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Évaluation des modèles psychologiques du contrôle inhibiteur au moyen de l'IRM fonctionnelle : Plausibilité physiologique, bases neurales et applications cliniques dans la maladie de parkinson

Marion Criaud

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UNIVERSITY OF TORONTO

**Evaluation des modèles psychologiques du contrôle inhibiteur au
moyen de l'IRM fonctionnelle:**

Plausibilité physiologique, bases neurales et applications cliniques dans la
maladie de parkinson

Thèse de doctorat – Spécialité Neurosciences

Présentée par **Marion CRIAUD**

le 18/12/2015

Sous la direction de

Pr. Philippe BOULINGUEZ & Pr. Antonio

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Résumé

La capacité à réprimer une action non désirée ou inopportune est au cœur du contrôle cognitif. Mais son étude est ardue parce qu'elle s'accommode mal des méthodes psychophysiologiques classiques qui cherchent à mettre en correspondance des marqueurs comportementaux et des modulations d'activité physiologique. En effet, lorsque la fonction d'inhibition est efficacement implémentée, tout comportement observable est supprimé! La conséquence de cette difficulté particulière est que les modèles psychologiques existants sont fragiles, et que les méthodes de neuroimagerie cherchant à identifier l'anatomie fonctionnelle de l'inhibition de réponse sur la base de ces modèles rapportent des résultats discordants.

La *première partie* de ce travail a consisté à utiliser une méthode méta-analytique (ALE) pour identifier les activations réactives et sélectives (l'inhibition est censée être déclenchée spécifiquement par le stimulus auquel il faut éviter de répondre) reproductibles entre les études disponibles. Nous avons en outre contrôlé l'effet de la difficulté variable des tâches de Go/NoGo. Les résultats montrent clairement que les travaux classiques confondent activations liées aux mécanismes d'inhibition et activations liées aux fonctions cognitives corolaires mises en jeu dans les tâches expérimentales.

Ce constat nous a amené à proposer dans la *seconde partie* un modèle alternatif d'inhibition, conçu comme un verrouillage anticipé et non-sélectif des mécanismes de déclenchement de l'action (contrôle proactif). Ce modèle a d'abord été testé au moyen de deux expériences psychophysiques. Les résultats, compatibles avec le modèle, suggèrent que l'inhibition proactive de l'initiation de l'action est le mode de fonctionnement par défaut du système exécutif. Le modèle proactif a ensuite été éprouvé en même temps que ses deux concurrents (réactif sélectif et réactif non-sélectif) à l'aide d'une étude IRMf événementielle. Ici, nous avons plus précisément testé les prédictions respectives de ces différents modèles concernant les réponses hémodynamiques censées être générées par chaque signal. Les résultats confirment que le modèle standard réactif sélectif est peu plausible, au contraire de ses deux concurrents plus récents et moins populaires.

La *troisième partie* de ce travail doctoral est consacrée aux conséquences cliniques de ce renversement théorique. En effet, alors que le modèle standard assume que l'impulsivité est la seule conséquence possible de troubles de l'inhibition, le modèle proactif prédit qu'un dysfonctionnement peut également se manifester par des difficultés à initier un mouvement. C'est ce que nous démontrons, en faisant le lien entre hyperactivation du réseau de contrôle proactif (estimée par IRMf) et lenteur à l'initiation du mouvement chez le patient parkinsonien akinétique.

Mots clés : Contrôle inhibiteur, fonctions exécutives, fMRI, méta-analyses, temps de réaction, maladie de Parkinson, akinésie, impulsivité

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Curriculum Vitae

Publications (in order of authorship)

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Criaud M, Wardak C, Ben Hamed S, Ballanger B, Boulinguez P. (2012). Proactive inhibitory control of response as the default state of executive control. *Frontiers in Psychology*, 3:59.

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Liste des abréviations

ACC: anterior cingulate cortex

BOLD: blood oxygenation level-dependant

Cn: caudate nucleus

DA: dopamine

DMS: Diagnostic and Statistical Manual of Mental Health Disorders

DLPFC: dorsolateral prefrontal cortex

EEG: électroencéphalographie

GB: ganglions de la base

GPI/GPe: globus pallidus interne/externe

ICD: impulse control disorder

IFG: inferior frontal gyrus

IPL: inferior parietal lobule

IRMf: imagerie par résonance magnétique fonctionnelle

MEG: magnétoencéphalographie

NA: noradrénaline

NAcc : noyau accumbens

PD: Parkinson's disease

Put: putamen

ROI: region of interest

SMA: supplementary motor area

SMC: supplementary motor cortex

S-R: stimulus-réponse

SSD: stop-signal delay

SSRT: Stop Signal Reaction Time

STN: sub-thalamic nucleus

TEP: tomographie par émission de positons

TMS: transcranial magnetic stimulation

TR: temps de réaction

Chapitre 1

L'inhibition au cœur du contrôle exécutif

Le contrôle du comportement humain, entendu au sens de la capacité individuelle à planifier et exécuter ses propres actions, est au centre des préoccupations de la Psychologie Cognitive. On trouve une variété de terminologies et de modèles de contrôle, qui se distinguent essentiellement par l'étendue assumée de leur champ d'application et de leur capacité de généralisation. Nous ne proposons pas ici de passer en revue de façon exhaustive les travaux de la Psychologie Cognitive abordant cette notion de contrôle, nous nous contentons juste dans ces premières lignes d'évoquer les acceptions les plus proches de notre sujet. L'objectif est à la fois de mieux le circonscrire et d'illustrer la difficulté de synthèse qui émane de cet éclatement lexical conceptuel.

1.1 Notion de Contrôle(s)

1.1.1 Le contrôle de l'action

Le contrôle de l'action (ou encore contrôle moteur ou sensorimoteur) peut être défini comme la fonction qui regroupe l'ensemble des processus qui concourent à la planification, l'exécution et la régulation de l'action (e.g., Desmurget and Grafton, 2000 ; Hommel et al., 2001 ; Hommel, 2009 ; Gaveau et al., 2014 ; Nattkemper et al., 2010 ; Prablanc et al., 2003 ; Turner et Desmurget, 2010). Le développement de ce champ théorique des sciences cognitives doit beaucoup au Pr Jeannerod, fondateur de l'institut éponyme au sein duquel ce travail de thèse a été mené (voir pour revue Gaveau et al., 2014 ; Jeannerod, 1988, 1990). Les mécanismes explicités dans les travaux se référant à cette acception du contrôle se réfèrent aux opérations basiques permettant la transformation d'un signal sensoriel en commandes motrices. Un aspect important et consensuel

des différents modèles recensés est que ces mécanismes ne sont pas uniquement sensorimoteurs, mais font appel à des fonctions éminemment cognitives, c'est à dire bouclées sur les mémoires du système. En effet, les opérations élémentaires de transformation de coordonnées entre les différents systèmes de référence utilisés dans les codages sensorimoteurs, aussi bien que les mécanismes d'élaboration de la commande musculaire, nécessitent l'utilisation de multiples représentations stockées en mémoire. Celles-ci concernent évidemment les propriétés des objets, de l'environnement ou du système musculo-squelettique, stockées dans les modèles internes du système. Mais elles concernent également la représentation du but de l'action et des attentes perceptives et autres prédictions des conséquences de l'action en cours d'élaboration (Figure 1).

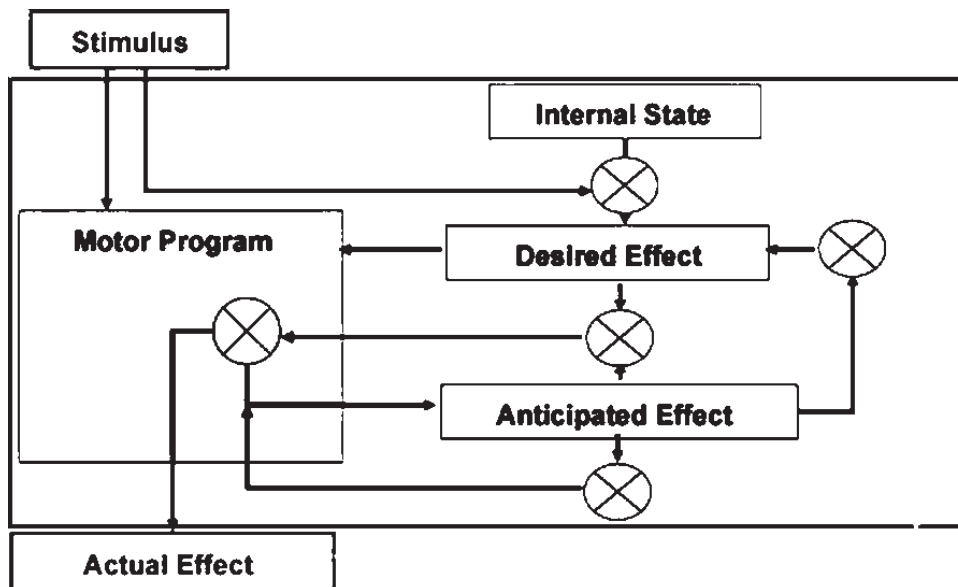


Figure 1 : Exemple de modèle de contrôle de l'action (Ziessler et al., 2004) illustrant la contribution des représentations liées à l'intention et aux attentes perceptives. On notera également l'implication des états internes et des processus d'anticipation des effets de l'action dans le contrôle des sorties motrices, qui mettent en exergue le fait que le contrôle sensorimoteur ne peut reposer que sur la cascade d'événements déclenchés par une stimulation.

Néanmoins, une critique de ces modèles est qu'ils sous-estiment ou ignorent une partie des représentations cognitives, et donc des mécanismes de contrôle associés, qui concourent à la génération d'une action (Hommel et al., 2001). En particulier, selon la théorie du codage des événements de Hommel et collaborateurs, les représentations qui sous-tendent la perception et l'action ne sont pas codées séparément mais plutôt au sein d'un média commun. Ceci implique que, plutôt que d'être des entités séparées, le codage des stimuli et des réponses ne sont pas de nature différente et se réfèrent à « des événements pour une tâche particulière et dans un contexte particulier » (Hommel et al., 2001, p.849). Ce constat invite à élargir le cadre théorique à des domaines moins centrés sur les processus sensorimoteurs élémentaires.

1.1.2 Le contrôle exécutif

Le contrôle exécutif se réfère à l'ensemble des processus qui contrôlent et régulent les autres processus de traitement de l'information (Baddeley et DellaSala, 1996 ; Garavan et al., 2002 ; Heyder et al., 2004). Une partie des mécanismes évoqués dans les modèles de contrôle de l'action répond à cette définition. Mais les fonctions exécutives ne se limitent pas dans leur application au domaine strictement sensorimoteur. Le contrôle exécutif s'applique à tous les types de traitement, depuis l'organisation et le rappel en mémoire et l'attention jusqu'aux mécanismes de motivation et de prise de décision, en passant par la régulation des émotions (Anderson et al., 2001 ; Hofmann et al., 2012; Kiyonaga et al., 2012 ; Logue et Gould, 2014 ; Miyake et al. 2000; Nigg, 2000 ; Tomita et al., 1999). La question qui se pose ici n'est pas de vérifier que les mécanismes décrits dans les approches conceptuelles de type « bottom-up » (les modèles du contrôle moteur partent des mécanismes élémentaires et remontent à certaines fonctions exécutives) correspondent bien à une partie des mécanismes décrits séparément dans

les modèles de type « top-down » (on part de modèles exécutifs et on éprouve leur caractère généralisable). La question est plutôt de savoir quels mécanismes décrits dans les modèles exécutifs mais pas dans les modèles de contrôle moteur sont susceptibles de rendre compte de la performance sensorimotrice. En d'autres termes, il est très probable que la liste des mécanismes exécutifs implicitement évoqués dans les modèles de contrôle moteur (modèles internes, attentes perceptives, prédictions...) ne soit pas exhaustive. Rapprocher ces deux champs permettrait : 1) d'enrichir les modèles du contrôle sensorimoteur trop souvent perçus comme un assemblage de processus élémentaires, et 2) de tester et amender les modèles exécutifs en utilisant des tâches sensorimotrices simples qui permettent de limiter les confusions potentielles entre fonctions cognitives complexes.

Il est classiquement admis que le contrôle exécutif repose sur trois fonctions de base : 1) les opérations de mémoire de travail comme le maintien et la mise à jour de l'information pertinente (*updating*), 2) la permutation de tâche ou de configuration mentale (*shifting*) (Hofmann et al., 2012 ; Miyake et al., 2000), et 3) l'inhibition des réponses impulsives (*inhibition*). L'*updating* correspond à la capacité de conservation de l'information dans un état actif, rapidement retrouvable, et protégé de la distraction. Le *shifting* réfère à la capacité à passer d'une configuration exécutive (prédisposition de règles d'actions et modes opératoires) à une autre. L'*inhibition* de réponse se rapporte à la capacité à inhiber délibérément une réponse dominante, automatique ou prépotente. Ces trois fonctions sont fonctionnellement distinctes et séparables expérimentalement, mais elles sont interdépendantes (Miyake et al., 2000). Le *shifting* dépend par exemple étroitement de la mémoire de travail. De même, le *shifting* nécessite l'*inhibition* des actions évoquées par la configuration exécutive qui doit être abandonnée. Cette interdépendance complique substantiellement l'étude isolée de chacune de ces fonctions. Néanmoins, comme le montrent les résultats de l'analyse factorielle confirmatoire appliquée à un ensemble de tâches

exécutives classiques de Miyake et collaborateurs, on peut affirmer que l'inhibition joue un rôle global et central dans le contrôle exécutif, et pas uniquement dans des tâches qui requièrent explicitement l'inhibition d'une réponse (Figure 2).

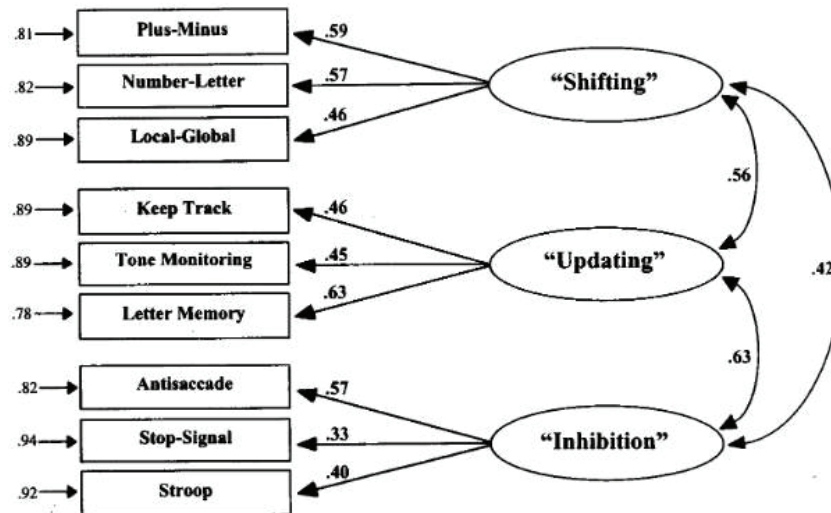


FIG. 2. The estimated three-factor model. Single-headed arrows have standardized factor loadings next to them. The loadings, all significant at the .05 level, are equivalent to standardized regression coefficients (beta weights) estimated with maximum likelihood estimation. The numbers at the ends of the smaller arrows are error terms. Squaring these terms gives an estimate of the variance for each task that is not accounted for by the latent construct. The curved, double-headed arrows have correlation coefficients next to them and indicate significant correlations between the latent variables.

Figure 2 : Unité et diversité des fonctions exécutives : Le modèle à trois facteurs (*Shifting*, *Updating*, *Inhibition*) de Miyake et collaborateurs, testé au moyen d'une analyse factorielle confirmatoire appliquée à un ensemble de tâches exécutives classiques (Local-Global, Letter Memory, Stroop...). Les trois facteurs sont à la fois séparables car plus fortement associés à des tâches qui sollicitent les fonctions inférées, et interdépendants car substantiellement corrélés. En d'autres termes, l'inhibition est susceptible de jouer un rôle clef même dans des tâches qui ne sont pas de nature exécutive. Tiré de Miyake et al. (2000).

1.1.3 Le contrôle cognitif

Le contrôle cognitif présente un spectre encore plus large de domaines d'application dans la mesure où il se réfère aux processus qui permettent l'adaptation en temps réel du traitement de l'information, et in fine du comportement, sur la base des buts internes et actualisés du sujet (Botvinick et al., 2001 ; Koechlin et al., 2003). Les modèles de contrôle cognitif se distinguent du *Shifting* des modèles des fonctions exécutives dans le sens où ils intègrent des opérations liées à

la représentation du contexte, que ce soit le contexte immédiat ou le contexte d'une information passée. Le contrôle cognitif est associé à un large ensemble de processus et n'est pas restreint à un domaine cognitif particulier. Le modèle hiérarchique et en cascade de Koechlin (2003) est particulièrement intéressant ici car il considère un niveau hiérarchiquement inférieur de contrôle dit « sensoriel », mais qui regroupe en fait sans les décrire les opérations de contrôle de l'action (ou contrôle sensorimoteur) entrevues en début de chapitre. Le modèle assume qu'un niveau de contrôle de l'information contextuelle hiérarchiquement supérieur guide la sélection des représentations sensorimotrices (association stimulus-réponse S-R) élaborées au niveau inférieur. Cette modulation est fonction des signaux qui accompagnent les stimuli sensoriels, et permet l'adaptation des réponses motrices au contexte immédiat. Un dernier niveau, nommé contrôle de l'information épisodique rend compte de la possibilité de modulation des traitements S-R sur la base d'informations non contemporaines de la stimulation.

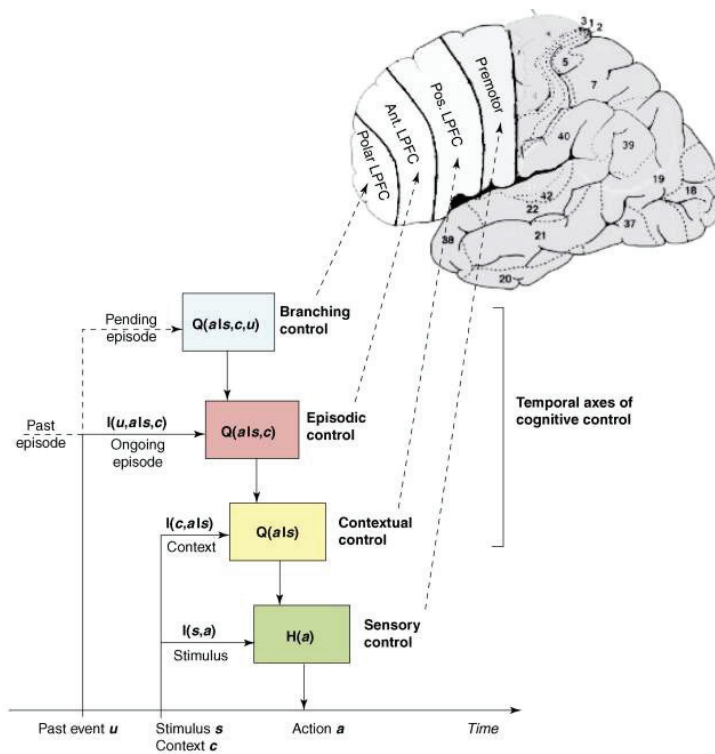


Figure 3 : L'architecture du contrôle cognitif dans le cortex préfrontal humain. Dans cette évolution du modèle de Koechlin (2003), une dimension supplémentaire est intégrée (Branching Control), qui étend la temporalité du modèle à l'influence d'événements plus antérieurs que ceux considérés dans la seule dimension épisodique. Tiré de Koechlin et Summerfield (2007).

Les modèles du contrôle cognitif s'appuient sur le fait que l'inhibition est un processus intrinsèque des mécanismes de prise de décision ou de sélection de réponse (e.g., Koechlin et al., 2003 ; Siegel et al., 2011). Ils assument que leur modélisation explicite n'est ainsi pas nécessaire (Figure 3). Les travaux sur le concept de contrôle cognitif revêtent pourtant une importance cruciale dans notre problématique dans le sens où ils permettent d'affirmer que **les mécanismes de contrôle ne peuvent pas être constitués uniquement d'une cascade d'événements déclenchés par les stimuli.**

1.2 L'inhibition de réponse

Réfréner nos actions, pensées et émotions non désirées ou inappropriées est au centre de notre vie quotidienne (Munakata et al., 2011). Sans cette faculté, l'Homme s'éloignerait de sa condition en étant soumis à ses impulsions, ses habitudes, ses automatismes (Bari et Robbins, 2013 ; Diamond, 2013; Logan et Cowan, 1984). Plus simplement, il se verrait très limité dans ses capacités d'adaptation immédiate à son environnement. Comment retenir le mouvement amical de la main initié en direction du chien qui, soudain, montre les crocs ? Comment résister à un troisième verre de Côte-rôtie 2005 alors que l'on doit reprendre la route ? Plus généralement, comment résister à la distraction ? à la gourmandise, la luxure, la colère, l'envie... ? L'importance de la fonction d'inhibition de réponse a suscité un nombre considérable de travaux depuis Thomas d'Aquin. Une recherche sur le Web of Science™ à la date de rédaction de ce manuscrit croisant les termes (response inhibition) et (control), centrée sur les domaines des neurosciences/neurologie, de la psychologie, de la physiologie et de la pharmacologie, et restreinte aux seuls travaux des dix dernières années rapporte... 44024 documents ! Nous ne proposons pas ici un rapport exhaustif de ces travaux, mais une analyse critique des théories et méthodes dominantes inspirée de l'étude des modèles de contrôle proposée en préambule.

