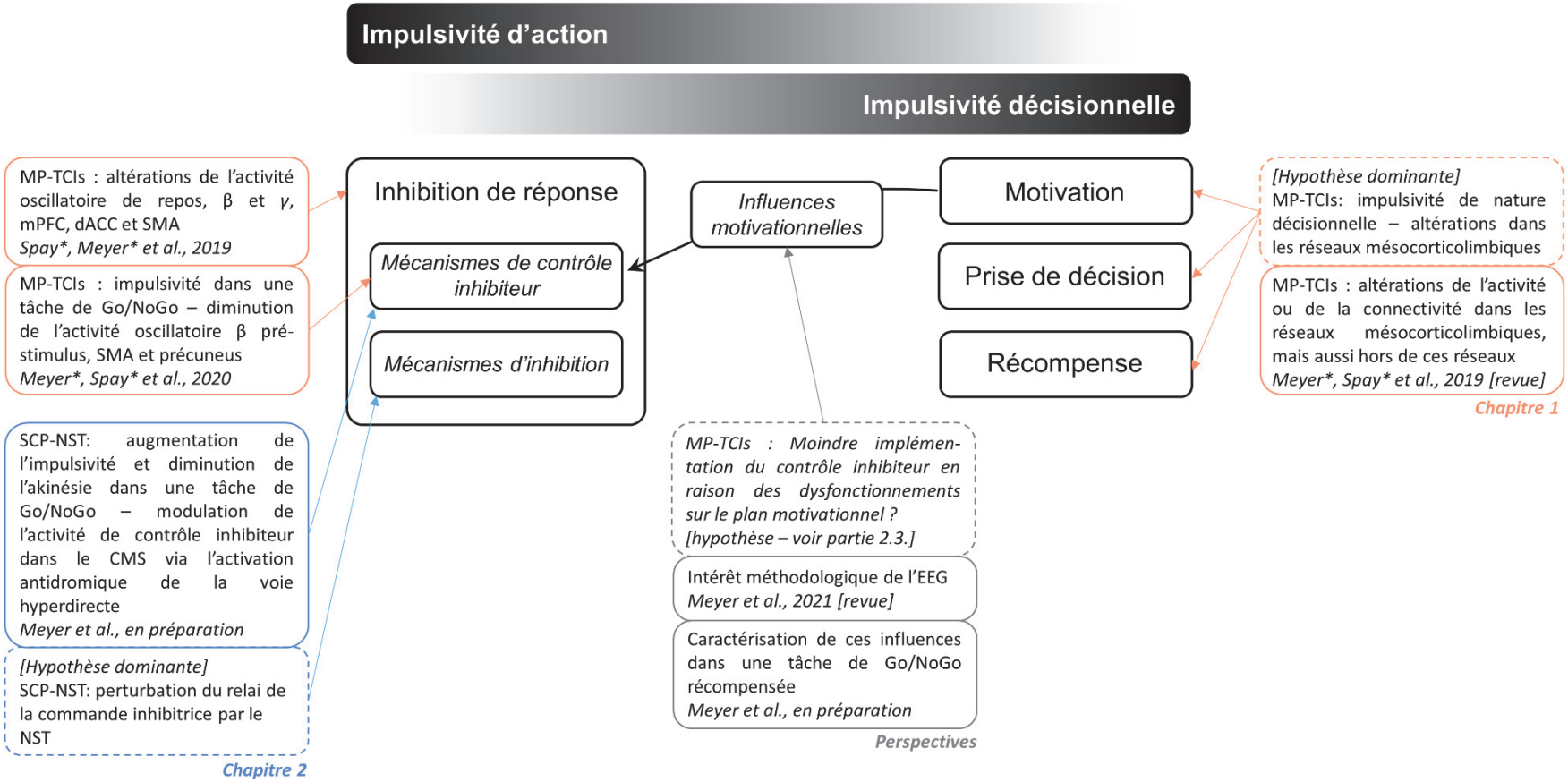

Figure 10 : Représentation schématique des apports de ce travail de thèse à la caractérisation des bases neuro-fonctionnelles de l'impulsivité dans la MP. La dichotomie classique entre impulsivité d'action et décisionnelle ne rendant pas compte de la complexité des mécanismes sous-jacents, nous avons adopté une approche visant à identifier précisément certains des mécanismes neurocognitifs impliqués. Dans le Chapitre 1 (encarts orange), nous avons remis en question l'hypothèse dominante selon laquelle l'impulsivité des patients atteints de TCIs est purement décisionnelle (c'est-à-dire relevant uniquement de dysfonctionnements des mécanismes de motivation, de prise de décision et de récompense), en apportant des éléments en faveur d'un déficit d'inhibition de réponse, et plus précisément d'une altération des mécanismes de contrôle inhibiteur au niveau cortical. Dans le Chapitre 2 (encarts bleu), nous avons montré que les effets de la SCP sur l'inhibition de réponse pourraient dépendre d'une modulation de l'activité corticale de contrôle inhibiteur en lien avec l'activation antidromique de la voie hyperdirecte, plutôt que d'effets sur l'activité locale du NST qui perturberaient le relai de la commande inhibitrice au niveau sous-cortical. Les perspectives immédiates de ce travail de thèse (encarts gris ; partie 4.2.) concernent l'étude du rôle des interactions entre motivation et contrôle inhibiteur dans l'impulsivité des TCIs. Le lecteur est renvoyé au texte principal pour détails.

Au final, nos résultats montrent que l'impulsivité dans la MP repose sur des bases neuro-fonctionnelles diverses. La SCP-NST semble affecter le contrôle inhibiteur au niveau cortical, un déficit retrouvé chez les patients souffrant de TCIs. Ces patients, quant à eux, sont également touchés par des dysfonctionnements des processus de traitement de la récompense, de motivation et de prise de décision (Figure 10). Bien qu'en dehors du cadre de ce travail de thèse, on notera que ces processus pourraient également être affectés par la SCP-NST. Le NST joue en effet un rôle important dans le traitement de récompense et la motivation (Baunez, 2016; Baunez and Lardeux, 2011; Baunez and Robbins, 1997; Baunez et al., 2002; Lardeux et al., 2009; Rossi et al., 2015; Zénon et al., 2016), et de nombreux travaux réalisés chez le rongeur montrent que sa stimulation peut affecter les fonctions associées (Baunez et al., 2007; Vachez and Creed, 2020). Mais les effets de la SCP-NST sur celles-ci chez le patient parkinsonien sont peu clairs, et dépendent probablement fortement de la position des contacts actifs (Aiello et al., 2019; Atkinson-Clement et al., 2019; Castrioto et al., 2014; Evens et al., 2015; Faggianelli et al., 2022; Irmen et al., 2018; Mosley et al., 2020; Petry-Schmelzer et al., 2019; Růžička et al., 2012; Scherrer et al., 2020; Seinstra et al., 2016; Seymour et al., 2016; Steinhardt et al., 2021; Volkmann et al., 2010).

4.2 Perspectives immédiates

Une perspective importante reste à explorer concernant l'impulsivité des patients avec TCIs, car les mécanismes de motivation et de contrôle inhibiteur ne sont pas indépendants (Figure 10, encarts gris). Une motivation exagérée pour la récompense est susceptible de conduire à une diminution des niveaux de contrôle appliqués. Autrement dit, il reste à déterminer si les patients souffrant de TCIs sont réellement confrontés à une incapacité à implémenter le contrôle, ou bien à une moindre volonté de l'implémenter, un objectif qui n'a pas pu être rempli dans le cadre de ce travail de thèse en raison de la crise sanitaire liée à la Covid-19. Nous avons cependant pu réaliser un travail préalable chez le sujet sain, visant à caractériser ces interactions entre motivation et contrôle inhibiteur. L'analyse des données expérimentales acquises dans le cadre de ce projet est toujours en cours à l'heure de l'écriture de ces lignes. Nous en dévoilons ici la démarche générale et les premiers résultats.

Il est devenu clair, ces dernières années, que le contrôle cognitif, y compris le contrôle inhibiteur, est motivé, c'est-à-dire qu'il peut être influencé de façon spécifique par des signaux motivationnels (Botvinick and Braver, 2015; Braver et al., 2014; Pessoa and Engelmann, 2010; Yee and Braver, 2018). Introduire et manipuler des récompenses monétaires au sein d'une tâche comportementale constitue un moyen simple de manipuler la motivation de façon extrinsèque. De nombreuses études ont donc ajouté ce type de récompenses dans des tâches de Go/NoGo ou de signal

stop. Les effets sur la performance comportementale dépendent alors largement de la façon dont sont introduites les récompenses : de façon générale, récompenser les réponses rapides au Go diminue la performance d'inhibition, tandis que récompenser les essais NoGo/Stop réussis améliore la performance d'inhibition (Boehler et al., 2012, 2014; Greenhouse and Wessel, 2013; Leotti and Wager, 2010; Padmala and Pessoa, 2010). Il a donc été proposé que, dans ce type de tâche, les sujets s'engagent dans un processus de prise de décision basé sur les valeurs associées aux différents modes de réponse (répondre vite au Go vs. éviter les erreurs au NoGo/Stop ; Dixon and Christoff, 2012; Leotti and Wager, 2010; Shenoy and Yu, 2011). Cette décision se traduirait par une modification du compromis vitesse-précision, implémentée via des ajustements proactifs (Greenhouse and Wessel, 2013; Verbruggen and McLaren, 2018). Cependant, la nature de ces ajustements proactifs reste peu claire. Nous avons fait l'hypothèse selon laquelle le niveau de contrôle inhibiteur proactif peut être adapté sur la base du contexte motivationnel, supportant ainsi les adaptations du compromis vitesse-précision dans une tâche d'inhibition impliquant des récompenses. Tout l'enjeu de cette hypothèse réside dans la capacité à distinguer les influences motivationnelles sur le niveau de contrôle inhibiteur appliqué de celles sur d'autres mécanismes co-occurrents, et notamment sur le niveau de préparation motrice. Cette capacité ne peut résulter que de l'utilisation de méthodes d'enregistrement et d'analyse de l'activité cérébrale dotées d'une une résolution temporelle suffisante pour distinguer de façon certaine l'activité pré- et post-stimulus, et s'appuyant également sur d'autres dimensions analytiques afin de maximiser le pouvoir de discrimination obtenu quant aux mécanismes neurocognitifs mis en jeu. Encore une fois, l'EEG nous apparaît comme une méthode optimale, à condition d'utiliser les solutions de traitement du signal permettant d'exploiter les dimensions spatiale et spectrale du signal, c'est-à-dire la séparation et la localisation de sources, ainsi que les analyses temps-fréquence.

Nous avons réalisé une revue systématique des études en EEG du traitement de la récompense, dans le but d'évaluer à quel point ces différentes options méthodologiques ont été employées dans la littérature existante (Meyer et al., 2021 ; présentée en annexe). Trois cent cinquante-neuf études réalisées chez le sujet sain ont été analysées. Nous avons montré que cette littérature s'est principalement intéressée à l'activité liée à la réception de la récompense, plutôt qu'à son anticipation (88% vs. 24% des études). Surtout, elle s'est principalement reposée sur l'analyse des potentiels évoqués (92%), n'utilisant que peu les analyses temps-fréquence (19%), les analyses de sources (12%) ou leur combinaison (2%). Dans cette revue, dont le ton est celui d'un article d'opinion, nous soutenons que la contribution que peuvent apporter les potentiels évoqués à notre compréhension des mécanismes neurocognitifs impliqués dans le traitement de la récompense est intrinsèquement limitée. Autrement dit, selon nous, le pouvoir de discrimination de l'EEG n'a pas été

exploité de façon optimale. Nous détaillons alors les bénéfices attendus de l'implémentation des méthodes proposées sur la base d'exemples de travaux existants.

Nous avons par la suite mis en œuvre une quatrième étude expérimentale chez le sujet sain visant à tester notre hypothèse d'adaptation du niveau de contrôle inhibiteur appliqué selon le contexte motivationnel. Nous avons pour cela conçu une version de notre tâche de Go/NoGo enrichie de récompenses monétaires (Figure 11), et nous sommes appuyés sur les solutions méthodologiques proposées dans notre article de revue. Dans un objectif de science robuste, transparente et reproductible, nous avons pré-enregistré cette étude. Le pré-enregistrement (plus connu sous la dénomination anglaise de « pre-registration ») consiste à spécifier les hypothèses, le design expérimental et les analyses statistiques prévues en amont de la réalisation de l'étude, et ce sur un registre dédié et publiquement accessible, tel que le site web dédié de l'Open Science Framework. Cette approche nouvelle, et encore assez peu utilisée, permet de respecter strictement le principe fondamental en sciences du test d'hypothèse. En effet, elle permet, au moment de la publication des résultats, de distinguer de façon extrêmement claire les résultats issus d'analyses confirmatoires, c'est-à-dire relevant du test des hypothèses formulées au moment de la conception du projet de recherche, de ceux issus d'analyses exploratoires. En prédéterminant de façon précise le plan d'analyse statistique, cette approche permet aussi de minimiser le phénomène dit des « degrés de liberté de l'expérimentateur », qui tend à augmenter le risque de faux positifs. Les objectifs et avantages de cette démarche sont décrits en détails dans (Nosek et al., 2018), et de nombreuses ressources sont disponibles sur le site web de l'Open Science Framework.[11] Notre pré-enregistrement est reproduit en annexe. Nous y avons décrit le design expérimental, l'ensemble des hypothèses et analyses statistiques concernant les données comportementales, ainsi que les hypothèses et la démarche générale d'analyse concernant les données EEG.

[11] Voir : https://www.cos.io/initiatives/prereg?_ga=2.174898594.1854068043.1643724960-2123788394.1643313669

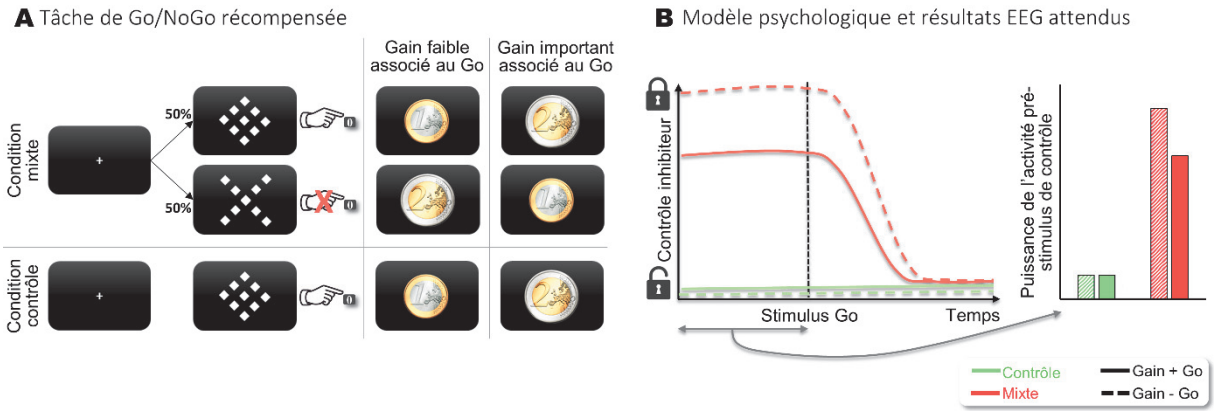

Figure 11 : Tâche de Go/NoGo récompensée et hypothèse principale concernant les interactions entre motivation et contrôle inhibiteur. (A) La tâche de Go/NoGo utilisée dans ce travail de thèse a été enrichie de récompenses monétaires. Les réponses correctes (réponses suffisamment rapides aux stimuli Go, selon un seuil prédéterminé pour chaque participant lors d'un entraînement, et non-réponses aux stimuli NoGo) sont récompensées, tandis que les erreurs n'entraînent pas de conséquences monétaires. Afin de maximiser leur motivation, les participants étaient avertis qu'ils recevraient une partie de leurs gains après l'expérience. La tâche est conçue pour faire varier le contexte motivationnel, en variant la magnitude des gains associés à chaque type d'essais. En effet, l'association de gains faibles aux réponses correctes aux stimuli Go et de gains importants aux réponses correctes aux stimuli NoGo est supposée créer un contexte motivationnel favorisant plutôt les réponses rapides aux stimuli Go, tandis que l'association inverse est supposée créer un contexte motivationnel favorisant plutôt l'absence d'erreurs dans les essais NoGo. (B) Dans cette tâche, les participants devraient donc adapter leur compromis vitesse-précision au contexte motivationnel. Nous faisons l'hypothèse que cette adaptation repose sur une modulation du niveau de contrôle inhibiteur proactif appliqué. Plus précisément, alors que l'application de contrôle inhibiteur proactif n'est pas requise dans la condition contrôle, et ce quel que soit le niveau de gain associé aux stimuli Go, pour la condition mixte, le niveau de contrôle appliqué devrait être plus élevé dans le contexte supposé favoriser l'absence d'erreurs dans les essais NoGo (« Mixte, Gain - Go ») que dans celui supposé favoriser les réponses rapides au Go (« Mixte, Gain + Go »). Si cette hypothèse est avérée, nous devrions observer des modulations de la puissance de l'activité EEG pré-stimulus correspondant au contrôle inhibiteur proactif selon un pattern correspondant à ces prédictions. Figure adaptée du pré-enregistrement (en annexe).

Les données ont été acquises à l'automne 2021, et sont en cours d'analyse au moment de l'écriture de ces lignes. Les premiers résultats comportementaux sont, dans l'ensemble, en accord avec l'idée d'une adaptation du compromis vitesse-précision au contexte motivationnel (Figure 12A). Concernant les données EEG, suite à la séparation de source de groupe, nous retrouvons le réseau attendu comme impliqué dans la tâche, composé de sources occipitales, médiales frontales et pariétales (Figure 12B). L'activité de ces sources reste à analyser selon les principes décrits dans notre pré-enregistrement afin de rechercher des indices d'adaptation du contrôle inhibiteur proactif au contexte motivationnel. Si nos hypothèses sont validées, la méthodologie proposée pourra être adaptée à l'étude du rôle des interactions entre troubles de la motivation et du contrôle inhibiteur dans l'impulsivité des patients parkinsoniens souffrant de TCIs, et pourquoi pas dans celle d'autres populations de patients.

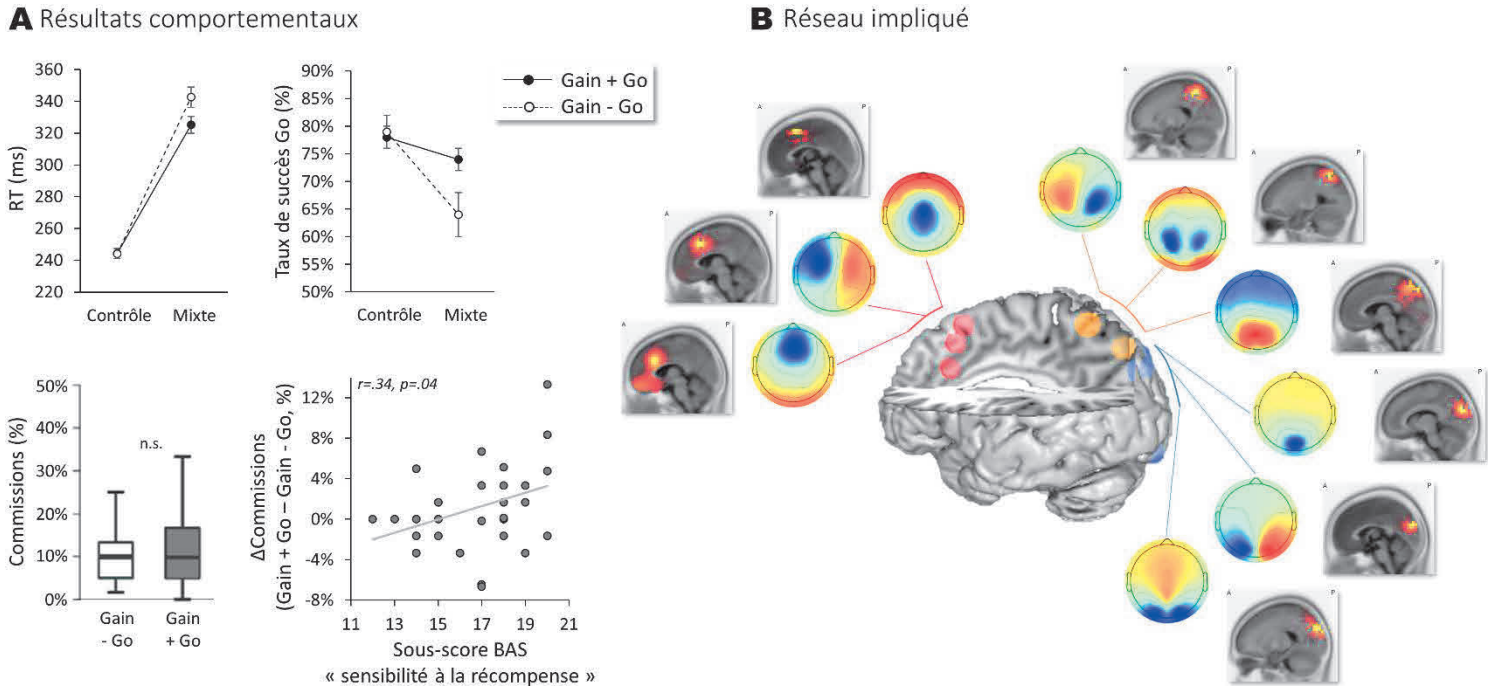

Figure 12 : Résultats comportementaux et réseau impliqué dans la tâche. (A) L'analyse des données comportementales a été réalisée, en suivant strictement le pré-enregistrement (en annexe). Ces premiers résultats sont, dans l'ensemble, en accord avec l'idée d'une adaptation du compromis vitesse-précision au contexte motivationnel. Tout d'abord, nous observons un effet de la condition, du contexte motivationnel, et un effet d'interaction sur le TR (F_s(1,28)=604,6 ; 16,8 ; 22,8 ; p_s <0,001). Spécifiquement, en accord avec notre hypothèse préenregistrée, le TR est plus court dans la condition mixte lorsque le contexte favorise les réponses rapides aux stimuli Go (condition « Mixte, Gain + Go ») plutôt que lorsqu'il favorise l'absence d'erreurs dans les essais NoGo (condition « Mixte, Gain - Go » ; p<0.001). Les résultats observés concernant les taux de réussite au Go (effet de la condition, du contexte motivationnel, et interaction, F_s (1,28)= 5,5 ; 12,6 ; 20,5 ; p_s<0,05) sont en accord avec ceux observés pour les taux de réaction, avec un taux de réussite au Go plus élevé dans la condition « Mixte, Gain + Go » que « Mixte, Gain - Go » (p<0.001). Cependant, contrairement à notre hypothèse préenregistrée, nous ne retrouvons pas d'effet significatif du contexte motivationnel sur le taux d'erreurs de commission (W=193,5, p=0,11, test unilatéral). Nous observons néanmoins une corrélation entre l'augmentation du taux d'erreurs de commission dans la condition « Mixte, Gain + Go » comparé à la condition mixte « Mixte, Gain - Go », et la sensibilité à la récompense telle qu'évaluée par l'échelle auto-rapportée « Behavioural Inhibition and Behavioural Activation System » (BIS/BAS, Carver and White, 1994) ; *r*=0,34, p=0,04, test unilatéral ; préenregistré comme analyse exploratoire). En d'autres termes, seuls les participants les plus sensibles à la récompense feraient plus d'erreurs de commission lorsque le contexte motivationnel favorise les réponses rapides aux stimuli Go. (B) Les données EEG ont été prétraitées, et la séparation de sources de groupe a été réalisée selon les méthodes utilisées dans le reste de ce travail de thèse et décrites dans notre pré-enregistrement. Comme attendu, nous avons identifié un réseau composé notamment de sources médiales frontales (en rouge ; aire motrice supplémentaire, cortex cingulaire antérieur, cortex préfrontal ventro-médian), pariétales (en orange ; précuneus), et occipitales (en bleu ; aires visuelles, cuneus). L'activité oscillatoire au sein de ces sources est en cours d'analyse.

4.3 Perspectives à long terme

Ce travail de thèse s'inscrit dans une démarche visant à déterminer précisément les dysfonctionnements neurocognitifs sous-jacents de l'impulsivité observée, que ce soit dans la MP ou dans d'autres populations de patients, afin de proposer, à terme, des traitements ciblant précisément ces dysfonctionnements. On peut imaginer, tout d'abord, des traitements pharmacologiques. Par exemple, des traitements visant le système noradrénergique pourraient être envisagés pour remédier aux troubles de contrôle inhibiteur, comme cela a déjà été proposé dans le cadre du trouble déficitaire de l'attention avec ou sans hyperactivité (Robbins, 2017). Dans la MP, il a été montré que l'atomoxetine, un inhibiteur de la recapture de la noradrénaline, peut améliorer la performance d'inhibition des patients, ainsi que restaurer l'activité des réseaux sous-jacents (Kehagia et al., 2014; O'Callaghan et al., 2021; Rae et al., 2016; Ye et al., 2015). Un essai clinique est déjà cours aux Hospices Civils de Lyon pour tester l'efficacité d'un autre agent noradrénergique, la clonidine, pour l'amélioration des TCIs (https://clinicaltrials.gov/ct2/show/NCT03552068). Par ailleurs, au-delà des traitements pharmacologiques, une autre piste intéressante pourrait être l'utilisation de la stimulation cérébrale non-invasive dans le but de moduler spécifiquement les réseaux supportant les mécanismes neurocognitifs incriminés, une approche développée actuellement dans le cadre d'autres symptômes neuropsychiatriques que l'impulsivité (Fox et al., 2014; Horn and Fox, 2020; Siddiqi et al., 2020). Enfin, au-delà de l'identification des dysfonctionnements neurocognitifs liés à l'impulsivité d'une population de patients, une approche de médecine personnalisée visant à déterminer et cibler les dysfonctionnements contribuant le plus fortement à l'impulsivité d'un patient pourrait être envisagée.

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Article de revue - Electrophysiological underpinnings of reward processing: Are we exploiting the full potential of EEG?

Garance M Meyer, Josep Marco-Pallarés, Philippe Boulinguez*, Guillaume Sescousse*. *Publié dans Neuroimage, 242(118478)*

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Review

Electrophysiological underpinnings of reward processing: Are we exploiting the full potential of EEG?

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ABSTRACT

Understanding how the brain processes reward is an important and complex endeavor, which has involved the use of a range of complementary neuroimaging tools, including electroencephalography (EEG). EEG has been praised for its high *temporal* resolution but, because the signal recorded at the scalp is a mixture of brain activities, it is often considered to have poor *spatial* resolution. Besides, EEG data analysis has most often relied on event-related potentials (ERPs) which cancel out non-phase locked oscillatory activity, thus limiting the functional discriminative power of EEG attainable through *spectral* analyses. Because these three dimensions -temporal, spatial and spectral- have been unequally leveraged in reward studies, we argue that the full potential of EEG has not been exploited. To back up our claim, we first performed a systematic survey of EEG studies assessing reward processing. Specifically, we report on the nature of the cognitive processes investigated (i.e., reward anticipation or reward outcome processing) and the methods used to collect and process the EEG data (i.e., event-related potential, time-frequency or source analyses). A total of 359 studies involving healthy subjects and the delivery of monetary rewards were surveyed. We show that reward anticipation has been overlooked (88% of studies investigated reward outcome processing, while only 24% investigated reward anticipation), and that time-frequency and source analyses (respectively reported by 19% and 12% of the studies) have not been widely adopted by the field yet, with ERPs still being the dominant methodology (92% of the studies). We argue that this focus on feedback-related ERPs provides a biased perspective on reward processing, by ignoring reward anticipation processes as well as a large part of the information contained in the EEG signal. Finally, we illustrate with selected examples how addressing these issues could benefit the field, relying on approaches combining time-frequency analyses, blind source separation and source localization.

1. Introduction

Reward processing is at the very heart of goal-directed behavior and decision-making. It has been shown to be impaired across a wide range of psychiatric disorders (Balodis and Potenza, 2015; Ng et al., 2019; Nusslock and Alloy, 2017), making it a potentially valuable transdiagnostic marker of mental health (Hägele et al., 2015). Understanding how the brain processes rewards is thus crucial, but remains a complex endeavor. First, reward processing comprises both anticipatory and outcome phases, each of them involving several processes co-occurring at various times scales. While reward anticipation corresponds to the cognitive operations that precede an incoming reward, including incentive valuation, probability estimation or motor preparation, reward outcome corresponds to those operations triggered by the actual delivery of the reward, including hedonic feelings, reward value update and behavioral reinforcement. Broadly speaking, incentive salience ('wanting'), hedonic impact ('liking'), and learning can be seen as the three core components of reward (Berridge et al., 2009; Berridge and Robinson, 2003). Second, reward processing involves large brain networks as well as various neuromodulators (Haber and Knutson, 2010; Kranz et al., 2010; Liu et al., 2011). This complexity thus requires the use of complementary neuroimaging techniques

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in order to gain a global understanding of reward processing in the brain.

Functional MRI and PET have been among the most popular techniques used to investigate reward processing and have helped characterize the underlying brain networks and neurochemistry. On the other hand, electroencephalography (EEG) has been leveraged for its fine temporal resolution, which can reveal the rapid brain dynamics that remain out of reach for fMRI and PET (Luck, 2014). As such, many EEG studies have tracked specific timed events associated with reward processing, most often through event-related potentials (ERPs) (see for reviews: Brunia et al., 2011; Foti and Weinberg, 2018; Glazer et al., 2018; Luft, 2014; Marco-Pallarés et al., 2015; Proudfit, 2015; Sambrook and Goslin, 2015; San Martín, 2012; Walsh and Anderson, 2012). However, a major limitation of EEG in general, and ERPs in particular, is that the signal recorded at the scalp is a mixture of a number of different brain activities arising from a number of different brain regions. The resulting mixing of brain activities is exacerbated by volume conduction, which causes activity from a single region to spread across a large part of the scalp (see Jackson and Bolger, 2014 for a comprehensive review on EEG signal generation). But confounds do not only arise from the limited spatial resolution inherent to the method. Simply considering event-related voltage deflections recorded between two sensors also neglects the fact that electrophysiological brain activity can occur through different frequency bands. Disentangling the temporal, spatial and functional overlaps of electrophysiological activities is thus a central issue to consider in order to optimally benefit from EEG . More or less advanced signal processing methods can enhance the discriminative power of EEG, by (1) considering the frequency content of the signal that provides functional signatures of neurocognitive processes, (2) using mathematical solutions to separate the functional sources of activity mixed in the overall electroencephalogram, and (3) estimating the anatomical origin of an electrophysiological marker.