Les modèles intégrés du contrôle exécutif montrent que l'inhibition de réponse est au cœur du(des) système(s) de contrôle, obligeant à envisager des interactions fortes avec d'autres formes de modulation du traitement (attention, mémoire, flexibilité...). Les modèles du contrôle cognitif montrent qu'il existe une dimension temporelle et hiérarchique, obligeant à prendre en considération l'implication de modulations des capacités de traitement avant même que le sujet ne soit stimulé. Pourtant, peu de travaux sur l'inhibition de réponse se sont inspirés de ces avancées des modélisations «macroscopiques» des systèmes de contrôle. La tendance inverse est observée. Beaucoup de travaux se sont plutôt attelés ces deux dernières décennies à «microscopiser» leurs investigations, en cherchant plus particulièrement à identifier les bases neurales des processus d'inhibition en s'inscrivant plutôt dans les domaines du contrôle sensorimoteur et du contrôle exécutif. Dans ce type de démarche, le modèle dominant d'inhibition de réponse n'est généralement pas questionné, mais considéré comme un postulat, voire un axiome...

1.2.1 Le modèle standard (idée directrice)

Les modèles dominants, quelles que soient leurs nuances, partent du même principe non démontré mais semblant intuitivement non contestable que l'inhibition de réponse repose sur une cascade de processus qui ne peuvent qu'être déclenchés par le stimulus auquel il convient de ne pas répondre (les crocs du chien ou la conscience subitement réveillée par la stimulation dans les exemples précédents). Comme tout mauvais postulat, il se trouve souvent renforcé par les résultats expérimentaux eux-mêmes. Les études d'imagerie cérébrale ont à ce sujet une tendance parfois forte à la tautologie en listant les activations induites par le stimulus d'intérêt, et en utilisant cette observation comme une preuve de la mise en jeu des mécanismes inférés (i.e., en démontrant a posteriori le postulat !).

Classiquement, l'inhibition de réponse est assimilée à un processus phasique et sélectif. Il est phasique dans le sens où il est bref, possède une phase et est généré par des stimuli (on parle également de processus réactif). Il est sélectif dans le sens où il est généré par un stimulus spécifique (celui auquel il convient d'éviter de répondre), mais pas par les autres. Le modèle (toujours) le plus populaire est le Race model proposé par Logan et Cowan il y a une trentaine d'années (1984). Les processus d'exécution et d'inhibition de l'action, tous deux phasiques, entrent en compétition pour l'atteinte d'un seuil d'activation (Figure 4). Si les processus d'exécution atteignent le seuil avant les processus d'inhibition, le mouvement est déclenché. Si les activations inhibitrices parviennent à atténuer suffisamment les activations excitatrices, le seuil n'est pas atteint et le mouvement n'est pas déclenché. C'est ce qui se passe par exemple lorsque le feu de circulation passe au vert, mais que la voiture qui s'apprête à bondir doit s'en empêcher parce qu'un piéton tente de traverser la route au dernier moment.

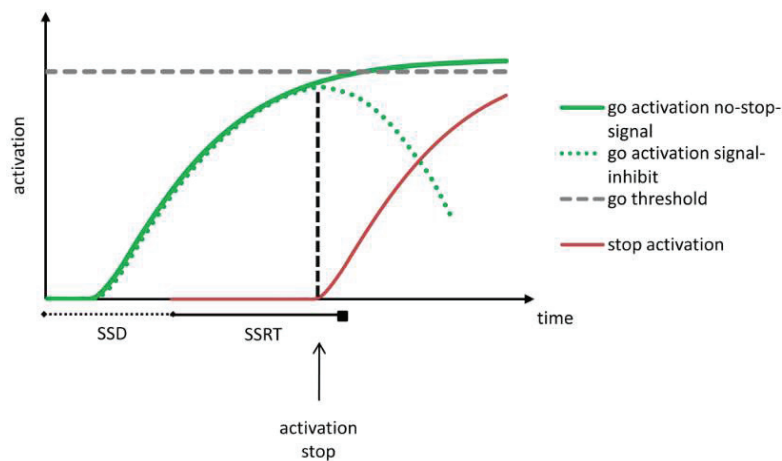


Figure 4 : Race Model. Ici, l'activation excitatrice est provoqué par la présentation d'un signal auquel le sujet doit répondre (go, vert), et l'activation inhibitrice est déclenchée par la présentation quelques dizaines ou centaines de ms plus tard d'un second signal requérant la suppression de la réponse motrice en cours d'élaboration (stop, rouge). Les mêmes mécanismes sont supposés être à l'œuvre lorsqu'un signal auquel il convient de ne pas répondre (nogo) est présenté isolément, à la différence que les activations antagonistes sont dans ce cas co-occurentes puisque déclenchées par le même stimulus. En effet, lorsque le sujet est conditionné à répondre, toute stimulation génère des activations motrices automatiques qu'il convient de supprimer lorsqu'il ne s'agit pas du stimulus-cible. *Illustration tirée de Verbruggen et Logan, 2008.*

Il existe des variantes de ce modèle général, qui s'appliquent essentiellement aux situations dans lesquelles le sujet doit faire un choix entre plusieurs réponses possibles. Ici la question n'est pas de supprimer l'activation d'une réponse qui requiert explicitement une inhibition (signaux stop ou nogo, voir Figure 4 et Figure 6). Il s'agit de supprimer les activations des réponses possibles mais non sélectionnées par les mécanismes décisionnels. Il peut s'agir d'une forme d'inhibition réactive, phasique et sélective conformément au modèle directeur, qui s'applique aux réponses activées automatiquement mais finalement non retenues par les processus de choix délibéré. Par exemple, si je peux attraper cette balle de la main droite ou de la main gauche, les deux réponses motrices sont automatiquement préparées dans le cortex moteur. Pour éviter un trouble majeur de coordination, une seule doit être sélectionnée (e.g., la gauche). Différentes raisons peuvent guider la sélection (e.g., choix de la main la plus habile, position des partenaires ou adversaires, etc...), ici n'est pas notre propos. La conséquence du choix de la réponse appropriée est la suppression de l'activité motrice de la réponse non sélectionnée (e.g., la droite). Choisir, c'est renoncer (Gide, 1897). Cette fonction d'inhibition est connue sous la terminologie de *dual-route model* (Ridderinkhof, 2002; van den Wildenberg et al., 2010) (Figure 5).

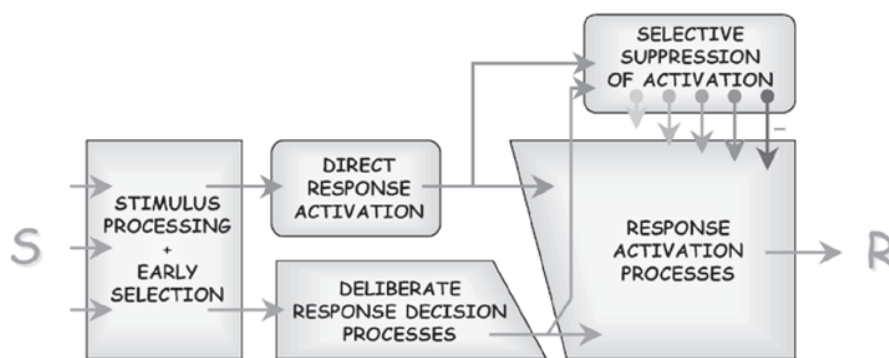


Figure 5 : Dual-route model. L'inhibition de l'activation automatique des réponses possibles mais non désirées est conçue comme un mécanisme réactif et hautement sélectif. Tiré de Ridderinkhof (2002).

Parmi les modèles les plus acceptés et les plus populaires, le plus décalé par rapport à la conception classique du *Race Model* est certainement le *Hold your Horses* de Michael Frank et collaborateurs (Frank, 2006, 2011; Franck et al., 2007 ; Wiecki et Frank, 2013). Ce modèle s'applique aux situations décisionnelles dites « gagnant-gagnant » dans lesquelles le sujet doit choisir une option parmi un ensemble d'options toutes gratifiantes (Que choisir en dessert: tartelette aux fraises? Fondant au chocolat? Mousse au citron?...). Il suggère que, dans ces situations, une inhibition globale est générée dans le but de supprimer toute réponse impulsive et de permettre au système de traitement de l'information de s'accorder plus de temps pour statuer sur la décision. L'inhibition est ici conçue comme *réactive*, mais elle est *non-sélective* dans la mesure où elle s'applique à toutes les réponses possibles (Figure 6). Cette conception se rapproche du modèle de contrôle de l'impulsion pour lequel l'inhibition s'applique, certes, à la réponse sélectionnée, mais est destinée à suspendre l'exécution effective du mouvement pour prévenir toute initiation de réponse prématurée (Duque et Ivry, 2009; Duque et al., 2010, 2012).

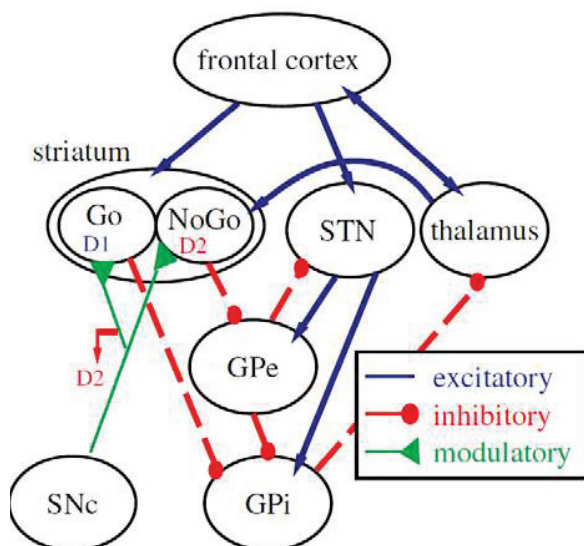


Figure 6 : The *Hold your Horses* model. L'inhibition globale de l'activation de toute réponse peut être générée en situation de choix complexe (opéré par le cortex frontal). Le signal d'inhibition (*global nogo*) est relayé par le noyau sous-thalamique qui, via l'activation du pallidum interne (GPi), atténue l'activité du thalamus et par voie de conséquence du cortex moteur. L'inhibition est conçue ici comme un mécanisme réactif mais non-sélectif. Tiré de Franck (2006).

1.2.2 Les méthodes comportementales d'investigation de l'inhibition de réponse

L'étude de l'inhibition de réponse peut se faire au moyen d'une variété de paradigmes comportementaux qui sont généralement considérés comme mettant à l'épreuve un mécanisme inhibiteur commun conforme au processus phasique que nous venons de présenter (voir Chambers et al., 2009 pour revue). Les paradigmes les plus couramment utilisés sont la tâche de Go/NoGo (Garavan et al., 1999; Picton et al., 2007), la tâche de stop (Logan, 1994; Verbruggen and Logan, 2009), et la tâche d'anti-saccades (Anderson et al., 2008 ; Butter et al., 1988; Hallet, 1978; Walker et al., 1998) (Figure 7).

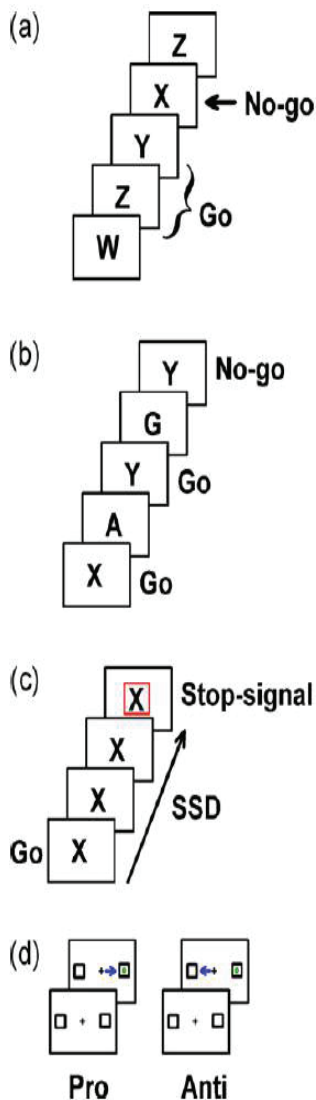


Figure 7 : Paradigmes classiques de mesure de l'inhibition de réponse. (a) Dans une tâche simple de Go/NoGo (e.g. Menon et al., 2001 ; Picton et al., 2007), les participants doivent apporter une réponse rapide à l'apparition de lettres cibles (e.g. W, Y, ou Z), mais inhiber la réponse quand un stimulus nogo est présenté (X). La performance est estimée au moyen du pourcentage de réponse aux stimuli nogo. (b) Une variation classique du Go/NoGo intègre une charge de mémoire de travail (e.g. Garavan et al., 1999; Hester et al., 2004). Ici les participants ont pour consigne de répondre rapidement à l'une ou l'autre des cibles présentées au sein d'une multitude de lettres (e.g. X ou Y). Cependant, si la lettre est la même que la cible précédente (e.g. Y suivi d'un Y), alors elle devient un nogo, comme illustré si contre. (c) Dans la tâche de stop (Logan, 1994), les participants doivent identifier une cible rapidement (e.g. X ou O; ici la cible est un X). Dans une minorité d'essais, un signal stop apparaît, ici représenté par le carré rouge (Chambers et al., 2006, 2007), souvent présenté sous la forme d'un stimulus auditif. Le signal stop indique aux participants qu'ils doivent supprimer leur réponse. Dans les essais stop, la variable essentielle est le délai du signal stop (SSD) : le temps (en ms) entre l'apparition de la cible et l'apparition du signal stop. Plus le SSD augmente, plus la probabilité d'inhiber correctement l'action diminue. La performance est mesurée grâce au temps de réaction au signal stop (SSRT), qui est calculé en soustrayant le SSD pour lequel les participants inhibent correctement 50% des essais stop et le temps de réaction moyen des participants dans les essais Go. Cette estimation vient de l'hypothèse d'une compétition entre les processus Go et Stop (voir Verbruggen et Logan, 2009). Chez les sujets sains, le SSRT se trouve autour de 150-200ms. Le signal stop doit être présenté 150-200ms avant le temps de réaction moyen pour pouvoir supprimer leur réponse dans 50% des essais stop. (d) Dans une tâche d'anti-saccade, les participants doivent soit exécuter une pro-saccade en direction d'une cible, soit supprimer la saccade initiale et exécuter une anti-saccade dans la direction opposée. Que la cible nécessaire une pro- ou anti-saccade est fixe (Hodgson et al., 2007), mais cela peut aussi être rendu aléatoire en utilisant un indice, comme la couleur du fond (Chikazoe et al., 2007). Le marqueur principal de l'inhibition de réponse est l'augmentation relative de l'intervalle entre l'apparition des anti- et pro-saccades. *Tiré de Chambers et al. (2009).*

Ces paradigmes ont été érigés en standards pour tester les capacités d'inhibition de réponse, que ce soit pour comprendre les mécanismes élémentaires et leurs bases neurales chez le sujet sain, ou leurs dysfonctionnements dans de nombreuses pathologies développementales, neurologiques ou psychiatriques. **Il existe pourtant plusieurs problèmes potentiels avec ces méthodes.**

1.3 Les obstacles à l'étude de l'inhibition de réponse

1.3.1 De la difficulté d'identification des marqueurs comportementaux de la fonction

L'étude du contrôle inhibiteur est rendue difficile par un obstacle majeur qui est lié à la nature même de la fonction. En effet, quelle que soit l'approche cognitive en psychologie, en neurosciences ou en clinique, la démarche inférentielle repose en premier lieu sur l'observation et la caractérisation du comportement. Il est évidemment ardu d'obtenir des marqueurs comportementaux précis lorsque la fonction d'intérêt est précisément destinée à supprimer le comportement. Le seul marqueur évident est un marqueur de dysfonctionnement : le taux d'erreur (e.g., erreurs de commission: le sujet a répondu à un stimulus non-cible ; anticipations : le sujet a répondu avant l'instruction...). Il n'est pas utilisé qu'en clinique, mais sert également à catégoriser les essais en imagerie fonctionnelle dans le but d'appliquer des contrastes (essais réussis vs. essais ratés) mettant en évidence les différences d'activation associées à la réussite ou à l'échec dans la tâche. Evidemment, ces activations sont susceptibles d'indexer de très nombreux dysfonctionnements situés en amont ou en aval des mécanismes d'inhibition plutôt que les mécanismes d'inhibition eux-mêmes (e.g., une difficulté à identifier un stimulus nogo peut facilement être confondue avec une difficulté à supprimer la réponse automatique à ce stimulus).

La chronométrie mentale (l'exploration des caractéristiques temporelles des traitements sur la base de chaque essai individuel, permettant d'inférer la durée des processus cognitifs isolés dans le design expérimental : Donders, 1868; Posner, 1978), outil privilégié d'investigation dans ce domaine des sciences cognitives, est inexploitable dans de nombreux paradigmes d'inhibition de réponse, au moins en tant qu'indicateur direct des mécanismes d'inhibition. Seul le paradigme du *Stop Signal Reaction Time Task* (SSRT) le permet (Figure 7). Mais sa validité a été mise en cause. En effet, le protocole impose une procédure dynamique de manipulation du SSRT (Boehler et al., 2012) susceptible d'induire la mise en place de stratégies dans le but de d'ajuster le niveau de préparation de la réponse pour en faciliter sa suppression (Jahfari et al., 2012). La tâche d'antisaccades permet également de mesurer une différence de temps de réaction (TR) entre essais pro- et anti- (Figure 7), mais ce différentiel exprime probablement moins l'inhibition de la réponse automatique que la reprogrammation complète du mouvement dans la direction opposée. Cette difficulté ne représente pas qu'une limite aux études comportementales. Elle est également une sérieuse limite aux méthodes d'investigation de l'activité cérébrale. En effet, utiliser un régresseur psychophysique permettant de corrélérer les variations d'activation aux variations du comportement individuel sur une base inter-essais permet l'interprétation d'une grande part de la variance totale du signal, que ce soit en IRMf ou en MEG/EEG (Albares et al., 2015a; Carp et al., 2010 ; Chee et al., 2008 ; Domagalik et al., 2014 ; Friston et al., 1997 ; Hilti et al., 2013 ; Knuth et al., 2006; Lehmann et al., 2006 ; Makeig, 2002 ; Michel and Murray, 2012 ; Ozyurt et Greenlee, 2011 ; Rousselet et al., 2011 ; Shah et al., 2004 ; Tark et Curtis, 2013 ; Yarkoni et al., 2009).

Enfin, il est possible de remettre en question l'idée que les différents paradigmes sondent les mêmes mécanismes de base de l'inhibition (e.g., Chambers et al., 2009; Garavan et al., 1999; Rubia et al., 2001). Par exemple, la nature de la tâche de Stop conditionne complètement le type

de mécanisme inhibiteur, qui peut difficilement être autre chose que réactif. En effet, le signal d'inhibition est consécutif au signal d'action, et il est clair qu'il s'agit là de l'inhibition « en ligne » d'une action en cours d'exécution. Lorsque le signal d'action et le signal d'inhibition sont uniques ou confondus, d'autres mécanismes sont théoriquement possibles, comme un verrouillage anticipé des mécanismes de déclenchement de l'action (Jaffard et al., 2007, 2008), une diminution généralisée de l'excitabilité corticomotrice (Cai et al., 2012 ; MacDonald et al., 2014), ou encore une modulation des seuils de décision (Forstmann et al., 2008, 2010). Sans remettre en question l'intervention de mécanismes réactifs et sélectifs dans des tâches comme le Go/NoGo, il est très probable que ces dernières intègrent une dimension supplémentaire par rapport à la tâche de Stop, dimension généralement retrouvée sous le terme de *Action Restraint*. C'est pour cette raison que **nous avons choisi de privilégier la tâche de Go/NoGo, plus susceptible de rendre compte de la possible diversité des mécanismes d'inhibition, dans notre démarche expérimentale.** Néanmoins, la variété et la complexité des protocoles (e.g., Figure 7a vs. Figure 7b) est également très susceptible de parasiter les mesures en induisant d'importantes confusions entre les différentes fonctions cognitives sollicitées dans une même tâche. Par exemple, une tâche de Go/NoGo qui sollicite des changements incessants de règles d'action requière considérablement les fonctions de mémoire de travail et de permutation de règles d'action (voir 1.1.2) en plus de l'inhibition de réponse. Une tâche de Go/NoGo qui sollicite des stimuli rares ou difficiles à identifier requière des ressources attentionnelles substantielles. **Cette variabilité des protocoles constitue une source d'ambiguïté considérable mais négligée.**

1.3.2 De la difficulté d'identification des marqueurs physiologiques de la fonction

Tout d'abord, si caractériser comportementalement le fonctionnement des mécanismes destinés à éviter de produire un comportement est difficile, inférer les bases neurales de ces mécanismes au moyen de ces mêmes paradigmes paraîtra pour le moins extrêmement ardu. En effet, si les méthodes comportementales sont incapables de révéler les véritables processus inhibiteurs, il y a peu de chances pour que les activations cérébrales associées correspondent à l'activité des processus inférés.

Ensuite, l'étude du contrôle inhibiteur est rendue difficile par un autre obstacle majeur, qui est lié aux limites propres des méthodes d'investigation de l'activité cérébrale. Chaque méthode offre une perspective spécifique sur les mécanismes physiologiques du contrôle inhibiteur, mais aucune ne permet de discerner sans ambiguïté les réseaux et la dynamique cérébrale des processus sous-jacents.