Indeed, because brain activity recorded with EEG is composed of oscillations that occur in different frequency bands, their separation via time-frequency analyses (which assess the spectral characteristics of the signal as a function of time) constitutes a first way to isolate activities that would otherwise overlap in time or space. Moreover, recent methodological advances, not specific to the EEG domain, offer various computational solutions to recover a set of source signals[1] from the mixed signals recorded at the sensor level. These are termed *Blind Source Separation* (BSS). BSS-based analyses are able to unmix most sources of the ongoing brain activity without a priori knowledge about the source signals or the mixing process. Additionally, *source localization* is a class of methods that aim to retrieve the anatomical generator(s) of an observed EEG activity. It relies on an inverse problem that, as an ill-posed problem, is non-unique and unstable (i.e., cannot be solved but only estimated). However, when applied on "clean" unmixed signals, source localization offers the opportunity to take full advantage of the spatial information contained in the EEG signal (He et al., 2018; Huster and Calhoun, 2018; Michel and Murray, 2012).

To summarize, the discriminative power of EEG analyses relies on three axes that are mutually beneficial: the temporal, spectral, and spatial dimensions (Fig. 1). Here, we perform a systematic survey of EEG studies investigating how the different methodological options that might contribute to disentangling brain activities confounded in the EEG signal have been employed to address current theoretical issues about reward processing. In other words, we aimed to check whether the full power of EEG has been exploited in the field. Specifically, we report on (1) the nature of the cognitive processes investigated (reward anticipation vs reward outcome processing) and (2) the methods used to collect and process the EEG data. Based on the results, we argue that a large proportion of previous studies investigating reward processing have used EEG in a suboptimal way. Indeed, we show that (1) reward anticipation has been overlooked and (2) the three axes for discriminative power have been unequally leveraged, revealing that some methodological developments have not been widely adopted by the field yet. We then discuss and illustrate with selected examples how doing so could bring novel insights to the field.

[1] Note that in the context of blind source separation, "source" should not be understood as an anatomical generator, but a functional generator. See section "Considering spatial information: localization and source separation" for discussion.

2. Systematic analysis

2.1. Methods

We searched the Pubmed and Web of Science databases for EEG studies of reward processing on 8/10/2019. To be included, studies had to (1) include a group of healthy subjects; (2) involve the delivery of monetary rewards; (3) report statistical analyses of brain activity related to the anticipation and/or receipt of rewards. Based on these criteria, 359 articles (out of 2469 retrieved records) were considered for our survey. Detailed information about the selection process as well as a flow chart are provided in the Supplementary Materials.

The following information was extracted from the abstracts or method sections of these articles: (1) nature of the cognitive processes investigated, i.e. reward anticipation and/or reward outcome processing; (2) methods used to collect and process the EEG data, i.e. technique used (e.g., EEG, EEG-fMRI…), and presence of ERP, time-frequency and/or source analyses. We chose to extract this information regarding data processing because it captures the use of the three axes for discriminative power of EEG. Indeed, while both ERPs and time-frequency analyses make use of the temporal dimension, only time-frequency analyses exploit the spectral dimension. By source analyses, we here refer to the methods that can contribute to enhanced spatial information, in particular source separation and/or localization methods.

2.2. Results

Among the 359 surveyed studies, a majority was interested in reward outcome processing (88%, 316 studies) as compared with reward anticipation (24%, 86 studies). While 92% (331 studies) reported ERP analyses, only 19% (70 studies) reported time-frequency analyses. Twelve percent (44 studies) performed source analyses (here meant as source separation and/or localization), and only 2% (8 studies) performed both time-frequency and source analyses. Finally, 4% of studies used EEG combined with another neuroimaging technique (EEG-fMRI: 14 studies, EEG-Magnetoencephalography (MEG): 1 study, EEG-PET: 1 study). Figs. 2 and 3 display the evolution of these proportions over the last 20 years.

3. Considering the diversity of reward processes

Our analysis revealed that EEG studies have investigated reward outcome processing more often than reward anticipation (88% vs 24%, Fig. 2). Incidentally, it is interesting to note that the field of EEG has mostly relied on gambling/guessing tasks (e.g., Gehring and Willoughby, 2002; Kujawa et al., 2013) as well as reinforcement learning tasks (e.g., Bellebaum et al., 2010; Cohen et al., 2007), well-suited to investigate reward outcome processing, while the field of fMRI has been more strongly influenced by paradigms such as the Monetary Incentive Delay task (Knutson et al., 2000) which was specifically developed to investigate anticipatory processes. We speculate that the overrepresentation of EEG studies investigating reward outcome processing might result from the combination of a theoretical interest for a trendy issue and the ease of use of available tools and markers. Indeed, the field has historically focused on the feedback-related negativity (FRN) and other feedback-related ERPs in the context of error processing and learning, in particular in relation with the influential reward prediction

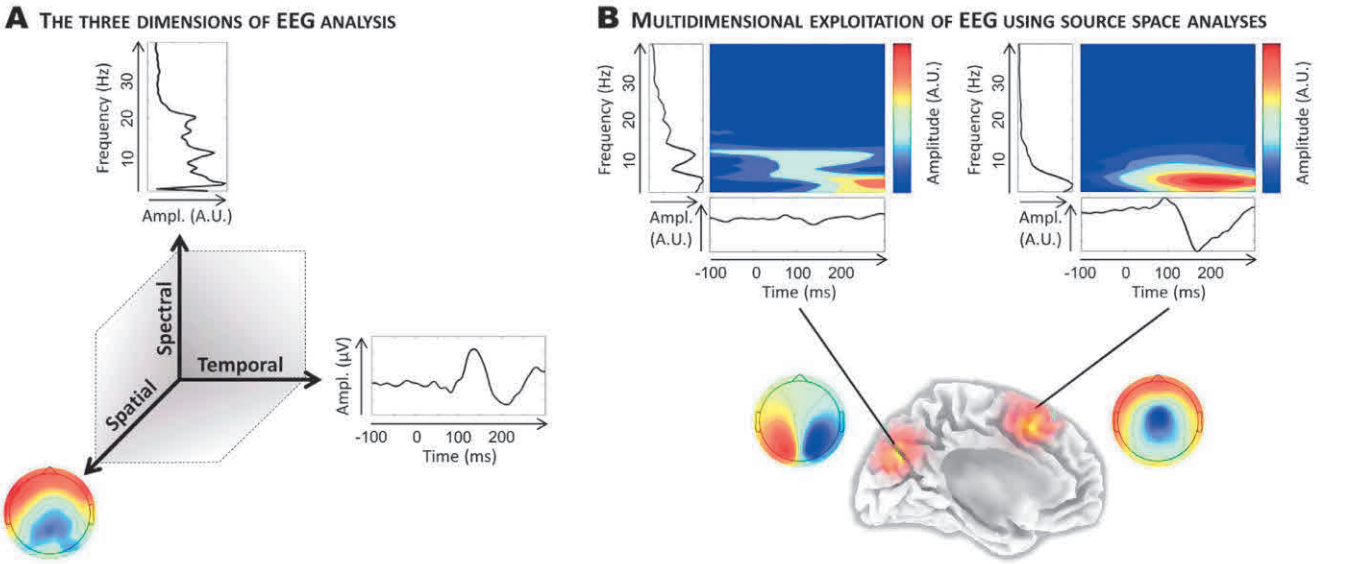

Fig. 1. The discriminative power of EEG relies on the exploitation of three analytical dimensions. The EEG signal recorded at the sensors is a time-series, which can be resolved along different analytical dimensions. (A) The high temporal resolution of the recorded time-series allows one to examine how it unfolds with time (*temporal* dimension) as well as its underlying oscillatory rhythmicity (*spectral* dimension). Considering the spectral content of the signal can help to distinguish brain processes or functions, because these may occur in different frequency bands. These two dimensions are often examined in isolation, using ERP analyses (that ignore the spectral dimension), or spectral analyses (that ignore the temporal dimension). ERP and static spectrum at electrode FCz are shown as illustrations. The third dimension, *spatial*, is reconstructed from the known position of the different sensors on the scalp. It is often considered as the weakness of EEG, and hence ignored. Indeed, while the topography of scalp activity can be examined (here, topography at 210ms is shown as an example), it may be poorly informative due to volume conduction. Yet, a range of solutions is available to take full advantage of the spatial information hidden in the scalp signal, including source separation and source localization methods. (B) Optimal discriminative power may be obtained when the three dimensions -temporal, spectral, spatial- are leveraged in combination, e.g., by using time-frequency analyses (that combine the temporal and spectral dimensions to examine event-related changes in the amplitude and phase of oscillations at specific frequencies) performed in the source space. Illustrations show, for two distinct sources, the static spectrum, back-projected ERP (at electrodes B4 and FCz, respectively), time-frequency map, topography, and localization (obtained using sLORETA). All illustrations are adapted from Albares et al., 2014. The reader is referred to the main text for details about the different signal processing options presented here.

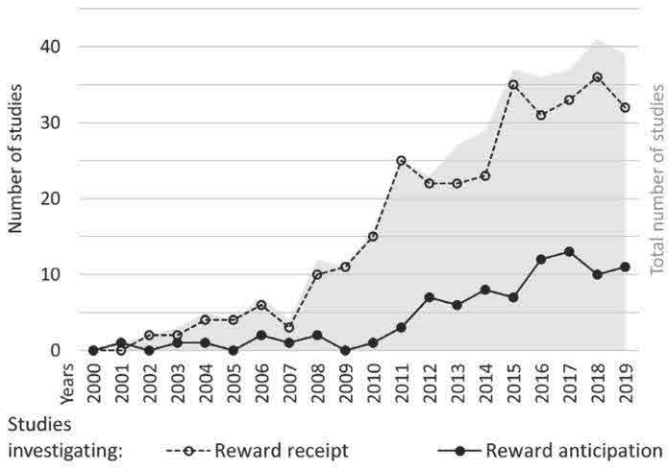

Fig. 2. EEG studies investigating reward outcome processing vs. reward anticipation. Much more studies have investigated reward processing at the outcome stage (by means of analyses of the feedback period, using comparisons such as win vs. loss or small vs. large gain), as compared with reward anticipation (for instance, analyses of the cue period, using comparisons such as expected win vs. expected loss).

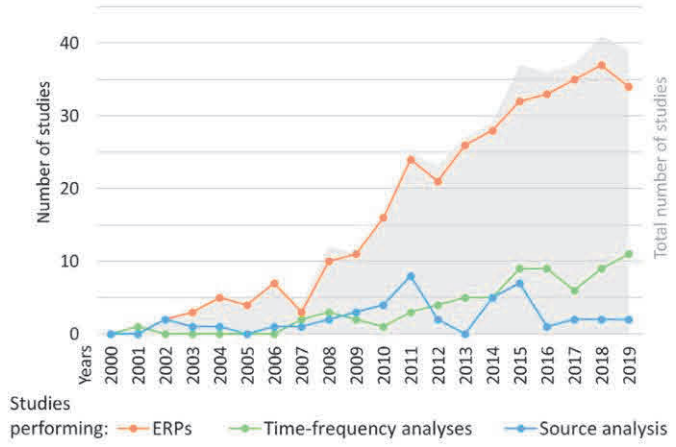

Fig. 3. EEG studies of reward processing made unequal use of the three dimensions for discriminative power. Most studies over the last 20 years have relied on ERP analyses. In contrast, time-frequency and source analyses have been performed by only a minority of studies. This demonstrates limited use of the spatial and spectral information. Note that no clear temporal evolution in the proportion of studies using ERPs, time-frequency analyses or source analyses can be seen.

error (RPE-FRN) framework (Holroyd and Coles, 2002; Sambrook and Goslin, 2015; Walsh and Anderson, 2012). Only later, the focus shifted to reward processing *per se* (Foti and Weinberg, 2018), putting reward anticipation in the spotlight. Additionally, reward anticipation processes were initially associated with subcortical areas (Schultz et al., 1997), which logically made EEG a less appropriate technique to investigate them, due to the difficulty of reaching deep brain areas.

Consistent with our observation, Glazer et al. (2018) noted that EEG studies neglect the "rich temporal heterogeneity of reward processing", by focusing on the reward outcome stage and disproportionately relying on the FRN. Glazer et al. thus called for "broadening the time course" of EEG components investigated in relation to reward processing. Based on the data presented here, we fully endorse this recommen-

dation. It should be emphasized that the high temporal resolution of EEG is particularly valuable here, since the brain signals related to reward anticipation and reward outcome processing are often problematically confounded when studied with fMRI, due to the sluggishness of the BOLD signal (e.g., Pornpattananangkul and Nusslock, 2016). However, "broadening the time course" may not be sufficient. Below, we discuss other equally important limitations that the field must overcome for using EEG in an optimal way to disentangle the neurocognitive processes of reward.

4. Considering oscillatory components

Although the informativeness and added value of time-frequency analyses have been previously highlighted in the context of reward processing and feedback learning (Cohen et al., 2011b; Marco-Pallarés et al., 2015), our systematic survey reveals that a large majority of studies keeps relying on ERPs to date, with only a small minority of studies reporting time-frequency analyses (e.g., in 2018, 37 out of 41 papers reported ERP analyses, while only 9 reported time-frequency analyses; Fig. 3). The problem is that ERP analyses are intrinsically limited in the insight they can provide about the neurocognitive mechanisms supporting reward processing.

The first reason is that ERP analyses only exploit a small part of the information contained in the EEG signal, as they ignore the spectral information and cancel out non-phase locked activity. For example, the ERPs following reward receipt show two characteristic components, the FRN and P300. Time-frequency analyses have shown that these components correspond to overlapping phase-locked delta and theta oscillatory activities (Bernat et al., 2015, 2011; Cohen et al., 2007). But, in the same time range (~250-450ms), time-frequency analyses have also shown a clear increase in high-beta band activity (20-35Hz) at frontal electrodes for gains compared with losses (Cohen et al., 2007; Doñamayor et al., 2012; HajiHosseini et al., 2015, 2012; HajiHosseini and Holroyd, 2015; Marco-Pallares et al., 2008; Marco-Pallarés et al., 2009; Mas-Herrero et al., 2015). Because this high-beta band activity is induced rather than phase-locked (as revealed by analyses considering evoked and induced activity separately, Li et al., 2016; or by using phase coherence analysis, Cohen et al., 2007), it does not contribute to the ERPs. More generally, it is common for high frequency oscillatory activity to be induced rather than phase-locked, and it is therefore rarely captured by ERP analyses.

The second reason is what is termed the component overlap issue. As summarized by Luck (2014), an ERP component is often conceptualized as "a scalp-recorded neural signal that is generated in a specific neuroanatomical module when a specific computational operation is performed" (p.66). In practice though, the EEG signal is a mixture of a number of different brain activities (because of their inherent temporal and/or spatial overlap, and because of volume conduction). As a consequence, ERP waveforms at the scalp are most often composed of several overlapping signals from different generators (Luck, 2014). As a result, the components under scrutiny (which are classically defined based on peaks and troughs in these waveforms) often have unclear generators. For example, the FRN is generally believed to be generated by the anterior cingulate cortex, but the contribution of other generators is still a matter of debate, even while this is the most studied EEG feature in the context of reward processing (Walsh and Anderson, 2012). Also, the functional meaning of ERP components can also be obscured because of overlapping cognitive operations. For example, the FRN was named as such because it was first understood as a negativity present in loss and not in gain conditions, but it was later suggested to reflect a positive-going deflection that would be present only in gain conditions, and would sum up with the "standard" response to feedback, a N200 (Holroyd et al., 2008; Proudfit, 2015). In other words, the FRN was thought to be due to the addition of a loss-related process, before being reinterpreted as being due to the addition of a gain-related process (Proudfit, 2015). To work around the component overlap issue, some of the studies analyzed here have used difference waves or principal component analysis (e.g. Foti et al., 2011a; Sambrook and Goslin, 2016). However, the issue of whether these outputs reflect a discrete process still stands (Dien, 2012; Luck, 2014). Considering spectral information provides an efficient solution capitalizing on the fact that temporally or spatially co-occurring processes may occur in different frequency bands. For instance, time-frequency analyses have shown that the FRN harbors two overlapping components (i.e., increased phase-locked delta activity to gains and increased phase-locked theta activity to losses) that have different generators and relate to different aspects of reward processing (Foti et al., 2015). It was also demonstrated that the phase-locked delta and theta activities giving rise to the ERPs waveforms in the FRN-P300 time range reflect more independent processes than their ERP counterparts (Bernat et al., 2015, 2011; Watts et al., 2017). However, time-frequency analyses are not a magic-wand solution to the component overlap issue. Volume conduction still applies, and there is obviously no one-to-one mapping between frequency bands and cognitive processes. There are numerous possible generators of a single oscillation, and a single oscillation potentially reflects different processes in different circuits (Cohen, 2017a; Karakaş and Barry, 2017). In other words, there may be situations where a same frequency band supports different processes that are close in time and/or space (see e.g. Mas-Herrero and Marco-Pallarés, 2016 for an illustration of co-occurring medial frontal theta band activities supporting distinct feedback-related processes).

Importantly, oscillations have a direct neurophysiological significance, and are not a mere by-product of brain function (Buzsáki and Draguhn, 2004). As a consequence, studying oscillations allows to adopt a more mechanistic perspective, as they can be directly linked to neurophysiological phenomena (see Cohen et al., 2011b for instance for a discussion in the context of feedback learning). In particular, they are thought to play an important role in neuronal communication, by allowing synchronization within local neuronal populations or between distant brain areas (Bonnefond et al., 2017; Buzsáki and Draguhn, 2004; Canolty and Knight, 2010; Fries, 2015; Varela et al., 2001). As such, studying oscillations offers a glimpse into the neural computations underlying cognitive processes (Donner and Siegel, 2011; Karakaş and Barry, 2017; Lopes da Silva, 2013; Siegel et al., 2012). In the context of reward processing, it has been proposed that the high-beta band activity following reward feedback may be a mechanism supporting the coupling within a frontostriatal-hippocampal network involved in the processing of unexpected or highly-relevant rewards in the context of learning (Marco-Pallarés et al., 2015; Wang et al., 2019). We note that this kind of network perspective justifies the use of connectivity analyses (see Bastos and Schoffelen, 2015; He et al., 2019 for reviews of connectivity approaches for EEG data). Indeed, EEG (or MEG) connectivity analyses are the only way to uncover rapid network dynamics non-invasively in humans (with the limitation that deep brain components of the target network may be more challenging to assess, see section "Considering spatial information: localization and source separation"). However, they are rarely performed in EEG studies of reward processing.

In conclusion, time-frequency analyses are a valuable complementary approach to the traditional ERP analyses, since scanning the frequency spectrum can provide a much more detailed picture of brain reward processing. We note that studies of reward anticipation using time-frequency analyses are particularly scarce (22 out of 359 surveyed studies to date, e.g., Pornpattananangkul and Nusslock, 2016; Reinhart and Woodman, 2014). Importantly, because time-frequency analyses alone do not circumvent the component overlap issue, it is essential to go beyond the study of power modulations in a specific frequency band at one or several electrodes. Rather, source separation and in-depth source-space analyses should be considered to get maximal discriminative power in the study of neurocognitive processes.

Box 1
Source localization issues.

The generators of brain electric fields are macroscopic post-synaptic potentials created by synchronized populations of pyramidal cells oriented perpendicularly to the cortical surface (Jackson and Bolger, 2014). The EEG signal thus captures only part of the neural activity of interest, and requires caution for functional interpretation of the localization of its generators. Nonetheless, when using dipole modelling -an approach that aims to model the recorded activity with a single or a few dipoles on the basis of a priori assumptions with respect to the number of these dipoles (model-driven inverse solutions)-, source localization is fatally biased if the number of dipoles is misestimated (Michel and Brunet, 2019). In contrast, distributed source modelling discretizes the source space into a large number of locations in the brain volume. It estimates the amplitude of all equivalent current dipole locations simultaneously to recover the source distribution with minimum overall energy that best fits scalp measurements (minimum norm solutions). This class of data-driven inverse solutions is theoretically more appropriate when the number of dipoles to model is unknown, which is particularly the case when complex cognitive tasks are used or when data are very noisy (Hauk and Stenroos, 2014; He et al., 2018; Yao and Dewald, 2005). Based on the observation that minimum norm solutions are biased toward superficial sources, weighting parameters have been introduced and form the class of weighted minimum norm solutions on which successful tools like sLORETA are based (Pascual-Marqui, 2002). These methods are accurate from a mathematical point of view in ideal noise conditions (Greenblatt et al., 2005; Pascual-Marqui, 2007; Sekihara et al., 2005). But despite convincing empirical comparisons, it is difficult to validate the accuracy of each solution for real EEG data (Grech et al., 2008), and issues of physiological plausibility remain. For instance, distributed methods which use norm constraints applied to the overall source space might provide too smooth solutions to be perfectly realistic (Pascual-Marqui et al., 2002). Moreover, representing an active segment of the cortical sheet by a small subset of focal dipoles can raise some issues of biological interpretability.

5. Considering spatial information: localization and source separation

EEG is reputed as having poor spatial resolution. In the traditional ERP approach, spatial information is thus simply ignored, by averaging the signal at one or several electrodes (Michel and Murray, 2012). Indeed, drawing conclusions from electrodes' position could be misleading, as there is no straightforward correspondence between the position of the electrode(s) at which an EEG feature is best observed and the brain area(s) generating it (i.e., an ERP which has a fronto-central topography does not necessarily have fronto-central areas as main generators). Source localization methods were developed to exploit the spatial information contained in the EEG signal, with the aim of countering the effects of volume conduction. These methods allow one to estimate the anatomical generators of an EEG feature of interest, based on head models and resolution of the inverse problem, for which several approaches exist (see He et al., 2018 for review, and Box 1 for details).

In our survey, 19% of studies used source localization, with most aiming to localize the source of ERPs. However, because ERPs are most often composed of several signals from different generators (the component overlap issue, see previous section), this approach runs the risk of lacking precision in most cases regardless of the computational reliability of the localization method used (e.g., Pascual-Marqui, 2002). As a consequence, uncertainties remain in studies using source localization to track the anatomo-functional bases of reward processing. For example, while many studies suggest that the anterior cingulate cortex is the main generator of the FRN (e.g., Bellebaum and Daum, 2008; Gehring and Willoughby, 2002; Hewig et al., 2007; Luu et al., 2003; Polezzi et al., 2010; Potts et al., 2006; Ruchsow et al., 2002; Zhou et al., 2010), some suggested a wider picture, by revealing a range of other potentially contributing generators (e.g., the inferior frontal gyrus, Martin and Potts, 2011; Ruchsow et al., 2002; the superior frontal gyrus, Bellebaum and Daum, 2008; the medial or superior temporal cortex, Bellebaum and Daum, 2008; De Pascalis et al., 2010; Kokmotou et al., 2017).

Unmixing the signals contributing to the overall electrical activity recorded on the scalp therefore appears as a major issue to disentangle the underlying neurocognitive mechanisms that are, by virtue of their overlap in time and space, potentially mixed in the experimental design. Blind source separation (BSS) methods can tackle this issue (Makeig et al., 2002). BSS is a data-driven ensemble of techniques originally from signal processing sciences, with a wide range of applications besides neuroscience (Comon and Jutten, 2010). In particular, BSS methods allow the separation of intermixed sources without a priori knowledge about the source signals or the mixing process. Thus, when applied to EEG data, they assume no a priori biophysical or topographical information. In other words, here the term "sources" does not refer to anatomical generators, but to functional entities that are separated based on their statistical properties (see Box 2 for details). In practice, source separation provides the researcher with a set of source estimates, which are composed of reconstructed source activities and topographies. By working directly on source activities, it is possible to move from classical electrode-space analyses to source-space analyses (either time-frequency or ERP analyses). Besides, topographies (i.e., the spatial projection of the source to the scalp) can be fed to source localization algorithms (Figure 4). Although separated on the basis of their statistical properties, the components resulting from BSS can still be expected to reflect the activity of distinct cortical areas (Delorme et al., 2012). For this reason, applying source localization on separated sources can maximize the use of the spatial information contained in the EEG signal (Onton et al., 2006). As an example, the current density map (obtained through distributed source modeling) of an ERP recorded at the scalp might be difficult to interpret when it is itself composed of a large number of generators that are distant and whose dynamics are not perfectly aligned in time. Separating (and localizing) sources might help to disentangle the different neural activities contributing to the overall ERP recorded at the scalp, thus limiting the superposition between neurocognitive mechanisms when interpreting current density maps. Indeed, BSS has proven useful in decomposing ERP responses into distinct events (e.g., Bridwell et al., 2015; Onton et al., 2006).

Source-space analyses offer other advantages. Because the signal of interest is better isolated, the method provides access to less energetic but potentially interesting features of the data that may be missed with classical analyses (Sutherland and Tang, 2006). Moreover, since connectivity analyses performed at the sensor level are compromised by volume conduction patterns, connectivity measures may best be derived from source activities after BSS (Brunner et al., 2016; Schoffelen and Gross, 2009)[2]. Despite these advantages, source separation and source-space analyses have been used by only one of the surveyed studies (Silvetti et al., 2014). In this study, independent component analysis was used to isolate one component for each subject on the basis of a topography consistent with a medial frontal source and an activity consistent with the error-related negativity (an ERP that is time-locked to the motor response and more negative following errors, and is believed to be generated by the medial frontal cortex). The activity of this component was then assessed during reward anticipation and outcome processing periods, providing arguments for the hypothesis that the same medial frontal source could be responsible for encoding error-related processes as well as reward expectation and prediction error.

To enhance spatial information, another possibility is to combine the millimeter resolution of fMRI with the unique ability of EEG to probe fast neural dynamics (He et al., 2018). This has been done by 14 (4%) of the studies included in our analysis, using a variety of approaches. For example, Mas-Herrero et al. (2015) used joint independent component analysis and showed that the high beta band activity induced by gains cor-

[2] When applied to source signals, vector autoregressive (VAR) models are useful tools for assessing information flow through lagged dependencies between source signals (e.g., Directed Transfer Function, Kaminski and Blinowska, 1991; Partial Directed Coherence, Baccalá and Sameshima, 2001).

Box 2
Blind source separation general principles and applications.

Numerous BSS approaches and algorithms can be applied to EEG signal processing in order to unmix potential overlapping neural processes. In contrast to source localization methods, these approaches do not aim to localize the generators based on biophysical assumptions. Rather, the general method relies on the assumption of a certain degree of independence between sources. Independent Component Analysis (ICA) is the most popular approach (Hyvärinen et al., 2001). It decorrelates the signals and reduces higher-order statistical dependencies in order to make the source signals as independent as possible (Delorme et al., 2007; Onton and Makeig, 2006). Various higher order statistics (HOS) algorithms use data distribution characteristics to perform the decomposition, with the main separation criteria being maximization of non-gaussianity (e.g., FASTICA, EFICA) or minimization of mutual information (e.g., INFOMAX, ExtINFOMAX). These algorithms decompose the EEG signal obtained from a specific number of electrodes into the same number of statistically maximally independent components. They are robust to Gaussian noise in the dataset but temporal information is lost. Second order statistics algorithms (SOS; e.g., SOBI, UWSOBI, WASOBI, AJDC; Sutherland and Tang, 2006; Tang et al., 2006, 2005) are interesting alternatives. They use time-frequency information to perform the decomposition, with spectral diversity as the main separation criterion. Indeed, they allow applying BSS on shorter time intervals and are more robust with respect to outliers (Congedo et al., 2008; Lio and Boulinguez, 2013; Tang, 2010).
Choosing a BSS method is not trivial. For instance, HOS-based BSS algorithms are optimal for removing non-brain artifacts and most of the Gaussian noise from the data (e.g., Lio and Boulinguez, 2013), while the benefits of SOS-based BSS algorithms in the temporal domain are well-suited for capturing trial-to-trial variations and analyzing single-trial ERPs (Sutherland and Tang, 2006; Tang et al., 2011; Zhang et al., 2014). SOS-based BSS is also especially adapted to group BSS, a method which aggregates data from all subjects to form a unique estimation of the mixing matrix for the whole group (Congedo et al., 2010; Eichele et al., 2011; Huster et al., 2015; Kovacevic and McIntosh, 2007; see Huster & Calhoun, 2018 for a special issue on multi-subject decomposition of EEG). Group BSS solves one of the major concerns with source separation, which is generalization across subjects. Indeed, when using BSS at the individual level, single-subject components have to be selected by hand (e.g., based on topography and time course similar to an ERP of interest, Silvetti et al., 2014) or matched across subjects by means of clustering algorithms for group analysis. This introduces subjectivity (in the selection or when setting the criteria for clustering), and difficulties with statistical analyses when only a subset of subjects contributes to a cluster. Indeed, because of interindividual anatomo-functional variability, building a unique mixing matrix for a group of subjects on the basis of their aggregated data violates the mandatory assumption that the mixing matrix is stationary (Lio and Boulinguez, 2018, 2013). Yet, SOS-based algorithms are more robust to mixing matrix distortions, leading more easily to generalization when similar spectral patterns are identified at neighboring locations, as compared with HOS-based algorithms which show a tendency for overlearning and over-separation (extraction of spurious information from non-stationary events) (Lio and Boulinguez, 2018, 2013). Importantly, even though using group BSS with SOS-based algorithms like SOBI allows direct matching of functionally equivalent components across subjects on the basis of their spectral signature, it does not prevent from analyzing the inter-individual variability of these sources by using the group filter to extract and compare individual component time-series (Huster and Raud, 2018).