L'EEG et la MEG offrent une résolution temporelle idéale pour étudier la dynamique de processus opérant dans une fenêtre temporelle extrêmement courte (<500 ms). Les méthodes électromagnétiques permettent l'analyse de deux types de phénomènes aux temporalités distinctes. Le premier phénomène est phasique. Il correspond aux potentiels évoqués, c'est-à-dire à l'activité synchronisée d'une masse neuronale qui génère des variations de champ électrique sur le scalp dans une relation temporelle stricte avec l'événement d'intérêt. Le second phénomène peut être tonique. Il correspond à la mesure de la puissance du signal dans une bande de fréquence et de ses modulations induites par des événements précis. Il s'agit d'une mesure de synchronisations/désynchronisations liées à un événement. L'EEG et la MEG possèdent un atout supplémentaire. Les analyses spectrales offrent en effet un pouvoir de discrimination additionnel grâce aux liens qui unissent des fonctions précises à une activité dans une bande de fréquences isolée. Ces signatures spectrales permettent en particulier de distinguer des processus excitateurs

et inhibiteurs (Bertrand et al., 1994 ; Bertrand et Tallon-Baudry, 2000 ; Huster et al., 2013; Jensen et Mazaheri, 2010 ; Klimesh et al., 2007 ; Siegel et al., 2012 ; Tallon-Baudry et Bertrand, 1999). Cependant, la nature du signal enregistré en EEG doit également être questionnée. Premièrement parce que l'activité EEG résulte essentiellement de l'activité postsynaptique (dendritique), et qu'elle ne représente donc pas l'output neuronal (Whittington et al., 2000). Deuxièmement parce que l'activité enregistrée à la surface du scalp est la résultante du mélange complexe de l'activité d'une multitude de sources (Kropotov et Ponomarev, 2009; Kropotov et al., 2011; Makeig et al., 1996; Tang et al., 2010) qu'il est difficile de démêler avec précision (Lio et Boulinguez, 2013). Enfin, le prix à payer pour une résolution temporelle optimale est bien sûr la faible résolution spatiale de la méthode, illustrée par les difficultés de localisation des sources d'activité (Koles, 1998), notamment lorsque celles-ci sont sous-corticales. Ceci pose un problème majeur pour l'étude de l'inhibition de réponse, puisque celle-ci repose en bonne partie sur l'activité des ganglions de la base (Alexander et Crutcher, 1990 ; Aron et Poldrack, 2006 ; Frank et al., 2007 ; Mink, 1996 ; Nambu et al., 2002 ; Zandbelt et Vink, 2010).

Les études de neuroimagerie basées sur l'analyse du signal BOLD utilisent une mesure indirecte de l'activité neurale. Les variations du niveau d'oxygénation sanguine par rapport à une condition de contrôle ne peuvent en aucun cas renseigner sur la nature excitatrice ou inhibitrice de l'activité neuronale (Buzsaki et al., 2007; Logothetis, 2008). De plus, l'IRMf (et à plus forte raison la TEP qui ne permet pas de mener des analyses liées aux événements), ne possède pas la résolution temporelle idéale pour distinguer la dynamique d'activités (excitatrices et inhibitrices) contemporaines intervenant dans des fenêtres temporelles très courtes. Malgré ces limites conséquentes, l'IRMf possède un avantage de taille dans l'étude de l'inhibition de réponse : son excellente résolution spatiale permet une identification précise de toutes les régions potentiellement clefs du contrôle inhibiteur, y compris sous-corticales. C'est pour cette raison que

nous avons choisi de privilégier dans cette étude l'IRMf comme outil d'investigation de la dynamique cérébrale des mécanismes d'inhibition.

1.4 Les réseaux de l'inhibition

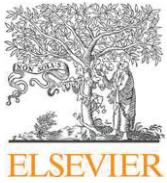
Avec les difficultés d'investigation que nous venons d'évoquer succinctement, il n'est pas surprenant que les données de neuroimagerie disponibles soient confuses, voire conflictuelles. Ces données semblent en tout cas en contradiction avec l'idée générale selon laquelle il existe un mécanisme inhibiteur commun de nature réactive et sélective. Le seul consensus qui semble se dégager est que l'inhibition de réponse engage un très large réseau cortical, principalement frontal, avec de complexes interactions sous-corticales (Aron, 2007 ; Aron, 2011 ; Banich et Depue, 2015; Chambers et al., 2009 ; Duann et al., 2009; Garavan et al., 1999; Garavan et al., 2002; Isoda et Hikosaka, 2007; Jahfari et al., 2012 ; Kelly et al., 2004 ; Konishi et al., 1999; Liddle et al., 2001 ; McNab et al., 2008 ; Menon et al., 2001 ; Mostofsky et al., 2003 ; Mostofsky et Simmonds, 2008; Picton et al., 2007 ; Rubia et al., 2001 ; Simmonds et al., 2008 ; Stinear et al., 2009; Sumner et al., 2007; Swick et al., 2011 ; Van den Wildenberg et al., 2006 ; Zandbelt et Vink, 2010). Cependant, si certains travaux ont eu une influence plus grande que d'autres (e.g., Aron et al., 2007), les données de la littérature ne nous semblent pas aussi cohérentes qu'il n'y paraît. Prenons l'exemple du rôle supposé du gyrus frontal inférieur droit, qui a été largement popularisé par Aron et ses collaborateurs. Il est regrettable qu'un nombre considérable de travaux d'imagerie ultérieurs aux premières investigations cliniques se soient contentés d'analyses en régions d'intérêt centrées sur cette structure, au détriment d'analyses en cerveau entier (e.g., Aron et al., 2007 ; Enriquez-Geppert et al., 2010). Les multiples travaux qui ont pourtant ignoré délibérément le possible rôle des autres régions cérébrales sont

malheureusement souvent considérés, dans des revues de questions plus quantitatives qu'analytiques, comme autant d'arguments en faveur du rôle prépondérant du gyrus frontal inférieur droit. Néanmoins, il n'est pas rare de ne pas retrouver cette région dans les analyses sur cerveau entier, mais d'en identifier d'autres comme le cortex dorsolateral pre-frontal (DLPFC), le gyrus frontal inférieur droit (IFG), l'aire motrice supplémentaire (SMA), l'insula, le lobule pariétal inférieur (IPL); voir Banich et Depue, 2015; Chambers et al., 2009; Mostofsky et Simmonds, 2008; Simmonds et al., 2008; Swick et al., 2011 pour revues.

Il nous a donc semblé important de procéder à une revue de la littérature à la fois critique, critériée et pondérée pour éviter ces biais d'interprétation et dresser un tableau plus objectif des réseaux de l'inhibition de réponse, au moins pour ce qui est des mécanismes mis en jeu dans le Go/NoGo et sondés au moyen de l'IRMf événementiel. Nous avons pour ce faire utilisé des outils méta-analytiques. La technique permet en effet de surpasser certaines limites des méthodes de neuroimagerie que nous n'avons pas évoquées en détail au paragraphe précédent, telles que la taille de l'échantillon ou l'inhomogénéité des populations (Eickhoff et al. 2009; Wager et al. 2009). La technique permet également de contourner certaines limites évoquées plus haut, en particulier celles liées à la diversité et la complexité des paradigmes utilisés, pourvu que les conditions expérimentales puissent être catégorisées et utilisées comme variables indépendantes dans l'analyse. La technique permet donc de localiser les activations liées à la fonction cognitive qui nous intéresse spécifiquement et qui sont reproductibles à travers la littérature, tout en contrôlant une partie des effets confondants liés à la variabilité des protocoles expérimentaux.

1.4.1. Méta-analyse

Article 1: Criaud M and Boulinguez P (2013). Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review. Neuroscience & Biobehavioral Reviews.



Review

Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review

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ABSTRACT

The popular go/no-go paradigm is supposed to ensure a reliable probing of response inhibition mechanisms. Functional magnetic resonance imaging (fMRI) studies have repeatedly found a large number of structures, usually including a right lateralized parieto-frontal network and the pre-supplementary motor area (pre-SMA). However, it is unlikely that all these regions are directly related to the mechanism that actively suppresses the motor command. Since most go/no-go designs involve complex stimulus identification/detection processes, these activations may rather reflect the engagement of different cognitive processes that are intrinsically related and quite difficult to disentangle. The current critical review is based on repeated meta-analyses of 30 go/no-go fMRI experiments using the Activation Likelihood Estimate method to contrast studies using simple vs. complex stimuli. The results show that most of the activity typically elicited by no-go signals, including pre-SMA hemodynamic response, is actually driven by the engagement of high attentional or working memory resources, not by inhibitory processes per se. Implications for current methods and theories of inhibitory control are discussed, and new lines of inquiry are proposed.

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1. Introduction

Response inhibition is a key process of executive control (Hofmann et al., 2012). As such, it arouses considerable interest in cognitive and clinical neuroscience. However, assessing a function which, by its very nature is intended to suppress overt measurable behavior, remains a challenge. The go/no-go paradigm has rapidly become one of the two most popular in the field with the stop-signal task (respectively 806 vs. 824 papers in the web of science at the time of writing). Thanks to its apparent simplicity, the go/no-go paradigm is supposed to ensure a reliable probing of response inhibition mechanisms. In this paradigm, subjects are simply instructed to provide a response to a “go” stimulus and to refrain from reacting to a “no-go” stimulus. The basic theoretical assumption is that inhibitory processes are phasic reactive mechanisms triggered by the external stimulus one must refrain to react to. Usually, the behavioral index of inhibitory control is the number of errors a subject makes on no-go trials (i.e., false alarms), while the most frequent imaging contrast consists in subtracting go from no-go brain activity. Event-related fMRI investigations allow separating go and no-go trials in simple mixed designs, and have been preferred for assessing the functional anatomy of response inhibition.

A large number of structures is involved in inhibitory control, reviewed by Swick et al. (2011). Go/no-go tasks activate many areas of the lateral frontal cortex (including superior, middle and inferior frontal gyri), the insula, the dorsal medial frontal cortex (including the supplementary and pre-supplementary motor areas), the anterior cingulate cortex, the inferior parietal cortex, the precuneus, as well as the striatum. However, neither all these regions, nor all of their activity, may be directly related to the inhibitory process itself, i.e., to the mechanism that actively gates or suppresses the motor command. Rather, these activations may reflect the engagement of different cognitive processes that are intrinsically related and quite difficult to disentangle in experimental designs (e.g., Chambers et al., 2009; Picton et al., 2007; Rubia et al., 2001; Rushworth and Taylor, 2007; Swick et al., 2011; Simmonds et al., 2008). Disagreement remains over the exact contribution made by each brain region (see Chambers et al., 2009 for review). Their activation during tasks requiring inhibitory control was also variously associated with conflict monitoring (Graf et al., 2011; Garavan et al., 2003), error detection (e.g., Menon et al., 2001; Simões-Franklin et al., 2010), attention (e.g., Duann et al., 2009; Hampshire et al., 2010; Sharp et al., 2010; Chikazoe et al., 2009a), working memory (Mostofsky et al., 2003; Simmonds et al., 2008), response selection (Simmonds et al., 2008; Mostofsky and Simmonds, 2008), task setting (e.g., Vallesi et al., 2009; Dosenbach et al., 2007; Konishi, 2011), or even integration of bottom-up sensory information with top-down response-related information (e.g., Dodds et al., 2011; Laurens et al., 2005). Yet, this type of assumption mostly arises from the observation of concurrent activations across studies handling these functions separately. Indeed, it is quite difficult to control several functions at the same time within a single fMRI study design. Meta-analysis techniques are especially appropriate to assess both the consistency and specificity of particular activation patterns across studies (Wager et al., 2009); they are likely to provide key empirical arguments for a critical review.

Searching for common activations between different inhibitory tasks represents a potential solution for identifying the regions that play a direct role in response inhibition. Indeed, it is generally

assumed that each standard paradigm assesses common, or at least closely related, inhibitory mechanisms (Chambers et al., 2009). In an extensive meta-analysis, Swick et al. (2011) found a restricted conjunction of activity between go/no-go and stop signal tasks. They concluded that the major role in inhibition is played by the anterior insula and the pre-SMA. However, it is still possible that go/no-go and stop signal tasks rely on specific neural processes of motor inhibition. This hypothesis is consistent with a different implication of the basal ganglia in the two tasks, as reported by the authors themselves.

Another method of isolating the extent of no-go induced brain activation due to the engagement of collateral cognitive functions consists in assessing the effects of the specific requirements of the experimental tasks across studies. Another influential meta-analysis demonstrated that the localization of no-go evoked activations within the frontal cortex depends on task complexity (Simmonds et al., 2008). Task complexity was assessed by contrasting “simple” with “complex” tasks. In “simple” tasks (five studies), the no-go stimulus–response association always remained the same. In “complex” tasks (six studies), the no-go stimulus–response association was manipulated based on information in working memory. The number of regions commonly activated during both simple and complex go/no-go tasks was small (pre-SMA and fusiform gyrus). However, because of the limited number of experiments available, Simmonds et al. could not consider factors other than working memory that may account for task complexity. It is possible that more general attentional processes are additionally recruited as tasks become more demanding, and may then directly account for go/no-go decisions (Chambers et al., 2009).

Here, we specifically investigate several dimensions that contribute to increased complexity, using the largest possible number of studies. We focus on three non-mutually exclusive dimensions: (1) the difficulty in identifying no-go signals, (2) the frequency of no-go signals among all signals, (3) the working memory load as described by Simmonds et al. (2008). We assume that these three dimensions are important confounds, because they engage multiple attentional control systems to a varying extent, especially selective attention (Braver et al., 2001; Sanaert et al., 2000) and sustained attention (Molloy and Parasuraman, 1996). Most published go/no-go studies use complex designs, with burdensome cognitive requirements in at least one of the three dimensions. Here, we review a large number of studies with respect to each of these dimensions, and investigate the potential confounding influence of cognitive load in each of the dimensions.

2. Materials and methods

2.1. Rationale

To isolate the possible core response inhibition system, we proceeded as follows. First, we identified the network that was significantly activated when processing no-go stimuli, considering all eligible studies as a whole. Then, the same studies were classified as “simple” or “complex” with regard to the three dimensions described above. For each dimension (no-go signals discriminability, no-go signals frequency, working memory load), a two-steps meta-analysis was performed. At a first level, the global “no-go” network was identified within each group (simple and complex study designs). At a second level, subtraction analyses were

performed between groups in order to uncover the “no-go” brain regions specifically activated when high attentional control or working memory load was required (complex > simple). The rationale was as follows: when no-go activity strictly reflects response inhibition, it is expected that no difference is observed between groups since all experimental procedures require refraining from reacting to no-go stimuli, whenever supplementary cognitive functions are required or not. Conversely, significant differences between groups are expected when the no-go activity is specific to the requirements of the complex tasks. Since most go-no-go studies use complex designs, it is likely that the results of a global meta-analysis including all types of experimental protocols are mainly driven by the effects specifically related to the involvement of parallel cognitive functions rather than response inhibition. Accordingly, we assume that only the regions evidenced in the global “no-go” network (all groups analysis) which do not overlap with those revealed by the three specific between-group contrasts should be considered as potential candidates for a direct role in response inhibition. Conversely, we assume that the overlapping regions should pinpoint the no-go activity which is actually driven by the engagement of high attentional or working memory resources, not by inhibitory processes per se.

2.2. Literature selection

We searched the Web of Science and Pubmed databases using the keywords ‘fMRI’ and ‘go/no-go’ (and all variants of this terminology). The inclusion criteria for this review were as follows:

- (1) Studies that used fMRI in healthy subjects were included. Studies in patients that did not provide separate results for the control group were excluded. We restricted our analysis to fMRI in order to have comparable resolution. This revealed 109 relevant papers.
- (2) Studies that used whole brain analyses were included and studies that used only a region of interest approach were excluded. Sixty-two of the 109 papers we found met the former criterion.
- (3) Studies that used event-related designs were included (16 used a block design, 41 an event-related and 5 a mixed design). Indeed, event-related designs are far more suitable to capture the specific activity of rare no-go trials than block designs where trials are intermixed. In addition, in block designs the subtractive rationale of the go/no-go vs. go contrast assumes that go trials are performed similarly in the two blocks. However, it is not at all the case (Boulinguez et al., 2009; Frank et al., 2007; Jaffard et al., 2007; Konishi et al., 1999).
- (4) Only studies that provided full three-dimensional coordinates in stereotactic space (either Talairach or MNI) were included. Twenty-nine studies remained. However, since each paper could have multiple experiments, the present meta-analysis was based on a total of 30 individual contrasts.

2.3. Selection of the contrasts used in the original studies

Several contrasts were used in the original studies to identify brain regions involved in no-go response inhibition. The activations included as a dependent variable in the present meta-analysis were only issued from the most reliable no-go vs. go contrast. We included all foci that survived the FWE, $p < 0.05$ threshold corrected for the whole brain (62% of the papers performed corrections at the single voxel level and 38% at the cluster level). MNI data were transformed to Talairach space when necessary (Laird et al., 2010; Lancaster et al., 2007; Talairach and Tournoux, 1988).

2.4. Categorization of the original experiments and determination of between-groups comparisons

All studies were sorted according to the level of cognitive resources required by their protocol. This was done across three dimensions (Table 1):

- (1) The complexity of identification of the no-go signals. Tasks involving only two stimuli (one go and one no-go, one bit of information) were considered as simple with regard to this criterion. Tasks involving more than two stimuli (usually several go for one no-go, >1 bit of information) were considered as complex. Among the 30 experiments included in the present meta-analysis, 17 were classified as complex and 13 as simple.
- (2) The probability of no-go signals. When go and no-go signals were equiprobable, the task was considered as simple. When the probability of a no-go stimulus was inferior to 50% (usually around one fifth of all trials; average = 20.5%), the task was considered as complex. Twenty studies were classified as complex and ten as simple.
- (3) The working memory load. When the no-go stimulus–response association was stable across the experiment, the task was considered as simple. When the no-go stimulus–response association was manipulated, the task was considered as complex. Indeed, frequently updating stimulus–response associations increases short-term working memory demands. Nine studies were classified as complex and twenty-one as simple.

2.5. Activation likelihood estimation

We first estimated concurrence of activations across all selected imaging studies to reveal the consistent no-go network. Then, we contrasted complex vs. simple conditions in each one of the three dimensions described above. These contrasts were performed to highlight no-go activations specifically observed for complex no-go stimuli. To this end, we used the widely used and validated activation likelihood estimation (ALE) method. We used the Ginger ALE 1.1 software (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002) and applied its standard settings. ALE maps of the foci issued from the selected studies were created using a full-width half maximum (FWHM) determined by means of the Turkeltaub method (Turkeltaub et al., 2012). Statistical significance was determined using permutation tests. Five thousand permutations were computed using the returned FWHM values. Tests were corrected for multiple comparisons using the false discovery rate (FDR) method with $p < 0.05$. Since the cluster threshold is dependent upon the number of experiments, it was defined specifically for each analysis. The maps of the ALE values were superimposed on a colin.nii atlas (Laird et al., 2005; Kochunov et al., 2002) using the Mango software (<http://ric.uthscsa.edu/mango/mango.html>) or MRICron software (<http://www.mccauslandcenter.sc.edu/mricron/mricron/>). Finally, we used Matlab© codes to calculate the amount of overlap between, on the one hand, the global no-go ALE map and, on the other hand, the ALE map of the specific activations induced by the additional attentional/working memory demands of the complex designs. For each cluster of the global conjunction analysis, this overlap score provided an estimation of the extent of no-go induced activation that might be accounted for by cognitive processes other than response inhibition per se.

3. Results

3.1. Distribution of the original experiments

Among the 30 experiments included, 24 (80%) were categorized as complex in at least one dimension (Table 1). Seventeen involved

Table 1
Studies included in the meta-analyses.

First Author	Year	<i>n</i>	Complexity of Identification (bit)	No-Go Frequency (%)	Working Memory Load
Borgwardt	2008	5	>1	11	–
Braver	2001	11	>1	17	–
Chikazoe	2009	52	>1	12.3	–
Cojan	2009	8	1	25	–
Danielmeier	2004	3	>1	50	–
Dibbets	2009	23	>1	14	+
Evers	2006	17	>1	14	+
Falconer	2008	6	1	25	–
Fassbender	2004	8	>1	48.6	–
Garavan	2002	16	>1	7	+
Garavan	1999	14	>1	14	+
Goghari	2009	8	1	20	–
Hare	2005	3	>1	30	–
Kaladjian	2009	16	1	50	–
Kaladjian	2009	20	1	50	–
Karch	2009	13	>1	33.3	+
Konishi	1999	1	1	50	–
Liddle	2001	23	1	50	–
Maltby	2005	5	1	20	–
Mazzola-Pomietto	2009	7	1	50	–
McNab	2008	6	>1	25	–
Mostofsky	2003	3	1	18	+
Ousdal	2008	2	>1	25	–
Rubia	2006	11	>1	12	–
Tamm	2004	7	>1	17	–
Van Gaal	2010	21	>1	50	+
Walther	2010	15	>1	20	–
Watanabe	2002	4	1	50	–
Zheng	2008	8	1	25	–

List of studies including first author, year of publication, number (*n*) of activation foci entered into the ALE meta-analyses, complexity of identification of the no-go signals (bit), frequency of no-go signals among all signals (%), and working memory load (+: studies using context-based stimuli; –: studies using stable stimuli).

more than one bit of information, 20 used a low probability of no-go occurrence, and nine reported varying stimulus–response associations. Only six experiments used a simple study design (20%).

3.2. Whole group analysis

The 30 experiments included in the study provided 342 foci (12 foci were outside the mask used by the algorithm). The results from the ALE analysis demonstrated concurrence in eleven main clusters distributed in nine brain regions (clusters details can be seen in Table 2): (1) the right inferior parietal lobule (IPL), (2) the right dorsolateral prefrontal cortex (DLPFC), including mainly the lateral portions of Brodmann area 9, (3) the right inferior frontal gyrus (IFG), extending to the insula, (4) the left supramarginal gyrus, (5) the left DLPFC, mostly restricted to the middle frontal gyrus, (6) the supplementary motor complex (SMC), extending to the anterior cingulate cortex (ACC), (7) the left insula, (8) the right superior temporal gyrus (STG), and (9) the left IFG (Fig. 1).

3.3. Effect of stimulus complexity

One hundred and twelve foci were identified in the studies using simple stimulus discrimination, and 230 were identified in the studies using complex stimulus discrimination (five and seven foci fall outside the mask, respectively). Five regions were found to be specifically activated when stimulus discrimination was complex: (1) the right supramarginal gyrus, extending both dorsally and ventrally, (2) the right IFG, (3) the left claustrum and the insula, (4) the right DLPFC, and (5) the SMC (Table 3).