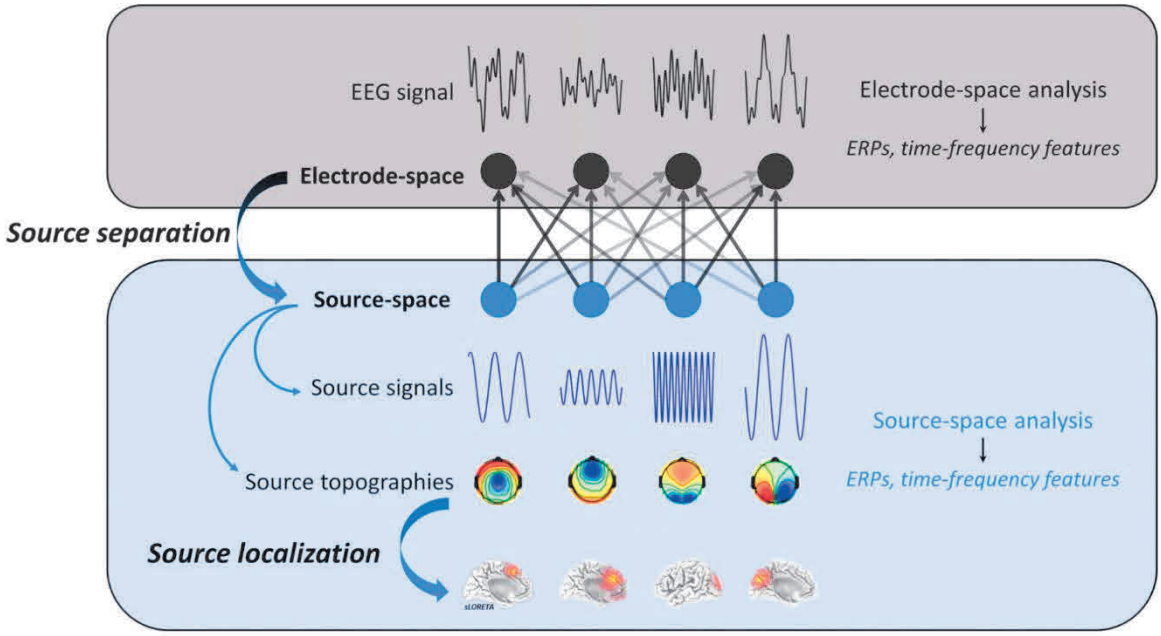

Fig. 4. Source separation at a glance. Source separation allows to unmix most sources of the ongoing brain activity. In practice, source separation returns the estimated source signals and topographies. Working directly with the source signals allows switching from classical electrode-space analyses to source-space analyses, regardless of the kind of analysis one aims to perform (ERP or time-frequency analyses). Besides, the source topographies can be used for localization (see text for details).

responds to the engagement of a fronto-striatal-hippocampal network identified with fMRI, providing support for previous hypotheses (Marco-Pallarés et al., 2015). Using regression of oscillatory power changes onto BOLD signal changes, Mas-Herrero and Marco-Pallarés (2016) showed that the sensitivity of midfrontal theta band activity to outcome valence and unsigned prediction error was correlated with the activation of the supplementary motor area and dorsomedial prefrontal cortex, respectively. Given the close proximity of these subregions of the medial frontal cortex, it would have been difficult with EEG alone to determine that the sensitivity of theta band activity to these variables reflects the engagement of two distinct regions rather than that of one single region encoding both processes.

Finally, the fact that a substantial part of the reward network is subcortical calls for a word of caution. While some authors have claimed that part of the reward feedback-related EEG activity may be generated by the striatum (Carlson et al., 2011; Foti et al., 2011a, 2015), the possibility to access subcortical, deep activity with EEG remains highly controversial (see Cohen et al., 2011a; Foti et al., 2011b for discussion) and cannot be considered as a genuine opportunity yet (but see Attal et al., 2012, 2009; Seeber et al., 2019). In any event, it is reasonable to consider that the activity we can observe with EEG is mostly cortical. Because of this major limitation of the EEG technique, standard and complementary neuroimaging tools will still be highly needed in the future.

6. Conclusion

Our survey of the literature reveals that a majority of EEG studies on reward processing have been designed to investigate how ex-

Box 3
How advanced methods in EEG analysis can help answer outstanding questions on reward processing.

- Using time-frequency and connectivity analyses to uncover the oscillatory mechanisms supporting the integration and transfer of information within the reward network
- Using source-space connectivity analyses to unravel the interaction between the reward network and the attentional, executive, or motor networks, that mediates the behavioral effects of reward
- Using source-space analyses to identify precise markers of neurocognitive dysfunctions in pathology (e.g., major depressive disorder, substance use disorder, behavioral addiction; McLoughlin et al., 2014)
- Leveraging the three axes for the discriminative power of EEG to isolate motivational from motor and attentional processes during reward anticipation (e.g., Reinhart and Woodman, 2014)
- Exploiting the fine temporal resolution of EEG to separate the brain signals related to reward anticipation and reward outcome processing, that are often problematically confounded when studied with fMRI (e.g., Alicart et al., 2015)

perimental manipulation of feedback valence, likelihood or magnitude, among other attributes, impacts the FRN amplitude (Glazer et al., 2018; Sambrook and Goslin, 2015; Walsh and Anderson, 2012). This approach provides limited insight. First, it overlooks reward anticipation. Second, investigating variations of one ERP at one or a few electrodes ignores a lot of the (spatial and spectral) information contained in EEG signal, providing a biased perspective on how the brain actually processes rewards. Indeed, time-frequency analyses of reward outcome processing unsurprisingly showed that different processes are confounded (e.g., those reflected in the evoked delta and theta band activities) or missed (e.g., those reflected in the induced beta band activity) in classical time-domain analyses. Paying more attention to reward anticipation and employing more recent methodological advances as discussed here will undoubtedly help to build a more comprehensive picture of the neurocognitive mechanisms underlying reward processing. We believe that it can help answer outstanding questions on reward processing (Box 3).

We want to highlight that, even though the analyses we describe here are more difficult to apply than classical ERP analyses, and may also require more resources (e.g., time, or data storage capacity), they are now greatly facilitated by available software (e.g., Fieldtrip, EEGlab; see Michel and Brunet, 2019 for a list of packages including source localization tools). Still, some precautions should be taken when applying them, as soon as the initial setup of the experiment. For instance, source localization requires higher density recordings (at least 64 electrodes, Seeck et al., 2017), efficient source separation needs long continuous time-series (e.g., Lio and Boulinguez, 2013), and accessing subtle features of the data requires a large number of trials (e.g. while 20 trials are enough to obtain a stable FRN in healthy subjects -Marco-Pallares et al., 2011-, a minimum of 50 can usually be recommended for time-frequency analyses, Cohen, 2017b). For more details, we refer the reader to the useful recommendations made in all the listed references of interest.

In conclusion, because EEG is inexpensive, non-invasive, and portable, there is great interest in using EEG features as potential biomarkers of cognitive processes or pathologies. We believe that using the methods discussed here could provide more precise and interpretable markers in reward studies.

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Data code availability

The data supporting the survey presented in this paper was extracted from published literature following a procedure described in the Supplementary Material. The full list of references and the derived data are available from the corresponding author on simple request.

Code availability: Not applicable.

Declarations of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118478.

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Supplementary material: Detailed methods

We searched the Pubmed database from 01/01/2000 to 8/10/2019 for EEG studies of reward processing, using the following terms: (reward OR incentive) AND (EEG OR electroencephalograph* OR ERP OR event-related potential OR oscillat*). For completeness, we also searched the Web of science database using the same terms.

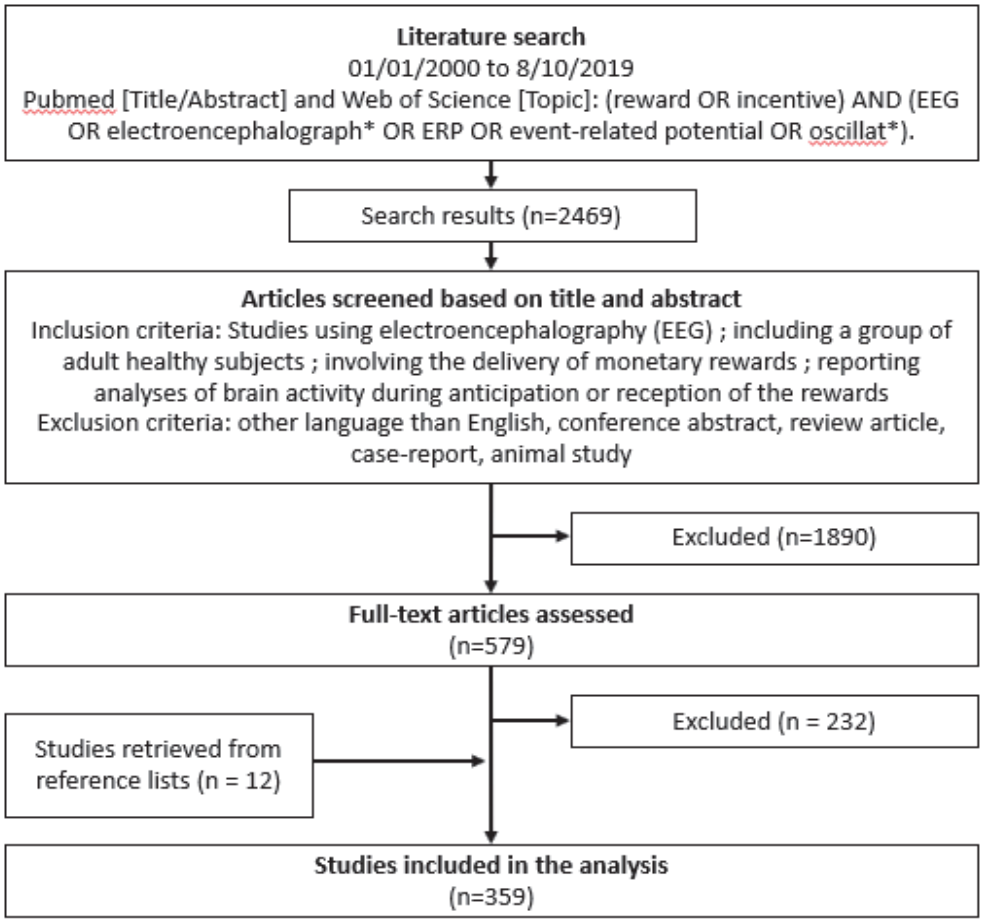
The inclusion criteria were:

- Studies using electroencephalography (EEG)
- Studies including a group of adult healthy subjects that are not under the influence of a drug, placebo or brain stimulation.
- Studies involving the delivery of monetary rewards to the subjects themselves. We chose to focus on monetary reward as different reward types may be processed in partially distinct networks (Sescousse et al. 2013), and as this is the most used type of reward (especially in EEG studies, probably because other rewarding stimuli such as food can raise issues with precise stimulus timing, which is crucial for EEG but less crucial for e.g. fMRI), allowing us to consider a large number of comparable EEG studies investigating reward processing. Studies using real amounts of money, hypothetical amounts of money or points exchanged for real amounts of money were considered. However, we note that there is evidence that hypothetical monetary rewards could produce different effects than actual monetary rewards (Camerer and Mobbs 2017).
- Studies reporting analyses of brain activity during anticipation or receipt of the rewards.
    - For anticipation, studies analyzing e.g. the cue period or the period preceding feedback onset in a MID task, or the reel spinning period in a slot machine task, and performing statistical comparisons such as low vs. high probability of reward, potential small vs. potential large reward, potential reward vs. no potential reward, potential gain vs. potential loss were included.

      We did not consider studies investigating reward anticipation at e.g. the target processing stage or during a memory retention period, or studies investigating a separated decision making period. Although we acknowledge that reward anticipation processes also occur at these stages, they may also be more easily confounded with other co-occurring processes without careful experimental design and analysis. A significant number of studies compared anticipation of the outcome of a small vs. large bet, with gains and losses being equiprobable. These studies were also excluded because only expectations about the magnitude, and not expectations about the valence, can be assumed.
    - For delivery, studies investigating e.g. the feedback presentation period, and performing statistical comparisons such as small vs. large reward, gain vs. loss, gain vs. no gain, or regression of the neural activity by reward level were included. Accordingly, some ERPs studies were excluded because they only compared difference waves (losses – gains) across various conditions, without testing them for statistical significance within conditions (i.e., testing them against 0 with a t-test). Others

common designs that were excluded include fair outcome vs. unfair outcome or loss vs. non-loss comparisons, as well as regression of the neural activity by a modeled reward prediction error.

The exclusion criteria were: other language than English, conference abstract, review article, case-report, animal study.



Supplementary figure 1: Flow chart of the selection process.

Supplementary Figure 1 summarizes the selection procedure. The search returned 1030 records from Pubmed and 2408 from Web of Science[12]. Among these, we identified 2469 unique records. 1890 were excluded based on title and abstract. 232 were excluded after the consultation of the method section of the remaining 579 articles. Twelve additional articles were retrieved from

[12] For comparison purpose, a similar search was performed on the Pubmed database for fMRI studies ((reward OR incentive) AND (fMRI)). This search returned 6854 records, suggesting that fMRI have been privileged over EEG in the study of reward processing.

reference lists of recent reviews on the topic (San Martín 2012; Walsh and Anderson 2012; Hauser et al. 2014; Luft 2014; Glazer et al. 2018). This led to a total of 359 (347+12) included articles.

The following information was extracted from the abstracts or method sections of the selected articles: technique used (e.g., EEG, EEG-fMRI...), presence of ERP analyses, presence of time-frequency analyses, presence of source analyses, presence of analyses focused on reward receipt, presence of analyses focused on reward anticipation.

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Matériel complémentaire - Resting state oscillations suggest a motor component of Parkinson's Impulse Control Disorders

Charlotte Spay*, Garance Meyer*, Bénédicte Ballanger, Roberto Cilia, Philippe Boulinguez. *Publié dans Clinical Neurophysiology, 130:2065-75*

Supplementary file 1

Supplementary file 2

SUPPLEMENTARY FILE 1

Spay C, Meyer G, et al. Resting state oscillations suggest a motor component of Parkinson's Impulse Control Disorders.

Supplementary Table 1: Literature-based predictions

	Motor impulsivity Motor, executive dysfunctions		**Decisional impulsivity** Cognitive, decisional dysfunctions	
Processes	Motor preparation, response inhibition		Motivation, valuation, decision, reward	
Cortical brain regions	Motor executive network		Mesocorticolimbic network	
	Dorsomedial Prefrontal Cortex	(1–3)	Orbitofrontal Cortex - Ventromedial Prefrontal Cortex	(15–19)
	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) *but see* (5,13,14)		
Frequency bands	Alpha (8-12Hz)	(3,26–30)	Delta (0.5-3.5Hz)	(41–47)
	Beta (13-30Hz)	(26–38)	Theta (4-7Hz)	(47–56)
	Gamma (>30Hz)	(39,40)		

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SUPPLEMENTARY FILE 2

Spay C, Meyer G, et al. Resting state oscillations suggest 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 $p<10^{-3}$
Levodopa	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.

Matériel complémentaire – Inhibitory control dysfunction in parkinsonian impulse control disorders

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Supplementary table 1

Supplementary table 2

Supplementary Table 1: Detailed EEG results.

ICs explaining more than 1% of variance				Statistical matching procedure	Group analysis
#	Expl. var. (%)	sLORETA centroid coordinates (MNI, x y z)	Probability map extent Brodmann Area	Significant frequency band	Significant Group x Condition interaction (F, p) Post-hoc comparisons (t, p)
1	15.9	-20 -100 -10	Lingual gyrus, Cuneus 17,18,19	Alpha	-
				Beta 1-2	-
				Beta 3	F(1,39)=5.20, p=.028 ICDs-: t=-1.73, p=.092 ICDs+: t=1.49, p=.14
2	9.7	-5 -70 -5	Lingual gyrus 18	Alpha	-
				Beta 1-2	-
				Beta 3	-
3	6.0	15 -75 55	Superior parietal lobule, Precuneus 7	Alpha	-
				Beta 1-2	F(1,39)=5.45, p=.025 ICDs-: t=-1.02, p=.31 ICDs+: t=2.33, p=.025 (Ctrl>Mix)
				Beta 3	-
4	4.1	35 -35 65 (7 -58 47)	Post-central gyrus, Pre-central gyrus, Precuneus 2, 3, 6, 7	Alpha	-
				Beta 1-2	F(1,39)=11.52, p=.0016 ICDs-: t=-3.91, p=.0004 (Mix>Ctrl) ICDs+: t=.77, p=.44
				Beta 3	-
				Low gamma	-
5	3.7	5 -55 70	Post-central gyrus, Precuneus 5, 7	Alpha	-
				Beta 1-2	-
				Beta 3	-

6	3.1	-20 -60 65	Superior parietal lobule, Precuneus 7	Alpha	-
				Beta 1-2	F(1,39)=11.35, p=.0017 ICDs-: t=-2.79, p=.008 (Mix>Ctrl) ICDs+: t=1.95, p=.058 (trend Ctrl>mix)
				Beta 3	-
				Low gamma	-
7	2.6	20 -90 -25	Fusiform gyrus 18	Alpha	-
				Beta 1-2	-
				Beta 3	-
8	2.5	5 5 70	Superior frontal gyrus, Medial frontal gyrus 6	Alpha	-
				Beta 1-2	F(1,39)=4.53, p=.040 ICDs-: t=-1.53, p=.134 ICDs+: t=1.48, p=.147
				Beta 3	F(1,39)=17.34, p=.00017 ICDs-: t=-3.01, p=.005 (Mix>Ctrl) ICDs+: t=2.88, p=.006 (Ctrl>mix)
				Low gamma	-
9	2.3	-30 -90 -20	Inferior occipital gyrus, Fusiform gyrus 18, 19	Alpha	-
				Beta 1-2	-
				Beta 3	-
10	1.7	25 -90 -25	Fusiform gyrus, Inferior occipital gyrus, Medial frontal gyrus, Post-central gyrus 3,6,18	Alpha	-
				Beta 1-2	F(1,39)=4.35, p=.044 ICDs-: t=-1.23, p=.227 ICDs+: t=1.74, p=.089
				Beta 3	-
				Low gamma	-
11	1.6	-30 -95 15	Middle occipital gyrus 19	Alpha	-
				Beta 1-2	-
				Beta 3	-

12	1.5	30 10 65 (5 22 34)	Middle frontal gyrus, Anterior cingulate 6, 32	Alpha	-
				Beta 1-2	-
				Beta 3	-
				Low gamma	-
13	1.2	-10 -90 35	Cuneus, Middle occipital gyrus 18, 19	Alpha	-
				Beta 1-2	-
				Beta 3	-
14	1.2	20 -95 -20	Fusiform gyrus, Lingual gyrus, Inferior occipital gyrus 17, 18	Alpha	-
				Beta 1-2	-
				Beta 3	-

Supplementary Table 2: Connectivity results.

From… **To…**	IC #4 – Beta 1-2 Lag (ms) – p-value	IC #6 – Beta 1-2 Lag (ms) – p-value	IC #8 - Beta 3 Lag (ms) – p-value
IC #3 - Alpha	-24ms - <.0001	-6ms - <.0001	119ms - <.0001
IC #3 - Beta 1-2	-151ms - .0001	-73ms - .0004	74ms - <.0001
IC #3 - Beta 3	17ms - <.0001	71ms - .0006	-17ms - <.0001
IC #4 - Alpha	0ms - <.0001	0ms - <.0001	77ms - <.0001
IC #4 - Beta 1-2	-	8ms - <.0001	58ms - <.0001
IC #4 - Beta 3	-17ms - <.0001	28ms - <.0001	78ms - <.0001
IC #4 - Low gamma	n.s.	n.s	n.s.
IC #5 - Alpha	29ms - <.0001	-3ms - <.0001	83ms - <.0001
IC #5 - Beta 1-2	-85ms - <.0001	-96ms - <.0001	-67ms - <.0001
IC #5 - Beta 3	40ms - <.0001	60ms - .0001	79ms - <.0001
IC #6 - Alpha	0ms - <.0001	0ms - <.0001	69ms - <.0001
IC #6 - Beta 1-2	-8ms - <.0001	-	-17ms - <.0001
IC #6 - Beta 3	-16ms - <.0001	-7ms - <.0001	1ms - <.0001
IC #6 - Low gamma	n.s.	n.s.	n.s.
IC #8 - Alpha	91ms - <.0001	108ms - <.0001	93ms - <.0001
IC #8 - Beta 1-2	-63ms - .0005	n.s.	n.s.
IC #8 - Beta 3	-58ms - <.0001	17ms - <.0001	-
IC #8 - Low gamma	n.s.	n.s.	n.s.
IC #10 - Alpha	62ms - <.0001	70ms - <.0001	101ms - <.0001
IC #10 - Beta 1-2	n.s.	-119ms - .0002	-61ms - <.0001
IC #10 - Beta 3	23ms - <.0001	-81ms - <.0001	96ms - <.0001
IC #10 - Low gamma	n.s.	n.s.	n.s.
IC #12 - Alpha	-10ms - <.0001	2ms - <.0001	0ms - <.0001
IC #12 - Beta 1-2	-81ms - <.0001	-125ms - <.0001	65ms - <.0001
IC #12 - Beta 3	-199ms - <.0001	-1ms - <.0001	39ms - .0002
IC #12 - Low gamma	n.s.	n.s.	n.s.

Article de revue - Functional imaging correlates of akinesia in Parkinson's disease: Still open issues

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Article

Supplementary file 1

Supplementary file 2

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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 ± 11.5 AR patients and 20.7 ± 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

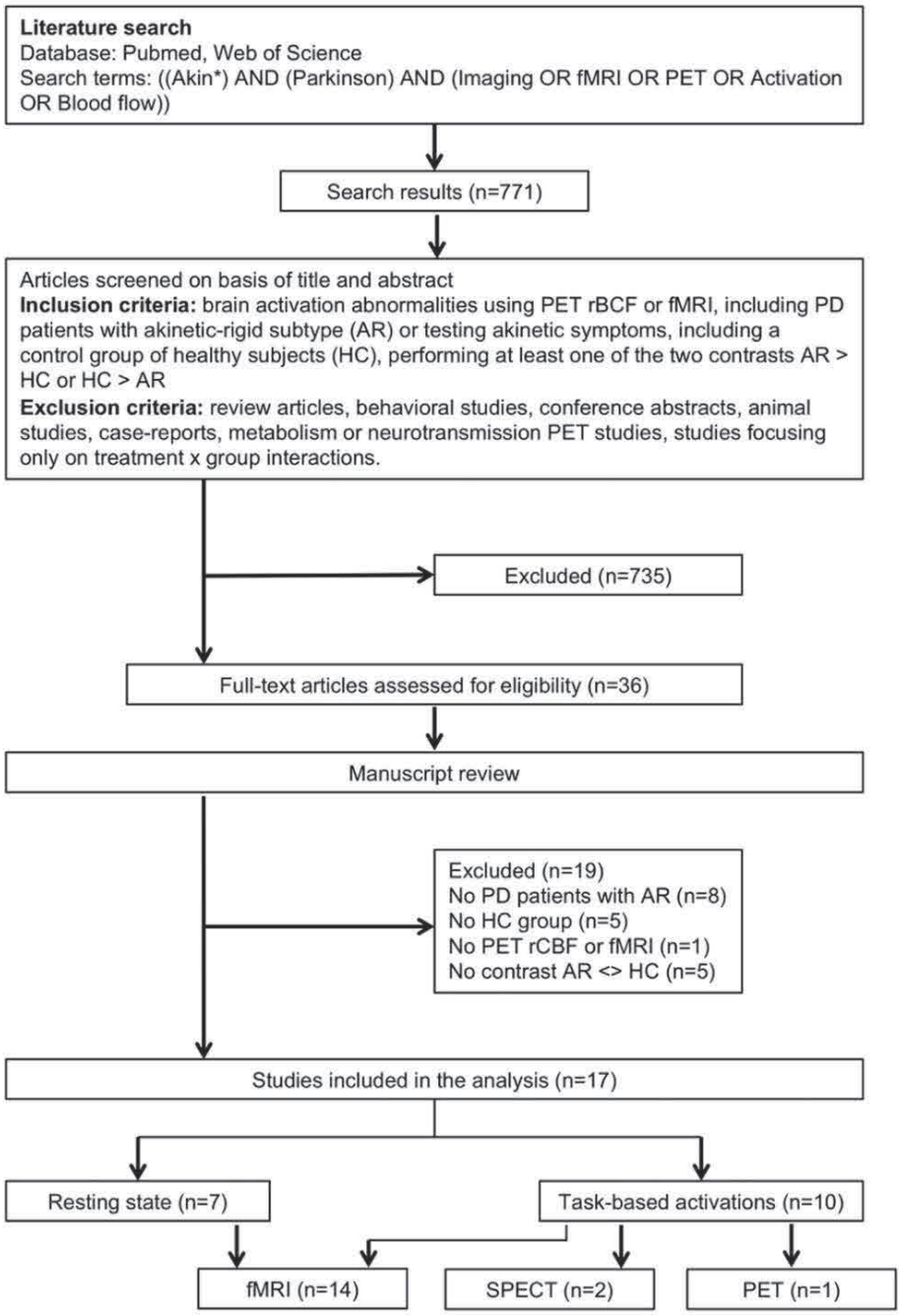

Fig. 1. Flow chart of publication selection for review, following PRISMA guidelines (Liberati et al., 2009).

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		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
#1	Hu 2017	(−) AR dominant 25/26/25	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. Ø
									AR > TD TD > AR	(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 lobule.
					Functional connectivity (FC) – Seed-based		(−)	*Seeds: regions showing differences in FCD between AR and TD*	AR > TD TD > AR	Ø (b) Lower FC in AR between the left cerebellum anterior lobule and the left primary somatosensory cortex, left superior frontal gyrus, right insula, right orbital inferior frontal gyrus.
#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	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.
									HC > AR	Decreased ReHo in the left middle and posterior cingulate gyrus/precuneus, right insula, left fusiform gyrus, vermis 4/5 and bilateral thalamus.
									AR > TD 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 lobule. Lower ReHo in AR in the left posterior cingulate, left thalamus, left superior frontal gyrus, left primary motor cortex, bilateral cerebellum.

(*continued on next page*)

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
#3	Hou 2017	(−) AR dominant . 21/21	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	Ø [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

(*continued on next page*)

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
										medial frontal cortex and the bilateral primary somatosensory cortex, right superior parietal lobule. Negative correlation between akinesia scores and FC between the posterior medial frontal cortex and the right inferior parietal lobule within the posterior medial frontal AR dominant.
#5	Guan 2017	(−) AR dominant 49/52/57	Drug naïve 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	Ø (a) [Voxel-wised analysis] Reduced network-based FC in the bilateral thalamus, occipital lobule, precuneus [ROI-based analysis] Reduced network-based FC in the bilateral thalamus.
									AR > TD TD > AR	Ø (a) [Voxel-wised analysis] Lower network-based FC in AR in the bilateral occipital lobule and right cerebellum posterior lobule [ROI-based analysis] Ø
					Intrinsic activity Eigenvector Centrality Mapping		(−)	*ROI: Bilateral caudate nucleus, putamen, pallidum, thalamus*	. AR > HC HC > AR AR > TD TD > AR	(b) Enhanced eigenvector centrality in the right caudate nucleus and right thalamus. Ø Ø Ø
#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	Ø Decreased VMHC values in the primary motor cortex.
									AR > TD TD > AR	Higher VMHC in AR in the cerebellum posterior lobule. Ø
#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*	. HC > AR . AR > HC	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
									AR > TD TD > AR	Ø Lower spontaneous brain activity in AR in the left and

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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
										right inferior parietal cortex, left posterior cingulate cortex within the DMN.
#8	Criaud 2016	Slowness in movement initiation PD patients without tremor . 12/15	ON	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	Increased pre-stimulus BOLD within several nodes of the proactive inhibitory network (caudate nucleus, precuneus, thalamus). Correlation between SMA activation and movement initiation latency. Increased movement initiation latency (akinesia) in AR compared to HC.
#9	Haslinger 2001	(−) AR without tremor 8/8	Drug naïve or OFF .ON	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 HC > AR	Increased activation in bilateral M1 and SMA in AR-ON compared to HC. Increased activation in bilateral S1 M1 in AR-OFF compared to HC. Decreased activation in preSMA/SMA in AR-OFF and AR-ON compared to HC.
#10	Buhmann 2003	(−) AR without tremor 8/10	Drug naïve. ON	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 . UAH > AH* . ON > OFF	Hypoactivation of the M1 and SMA in AR compared to HC (drug-naïve). Hypoactivation of the contralateral M1 in AH compared to UAH (drug-naïve). Hyperactivation of the M1 contralateral to the affected hand and bilateral SMA after L-dopa (ON) compared to drug-naïve.
#11	Sabatini . 2000	(−) AR without tremor . 6/6	OFF	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	Increased fMRI signal in the bilateral primary sensorimotor cortex, bilateral premotor cortex, inferior parietal cortex, caudal part of the SMA and ACC in AR compared to HC. Decreased fMRI signal in the rostral part of the SMA, in the right dorsolateral prefrontal cortex, in the left lateral premotor cortex and left inferior parietal cortex.
#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	(a) During synchronization phase, increased activity in

(*continued on next page*)

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
		(−) 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. Ø
#13	Yu . 2007	(−) PD patients without tremor . 8/8	OFF	fMRI BOLD	Task-based activations Block design	"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"	Motor Task Ext. . *Automatic* vs. *cognitively controlled thumb pressing movements*	*Whole brain (ROI mask based on group comparison)*	. AR > HC . HC > AR	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	(−) AR dominant . 8/14/9	OFF	.fMRI BOLD	Task-based activations . Block design	"to understand the clinical heterogeneity between TD and AR subtypes"	Motor Task Int. . *Internally-guided sequential finger tapping task*	*ROI: CTC/STC circuits*	. AR > HC . AR > TD	After adjusting for age, significant increase of the % of voxels activated in controlateral 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	(−) AR without tremor . 15;11/15	ON .OFF (between groups)	SPECT . rCBF	Task-based activations . Block design	"to assess whether the motor activation in the SMA is impaired or not when akinetic PD patients are treated with levodopa"	Motor Task Int. . *Sequential finger-to-thumb opposition movements*	*ROI: SMA. S1 M1*	. AR > HC . HC > AR	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	(−) AR without tremor . 12;16/12	ON . OFF (between groups)	SPECT . rCBF	Task-based activations . Block design	"to compare rCBF changes induced by a motor task in the cerebellar hemisphere of	Motor Task Int. . *Sequential finger-to-thumb*	*ROI: CerebellumS1 M1, SMA*	. AR > HC	Overactivation in the ipsilateral cerebellum in AR-OFF compared to HC and AR-ON.