3.4. Effect of no-go frequency

Ninety-five foci were identified in the studies using equiprobable no-go signals (simple task), and 247 were identified in the

studies using infrequent no-go signals (complex task). Seven and five foci fall outside the mask, respectively. Two regions were found to be specifically activated when the task was considered as complex (infrequent no-go stimuli): 1) the SMC, extending to the ACC and 2) the right DLPFC (Table 4).

3.5. Effect of working memory load

Two hundred and thirty five foci were identified in the studies using stable go and no-go signals (simple task), and 107 were identified in the studies using context-based stimuli (complex task). Seven and five foci fall outside the mask, respectively. Five clusters distributed were found to be specifically activated when the task was considered as complex (high working memory load): (1) the left IPL, (2) the right DLPFC, (3) the insula and the IFG, (4) the left posterior lateral frontal cortex/lateral portion of the SMC, and (5) the SMC (Table 5).

3.6. Overlap scores

All in all, the overlap rate between the analyses of the whole group and the repeated sub-groups exceeds half of the total brain volume that was more activated by no-go than by go stimuli (51.1%). Two clusters in the left hemisphere (#4 in the left IPL and #5 in the mid-DLPFC), two clusters in the right hemisphere (#8 in the STG and #9 the IFG), and one cluster in the medial prefrontal cortex (#11) showed no overlap at all (Table 2). Two clusters showed full overlap: one in the left hemisphere (#7 in the claustrum and insula) and one in the right (#6 in the SMC). The other four clusters showed partial overlap: one in the IPL (#1: 56%), one in the right mid-DLPFC (#2: 70%), one in the IFG/insula (#3: 58%), and one in the left SMC (#10: 54%). The total percentage of overlap in the SMC (#6 and #10 merged) was 87.4%.

Table 2
No-go clusters issued from the whole group ALE meta-analysis (global no-go network).

Cluster	Side	BA	Brain Region	Vol (mm ³)	W. Center	Overlap (%)
#1	R	40	Inferior Parietal Lobule	4648	46, -52, 37	56
	R	7	Superior Parietal Lobule			
	R	7	Inferior Parietal Lobule			
	R	39	Superior Temporal Gyrus			
	R	40	Supramarginal Gyrus			
	R	39	Angular Gyrus			
	R	39	Middle Temporal Gyrus			
#2	R	9	Middle Frontal Gyrus	2208	41, 32, 30	70
	R	9	Superior Frontal Gyrus			
	R	10	Middle Frontal Gyrus			
	R	46	Middle Frontal Gyrus			
	R	9	Precentral Gyrus			
	R	9	Inferior Frontal Gyrus			
	R	45	Inferior Frontal Gyrus			
#3	R	47	Inferior Frontal Gyrus	1552	35, 21, -2	58
	R	13	Insula			
	R	^a	Clastrum			
	R	47	Insula			
	R	45	Inferior Frontal Gyrus			
#4	L	40	Supramarginal Gyrus	1064	-56, -51, 30	0
	L	39	Superior Temporal Gyrus			
	L	40	Inferior Parietal Gyrus			
#5	L	46	Middle Frontal Gyrus	736	-44, 20, 28	0
	L	9	Precentral Gyrus			
	L	9	Middle Frontal Gyrus			
	L	8	Middle Frontal Gyrus			
	L	45	Inferior Frontal Gyrus			
	L	9	Inferior Frontal Gyrus			
#6	R	6	Superior Frontal Gyrus	712	10, 10, 58	98
	R	6	Medial Frontal Gyrus			
#7	L	47	Inferior Frontal Gyrus	368	-33, 19, -3	100
	L	13	Insula			
	L	^a	Clastrum			
#8	R	22	Superior Temporal Gyrus	280	57, -20, -1	0
	R	21	Superior Temporal Gyrus			
	R	21	Middle Temporal Gyrus			
#9	R	9	Inferior Frontal Gyrus	240	46, 9, 28	0
	R	9	Middle Frontal Gyrus			
#10	L	6	Medial Frontal Gyrus	224	-0, 15, 43	54
	L	32	Cingulate Gyrus			
#11	L	10	Medial Frontal Gyrus	160	-36, 53, 11	0
	L	10	Superior Frontal Gyrus			

Significant cluster location from the go/no-go vs. go contrast meta-analysis, thresholded at $p < 0.05$ (FDR-corrected for multiple comparisons), with the side (R: right, L: left), the Brodmann's area (BA), the region, the volume of the cluster (mm³), the weighted center (W. Center) in Talairach coordinates (x, y, z) and the percentage of overlap with the regions specifically activated by increased cognitive requirements in complex no-go designs.

^a BA not available.

4. Discussion

We critically reviewed 109 published fMRI experiments that examined the cerebral network supporting response inhibition by means of go/no-go paradigms. The global ALE meta-analysis performed on the 30 experiments suitable for inclusion in the analysis corroborates the usual view that processing no-go signals activates a predominantly right-lateralized network that involves the dorsolateral and inferior frontal cortices, the IPL, as well as the SMC, the ACC and the insula. The key element of the present work was to perform a series of complementary analyses among the same 30 experiments to disentangle the different functions potentially confounded in the no-go effect. To this end, we divided the 30 experiments into sub-groups of studies using complex as opposed to simple task designs, and did so repeatedly along several dimensions. The resulting groups were contrasted to uncover the brain regions specifically activated when high attentional control or working memory load was required. Then, we compared these

regions with those identified in the global no-go network, assuming that overlaps should evidence the no-go induced activity that is accounted for by parallel cognitive functions rather than by a direct role in response inhibition. We reported large overlaps between the global no-go network and the regions specifically involved in various aspects of perceptual processing (Fig. 2). The present results thus raise the question of what are the best candidates for a direct role in response inhibition. However, before exploring this issue, we address methodological concerns that could impact on the interpretation of the data.

4.1. Methodological considerations

First, the most frequent imaging contrast, i.e., the most appropriate for a meta-analysis, consists in subtracting go from no-go brain activity. Yet, it is not ideal. Indeed, far more ideal are the contrasts between no-go and oddball trials to control for the low frequency oddball effect (Braver et al., 2001), or no-go with failed

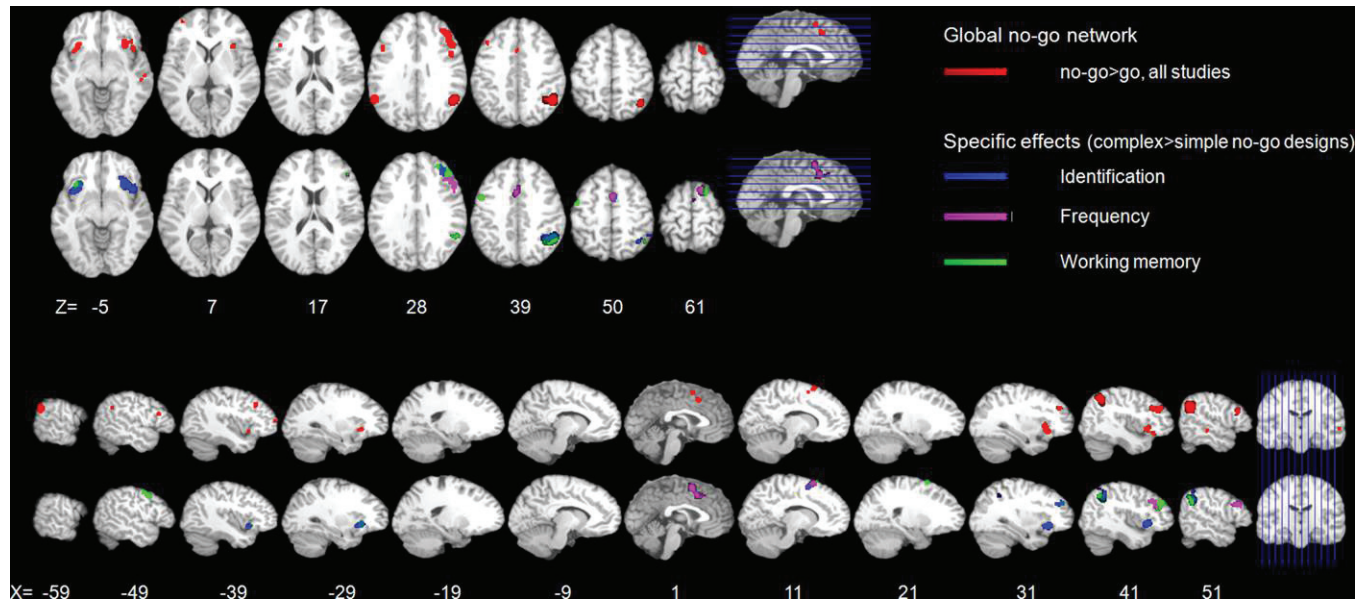


Fig. 1. ALE maps showing significant no-go induced activation clusters overlaid on the optimized Sample template (Kochunov et al., 2002). Red: concurrence of no-go induced activation across all studies. Blue: no-go induced activations specifically observed in tasks using complex no-go signals (amount of information conveyed by a no-go signal > 1 bit). Pink: no-go induced activations specifically observed in tasks using low probability no-go signals (mean probability: 0.205). Green: no-go induced activations specifically observed in tasks manipulating no-go stimulus–response association on the basis of information in working memory.

Table 3
No-go clusters specifically activated in studies using complex stimulus identification.

Cluster	Side	BA	Brain Region	Vol. (mm ³)	Weighted Center
#1	R	40	Inferior Parietal Lobule	2400	43, –48, 42
	R	40	Supramarginal Gyrus		
	R	7	Superior Parietal Lobule		
	R	39	Superior Temporal Gyrus		
#2	R	47	Inferior Frontal Gyrus	2048	35, 22, –3
	R	^a	Clastrum		
	R	^a	Putamen		
	R	47	Insula		
#3	L	47	Inferior Frontal Gyrus	992	–33, 18, –3
	L	13	Insula		
	L	^a	Clastrum		
#4	R	9	Middle Frontal Gyrus	672	35, 41, 28
	R	9	Superior Frontal Gyrus		
	R	10	Middle Frontal Gyrus		
#5	R	6	Superior Frontal Gyrus	664	9, 6, 55
	R	6	Medial Frontal Gyrus		

Significant cluster location showing the difference between tasks using complex no-go signals (>1 bit) and tasks using simple no-go signals (1 bit), obtained from the corresponding subtraction meta-analysis, thresholded at $p < 0.05$ (FDR-corrected for multiple comparisons), with the side (R: right, L: left), the Brodmann's area (BA), the region, the volume of the cluster (mm³) and the weighted center (W. Center) in Talairach coordinates (x, y, z).

^a BA not available

Table 4
No-go clusters specifically activated in studies using low frequency no-go signals.

Cluster	Side	BA ^a	Brain Region	Vol (mm ³)	Weighted Center
#1	R	6	Superior Frontal Gyrus	2712	6, 9, 52
	R	6	Medial Frontal Gyrus		
	R	32	Cingulate Gyrus		
	L	24	Cingulate Gyrus		
	L	32	Medial Frontal Gyrus		
	L	8	Medial Frontal Gyrus		
#2	R	9	Middle Frontal Gyrus	1792	45, 26, 29
	R	46	Middle Frontal Gyrus		
	R	9	Precentral Gyrus		
	R	9	Inferior Frontal Gyrus		

Significant cluster location showing the difference between tasks using low (<50%, mean: 20.5%) and tasks using equiprobable (50%) no-go signals, obtained from the corresponding subtraction meta-analysis, thresholded at $p < 0.05$ (FDR-corrected for multiple comparisons), with the side (R: right, L: left), the Brodmann's area (BA), the region, the volume of the cluster (mm³) and the weighted center (W. Center) in Talairach coordinates (x, y, z).

^a BA not available.

Table 5

No-go clusters specifically activated in studies manipulating no-go stimulus–response association on the basis of information in working memory.

Cluster	Side	BA	Brain Region	Vol (mm ³)	Weighted Center
#1	R	40	Inferior Parietal Lobule	2864	45, –50, 37
	R	40	Supramarginal Gyrus		
	R	7	Superior Parietal Lobule		
	R	7	Inferior Parietal Lobule		
	R	39	Angular Gyrus		
	R	39	Superior Temporal Gyrus		
#2	R	9	Superior Frontal Gyrus	1504	40, 38, 27
	R	46	Middle Frontal Gyrus		
	R	9	Middle Frontal Gyrus		
	R	10	Middle Frontal Gyrus		
#3	L	13	Insula	672	–32, 22, –2
	L	47	Inferior Frontal Gyrus		
	L	^a	Clastrum		
#4	L	6	Precentral Gyrus	608	–47, 1, 44
	L	6	Middle Frontal Gyrus		
	L	8	Middle Frontal Gyrus		
	L	9	Middle Frontal Gyrus		
#5	R	6	Superior Frontal Gyrus	488	16, 13, 62
	R	6	Middle Frontal Gyrus		

Significant cluster location showing the difference between tasks manipulating or not no-go stimulus–response association on the basis of information in working memory, obtained from the corresponding subtraction meta-analysis, thresholded at $p < 0.05$ (FDR-corrected for multiple comparisons), with the side (R: right, L: left), the Brodmann's area (BA), the region, the volume of the cluster (mm³) and the weighted center (W. Center) in Talairach coordinates (x, y, z).

^a BA not available

no-go trials (Padmala and Pessoa, 2010). However, too few studies that use these contrasts are available to allow consideration in a meta-analysis.

Second, it is acknowledged that the ALE maps do not represent the significant volume of activation observed for one contrast across studies. Indeed, in ALE analyses, the unique dependent variable taken into account is the location of the voxel of the peak activation reported for each cluster of each study included in the meta-analysis. This voxel is then equated to the center of a three-dimensional Gaussian function, but the magnitude and extent of activation for each cluster are not taken into account, nor is the statistical power of each study. Accordingly, while the ALE method probably provides a reliable estimate of the probability of localization of consistent activation peaks, in the absence of any weighting scheme in the analysis the output maps do not provide a

trustworthy approximation of the actual volume of activation. Therefore, one must be careful when comparing the maps produced by different ALE analyses. A consistent neurological activity within a unique brain region may produce only partially overlapping maps for two groups of studies. This creates a problem when interpreting partial overlaps for a region of interest. Does the non overlapping part of a cluster pinpoint the involvement of a different, contiguous, co-occurring function? Or does the discrepancy simply result from the uncertainty of the measurement? We assume that a good percentage of overlap between two clusters respectively issued from our global and our specific ALE analyses is indicative of a good probability that the two clusters account for the same function. Yet, it must be clearly acknowledged that an activation overlap could also be due to a functional overlap since the same region can be involved in different functions. It is just unlikely that the multiple parallel

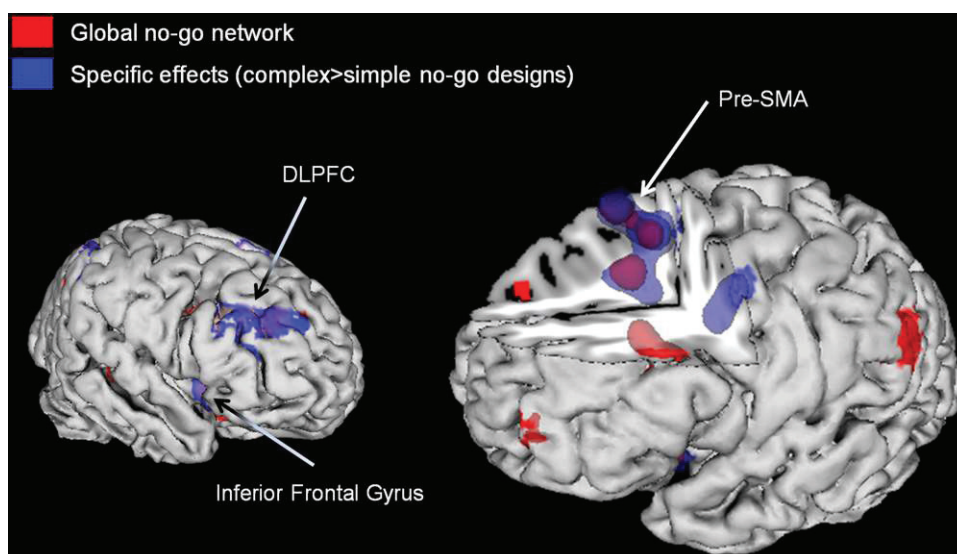


Fig. 2. Overlap between the global no-go network (red) and the regions specifically activated by increased cognitive requirements in complex no-go designs (blue). Most of the no-go activity typically observed in the right DLPFC, right inferior frontal gyrus and pre-SMA is actually driven by the engagement of high attentional/working memory resources, not by inhibitory processes per se.

cognitive functions isolated in this meta-analysis all have identical anatomo-functional properties with the core response inhibition system.

Third, according to our rationale, the regions evidenced in the global analysis but not in the specific analyses represent the best candidates for a genuine role in response inhibition. However, the observation of non-overlapping areas does not provide indisputable evidence for a direct role of these regions in inhibition. It must be kept in mind that the independent variables used to categorize the original studies according to their level of task complexity certainly do not allow all the cognitive functions indirectly related to response inhibition to be identified. Therefore, the key outcomes of the present study concern the regions from the global no-go network whose activity was found to be accounted for by attention and working memory. Indeed, while our method allows some brain regions to be excluded from the list of most probable candidates for a direct role in no-go response inhibition, it does not allow clear-cut identification of the brain regions which do play a straight role in inhibition.

4.2. Lateral cortical no-go activations

In two seminal meta-analyses, Swick et al. (2011) and Simmonds et al. (2008) hypothesized that the right lateral parieto-frontal network emphasized in most previous go/no-go studies does not belong to the core response inhibition system. The authors proposed that the role of this network may rather be related to attention. The results of the present meta-analysis suggest that, indeed, a large part of this parieto-frontal no-go activity is driven by the engagement of high attentional and working memory resources, not by inhibitory processes per se. The mean percentages of overlap found in the right DLPFC (70%), the right IFG (55.5%) and the right IPL (56%) are consistent with the frequent observations in tasks that do not require inhibitory control, that: (1) the DLPFC, the IPL and the IFG are consistently associated with tasks requiring working memory maintenance and stimulus retrieval (D'Esposito et al., 1998; Smith and Jonides, 1999; Owen et al., 1999; Duncan and Owen, 2000; Collette and Van der Linden, 2002; Derrfuss et al., 2004; Brass et al., 2005), (2) the right DLPFC and the right IPL are recruited during sustained attention (Banich et al., 2009; Lawrence, 2003; Coull et al., 1996; Fassbender et al., 2004, 2006), (3) the right IFG, the right IPL and the right STG play a central role in alerting and shifting attention to unpredictable, salient events (McCarthy et al., 1997; Sturm and Willmes, 2001; Corbetta and Shulman, 2002; Fan et al., 2005; Shulman et al., 2010; Banich et al., 2009), and (4) the whole right frontoparietal cortical network is activated when discrimination paradigms request object-based selective attention (Hopfinger et al., 2000; Degerman et al., 2006; Prado et al., 2011). These attentional functions are inevitably called upon to take part in the global processing of no-go signals in complex designs. In addition, it is noteworthy that some studies of inhibitory control using different or adapted experimental paradigms also support the attentional hypothesis (e.g., Fassbender et al., 2004, 2006; Li et al., 2006; Dodds et al., 2011; Duann et al., 2009; Krämer et al., in press; Hester et al., 2004; Sharp et al., 2010). This substantial confound is due to the fact that most go/no-go studies (80% of the papers included in this meta-analysis) use experimental designs handling complex no-go signals. These stimuli are difficult to identify because of their low distinctiveness and/or their low probability of occurrence and/or the high working memory load they require.

The recurrence of this methodological feature may appear somewhat surprising. Indeed, it has been long established that the amount of information conveyed by a stimulus, i.e., its complexity, depends both on the number of alternatives from which it could be chosen, and on the number of times it could occur (Hyman, 1953). The justification for the use of complex designs in

go/no-go studies relies on the aim to elucidate the distinct roles played by different cortical structures in three major aspects of behavioral control: inhibition, error detection, and behavioral correction (e.g., Garavan et al., 2002). This strategy has proven useful for dissociating these three executive functions with fMRI (Fassbender et al., 2004; Garavan et al., 1999, 2003; Hester et al., 2004; Kelly et al., 2004). However, the present meta-analysis strongly suggests that this method generates a number of other confounds regarding the activity attributed to inhibition per se. Conversely, the alternative classical go/no-go task design that involves only two stimuli (a go stimulus and a no-go stimulus) cannot easily assess all these adaptive functions. Yet this type of design is supposed to assess basic inhibitory processes as well (Kiehl et al., 2000; Liddle et al., 2001; Mostofsky et al., 2003; Watanabe et al., 2002), but with a much lower cognitive load. As a consequence, go/no-go tasks using two simple stimuli pose a limited risk to introduce confounds with parallel cognitive functions such as attention, working memory or response selection. Finally, whatever the number of stimuli used in the design, the task is most often weighted towards go stimuli in order to build up a prepotent tendency to respond. It is typically argued that this strategy increases the inhibitory effort necessary to successfully withhold responses to no-go stimuli, i.e., that this strategy enhances the inhibitory brain activity elicited by no-go stimuli. In practice, weighting the task towards go stimuli is classically achieved by speeding reaction time, irrespective of the complexity of the design. Yet, many authors consider that for an inhibition task to have reasonable inhibitory load and behavioral validity, the percentage of trials that require refraining from reacting also needs to be low to build up a predominant tendency to respond (see Table 1). This is a divisive issue. A sizable part of go/no-go studies (e.g., 30% of those included in the present meta-analysis) use equiprobable go and no-go signals (see Table 1). While making a response prepotent is undoubtedly useful when using complex choice reaction time tasks, it is theoretically not necessary, at least when using simple reaction time tasks that involve only one motor response to a single go stimulus. Indeed, there is now abundant evidence that no-go stimuli trigger automatic motor activations that require active inhibition to avoid overt erroneous responses, regardless of their relative frequency. These no-go locked motor activations were clearly observed centrally using MEG (e.g., Endo et al., 1999), fMRI (e.g., Jaffard et al., 2007) or even EEG (e.g., Boulinguez et al., 2009), and peripherally by means of subthreshold electromyographic activity in the muscles involved in the response (e.g., Boulinguez et al., 2008). In other words, these studies strongly suggest that there could be no better way to evoke a strong tendency to produce automatic motor responses than using simple reaction time tasks mixing equiprobable go and no-go stimuli. This controversial question is not trivial for interpreting the outcomes of this meta-analysis. Indeed, while the present results call for drastically simplifying study designs in investigations of response inhibition, the proponents of the low no-go frequency method usually consider that a go/no-go task with 50% no-go trials is not a proper go/no-go task (e.g., Casey et al., 1997). They consider that this type of task consists in ignoring non-targets rather than inhibiting no-gos. This position refutes our rationale regarding the meaning of the effect of no-go frequency and our interpretation in terms of attentional modulations (right DLPFC and SMC, Table 4). Adopting this position leads to interpret "low frequency no-go" clusters as reflecting precisely the involvement of response inhibition.