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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
						akinetic PD or HC receiving or not levodopa"	*opposition movements*		. HC > AR	Hypoactivation in the SMA in AR-OFF compared to HC and AR-ON.
#17	Samuel . 2001	(−) PD patients without tremor . 6/6	OFF	PET . rCBF	Task-based activations . Block design	"to explore what is less activated in PD than in HC when executing or imaging movements"	Motor Task Ext. . *Paced single joystick movements in a freely chosen direction.* . Motor Imagery Task	*Whole brain*	. HC > AR	(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: Akinetic-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 naïve: Patients who never experienced dopaminergic medication. Ext.: Externally driven. Int.: Internally driven -self-initiated-. AH: Affected –Akinetic- Hand. UAH: Unaffected -non-akinetic- 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.

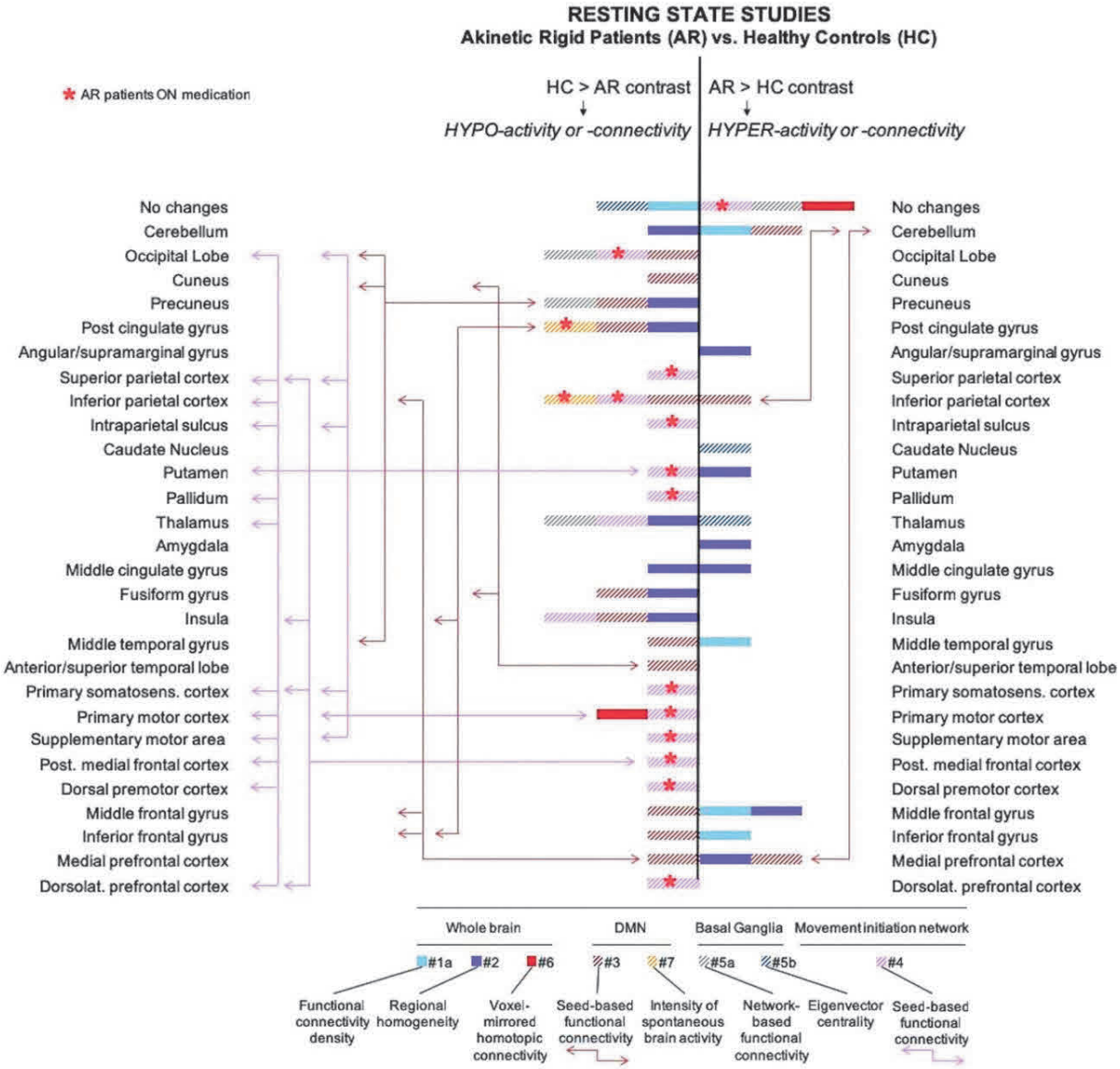

Fig. 2. Results of the neuroimaging studies using resting state approaches and comparing AR to HS subjects to assess the neural bases of akinesia. Arrows between two distinct brain regions indicate abnormal connectivity in seed-based functional connectivity studies. Studies assessing AR patients ON medication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

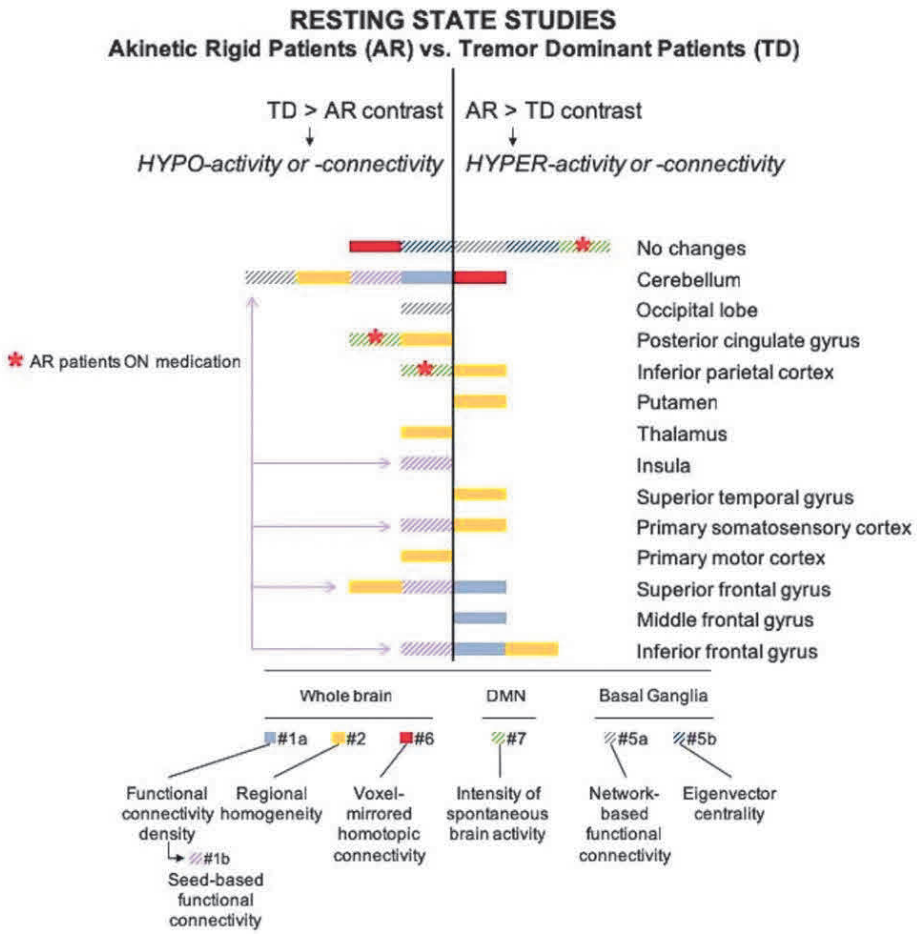

Fig. 3. Results of the neuroimaging studies using resting state approaches and comparing AR to TD subjects to assess the neural bases of akinesia. Arrows between two distinct brain regions indicate abnormal connectivity in seed-based functional connectivity studies. Studies assessing AR patients ON medication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

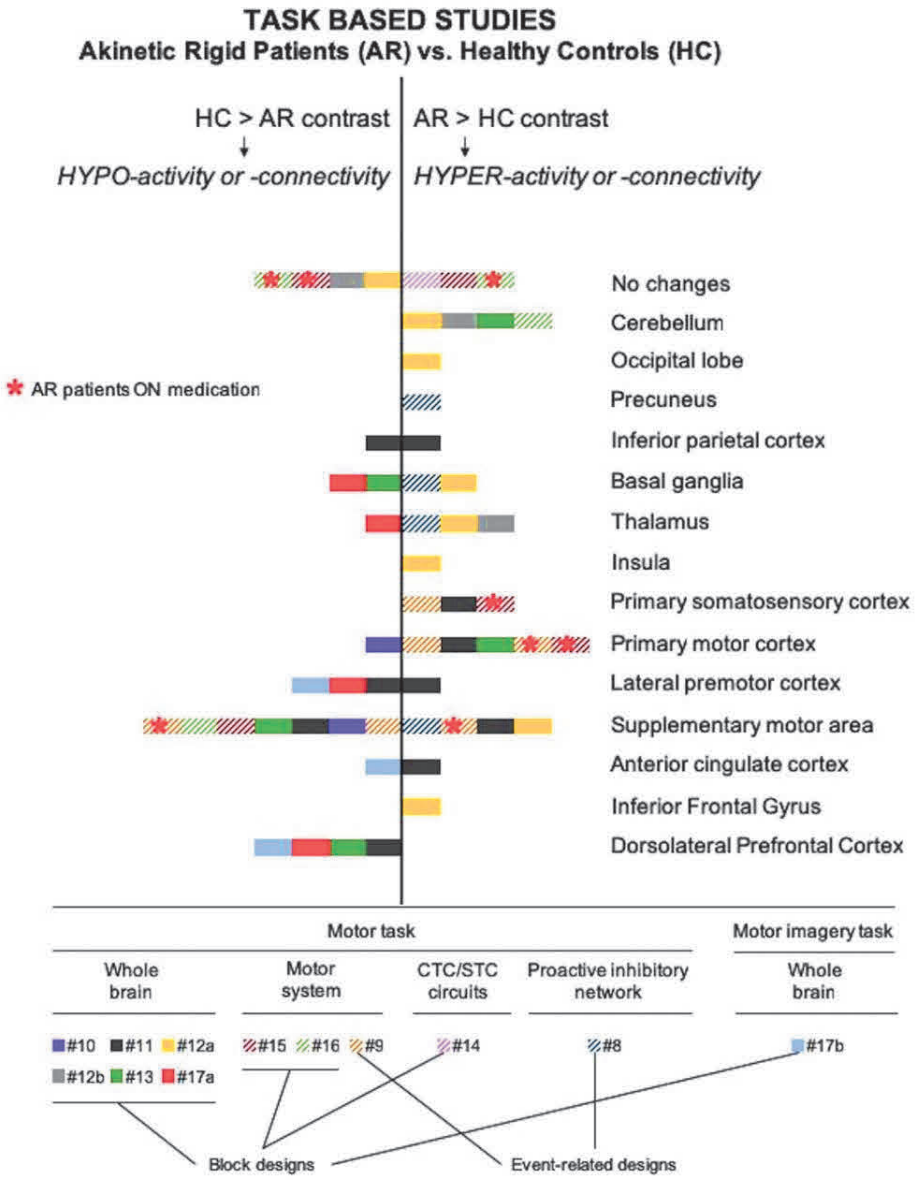

Fig. 4. Results of the neuroimaging studies using task-based approaches and comparing AR to HS subjects to assess the neural bases of akinesia. Studies assessing AR patients ON medication are indicated by red stars.

(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-thalamo-cortical loops and executive functions (Albares et al., 2015b; Chamberlain et al., 2009; Faggiani and Benazzouz, 2017; Spay et al., 2018), but also about the serotoninergic (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 unspecific 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 (1rst 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[2]
Guan, 2017	56.0 ± 9.9	4.4 ± 4.0	23/26	Non-demented[1] *(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[2]	6 ± 4 / 7 ± 6[2]	17/9	Non-demented *(NR)*	23 ± 10 / 25 ± 7[3]
Rascol, 1997	61 ± 3 / 60 ± 2[2]	6 ± 1 / 8 ± 1[2]	NR	Non-demented *(NR)*	26 ± 4 / 22 ± 3[3]
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 – [1]Patients with cognitive impairment were excluded according to MMSE and the criteria suitable for Chinese population – [2]UPDRS-III ON medication: 20.0 ± 13.2 – [3]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 *Potential confounds between the effects of disease and akinesia*				
#2 Zhang et al., 2015	Unclear	UPDRS Ratio derived from mean AR and tremor score based on UPDRS-III *Potential confounds between the effects of disease and akinesia*				
#3 Hou et al., 2017	Unclear	UPDRS Ratio derived from tremor and non tremor score based on UPDRS-III *Potential confounds between the effects of disease and akinesia*			Seeds and ROI (DMN) *Potential omission of effects outside the regions of interest*	
#4 Hensel et al., 2018		UPDRS UPDRS-III it 31 *Potential confounds between akinesia, bradykinesia and hypokinesia*	No exclusion criteria regarding dementia *Potential confound with the effect of dementia*		Seeds and ROIs (seed-specific networks) *Potential omission of effects outside the regions of interest*	

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

#11 Sabatini et al., 2000	Unclear	Unclear	No statistical testing of between groups match. No data on dementia	6 AR / 6 HC	No motion correction	No statistical correction for multiple comparisons
	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*
#12 Ceresa et al., 2006	Unclear	Unclear	No exclusion criteria regarding dementia	10 AR / 11 HC		
	Potential confounds between the effects of disease and akinesia		*Possible confound with the effect of dementia*	*Insufficient sampling*		
#13 Yu et al., 2007	Unclear	Unclear		8 AR / 7 HC		
	Potential confounds between the effects of disease and akinesia			*Insufficient sampling*		
#14 Lewis et al., 2011	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
	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*
#15 Rascol et al., 1994	Unclear	? "AR syndrome without tremor"		15 ON / 11 OFF / 15 HC	No motion correction ROI (SMA, S1M1)	No statistical correction for multiple comparisons
	Potential confounds between the effects of disease and akinesia			*Insufficient sampling*	*Possible source of spurious associations* *Potential omission of effects outside the regions of interest*	*Possible source of spurious associations*
#16 Rascol et al., 1997	Unclear	Unclear		12 OFF / 16 ON / 12 HC	No motion correction ROI (SMA, S1M1)	No statistical correction for multiple comparisons
	Potential confounds between the effects of disease and akinesia			*Insufficient sampling*	*Possible source of spurious associations* *Potential omission of effects outside the regions of interest*	*Possible source of spurious associations*
#17 Samuel et al., 2001	Unclear	Unclear	Groups unmatched for age and sex	6 AR / 6 HC	No motion correction	No statistical correction for multiple comparisons
	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*

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

Pré-enregistrement pour le projet “Modulation of proactive inhibitory control by the introduction of monetary rewards”

Garance Meyer, Guillaume Sescousse, Philippe Boulinguez - Déposé sur le site web Open Science Framework le 24/10/2021 (https://osf.io/mpxbj/)

Embargoed pre-registration for the project:

"MODULATION OF PROACTIVE INHIBITORY CONTROL BY THE INTRODUCTION OF MONETARY REWARDS"

https://osf.io/mpxbj/
Registered on 10/24/2021 - Embargoed until 10/22/2025.