Despite the fact that the interpretation of non-overlapping areas is doomed to remain as speculation, it is tempting to discuss the activity within the global no-go network which is not accounted for by the cognitive functions isolated in our specific contrasts. Interestingly, such activity is reported bilaterally. Among the acknowledged right lateralized no-go network, only the two

smallest clusters of our global conjunction analysis (in the STG and in the DLPFC) showed no overlap. Since it has not been emphasized with respect to right prefrontal regions in most previous go/no-go studies, the role of the STG remains obscure. It may play a direct role in response inhibition. Consistent with this view, this region was found to be hypoactivated when subjects with Attention-Deficit/Hyperactivity Disorder (ADHD), a disease characterized by inhibitory control deficits, performed a go/no-go task (Solanto et al., 2009). This hypothesis, however, finds little support in the acknowledged connectivity of the STG with the motor system and does not fit with previous meta-analyses (Swick et al., 2011; Simmonds et al., 2008). The alternative interpretation, i.e., the idea that its function in response inhibition is indirect anyway, is conversely supported by studies of cognitive functions that were not assessed in the present analysis. For instance, Karnath et al. (2001) have suggested that the critical locus of neurological damage in neglect patients may lie in this region. While still controversial (Corbetta and Shulman, 2011; Fink et al., 2003; Vallar and Perani, 1986; Vallesi and Crescentini, 2011), this observation supports the view that the STG may play a critical role in visuospatial attention. Also the STG supports other attentional modulations related to decisional mechanisms, such as assigning relative values to the options under consideration in order to bias response alternatives (Lim et al., 2011). It is likely that the underlying functions are enhanced when processing no-go signals.

Although not often underlined in go/no-go studies, consistent no-go activation within left parieto-frontal regions (IPL and DLPFC) was reported in our global conjunction analysis. To our knowledge, these regions have rarely been suspected to be directly involved in suppressing motor activation (but see Hirose et al., 2012 for recent evidence). However, the left mid-DLPFC has been proved to play a central role in perceptual decision-making by setting a threshold on the accumulated evidence required to trigger accurate response execution (Forstmann et al., 2008, Table S1; Vallesi et al., 2012; Wenzlaff et al., 2011). Consistent with our results, this function is supposedly involved in each go/no-go task reviewed in the present paper. The IPL also plays a critical role in the decision to act or not in go/no-go situations as it supports motor intention (Desmurget et al., 2009; Desmurget and Sirigu, 2012). This view is especially consistent with previous observations from our group that the left IPL plays a role in response inhibition by attenuating activity within the motor circuitry including SMA, Putamen and M1 (Jaffard et al., 2008).

4.3. Dorsomedial frontal cortical activity

The most striking result of the present meta-analysis is the finding that the no-go induced activity in the SMC, as well as in the left insula, is explained by increased attentional and working memory load (all in all, SMC exhibits 87.4% overlap and the left insula 100%). These results appear to suggest that the most expected brain regions (pre-SMA in particular) actually do not play a direct role in response inhibition. Obviously, there is too much evidence from clinical (e.g., Chen et al., 2009; Nachev et al., 2008; Paus, 2001; Picton et al., 2007; Sumner et al., 2007) and brain stimulation (Cai et al., 2012; Chambers et al., 2007)¹ studies that the SMC has a critical role in inhibiting motor responses to draw such a conclusion. Instead, we assume that this observation indicates that only the reflexive activity of the pre-SMA is not directly related to the suppression of motor action. Indeed, standard fMRI contrasts are based on the activation elicited by the no-go signal, which means

that the focus is entirely on reactive processes. We do believe that pre-SMA plays a central role in inhibitory control, but challenge the idea that this area triggers a cancellation signal specifically in reaction to the no-go stimulus. Pre-SMA contributes to many “reactive” functions that are involved in cognitive control. In particular, pre-SMA is responsive to conflict detection and is involved in adjusting response thresholds or switching from one action rule to another (e.g., Ball et al., 1999; Barber and Carter, 2005; Isoda and Hikosaka, 2007; see Nachev et al., 2008 for extensive review). In other words, its activity is undoubtedly enhanced when the complexity of the condition–action associations increases (Simmonds et al., 2008). It is therefore very likely that such activity is mostly reflected in the standard no-go > go contrasts, as suggested by the present meta-analysis.

4.4. The no-go network as part of a generic cognitive control system

The present study followed up on previous reviews providing clues against the idea that the format of the go/no-go task allows for examination of response inhibition under conditions in which other cognitive processes are minimized (e.g., Chambers et al., 2009; Simmonds et al., 2008; Swick et al., 2011). Here, we provide arguments suggesting that, with this paradigm, most of the activity classically attributed to response inhibition may in fact be attributable to other, more general, cognitive processes. This hypothesis is to be understood within the framework of more generic models of attention and executive control.

According to the simple standard taxonomy, executive functioning is composed of three basic modules (Hofmann et al., 2012; Miyake et al., 2000). Inhibition of prepotent impulses is considered as a basic executive function on its own, justifying the development of independent neuroimaging research programs. However, the wider model of executive functioning also integrates working memory operations and mental set shifting. The former module contributes to the maintenance and updating of relevant information. The latter refers to the ability to shift back and forth between multiple tasks or mental sets. Classically, different experimental tasks are used by researchers who aim at testing specifically each one of these three basic functions (see Miyake et al., 2000 for review). There is good agreement, however, that the accurate and independent assessment of each one of these modules is challenging because complex tasks inevitably tap into a combination of these three executive sub-functions (see also Jurado and Rosselli, 2007). This is especially the case of complex go/no-go paradigms in which numerous stimuli are presented, or even worse, in which stimulus–response association is manipulated based on information in working memory. From this perspective, it is not surprising at all to observe large overlaps between the “no-go” network and brain regions responsible for working memory operations and mental set shifting as identified in tasks which do not require response inhibition. These overlaps, i.e., the potential functional confounds in go/no-go paradigms, do not only concern the prefrontal cortex. They also involve posterior regions in the parietal and temporal cortices.

Similarly, neuroanatomical models of attentional control clearly state that attentional processing is sufficient to activate a large part of the “no-go” network in tasks that do not require explicit inhibition of response (Corbetta and Shulman, 2002, 2011). The model assumes the interplay of two cortical networks, the so-called dorsal and ventral frontoparietal networks, respectively involved in the top-down and stimulus-driven control of visual processing. The dorsal network is responsible for the generation and application of attentional sets (e.g., defining selection criteria for stimulus processing) and involves the superior parietal

¹ These studies assessed the role of the SMC in response inhibition with stop-signal tasks. To our knowledge, no study assessing the role of the SMC in response inhibition by means of TMS used a go/no-go paradigm.

and frontal cortices bilaterally (see also Mesulam's and Posner's models; Mesulam, 1998; Posner and Petersen, 1990). This system is supposed to link relevant sensory representations to relevant motor representations. The ventral network is involved in the detection of behaviorally relevant stimuli and acts as a "circuit breaker" for the dorsal system when appropriate. It is composed posteriorly of the IPL and STG, and anteriorly of the IFG and middle frontal gyrus. Importantly, the ventral network has a clear right lateralization pattern consistent with the no-go lateralization pattern (Shulman et al., 2010). Its anterior node would be involved in novelty detection while its posterior node would subsequently interrupt ongoing top-down control by means of its connections with the dorsal network. Once again, from this perspective it is not surprising to observe large overlaps between the "no-go" network and the brain regions responsible for selective and non-spatial attention when the task does not require inhibitory control.

Munakata et al. (2012) recently called for using a unified framework integrating cognitive models of attention and working memory for understanding inhibitory control and prefrontal cortex function. They argued that prefrontal areas would be primarily specialized for actively representing and maintaining abstract information relevant for cognitive control over behavior (see also Miller and Cohen, 2001 for earlier relevant review), not for inhibitory control per se. In line with this view, the present study strongly suggests that both the prefrontal and posterior regions, which are commonly believed to be the source of inhibitory control in go/no-go tasks, actually have a more general function. The right inferior frontal cortex would mediate the attentional processing of task relevant cues, i.e., would support the detection of no-go signals. The DLPFC would actively maintain information in working memory necessary to make decisions (stimuli, goals, contexts and task sets). The IPL and STG would sustain attention and maintain representations of stimulus–response associations, or conversely act as a circuit breaker when facing no-go signals. This network of regions would relay the information about when it is appropriate to refrain from reacting to the interconnected SMC (Narayana et al., 2012). By contrast with the above-mentioned cortical "no-go regions", there is strong agreement in the literature regarding the pivotal role of the SMC in inhibitory control. Thanks to its projections to the basal ganglia, the SMC finds itself in a key position to play this direct role (Inase et al., 1999; Hikosaka and Isoda, 2010; Nachev et al., 2008). However, the most puzzling result of the present study is the observation that the activity induced by no-go signals in the SMC is fully accounted for by the attentional and working memory requirements of the task. On the one hand, this conclusion is consistent with the accepted idea that the SMC supports various functions including operations that involve working memory, response selection and attention (Derrfuss et al., 2004; Rushworth et al., 2004). On the other hand, it is hard to reconcile with most clinical, imaging and stimulation studies of inhibitory control (Aron, 2007, 2011; Cai et al., 2012; Chambers et al., 2007, 2009; Picton et al., 2007; Sumner et al., 2007; Wardak, 2011). This striking result might be indicative of a more general bias in the theoretical (and derived methodological) underpinnings of go/no-go studies, and might call for revisiting the dominant theoretical model (and derived methods).

4.5. Revisiting the model

While stop-signal tasks undoubtedly probe reactive inhibition (Verbruggen and Logan, 2008b, 2009), this is more questionable for go/no-go tasks. Yet, standard go/no-go paradigms are guided by the postulate that inhibitory processes are phasic reactive mechanisms triggered by *the external stimulus one must refrain from reacting to* as in stop-signal tasks. This postulate asserts that no

inhibition is involved in go trials. Actually, this is very unlikely (e.g., Boulinguez et al., 2009; Jaffard et al., 2007; Konishi et al., 1999). Both go and no-go stimuli induce inhibition because the experimental protocols introduce uncertainty about the next event to come. Hence, subjects are forced to withhold fast automatic responses *to any upcoming event* when facing conflict decisions in order to allow themselves more time to integrate perceptual information and settle on the appropriate choice (e.g., Frank et al., 2007). This means that most common fMRI designs are probably inappropriate for proving response inhibition in go/no-go studies. Indeed, the BOLD activity induced by inhibitory control cannot survive the standard no-go > go contrast, given that the function is systematically involved in both conditions. This is quite consistent with the results of this meta-analysis. An appropriate control condition in which inhibition is not involved is necessary to prove the actual inhibitory activity. This can be achieved by introducing go trials in which subjects know in advance that there is no need to refrain from reacting (e.g., Jaffard et al., 2007; Criaud et al., 2012). By implementing these recommendations, we recently suggested that response inhibition in this type of task relies on proactive rather than on reactive mechanisms (Boulinguez et al., 2008, 2009; Jaffard et al., 2007, 2008; Criaud et al., 2012). Proactive inhibitory control would operate as a gating mechanism acting on movement initiation processes. According to the model, preventing automatic reaction to no-go (as well as to go) stimuli would mostly rely on tonic processes modulating the baseline activity of cortico-striatal connections. This locking state would be released reactively after the go signal had been identified, allowing a slow but controlled response. Incidentally, the locking state can also be released at any time depending on subjects' expectations of upcoming events. This control would mainly activate a medial parieto-frontal network composed of the SMC, the dorsomedial prefrontal cortex (BA 9/10) and the precuneus/posterior cingulate cortex, in addition to the left IPL (Jaffard et al., 2007, 2008). This ability to switch between proactive inhibition of response and automatic reactivity would represent a basic function of behavioral control (see also Hikosaka and Isoda, 2010 as well as Forstmann et al., 2010). Proactive control in response inhibition has recently become a matter of hot debate (e.g., Aron, 2011; Ballanger, 2009; Ballanger et al., 2009; Chikazoe et al., 2009b; Lo et al., 2009; Mazaheri et al., 2009; Boy et al., 2010; Chen et al., 2010; Claffey et al., 2010; Duque et al., 2010; Filevich et al., 2012; Karayanidis et al., 2010, 2011; Ullsperger and King, 2010; Verbruggen and Logan, 2008a; Wardak, 2011; Zandbelt and Vink, 2010; Zandbelt et al., 2012). More generally, the distinction between proactive and reactive modes of control now appears central for understanding the functional anatomy and the temporal dynamics of cognitive control processes, especially when assessing interindividual variability with fMRI (Braver et al., 2009). However, future advances in the field may rely on the amendment of standard theoretical backgrounds, experimental protocols and fMRI designs. To reveal the actual functional anatomy of no-go response inhibition, we especially suggest setting up simple go/no-go imaging designs that allow analysis of the intrinsic brain activity preceding stimulation, when prevention of reaction is required (go/no-go) as compared to when it is not (go only).

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1.4.2. Conclusion

La méta-analyse présentée dans ce premier article permet de confirmer que des stimuli auxquels il convient de ne pas répondre (nogo) activent de façon reproductible, par rapport à des stimuli requérant une réponse motrice, un très large réseau composé de 11 clusters distribué dans 9 régions : 1) le lobule pariétal inférieur (IPL) droit, 2) le cortex dorsolatéral préfrontal (DLPFC) droit, 3) le gyrus frontal inférieur (IFG) droit s'étendant jusqu'à l'insula, 4) le gyrus supramarginal gauche, 5) le DLPFC gauche, 6) le complexe moteur supplémentaire (SMC) s'étendant jusqu'au cortex cingulaire antérieur (ACC), 7) l'insula, 8) le gyrus temporal supérieur droit, et 9) l'IFG gauche. Evidemment, aucune de ces activations n'est surprenante. La surprise de cette première analyse vient plutôt de l'absence d'activation statistiquement reproductible dans les ganglions de la base.

Cependant, lorsque l'on contrôle a posteriori la difficulté d'identification de la cible, la fréquence des stimuli nogo, et la charge en mémoire de travail, on démontre que toutes les activations significatives sans ce contrôle dans le réseau classique d'inhibition (SMC, ACC, IPL droit, DLPFC droit, IFG droit) sont en fait dues à la difficulté de la tâche. Ceci signifie que, à cause de paradigmes complexes imposant une charge cognitive trop lourde, les travaux classiques confondent probablement activations liées aux mécanismes d'inhibition et activations liées aux fonctions cognitives corolaires mises en jeu dans les tâches. Cette conclusion pose un ensemble de questions très claires : Existe-t-il vraiment une forme d'inhibition réactive et sélective ? Dans la négative, comment l'inhibition de réponse est-elle mise en œuvre dans une tâche de Go/NoGo ? Comment réinterpréter les travaux cliniques s'appuyant sur les outils méthodologiques et modèles théoriques standards de l'inhibition de réponse ?

Chapitre 2

Modélisation psychologique de l'inhibition de réponse: Contributions combinées de la psychophysique et de la neuroimagerie

Le premier chapitre a permis de remettre en question la modélisation standard, purement réactive et sélective, du contrôle inhibiteur. En effet, la méta-analyse appliquée à l'ensemble des études d'IRMf incluables n'a pas révélé d'activations reproductibles conformes aux données issues des travaux les plus populaires. En d'autres termes, nous n'avons pas trouvé d'indices attestant de la plausibilité biologique de ce modèle. L'étape suivante consiste à réfléchir à un modèle alternatif tout en continuant à tester le modèle standard afin de cumuler plus d'absence d'évidences avant d'envisager d'accepter l'hypothèse nulle...

2.1 Un nouveau modèle d'inhibition de réponse : le control inhibiteur proactif

2.1.1 Le contrôle inhibiteur proactif : un mode de contrôle anticipé

Les résultats de travaux ne s'intéressant pas directement à l'inhibition de réponse permettent de dresser une esquisse de modèle inhibiteur alternatif (Albares et al., 2011¹ ; Boulinguez et al., 2008, 2009; Jaffard et al., 2007, 2008). En effet, cette série d'études avait pour objectif initial de sonder les mécanismes d'orientation de l'attention et d'alerte au moyen d'une méthode classique d'amorçage inspirée des travaux princeps de Posner (Posner, 1980, 2004 2008; Posner et Petersen, 1990). Fortuitement, l'introduction d'une condition de contrôle quasiment jamais

¹ Cet article, que j'ai signé en tant que co-premier auteur, a fait l'objet d'une partie de mon travail pré-doctoral, (Annexe 1).

utilisée dans les designs classiques a permis de révéler un biais considérable des méthodes d'amorçage. Ce biais est lié aux activations motrices automatiquement générées par la présentation du signal d'amorce indiquant l'imminence ou la localisation de la cible à venir. Si ces activations excitatrices ne sont pas réprimées, elles donnent lieu à des réponses impulsives de type erreur de commission. Il a été supposé qu'un mécanisme exécutif devait nécessairement être mis en œuvre pour y parvenir. Il reposerait sur le verrouillage anticipé des processus d'initiation du mouvement lorsque la situation événementielle est incertaine. L'inhibition serait active et effective avant l'apparition des stimuli, elle serait proactive. Elle s'appliquerait indifféremment à tous les stimuli présentés, elle serait en ce sens non-sélective. Le but de ce contrôle inhibiteur proactif serait d'empêcher le déclenchement de mouvements potentiellement inappropriés à la situation, ou non-désirés, en verrouillant le déclenchement de tout mouvement. Ce contrôle serait mis en place lorsque le contexte est incertain, autrement-dit dans la plupart des situations de la vie quotidienne.

2.1.2 La nécessaire adaptation des paradigmes expérimentaux

La mise en évidence expérimentale du contrôle inhibiteur proactif nécessite une adaptation des paradigmes classiques d'étude du contrôle de l'action. Pour illustrer ce point, nous nous référerons à une tâche typique de l'étude de la restriction d'action : la tâche de Go/NoGo. D'après le modèle d'inhibition proactive non sélective, ce n'est pas l'identification du signal nogo qui déclencherait les activations inhibitrices, mais c'est au contraire l'identification du signal go qui induirait la levée de l'inhibition. Le modèle suppose que le contrôle inhibiteur serait implémenté en condition d'incertitude mais ne le serait pas lorsque le contexte ne recèle pas d'incertitude. Dans cette condition précise, le sujet est censé laisser libre court aux automatismes

sensorimoteurs via les processus d'activation directe (Boulinguez et al., 2008; McBride et al., 2012; Sumner & Husain, 2008).

La mise en évidence des mécanismes proactifs non sélectifs passe donc par : 1) l'utilisation d'une condition de contrôle dans laquelle les participants sont certains avant le début d'un essai que la situation ne comporte pas d'incertitude, 2) l'enregistrement de l'activité cérébrale au cours de la période qui précède l'apparition des stimuli. Par ailleurs, l'utilisation de cette condition de contrôle possède un avantage supplémentaire. Elle permet d'obtenir un marqueur psychophysique de l'inhibition. En effet, les processus d'activation directe non inhibés dans la condition de contrôle génèrent des temps de réaction très courts. Au contraire, les temps de réaction aux stimuli Go de la condition expérimentale sont beaucoup plus longs car l'inhibition doit d'abord être levée suite à l'identification de la cible pour donner lieu à la production d'une réponse volontaire après réinitiation de la réponse activée (voir aussi MacDonald et al., 2014). La différence de TR entre les deux conditions indexerait ainsi le temps nécessaire au déverrouillage des mécanismes d'initiation de l'action (Ballanger et al., 2009; Boulinguez et al., 2009; Jaffard et al., 2007; 2008). Ce mécanisme exécutif consistant à permettre le passage d'un mode contrôlé (i.e. inhibé) à un mode automatique (i.e. non-inhibé) est évocateur de travaux de référence ne concernant pas directement les modèles d'inhibition (Hikosaka et Isoda, 2010 ; Isoda et Hikosaka, 2007).

2.1.3 Caractéristiques du contrôle inhibiteur proactif

Contrairement à la façon dont elles sont parfois présentées, les deux principales théories du contrôle inhibiteur ne sont certainement pas mutuellement exclusives (Aron, 2011). Ceci suggère que leurs effets sur le comportement, mais également sur l'activité cérébrale sous-tendant ce

comportement, sont potentiellement confondus. Clarifier le rôle respectif de chacune de ces formes de contrôle passe en premier lieu par une meilleure compréhension du contrôle inhibiteur proactif. Tout d'abord parce que l'immense majorité des travaux ignore complètement sa possible implication, ou pour le moins n'intègre pas cette dualité des niveaux de contrôle. Ensuite, parce que les travaux qui s'y sont intéressés ont laissé un certain nombre de questions en suspens. La question majeure concerne la nature de ce contrôle top-down. On suppose que ce contrôle consiste à passer alternativement d'un état verrouillé empêchant tout déclenchement de réponse à un état déverrouillé laissant libre cours aux automatismes sensorimoteurs. Ce que l'on ignore c'est comment et quand ces transitions sont contrôlées. L'inhibition est-elle implémentée dès lors que le contexte devient ambigu ou conflictuel? Est-elle transitoire ou soutenue? Au contraire, l'inhibition est-elle l'état par défaut du système exécutif, supposant que le contrôle consisterait plutôt à lever l'état d'inhibition lorsque l'incertitude événementielle disparaît? Les réponses à ces questions ne sont pas seulement susceptibles d'être utiles à l'actualisation des modèles psychologiques. Elles sont fondamentales d'un point de vue méthodologique en imagerie cérébrale. Elles permettront en effet de guider les techniques de traitement du signal vers les périodes ou modes d'activation susceptibles de mieux rendre compte de l'activité de contrôle inhibiteur. La partie expérimentale de ce travail respecte cette démarche. Deux expériences comportementales ont dans un premier temps été menées pour caractériser la dynamique du contrôle inhibiteur proactif.

2.1.4 Données comportementales

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Proactive inhibitory control of response as the default state of executive control

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Refraining from reacting does not only involve reactive inhibitory mechanisms. It was recently found that inhibitory control also relies strongly on proactive mechanisms. However, since most available studies have focused on reactive stopping, little is known about how proactive inhibition of response is implemented. Two behavioral experiments were conducted to identify the temporal dynamics of this executive function. They manipulated respectively the time during which inhibitory control must be sustained until a stimulus occurs, and the time limit allowed to set up inhibition before a stimulus occurs. The results show that inhibitory control is not set up after but before instruction, and is not transient and sporadic but sustained across time. Consistent with our previous neuroimaging findings, these results suggest that proactive inhibition of response is the default mode of executive control. This implies that top-down control of sensorimotor reactivity would consist of a temporary release (up to several seconds), when appropriate (when the environment becomes predictable), of the default locking state. This conclusion is discussed with regard to current anatomo-functional models of inhibitory control, and to methodological features of studies of attention and sensorimotor control.

Keywords: executive control, response inhibition, go/nogo, alertness, warning, psychophysics, human

INTRODUCTION

Self-control relies on the ability to countermand inappropriate stimulus-driven response impulses. Several inhibitory mechanisms may contribute to the process of refraining from reacting. These are either phasic, reactive processes triggered by the external stimulus itself, or tonic, proactive processes driven by top-down control. While the former involve online control of ongoing responses, the latter entail anticipatory locking of movement triggering mechanisms.

Most available studies have focused on reactive stopping. However, recent developments in the cognitive neuroscience of inhibitory control have highlighted the probable role of proactive mechanisms in inhibitory control (see Aron, 2011 for review). Proactive inhibitory control of action might take various forms such as adjusting the level of motor readiness, gating movement triggering mechanisms non-selectively or, conversely, inhibiting a particular response tendency. Importantly, proactive and reactive mechanisms are probably not mutually exclusive but rather interact for efficient inhibitory control (Verbruggen and Logan, 2008; Ballanger, 2009; Ballanger et al., 2009; Chikazoe et al., 2009; Lo et al., 2009; Mazaheri et al., 2009; Boy et al., 2010c; Chen et al., 2010; Claffey et al., 2010; Duque et al., 2010; Karayanidis et al., 2010, 2011; Ullsperger and King, 2010; Zandbelt and Vink, 2010). Nevertheless, current models of inhibitory control are mainly based on studies that have investigated reactive mechanisms, and still very little is known about the recent notion of proactive inhibitory control.

The major obstacle for identifying proactive inhibitory control (Figure 1) is that it is almost always involved in stimulus-response paradigms (Jaffard et al., 2007). Indeed, when the experimental protocol introduces uncertainty about the next event to come (e.g., will it be a go or a nogo stimulus? a cue or a target? a square or a circle?), as is usually the case in mixed-block designs, subjects are forced to withhold automatic responses to any upcoming event in order to avoid erroneous responses. This creates a serious problem with respect to the meaning of the control conditions or baseline activities classically used to refer to the effects of interest. For example, the metabolic activity induced by proactive inhibitory control does not survive standard neuroimaging contrasts like nogo > go or cue > no-cue trials because the function is systematically involved in both conditions. Similarly, the persistent neuronal activity observed before a stimulus and pinpointing top-down inhibitory control in the absence of sensory input vanishes when a short epoch preceding the first event of interest is used as a baseline for event-related potentials in electroencephalographic or electrophysiological recordings. Thus, identifying proactive inhibitory control requires the use of an unbiased control condition performed in an independent block of trials in which response triggering mechanisms are not locked in advance (e.g., only go trials are presented apart from the other conditions of interest and are compared to go trials presented randomly in a mixed-design). Using appropriate control conditions and baselines in order to take into account the effect of proactive inhibitory control is central for the proper interpretation of the

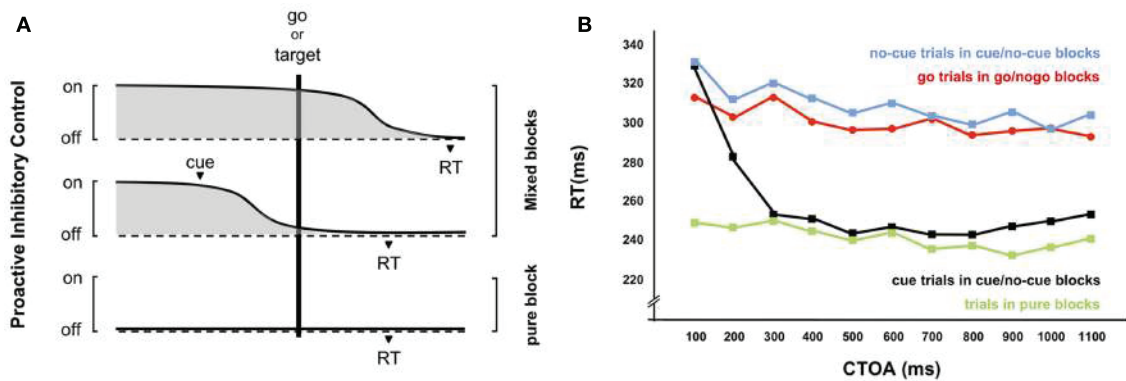


FIGURE 1 | The proactive inhibitory control model. (A) Hypothetical dynamics of proactive inhibitory control. When there is uncertainty about upcoming stimuli, as in standard mixed-block designs (e.g., go intermixed with nogo trials in go/nogo protocols – Figure 2A, cue intermixed with no-cue trials in cue/target protocols – Figure 3), tonic response inhibition is required to prevent false alarms (automatic responses to nogo or to cue stimuli). This implies that inhibitory control cannot be lifted until the first stimulus has been identified (a go or a nogo, a cue or a target). As a consequence, proactive inhibitory control is maximum at target occurrence in go and no-cue trials (upper part), two conditions usually considered as regular control conditions in standard designs. Accordingly, the mechanism of action of a warning signal may simply consist in unbolting the gate before a target occurs (middle part). Importantly, no proactive inhibitory control is required in conditions in which only targets are presented (pure-blocks, lower part), providing an unbiased baseline rarely considered in psychophysical setups. **(B)** Behavioral correlates of proactive inhibitory control. Go trials in go/nogo protocols as well as no-cue trials in cue/target protocols show a dramatic increase in reaction times (RT) with respect to no-cue trials performed apart in pure-blocks. The former condition involves proactive inhibition while the latter does not. The model assumes that when a go signal is presented (or when a target occurs without being preceded by a warning cue), the stimulus needs first to be identified to allow the release of inhibitory control and, hence, movement initiation. If a warning cue is presented sufficiently in advance of the target (cue–target

onset asynchrony, CTOA ≥ 300 ms), proactive inhibitory control has already been released at target occurrence and fast automatic responses to subsequent stimuli are generated in a similar way to no-cue trials performed apart in pure-blocks. (adapted from Jaffard et al., 2007). Yet, it could be argued that the RT change could be accounted for exclusively by (1) the addition of a visual discrimination process to the task in mixed-blocks, and (2) a linear rise to threshold model of motor preparation. Importantly, we previously tested and rejected this hypothesis. First, visual discrimination is a prerequisite in mixed designs, but ERP markers of inhibition are systematically locked to the process (e.g., Boulinguez et al., 2009). Second, electrophysiological measures of the activity of the muscles involved in response execution show that errors do not linearly increase as CTOA increases, as predicted by motor preparation effects. They are conversely composed of impulsive activations triggered by the first stimulus (Boulinguez et al., 2008; see also Sinclair and Hammond, 2008, 2009 for convincing evidence arising from studies using transcranial magnetic stimulation during foreperiods of warned RT privileging the inhibitory over the preparatory account). Finally, neuroimaging studies revealed that brain activity preceding stimulus presentation is coupled with changes in the motor brake circuitry (SMA, ventral anterior nucleus of the thalamus, primary motor cortex, putamen and inferior parietal lobule: Jaffard et al., 2007, 2008) and modulated by STN stimulation (Ballanger et al., 2009). In other words, proactive inhibitory control likely involves the anticipated suppression of the neuronal processes underlying movement initiation.

neural mechanisms underlying the numerous cognitive functions usually tested with cue–target protocols (e.g., attention, decision making, executive control). Otherwise, this may lead to reversed interpretations of typical behavioral outcomes (Jaffard et al., 2007; Albares et al., 2011) or brain activations (Jaffard et al., 2007, 2008; Boulinguez et al., 2009). Taking into account the involvement of proactive inhibitory control in stimulus response experiments may help resolving long-lasting controversies about attention and cognitive control (Kok et al., 2006; Anderson, 2011).

The proactive inhibitory control model hypothesizes that subjects can switch from controlled inhibition of response (anticipated suppression of the neuronal processes underlying movement initiation) to automatic processing of sensorimotor information (unlocked state) depending on their expectations of upcoming events (see also Hikosaka and Isoda, 2010). Obviously, this control contributes to long-lasting task setting (the configuration of cognitive processes that is actively maintained for subsequent performance in the task; Sakai, 2008; Vallesi et al., 2009), but this switch can also be performed with short delays within the course of a trial. Indeed, the time required to release proactive inhibitory control was estimated at less than 300 ms (Jaffard et al.,

2007; Figure 1). But how proactive inhibitory control can be implemented remains elusive. It may be set up when the context becomes ambiguous or potentially conflicting. According to this view, executive control would consist of applying temporary inhibition when necessary. Conversely, proactive inhibition may be the default state of the executive system, meaning that top-down control of sensorimotor reactivity would consist of releasing temporarily proactive inhibitory control. The latter hypothesis is compatible with recent functional magnetic resonance imaging (fMRI) observations revealing large overlaps between the mysterious “Default Mode Network” of brain function and the structures involved in the tonic inhibition state (Jaffard et al., 2008), yet no direct behavioral support for this hypothesis is available.

Here we test these two hypotheses and assess the dynamics of proactive inhibitory control by asking two questions: First, can this control be sustained over long periods of time (several seconds) or is it transient? Second, how long does it take to set up proactive inhibitory control? Two behavioral experiments were conducted. They manipulated the time during which inhibitory control must be sustained until a stimulus occurs, and the time limit allowed to set up inhibition before a stimulus occurs.

EXPERIMENT 1

Experiment 1 was adapted from classical go/nogo tasks. Subjects were asked to react to a go stimulus by means of a button press with the right thumb, and to withhold responses to an equiprobable nogo stimulus. Since we previously showed that proactive inhibitory control is largely involved in this kind of task (Jaffard et al., 2007), we also added a control condition in which it was not involved, i.e., go trials performed apart for which there is no need to refrain from reacting. In the go/nogo condition, we manipulated the time during which proactive inhibitory control had to be sustained by varying the delay between the beginning of a trial and the go or nogo stimulus presentation (Figure 2A).

MATERIALS AND METHODS

Subjects

Nineteen naive subjects (ages: 23–38, 11 females) with normal vision participated in the experiment. The experimental protocol was preapproved by the local ethical committee in Biomedical Research (comité de protection des personnes sud-est IV, No. CPP 11/025). All participants gave written informed consent.

Apparatus and procedure

The subjects were seated in a darkened room in front of a screen placed 50 cm from their eyes. Each subject's head was fixed using a chinrest to maintain the viewing distance and stabilize the head. Stimuli were presented and data were acquired using Presentation™. A red cross (0.4 cm × 0.4 cm) placed at the center of the screen and set at the subject's eye level served as a fixation point. Its appearance indicated the beginning of the trial and it lasted until the end of the trial. It could be replaced by a go stimulus (a 2.5-cm ∅ white circle centered on the screen, 2.9° of visual angle), a nogo stimulus (a 2 cm × 2 cm white "X" centered on the screen, 2.3° of visual angle), or no stimulus at all (catch trials, 15% of trials). Pre-stimulus delays (time between the beginning of a trial and stimulus presentation, i.e., the time during which proactive inhibitory control had to be sustained) varied from 2 to 6 s by steps of 500 ms. The inter-trial interval was fixed to 1 s. Subjects were asked to react as fast as possible to go stimuli by pressing a button with the right thumb while maintaining their error rate (responses in absence of go stimulus, responses to nogo stimuli or missed go stimuli) below 10%. They were informed about the evolution of their mean error rate after each error.

In order to introduce a control condition in which proactive inhibitory control was not involved, we added another kind of trial: a condition which did not require subjects to sustain proactive inhibitory control after the trial start and during the course of the pre-stimulus delay. In 35.7% of the trials, the central fixation point could turn white at the beginning of a trial, indicating that no nogo stimulus would be presented (only go/control – "white_cross" trials, 80% and catch trials, 20%). This condition enabled subjects to react automatically to any upcoming event. After a training session of 50 trials, "white_cross" and "red_cross" conditions were presented randomly in mini-blocks of 20 trials. All in all, 36 trials were presented for each condition of interest: Go/nogo (go presented in the red_cross condition, i.e., with stimulus uncertainty), nogo (red_cross condition), and go/control (go presented in the

white_cross condition, i.e., without uncertainty about the identity of the upcoming stimulus).

Data analysis

False alarm rate. A nine Pre-stimulus delay (2; 2.5; 3; 3.5; 4; 4.5; 5; 5.5; 6 s) ANOVA with repeated-measures was applied to the False Alarm rate (number of responses to the nogo stimulus/number of nogo stimuli).

Reaction time (the time between a go stimulus presentation and the button press response).

In order to avoid potential biases due to the classical lengthening of RT distribution's tail, we performed the statistical analysis of RT on log transformed data (neperian logarithm). A 2 Go (go/nogo vs. go/control) × 9 Pre-stimulus delay (2; 2.5; 3; 3.5; 4; 4.5; 5; 5.5; 6 s) ANOVA with repeated-measures was applied. *Post hoc* comparisons were performed when necessary using Newman–Keuls tests.

RESULTS

False alarms

No significant effect was observed. The false alarm rate was low for all values of pre-stimulus delay (mean 0.158 ± 0.026).

Reaction time

Reaction time (RT) results are presented in Figure 2B. A main effect of Go [$F(1, 18) = 131, p < 0.001; \eta^2 = 0.88$] showed shorter RT to go stimuli in the go/control condition (RT: 293 ± 43 ms) than in the go/nogo condition (RT: 376 ± 61 ms). A main effect of Pre-stimulus delay was also observed [$F(8, 144) = 10.5, p < 0.001; \eta^2 = 0.37$]. *Post hoc* analyses revealed that RT decreased as a function of Pre-stimulus delay up to 3 s (376 ± 76 vs. 359 ± 66 vs. 341 ± 67 for 2, 2.5, and 3 s delays respectively, $ps < 0.05$). No significant difference was observed between Pre-stimulus delay conditions above 3 s. No significant interaction between go and Pre-stimulus delay factors was observed.

DISCUSSION

The suppression of actions that are inappropriate in a given context does not only rely on phasic, reactive inhibitory mechanisms triggered by a nogo signal. Knowing that inhibitory control of response may be required also involves anticipated adjustments. Indeed, in accordance with the results of the present experiment, the insertion of nogo signals in a series of trials delays response latency in go trials with respect to an appropriate go/control condition (Menon et al., 2001; Jaffard et al., 2007). Unfortunately, proper go/control conditions are not systematically or appropriately used or discussed in go/nogo tasks, and the mechanisms by which these anticipated modulations operate have long been ignored or neglected. Some studies have attributed proactive modulations of brain activity and related behavioral outcomes in inhibition tasks to varying levels of sustained attention (Mazaheri et al., 2009) or response readiness (van den Wildenberg et al., 2002). However, recent converging evidence indicates that foreknowledge of potentially conflicting upcoming events results in setting up a control set whereby inhibitory control of response is applied in advance (Jaffard et al., 2007, 2008; Boulinguez et al., 2008, 2009; Chikazoe et al., 2009; Lo et al., 2009; Boy et al., 2010c; Chen et al., 2010;

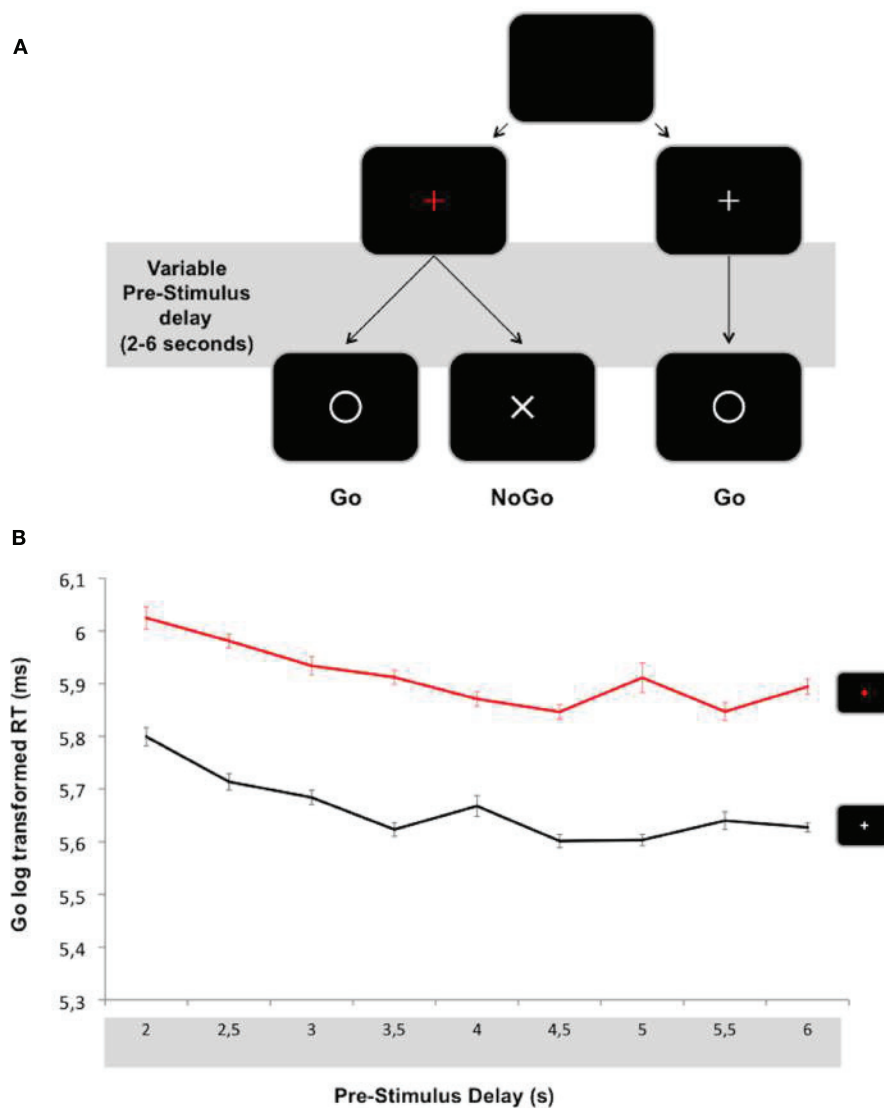


FIGURE 2 | (A) Overview of Experiment 1 (catch trials are not represented). Subjects are instructed to react to the presentation of a go signal (O) by pressing a button as fast as possible. At the beginning of a trial, the central fixation point (+) turns either red or white, indicating respectively that nogo stimuli (X) can or cannot be presented. In the

former condition, subjects must refrain from reacting in order to avoid responses to nogo stimuli. In the latter condition, subjects can react automatically to any upcoming target. **(B)** Mean reaction time to go/nogo (red line) and go/control (black line) stimuli plotted as a function of pre-stimulus delay. Vertical bars indicate standard error of the means.

Claffey et al., 2010; Stuphorn et al., 2010; Aron, 2011). Obviously, such an inhibitory state strongly affects performance in go/nogo trials because proactive response inhibition is at a maximum at stimulus occurrence, in contrast with go/control trials in which no proactive inhibitory control applies since subjects do not need to withhold responses to upcoming stimuli. Accordingly, it is likely that the go/control vs. go/nogo RT difference is mostly due to the involvement of proactive inhibitory control. More precisely, this difference indexes the time required to release proactive inhibitory control of response after the stimulus has been identified as the go signal (Jaffard et al., 2007).

Based on this postulate, the results of Experiment 1 clearly suggest that proactive inhibitory control is not transient but can be

sustained over several seconds (at least 6) since the go/control vs. go/nogo RT difference remains constant over increasing foreperiods (83 ms, **Figure 2B**). In particular, this main effect does not interact with the effect of foreperiod duration classically observed on RT when the distribution of pre-stimulus delays is uniform (Los and Van Den Heuvel, 2001). The observation that RT decreases as pre-stimulus delay increases (observed only from 2 to 3 s pre-stimulus delays in the present experiment) is usually attributed to the fact that non-specific preparation develops in accordance with the conditional probability of stimulus occurrence (the more time elapses, the greater the chance that a target will occur). Since this outcome is identical for the go/control and go/nogo conditions in our experiment, it can be asserted that proactive inhibitory

control is not confounded with motor preparation. In other words, this observation supports the view that proactive inhibitory control of response does not only rely on the modulation of motor corticospinal excitability, but also involves independent breaking circuits acting on the command function for initiating a motor program (Jaffard et al., 2008).