CONTRIBUTORS

Garance Meyer, Guillaume Sescousse, and Philippe Boulinguez

DESCRIPTION

Impulsivity is an important feature of a range of psychiatric diseases. A large body of work has ascertained its multifaceted nature (Dalley and Robbins, 2017; Evenden, 1999). Yet, deficits of cognitive control, and in particular of inhibitory control, constitute one of the core dimensions of impulsivity (Bari and Robbins, 2013; Heatherton and Wagner, 2011). Recently, our understanding of these mechanisms has been broadened by the demonstration of specific motivational influences on cognitive control (Botvinick and Braver, 2015; Braver et al., 2014; Yee and Braver, 2018). In other words, it is now clear that control is motivated. This offers a new perspective on impulsivity. Indeed, impulsive behaviors that seemingly reflect deficits of inhibitory control may rather reflect a reduced motivation to exert control (Cools et al., 2019). Thus, furthering our understanding of the interactions between motivation and inhibitory control may open new avenues in impulsivity research.

Motivation can be easily manipulated by introducing monetary rewards into response inhibition paradigms such as the Go/NoGo and the Stop Signal tasks. Previous work has demonstrated that the exact distribution of the rewards largely influences the results. Indeed, rewarding fast responses to the Go stimuli tends to reduce inhibitory performance, while rewarding the successful NoGo or Stop trials improves it (Boehler et al., 2012, 2014; Greenhouse and Wessel, 2013; Leotti and Wager, 2010; Padmala and Pessoa, 2010). Thus, it has been proposed that, in these tasks, subjects may engage in decision-making based on the values associated to the possible response styles (i.e., favoring fast responses to the Go, or favoring the avoidance of wrong responses to the NoGo/Stop stimuli) (Dixon and Christoff, 2012; Leotti and Wager, 2010; Shenoy and Yu, 2011). In other words, subjects make decisions about the optimal speed-accuracy trade-off, which would be implemented through proactive adjustments (Greenhouse and Wessel, 2013; Verbruggen and McLaren, 2018). However, the exact nature of these proactive adjustments remains unclear.

In this study, we will test the hypothesis that the speed-accuracy trade-off adaptation in a rewarded response inhibition task relies on modulations of proactive inhibitory control, a mechanism intended to lock movement initiation in order to avoid impulsive responding. We specifically aim to distinguish motivational influences on the applied levels of proactive inhibitory control vs. on the levels of motor preparation (i.e., invigoration of the motor response). To this aim, we will use high density EEG coupled to advanced signal processing methods to assess neural markers of motor preparation and proactive inhibitory control. The preregistration primarily concerns the behavioral data, but the hypotheses and planned analyses regarding the EEG data are also briefly described.

HYPOTHESES

(1) In a rewarded Go/NoGo task, if subjects adapt their speed-accuracy trade-offs based on the motivational context, we will observe shorter reaction times (RTs) and higher commission error rate when the reward distribution favors fast responses to the Go (at the expense of accuracy to the NoGo), i.e., when there is higher motivation for fast Go responses than for accurate response inhibition to the NoGo.

(2) If this adaptation relies on the adaptation of proactive inhibitory control, we will also observe less powerful pre-stimulus alpha and/or beta oscillatory activities in medial sources when the reward distribution favors fast responses to the Go (at the expense of accuracy to the NoGo), i.e., when there is higher motivation for fast Go responses than for accurate response inhibition to the NoGo. Indeed, pre-stimulus alpha and beta activities in medial sources such as the medial prefrontal cortex, the SMA and the precuneus are believed to be markers of proactive inhibitory control. Conversely, because no inhibitory control is required in the control condition (in which only Go trials are presented), we expect a task condition * motivational context interaction effect.

(3) In contrast, if this adaptation relies on the enhancement of motor activity (i.e., invigoration of motor preparation), we will also observe more powerful pre- and post-stimulus activities in motor sources (primary motor and premotor cortex) when the reward distribution favors fast responses to the Go (at the expense of accuracy to the NoGo), i.e., when there is higher motivation for fast Go responses than for accurate response inhibition to the NoGo. More precisely, we expect a main effect of motivational context. Note that hypotheses (2) and (3) are not mutually exclusive. The main predictions are summarized in the figure below. The task conditions are described in more detail in the Study design section.

DESIGN PLAN

Study type

Experiment - A researcher randomly assigns treatments to study subjects, this includes field or lab experiments. This is also known as an intervention experiment and includes randomized controlled trials.

Blinding

No blinding is involved in this study.

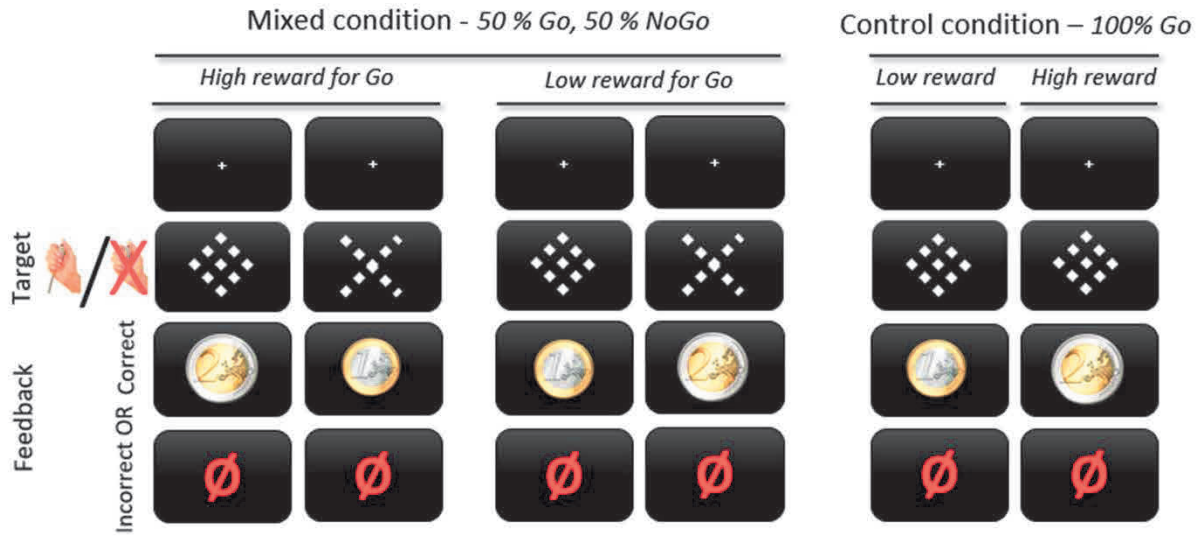
Study design

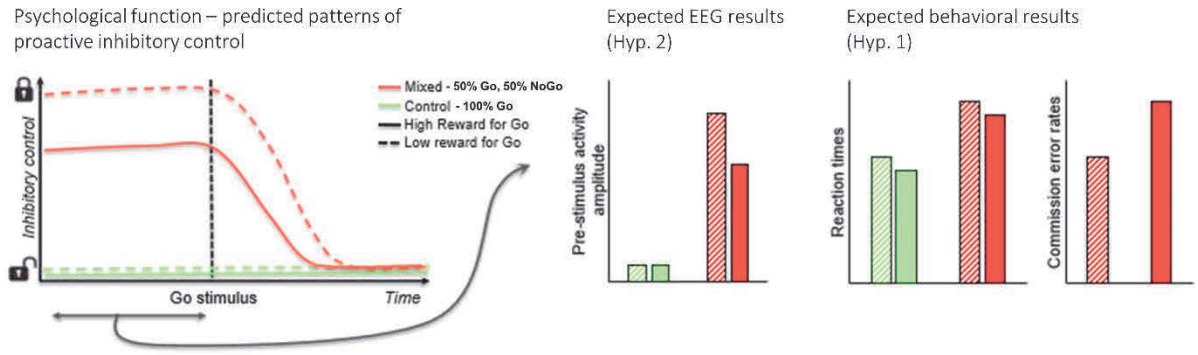
The study design involves 2 task conditions (control = 100% Go vs. mixed = 50% Go, 50% NoGo) x 2 reward contexts (High reward for Go vs. Low reward for Go). This is a repeated measures design, with both factors being within-subjects factors. Participants will complete a behavioral task based on a variant of the Go/NoGo task, with the addition of monetary rewards. In this task, participants will be required to respond as fast as possible to the Go stimulus (a white diamond), and to refrain from responding to the NoGo stimulus (a white cross). Control condition means that only Go stimuli are presented within a block, while equiprobable Go and NoGo are presented within the same block for the mixed condition. Monetary gains are obtained in Go trials if reaction time is fast enough, as well as in correct NoGo trials (i.e., successful inhibition of the response). The threshold for “fast enough” responses to the Go will be determined individually and separately for the mixed and control

conditions during a training phase. In order to manipulate the motivational context, we will use two levels of rewards (1€ vs. 2€), leading to a total of four conditions corresponding to the 2 x 2 design (see the figure below):

- Control/High reward for Go condition: fast responses to the Go lead to a gain of 2€;
- Control/Low reward for Go condition: fast responses to the Go lead to a gain of 1€;
- Mixed/High reward for Go condition: fast responses to the Go lead to a gain of 2€, while correct NoGo trials lead to a gain of 1€;
- Mixed/Low reward for Go condition: fast responses to the Go lead to a gain of 1€, while correct NoGo trials lead to a gain of 2€;

Participants will complete 2 blocks of each condition in a pseudo-randomized order, leading to a total of 60 trials per trial type.





Randomization

No randomization is involved in this study.

SAMPLING PLAN

Existing Data

Registration prior to analysis of the data

Explanation of existing data

The pre-registration was originally prepared before collecting the data, and was fine-tuned during data collection (but completely independently of data collection). Thus, at the time of registration, data has been fully collected by G.M. but has not been analyzed or examined in any way.

Data collection procedures

The target population is young healthy subjects. Participants will be recruited through announcements via the laboratory mailing list, social networks and word-of-mouth. Participants will be paid 25€ for their participation. They will also obtain a performance-dependent bonus up to an amount of 90€ (expected average amount: 72€), corresponding to the gain of a randomly selected task block among the 4 best blocks of the participant. Note that participants will be told that the random selection is performed among all the blocks, in order to keep them motivated for all the blocks. The performance-dependent bonus is essential because hypothetical money can have different effects than real money (e.g., Xu et al., 2018).

Inclusion criteria will be: Age between 18 and 55 years old, male or female, absence of known psychiatric or neurological disease, with normal or corrected to normal vision, without a priori knowledge about the goal of the study.

Exclusion criteria will be: Substance abuse or addiction, excepted tobacco.

Sample size

We will attempt to recruit 30 participants.

Sample size rationale

The sample size was initially determined based on methodological knowledge regarding EEG analyses. A sensitivity analysis was then performed. Indeed, to the best of our knowledge, no EEG study used a similar behavioral task. Thus, effect sizes for EEG analyses could not be estimated. However, a sample size of N=30 appears reasonable based on a survey of the sample sizes in the EEG literature as well as on methodological work evaluating the sample size required for optimal group blind source separation (Lio and Boulinguez, 2013, 2018).

According to a sensitivity analysis performed with G*Power, this sample size is also sufficient to detect the main expected behavioral effects (i.e., effect of motivational context and task condition on RT). Indeed, considering the use of a repeated measure ANOVA for analysis of RT, N=30, alpha=0.05, 1-beta=0.95, and a correlation between repeated measures of 0.8 (based on pilot data obtained with a similar task), we can detect effect sizes superior to f=0.22 for main effects of motivational context or task condition. This correspond to a small to medium effect size, while we rather expect large effect sizes:

- The effect size of task condition on RT was estimated at f=5.6 based on pilot data (i.e., very large effect).
- In Greenhouse and Wessel (2013), who used similar manipulation of motivational context, the effect size of motivational context on RT was dz=1.5 (i.e., very large effect).

Stopping rule

Data collection will end after reaching the desired sample size. Data will not be analyzed or examined until all the observations have been collected.

VARIABLES

Manipulated variables

The manipulated variables are motivational context (high vs. low reward for Go) and task condition (control vs. mixed). Please refer to the "study design" section above for details.

Measured variables

Principle of EEG analyses: We will use electroencephalography and advanced signal processing methods to reveal markers of the neurocognitive processes of interest (i.e., proactive inhibitory control and motor preparation) directly at the source level. Briefly, preprocessing will involve downsampling, re-referencing the data to average reference, filtering (1-48Hz), rejection of corrupted epochs and individual ICA for rejection of artifactual components (eye movements, ballistocardiac noise…). We will perform group blind source separation to reveal the cortical network involved in the task (Lio and Boulinguez, 2013, 2018). The selection of the medial and motor sources of interest follows from previous work from our group (e.g., Albares et al., 2014; Meyer et al., 2020; Spay et al., 2018).

Measured variables to be used in confirmatory analyses:

- For Hypothesis 1: Mean Go reaction time (in ms) for each of the four conditions, after exclusion of RTs <150ms (that most likely correspond to responses initiated before the actual target onset); Commission error rate for the mixed conditions, Nresponse to NoGo / NNoGo.
- For Hypothesis 2: Amplitude of pre-stimulus alpha and beta activities in medial sources.
- For Hypothesis 3: Amplitude of pre- and post-stimulus activities in motor sources (primary motor and premotor cortex).

Other measured variables:

- Go hit rate for each of the four conditions, calculated as (NFast enough Go responses / NGo);
- Amount of money won for each condition;
- Reward responsiveness as assessed by the BIS/BAS scale (Caci et al., 2007).

Indices

Mean reaction times and hit or commission rates will be computed as explained above. No behavioral variables will be combined into indices for confirmatory analyses.

ANALYSIS PLAN

Statistical models

Reaction times and EEG variables will be analyzed using repeated measures ANOVAs with factors Task condition (two levels: Control vs Mixed, within subject) and Motivational context (two levels: High vs Low reward for Go, within subject) Commission error rates will be analyzed using a Wilcoxon signed-rank test (Mixed/High reward for Go condition vs Mixed/Low reward for Go condition, one-tailed).

Transformations

We do not plan to use transformations on the behavioral data, unless the distribution of reaction times largely departs from normality.

Inference criteria

We will regard the standard $p<0.05$ threshold as the criteria for statistically significant results.

Data exclusion

We may exclude participants based on extreme behavior during the task. In particular, we may exclude participants based on extremely high commission error rate, omission error rate or false alarm (i.e., response occurring before the stimulus presentation) rate. However, in the absence of previous experience with this task, we cannot provide precise thresholds for such cases. EEG data from individual participants may be excluded in case of acquisition issues or unusual artifacts. Moreover, the EEG preprocessing pipeline will include rejection of noisy epochs.

Missing data

Data from individual participants will be excluded if mean reaction times, hit rates or commission rates are not available for each of the conditions, i.e. if the intended number of trials is not completed.

Exploratory analysis

We plan to explore the relationships between reward sensitivity as evaluated based on the BIS/BAS scale and the strength of motivational influences as assessed based on the behavior and on the EEG activities corresponding to proactive inhibitory control and motor preparation. We plan to perform exploratory analyses of the EEG data (i.e., other sources and frequency bands) in order to characterize the complete cortical network involved in the task.

AFFILIATIONS

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