While we now know that proactive inhibitory control can be sustained for relatively long periods of time (present data) and can be released when appropriate within extremely short delays (<300 ms, e.g., Jaffard et al., 2007, 2008; Boulinguez et al., 2009), a major issue remains regarding its dynamics: how is proactive inhibitory control implemented? Theoretically, two opposite hypotheses can be put forward: (1) Proactive inhibitory control is set up as soon as there is uncertainty about upcoming events, and is sustained until this uncertainty vanishes (the temporary set hypothesis). (2) Proactive inhibitory control is the default state of executive control, and can be actively released when an upcoming event becomes predictable (the default state hypothesis). These two hypotheses make specific predictions that are tested in Experiment 2.

EXPERIMENT 2

Experiment 2 (Figure 3) was adapted from the standard warned visual detection task. The original task allows the dynamics

of proactive inhibitory control to be revealed because it separates in time the implementation of proactive inhibitory control, its release, and target presentation (Jaffard et al., 2007, 2008; Boulinguez et al., 2008, 2009), while the last two events occur simultaneously in go/nogo-like protocols. It was adapted in the sense that we used instruction signals as in Experiment 1 to inform subjects about the experimental condition (red and white crosses), rather than performing these conditions in two separate blocks of trials. Subjects were asked to react to a target, which might or might not be preceded by a warning cue, by means of a button press with the right thumb. In other words, they were implicitly asked to withhold responses to unpredictable cues. We manipulated the time limit to set up proactive inhibitory control by varying the delay between the beginning of a trial (instruction) and the stimulus presentation (cue or target, Figure 3). We focused on the period 0–2 s after the trial started, which was ignored in Experiment 1.

MATERIALS AND METHODS

Subjects

Twenty-five naive subjects (ages: 21–28, 17 females) with normal vision participated in the experiment. The experimental protocol was preapproved by the local ethical committee in Biomedical Research (comité de protection des personnes sud-est IV, No. CPP 11/025). All participants gave written informed consent.

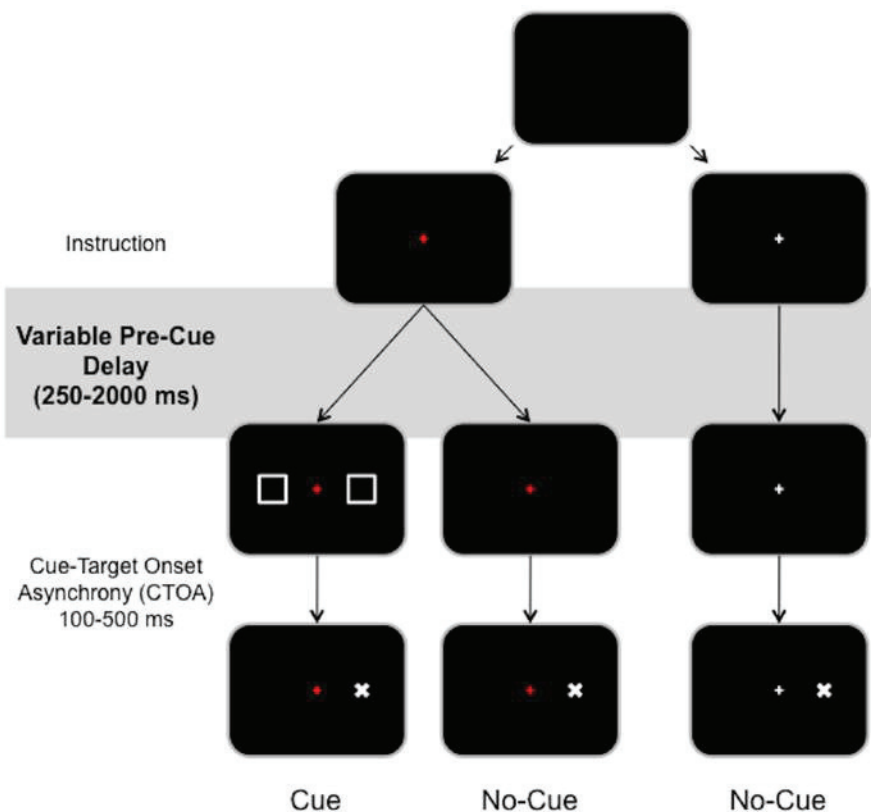


FIGURE 3 | Overview of Experiment 2. Subjects are instructed to react to the presentation of the target (X) by pressing a button as fast as possible. At the beginning of a trial, the central fixation point (+) turns either red or white, indicating respectively that a warning cue (two peripheral squares) can or

cannot be presented before target occurrence. In the former condition, subjects must refrain from reacting in order to avoid responses to the warning cue. In the latter condition, subjects can react automatically to any upcoming target.

Apparatus and procedure

While keeping their gaze fixed on a central fixation point (a 0.4 cm × 0.4 cm cross at the center of the screen), the subjects were asked to react as quickly as possible to a visual target that might or might not be preceded by a neutral warning signal. The neutral cue was composed of two 1.8 cm × 1.8 cm squares (2.06° of visual angle) located 6.9° to the left and right of the fixation point (duration 50 ms). The target was a 0.6 cm × 0.5 cm “X” (0.69 × 0.57° of visual angle) located either at 6.9° to the left or right of the fixation point (duration 50 ms).

As in Experiment 1, the central fixation point could be red or white when displayed at the beginning of a trial. A red cross indicated that a target could be preceded by a neutral warning signal (75%) or not (25%). A white cross indicated that no warning signal would be presented before a target (100% targets). In other words, this control condition did not require subjects to sustain proactive inhibitory control during the course of the pre-stimulus delay. We manipulated the time allowed to implement proactive inhibitory control by varying the delay between the beginning of a trial (instruction) and stimulus presentation (cue or target; **Figure 3**). Pre-stimulus delays varied randomly from 250 to 2000 ms in steps of 250 ms.

We also manipulated cue–target onset asynchrony (CTOA). Based on previous findings showing that the release of inhibitory control triggered by cue presentation takes less than 300 ms (Jaffard et al., 2007, 2008; Boulinguez et al., 2008, 2009), we used three CTOA levels that surround this value (100, 300, and 500 ms). Short CTOA (100 ms) is classically characterized by long RT because proactive inhibitory control is still engaged at target occurrence, whereas long CTOA (300, 500 ms) is characterized by short RT because proactive inhibitory control has already been released at target occurrence. Importantly, RT values for long CTOA were always found to be identical to RT observed in a control condition in which only targets were presented and for which no proactive inhibitory control was required (Jaffard et al., 2007, 2008; Boulinguez et al., 2008, 2009). In other words, long CTOA also provide a reliable control condition.

After a training session of 50 trials, “white_cross” and “red_cross” conditions were presented randomly in 10 mini-blocks of 40 trials. All in all, 240 cue trials (80 for each CTOA condition), plus 80 red_cross_no_cue trials, plus 80 white_cross_no_cue trials were presented. For each one of these conditions, 10 trials were presented for each pre-stimulus delay.

Data analysis

False alarms. False alarms were defined as responses to the cue. There are easily detectable when the button press occurs before the target. However, there are less easy to detect when the delay between the cue and the target is short. In order to detect responses to cues given after the target was presented for short CTOA trials, we also applied a cut-off filter to RT < 150 ms. These very short RT, outside the regular distribution, were considered as false alarms in cue target trials. An eight Pre-stimulus delay (250; 500; 750; 1000; 1250; 1500; 1750; 2000 ms) ANOVA was applied to False Alarm rate (number of responses to the cue/number of cue trials).

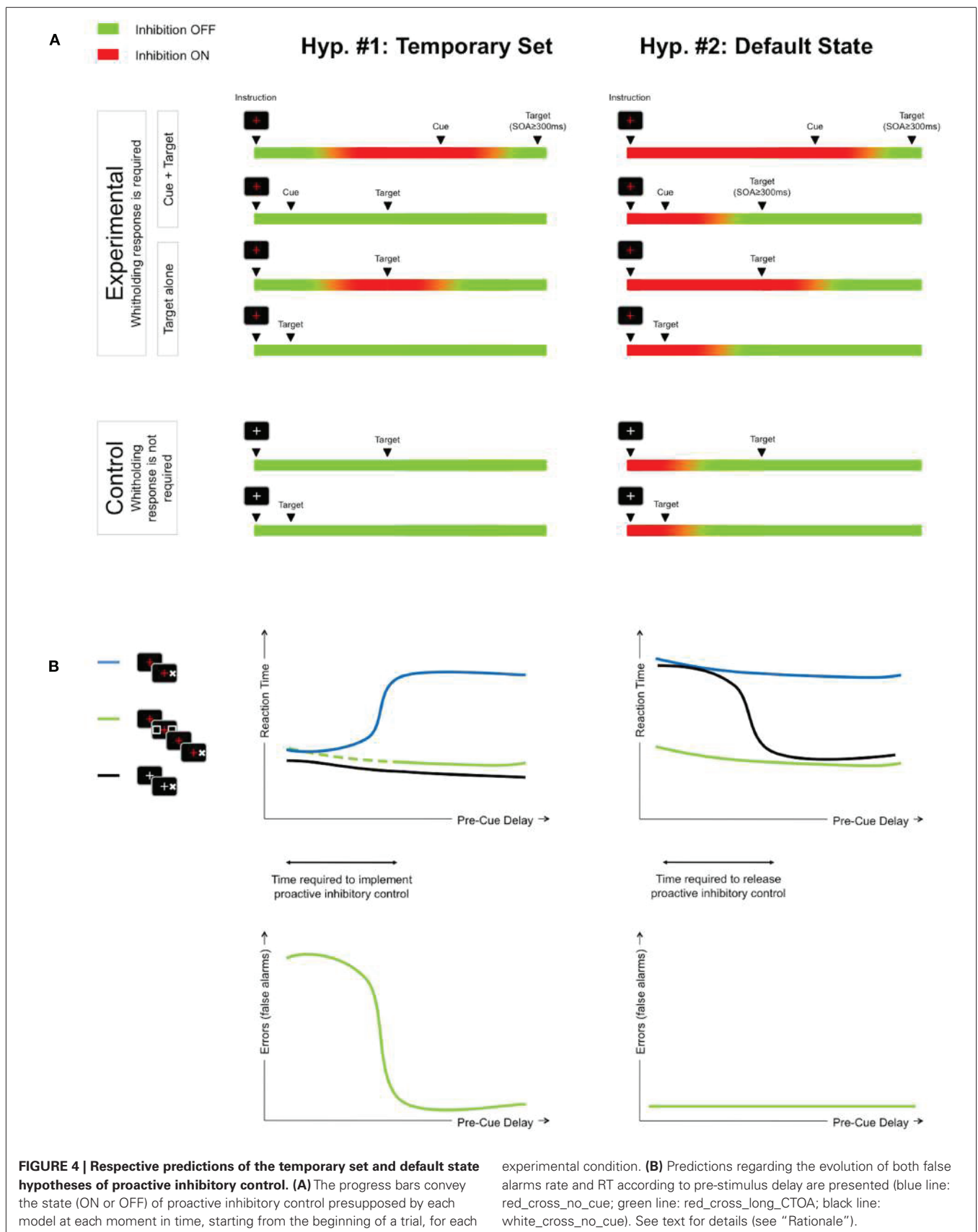
Pre-processing of RT data. We first analyzed cue trials RT according to CTOA and Pre-stimulus delay. The goal of this pre-processing is to check that CTOA ≥ 300 ms are long enough to allow subjects to release proactive inhibition, i.e., to insure that it is correct to consider long CTOA as a proper control condition. According to the model of proactive inhibitory control, this statement implies that longer RTs are observed for short (100 ms) than for long (≥ 300 ms) CTOA, and that RT stabilizes after CTOA 300 ms. A three CTOA (100, 300, 500 ms) ANOVA confirmed that long CTOA (500 and 300 ms) provides shorter RT than short CTOA (100 ms; respectively 252 and 254 vs. 307 ms; $F(2, 48) = 147$; $p < 0.001$, $ps < 0.001$ for *post hoc* Newman–Keuls tests). Individual analyses (*t*-tests) revealed that this effect was significant for each of our 25 subjects. Since no significant difference was observed between CTOA 500 and CTOA 300, we collapsed these two conditions, referred to as “long_CTOA” in the following sections, for the main data analyses.

Reaction time. Since switching from controlled inhibition to automatic sensorimotor reactivity may involve great interindividual variability with regard to switch timing (in addition to basic RT interindividual variability), we performed individual analyses to categorize each subject’s behavior with respect to the specific predictions of our two hypotheses. Unpaired two-sample *t*-tests were used to compare the RTs of cue and no-cue conditions for each pre-stimulus delay. More precisely, we compared “red_cross_no_cue,” “white_cross_no_cue,” and “red_cross_long_CTOA” conditions. The false alarm rate (number of responses to cues/number of cues, all CTOA collapsed) for each pre-stimulus delay was assessed by means of unpaired two-sample *t*-tests.

RATIONALE

Figure 4 presents the specific predictions of the two opposite hypotheses.

If proactive inhibitory control is set up when uncertainty about upcoming events occurs (temporary set hypothesis), then, in our experimental design, set up is induced by the presentation of the red cross. According to this hypothesis (**Figure 4**, left side), the time required to implement proactive inhibitory control can easily be estimated on the basis of the analysis of cued trials performance (green lines). Indeed, when the cue appears before set up is completed, the false alarm rate (responses to cues) is expected to be maximum (with minimum RT to cues). When the cue appears after set up is completed, no false alarm is expected. This hypothesis suggests that the switch time from maximum to minimum false alarm rate reflects the time required to set up inhibitory control. No-cue trials in the uncertainty condition (red_cross, blue lines) provide specific predictions about the duration of this mechanism. Indeed, if the target appears within short delays, very short RTs are expected because proactive inhibitory control is not set yet. Conversely, if the target appears after a sufficient delay, long RTs are expected because inhibition is ON at target occurrence. The switch time from minimum to maximum RT is also supposed to index the time required to set up inhibitory control. Finally, no-cue trials in the control condition (white_cross, i.e., no need to set up proactive inhibitory control; black lines) predict short RT whatever the pre-stimulus delay.



The default state hypothesis makes opposite predictions. If proactive inhibitory control is the default state of executive control, this means it is already set at the trial start and must just be released after any event (white cross or warning cue) indicates that there is no more uncertainty about the identity of the next stimulus. According to this hypothesis (Figure 4, right side), the time required to release default inhibitory control can be estimated on the basis of the analysis of no-cue trials in the control condition (white_cross, i.e., no need to sustain proactive inhibitory control; black lines). Indeed, if the target appears too soon after instruction presentation, i.e., while inhibitory control is still ON, then long RTs are expected. Conversely, if the target is presented after a sufficient delay, i.e., after inhibitory control has been released, short RTs are expected. This hypothesis suggests that the switch time from long to short RT reflects the time required to release the default state of inhibitory control. Since this control is already ON at the trial start, this hypothesis also predicts that the rate of false alarms will remain low whatever the duration of the pre-stimulus period for cued trials (green lines), as well as RT to targets with long CTOA. Finally, no-cue trials in the red_cross condition (blue lines) are expected to provide long RTs whatever the pre-stimulus delay because inhibitory control is always supposed to be ON at target occurrence.

To test these predictions, we performed individual statistical analyses. We first contrasted red_cross_no_cue with white_cross_no_cue conditions, assuming that inhibition is ON in the red_cross_no_cue condition when a significant difference is observed. If inhibition is ON in both conditions, no significant difference but long RT are expected. If inhibition is OFF in both conditions, no significant difference but short RT are expected. Then we contrasted white_cross_no_cue with red_cross_long_CTOA conditions, assuming that inhibition is ON in the white_cross_no_cue condition when a significant difference is observed, and OFF when there is no significant difference (see Figure 4; Table 1).

RESULTS

False alarms

No significant effect was observed. The false alarm rate was low for all values of pre-stimulus delay (mean 0.037 ± 0.004).

Reaction time

Individual results are presented in Table 1 and Figure 5. Twenty-two of the 25 subjects showed similar patterns consistent with the predictions of Hypothesis #2 (Figure 4).

Thus, we calculated a normalized RT in order to better illustrate the switch of the white_cross_no_cue condition from one control condition (inhibition ON) to the other (inhibition OFF) as pre-stimulus delay elapses (Figures 4 and 5A). White_cross_no_cue (black line) data were transformed with respect to statistical comparisons with red_cross_no_cue (blue line) and red_cross_long_CTOA (green line) control conditions for each pre-stimulus delay. When white_cross_no_cue is not different from red_cross_no_cue, RT is maximum. Accordingly, it was inferred that inhibition is ON at target occurrence and the value 1 was attributed to normalized white_cross_no_cue RT. Conversely, when white_cross_no_cue is not different from

red_cross_long_CTOA, RT is minimum. Thus, it was inferred that inhibition was OFF at target occurrence and the value 0 was attributed to normalized white_cross_no_cue RT. When significant differences were reported, corresponding normalized values were calculated as follows:

Normalized RT

$$= \frac{[(\text{red_cross_no_cue}) - (\text{red_cross_long_CTOA})]}{[(\text{white_cross_no_cue}) - (\text{red_cross_long_CTOA})]}$$

Normalized RT data were then fitted by a logistic function (Figure 5A, right) which best represents the switch from one state to the other. A Chi-square was used to test the validity of this fit. Observed and theoretical distributions were not significantly different for any of the 22 subjects who showed patterns consistent with the predictions of Hypothesis #2 ($p_s > 0.97$; Table 1).

The time required to start releasing inhibitory control after a trial start in the white_cross_no_cue condition can be estimated as the time the fitted logistic function reports values < 1 . The time inhibitory control is fully released in the white_cross_no_cue condition can be estimated as the time the fitted logistic function reaches 0. The difference between these two events represents the mean duration of the process in charge of releasing proactive inhibitory control after the uncertainty about the nature of the upcoming event has vanished. Figure 5B shows that the timing of these events is variable across subjects (mean duration: 600 ± 664 ms).

Among the three remaining subjects, two (s8, s12) showed no difference between the red_cross_no_cue and white_cross_no_cue conditions. The other subject (s19) showed significant differences between the red_cross_no_cue and white_cross_no_cue conditions beginning 1750 ms after trial start. However, RT in the white_cross_no_cue condition remained longer than in the red_cross_long_CTOA control condition for all pre-stimulus delays. These two patterns do not fit all predictions of Hypothesis #2, but are in total contradiction with the predictions of Hypothesis #1.

DISCUSSION

Eighty-eight percent of the subjects revealed clear patterns of results fitting perfectly the predictions of the default state hypothesis (Figures 4 and 5A,B). Among the other subjects, two did not take into account the instruction to react freely to upcoming events (white_cross condition), or were unable to release inhibitory control in due time after trial start. Nevertheless, inhibitory control was also already set at trial start for these subjects, who were able to release it after the presentation of a warning cue in less than 300 ms like the other subjects. The other atypical subject seemed able to follow the instruction to release inhibitory control after the trial start (white_cross condition). However, his RT pattern suggests that this mechanism remained uncompleted 2 s after the trial start.

All together, these results suggest that (1) proactive inhibitory control is the default state of executive control because it is already set at the trial start for all subjects, (2) the dynamics of proactive inhibitory control of response is variable among subjects and is heterogeneous depending on the instructing stimulus: While

Table 1 | Individual RT analyses of Experiment 2.

Subject	Test	Pre-stimulus delay (ms)								Logistic fn fit Chi-square (<i>p</i>)
		250	500	750	1000	1250	1500	1750	2000	
s1	#1	- (380)	*	*	*	*	*	*	*	
	#2	*	*	- (232)	-	-	-	-	-	
	Norm.	1	0.29	0	0	0	0	0	0	1
s2	#1	-	- (457)	*	*	*	*	*	*	
	#2	*	*	- (276)	-	-	-	-	-	
	Norm.	1	1	0	0	0	0	0	0	1
s3	#1	- (477)	-	-	*	*	*	*	*	
	#2	*	-	-	- (249)	-	-	-	-	
	Norm.	1	0.54	0.20	0	0	0	0	0	1
s4	#1	- (431)	*	-	*	-	*	*	*	
	#2	*	*	-	-	-	- (268)	-	-	
	Norm.	1	0.41	0.43	0	0.47	0	0	0	0.97
s5	#1	- (403)	-	-	*	-	-	*	*	
	#2	-	-	-	-	-	-	- (300)	-	
	Norm.	0.55	-0.55	0.59	0	0.24	0.25	0	0	0.99
s6	#1	- (396)	*	*	*	*	*	*	*	
	#2	*	*	- (274)	-	-	-	-	-	
	Norm.	1	0.39	0	0	0	0	0	0	1
s7	#1	-	-	-	-	- (301)	-	-	*	
	#2	*	*	*	*	*	-	-	- (235)	
	Norm.	1	1	1	1	1	0.34	0.44	0	0.99
s8	#1	-	-	-	-	-	- (299)	*	*	
	#2	*	*	*	*	*	*	*	*(239)	
	Norm.	1	1	1	1	1	1	0.63	1.1	-
s9	#1	-	- (325)	-	-	*	*	*	*	
	#2	*	*	-	-	- (215)	-	-	-	
	Norm.	1	1	0.36	0.17	0	0	0	0	0.99
s10	#1	-	- (340)	*	*	*	*	*	*	
	#2	*	*	- (236)	-	-	-	-	-	
	Norm.	1	1	0	0	0	0	0	0	1
s11	#1	-	- (351)	*	*	*	*	*	*	
	#2	*	*	*	- (237)	-	-	-	-	
	Norm.	1	1	0.29	0	0	0	0	0	1
s12	#1	- (450)	-	-	-	-	-	-	-	
	#2	*(297)	*	*	*	*	*	*	*	
	Norm.	1	1	1	1	1	1	1	1	-
s13	#1	*(504)	*	*	*	*	*	*	*	
	#2	*	- (242)	-	-	-	-	-	-	
	Norm.	0.33	0	0	0	0	0	0	0	1
s14	#1	- (405)	*	*	*	*	*	*	*	
	#2	*	- (243)	-	-	-	-	-	-	
	Norm.	1	0	0	0	0	0	0	0	1
s15	#1	- (372)	*	*	*	*	*	*	*	
	#2	-	- (247)	-	-	-	-	-	-	
	Norm.	0.75	0	0	0	0	0	0	0	1
s16	#1	- (414)	-	-	*	*	*	*	*	
	#2	*	-	-	- (234)	-	-	-	-	
	Norm.	1	0.46	0.20	0	0	0	0	0	0.99
s17	#1	- (347)	*	*	*	*	*	*	*	

(Continued)

Table 1 | Continued

Subject	Test	Pre-stimulus delay (ms)								Logistic fn fit Chi-square (<i>p</i>)
		250	500	750	1000	1250	1500	1750	2000	
s18	#2	-	-(248)	-	-	-	-	-	-	1
	Norm.	0.62	0	0	0	0	0	0	0	
s19	#1	-	<u>-(351)</u>	-	-	-	*	*	*	0.99
	#2	*	*	-	-	-	-(222)	-	-	
s20	Norm.	1	1	0.48	0.26	0.30	0	0	0	-
	#1	-	<u>-(352)</u>	-	-	-	-	-	-	
s21	#2	*	*	*	*	*	*	-	-(242)	1
	Norm.	1	1	1	1	1	1	0.42	0.28	
s22	#1	-	<u>-(455)</u>	*	*	*	*	*	*	1
	#2	*	*	-(253)	-	-	-	-	-	
s23	Norm.	1	1	0	0	0	0	0	0	1
	#1	-	<u>-(467)</u>	-	*	*	*	*	*	
s24	#2	*	*	-	-(279)	-	-	-	-	1
	Norm.	1	1	0.70	0	0	0	0	0	
s25	#1	-	-	<u>-(286)</u>	*	*	*	*	*	0.99
	#2	*	*	*	*	*	-(230)	-	-	
s25	Norm.	1	1	1	0.058	0.27	0	0	0	0.99
	#1	-	-	-	<u>-(347)</u>	-	-	*	*	
s25	#2	*	*	*	*	-	-	-(244)	-	0.99
	Norm.	1	1	1	1	0.19	0.33	0	0	

Unpaired two-sample *t*-tests were used to compare red_cross_no_cue with white_cross_no_cue conditions (comparison #1) and white_cross_no_cue with red_cross_long_CTOA conditions (comparison #2) for each pre-stimulus delay (-, no significant difference; **p* < 0.0031 – corrected for multiple comparisons). Normalized white_cross_no_cue RT (Norm.) is reported for each condition (see text and **Figure 5** for details). The value 1 indicates that inhibition is ON at target occurrence. The value 0 indicates that inhibition is OFF at target occurrence. Mean red_cross_no_cue RT (underlined) is given for the last condition of pre-stimulus delay for which inhibitory control is still ON at target occurrence. Mean red_cross_long_CTOA RT (bold) is given for the first condition of pre-stimulus delay for which inhibitory control significantly reaches the OFF state. The *p*-values obtained when testing the validity of the logistic function fit (Chi-square) are reported in the last column.

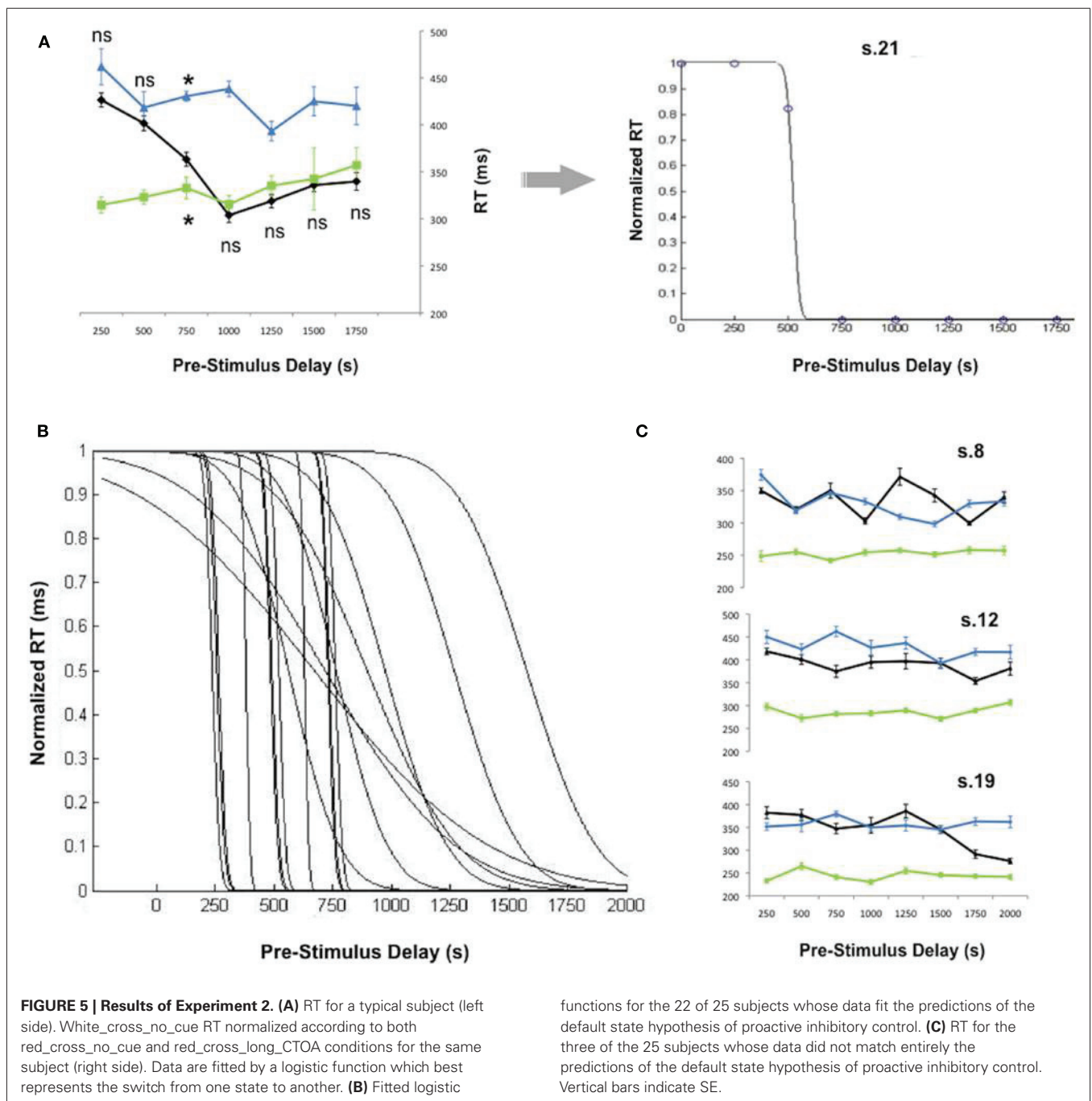
an exogenous alerting cue allows a rapid (<300 ms) release of inhibitory control for all subjects, a symbolic instruction cue induces a longer and more variable switch to an automatic mode of sensorimotor processing (≥ 500 ms).

GENERAL DISCUSSION

Proactive control may better account for efficient inhibition of inappropriate responses than reactive control (Aron, 2011). However, the mechanisms involved in the preparation to inhibit motor responses are still unclear. Brain activations (or deactivations) observed in the pre-stimulus period in tasks requiring subjects to refrain from reacting have been variously attributed to sustained attention (Coull et al., 1996; Coull, 1998; Mazaheri et al., 2009, 2011), motor corticospinal excitability reduction (Duque and Ivry, 2009; Sinclair and Hammond, 2009; Stinear et al., 2009), response threshold (Forstmann et al., 2008; Verbruggen and Logan, 2008), or increase in working memory load (Coull et al., 1996; McNab et al., 2008). Without refuting the direct or indirect roles these

functions play in controlling motor outputs, we assume, based on recent findings, that the main neurocognitive mechanism involved in proactive inhibitory control is an active braking process that locks movement initiation processes in anticipation of stimulus occurrence (Jaffard et al., 2007, 2008 summarized in **Figure 1**; see also Brass and Haggard, 2007; Jahfari et al., 2009). However, how this control is set up is still unknown.

What is accepted is the fact that proactive inhibition is controlled according to the goals of the subject (Aron, 2011). The standard view implicitly suggests that this control is set up when the context becomes ambiguous or potentially conflicting. In other words, executive control would consist of generating a top-down signal to gate the neural mechanisms responsible for movement triggering as long as uncertainty remains. The results of the present experiment clearly contradict this view. Proactive inhibition of response is probably the default state of executive control. This means that applying control would conversely consist of generating a top-down signal that unlocks the neural mechanisms



responsible for movement triggering as soon as uncertainty about the next event had vanished. This release is not transient and probably does not act like a burst locked to the motor response, but can be sustained for several seconds. At first glance this mechanism seems counter-intuitive, but it is probably the most effective means of regulating voluntary vs. automatic modes of action control. While the ability to allow or to override automatic motor activations is a core feature of flexible and adaptive behavior, in everyday life, most of the time we must refrain from reacting to stimuli overflows. Indeed, all kinds of sensory stimulation may provide important sources of motor excitation that can trigger

undesired movements (Endo et al., 1999; Tipper, 2001; Aron, 2007; Minelli et al., 2007; Boulinguez et al., 2008; Mele et al., 2008; Sumner and Husain, 2008). Only occasionally do we decide that acting or reacting may be appropriate. Accordingly, setting-up proactive inhibitory control each time the environment becomes potentially stimulating would be particularly inefficient, especially when the context is poorly predictable. In addition, from an ecological point of view, efficient control with reduced energy costs assumes that executive control consists of occasionally releasing, for short and appropriate periods of time, the default, effortless, mode of control that locks the neural mechanisms responsible for movement

initiation. This mechanism is reminiscent of the neuroethological model of tonic inhibition/disinhibition that accounts for the control of motor programs both in vertebrate and invertebrate animals (Benjamin et al., 2010).

Obviously, the functional anatomy of this top-down control is still a hot matter of debate. Improving psychological models of proactive inhibitory control is required to feed future neuroimaging studies and contribute to a better understanding of the neural systems supporting this executive function. For instance, the knowledge that proactive inhibitory control is probably the default state of the executive system and that the top-down signal of interest may be locked to the “releasing” period should inspire future experimental settings aiming at distinguishing executive from attentional and sensorimotor processes (Jaffard et al., 2007, 2008). So far, it seems that proactive and reactive inhibition may engage partially overlapping brain networks, including especially the presupplementary motor area (preSMA), the right inferior frontal cortex, the subthalamic nucleus (STN), and the striatum (Vink et al., 2005; Ballanger et al., 2009; Jahfari et al., 2009; Zandbelt and Vink, 2010; Aron, 2011) as well as the supplementary motor area and the inferior parietal cortex (Menon et al., 2001; Rubia et al., 2001; Jaffard et al., 2008; Boy et al., 2010a,b; Chen et al., 2010; Swick et al., 2011; Wardak, 2011) with downstream effects on M1 excitability (Duque and Ivry, 2009; Sinclair and Hammond, 2009; Stinear et al., 2009; Claffey et al., 2010). In other words, the stopping network would be preactivated by preparing to inhibit (Aron, 2011). However, while highly probable, this provisional conclusion must be considered carefully because the respective effects of proactive and reactive mechanisms are difficult to disentangle one from the other with standard metabolic brain imaging methods (Jaffard et al., 2007, 2008; Boulinguez et al., 2008, 2009), and also because the physiological correlates of inhibition remain ambiguous (Lauritzen, 2001; Aron, 2007; Buzsáki et al., 2007). In addition, even when brain activity preceding stimulus processing

is carefully isolated, it remains difficult to sort out proactive inhibition of response initiation from other functions involved in cognitive control like error monitoring (Rushworth and Taylor, 2007; Eichele et al., 2008) and task setting (Vallesi et al., 2009).

The conclusions of Experiment 2 are particularly reminiscent of our previous fMRI investigations suggesting that inhibitory control may be one of the functions of the “default mode of brain function” (Jaffard et al., 2007, 2008). Indeed, the mPFC (together with the precuneus/posterior cingulate and inferior parietal cortex also identified in the above mentioned studies, see Hagmann et al., 2008, for supporting anatomo-functional description) is characterized by important “intrinsic” activity during resting states (Raichle et al., 2001; Raichle, 2006; Raichle and Snyder, 2007). It is noteworthy that this activity is especially evidenced in experiments in which subjects are explicitly instructed to “refrain from moving and reacting” in passive viewing conditions (Mazoyer et al., 2001). The meaning of these resting state activations is still controversial. By providing behavioral evidence that proactive inhibition of response is the default mode of executive control, the present data strongly support our former suggestion that the activity at rest may be partly due to an active and sustained process consisting of locking movement initiation mechanisms. Nevertheless, understanding the intrinsic brain activity preceding stimulation is still a challenge of critical importance, and a large amount of work is still needed to understand precisely how proactive inhibitory control works. We hope that the findings described in this paper will suggest theoretical and methodological lines of inquiry that will contribute to achieving this goal.

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2.1.5 Conclusion

Adam Aron lui-même, pourtant ardent promoteur du modèle standard réactif et sélectif, a suggéré dans un article de revue publié à peu près en même temps que ce travail original que le contrôle proactif pourrait avoir une place plus importante que le contrôle réactif dans l'inhibition de réponse (Aron, 2011). Cependant, si nous considérons évidemment avec un grand intérêt cette conclusion, nous nous devons de rappeler que la conceptualisation du contrôle proactif par Aron est quelque peu différente de la nôtre. Alors que lui l'entend comme une forme de préparation à inhiber, i.e., une préactivation des processus inhibiteurs réactifs susceptibles d'être sollicités, nos résultats renforcent l'idée selon laquelle l'inhibition proactive peut agir comme un mécanisme de verrouillage en amont des processus d'initiation de l'action. Néanmoins, les deux conceptions ne sont pas mutuellement exclusives, et nos données n'invalident la conceptualisation d'Aron (2011).

La conclusion principale de cette série d'expériences psychophysiques est que le contrôle proactif tel que nous le concevons représenterait l'état par défaut du système exécutif. Il serait mis en œuvre dès lors qu'une incertitude événementielle pèse sur l'environnement, et serait levé pour de courtes périodes pendant lesquelles l'incertitude est elle-même levée. Cette idée fait sens d'un point de vue écologique. En effet, dans la vie de tous les jours, nous devons la plupart du temps nous abstenir de réagir à l'arrivée continue de stimuli. Nous décidons seulement occasionnellement que réagir peut être approprié. Par conséquent, mettre en place le contrôle inhibiteur proactif à chaque fois que l'environnement devient potentiellement stimulant serait particulièrement inefficace, surtout quand le contexte est peu prédictible. De plus, un contrôle efficace avec un coût énergétique réduit suppose que le contrôle exécutif consiste en la levée occasionnelle, pour une période courte et appropriée, du mode de contrôle par défaut qui

verrouille les mécanismes neuraux responsable de l'initiation du mouvement. Ceci amène naturellement à la question de l'existence même d'un contrôle top-down. S'il s'agit d'un état par défaut, alors il est envisageable que celui-ci soit strictement physiologique et autonome, comme le suggèrent les connaissances actuelles des boucles frontobasales, circuiterie élémentaire de l'inhibition (Mink 1996). En effet, il est admis que le globus pallidus interne (GPi) inhibe toniquement le thalamus, ce qui a pour conséquence d'atténuer l'activité de ses cibles thalamocorticales dans les états « de repos ». Or, si notre idée d'un déverrouillage transitoire est compatible avec cette observation, elle ne l'est pas avec le mode d'action connu des structures corticales sur les GB. En effet, seules des activités phasiques et transitoires ont été identifiées concernant le contrôle exercé par les structures frontales sur les ganglions de la base (Aron, 2007), et l'activité spontanée du GPi n'est pas censée être sous contrôle direct (Mink, 1996).

Nous suggérons que l'existence d'un tel contrôle a pu échapper aux psychologues et aux neuroimageurs pour des raisons méthodologiques très claires : les designs classiques ne permettent pas l'étude du contrôle inhibiteur proactif. Considérés conjointement aux résultats de notre méta-analyse, ces données comportementales nous invitent à revisiter la plausibilité physiologique et les bases neurales des différents modèles de l'inhibition de réponse.

2.2 Plausibilité physiologique des modèles d'inhibition de réponse

Il est important de rappeler que les différents modèles théoriques d'inhibition ne sont selon nous pas mutuellement exclusifs, mais concourent possiblement ensemble à l'optimisation de l'inhibition de réponse. Bien qu'il existe un modèle dominant et des méthodes standardisées, cette possible pluralité de mécanismes doit être envisagée pour mieux comprendre l'inhibition de

réponse et ses dysfonctionnements. L'observation simultanée de l'activité physiologique prédite par chacun des modèles est nécessaire pour répondre à cette question.

2.2.1 Principes directeurs

Nous avons vu dans le chapitre 1 que l'étude contrôle inhibiteur en IRMf possède certaines contraintes auxquelles il faut être particulièrement attentif. Mais cet outil de neuroimagerie reste notre premier choix pour l'investigation du réseau cérébral de l'inhibition de réponse. En effet, une bonne résolution spatiale et temporelle est nécessaire à l'identification de la dynamique des réseaux de l'inhibition, au niveau cortical et sous-cortical. L'EEG/MEG ne semble donc pas être la technique idéale, malgré l'intérêt de son excellente précision temporelle et de son pouvoir de discrimination spectrale déjà démontré par notre équipe dans ce contexte (Albares et al., 2014, 2015b ; Lio et Boulinguez, 2013).

Ici, nous proposons de tester chaque modèle (réactif sélectif, réactif non-sélectif, proactif non-sélectif) au regard des réponses hémodynamiques qu'il prédit. Nous proposons de le faire au moyen d'un protocole expérimental amendé selon les recommandations méthodologiques formulées à l'issue de notre méta-analyse, permettant de limiter les confusions potentielles entre processus d'inhibition et autres processus corolaires. Cette stratégie permettra dans un premier temps d'évaluer la plausibilité physiologique de chaque modèle et, le cas échéant dans un deuxième temps d'en déterminer les supports anatomo-fonctionnels.

2.2.4 Données empiriques

Article 3: Criaud M et al. (Submitted). From reactive to proactive and non-selective control in go/nogo tasks: Testing the respective predictions of conflicting psychological models with event-related fMRI. Cortex

**From reactive to proactive and non-selective control in go/nogo tasks:
Testing the physiological plausibility of conflicting psychological models of
response inhibition with event-related fMRI**

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From reactive to proactive and non-selective control in go/nogo tasks: Testing the physiological plausibility of conflicting psychological models of response inhibition with event-related fMRI

Key words: response inhibition; fMRI; attention; cognitive control.

Abstract: The standard psychological model of response inhibition in go/nogo (GNG) tasks assumes that inhibitory processes are reactively and selectively triggered by the stimulus subjects must refrain from reacting to. However, the validity of event-related fMRI analyses has been challenged because classical designs engage burdensome cognitive requirements that confound the processes of interest. In addition, alternative psychological models have recently been proposed, suggesting that action restraint in GNG tasks could rather rely on reactive but non-selective mechanisms (all automatic responses are automatically inhibited in uncertain contexts) or on proactive and non-selective mechanisms (a gating function by which reaction to any stimulus is prevented in anticipation of stimulation when the situation is unpredictable). Here we assessed the physiological plausibility of these three conflicting psychological models by testing their respective predictions regarding event-related BOLD modulations. To this aim, we used a single fMRI design which: 1) limits the confounds between response inhibition and parallel processes involved in more general aspects of cognitive control; and 2) allows recording of the different hemodynamic patterns of brain activation predicted by each model. We only found BOLD dynamics consistent with non-selective models. The identification of functionally distinct sub-regions respectively involved in proactive and reactive control indicates that proactive control does not simply consist in pre-activating the functional modules of the reactive control network when the need to inhibit can be anticipated. These results provide new theoretical and methodological lines of inquiry for the study of basic functions of behavioral control and related disorders.

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2 **Abbreviations:** fMRI, functional magnetic resonance imaging; SST, stop signal task; GNG,
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4 go/nogo; BOLD, blood-oxygen-level dependent; LED, light-emitting diode; RT, reaction
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6 time; SPM: Statistical Parametric Mapping; MNI: Montreal Neurological Institute; HRF,
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8 hemodynamic response function; SMA, the supplementary motor area; dmFC, dorsomedial
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10 frontal; DLPFC: dorsolateral pre-frontal cortex; IFG: inferior frontal gyrus; IPL: inferior
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12 parietal lobule; TMS: transcranial magnetic stimulation; STG: superior temporal gyrus; MTG:
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14 Middle temporal gyrus , TPJ: temporo-parietal junction; FP: fixation point.
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1. Introduction

How the brain implements inhibition of response to external stimuli is highly controversial. Behavioural inhibition has long been associated with volitional, reactive and selective processes, i.e., processes that are: 1) a result of a voluntary decision, 2) triggered by external signals, and 3) specifically instructed by the stimulus subjects must refrain from reacting to and/or selectively directed at one particular movement (e.g., Aron, 2007; Boy, Clarke, & Sumner, 2008; Boy, Husain, Singh, & Sumner, 2010; Chambers, Garavan, & Bellgrove, 2009; Garavan, Ross, & Stein, 1999; Logan & Cowan, 1984; Swick, Ashley, & Turken, 2011; van den Wildenberg et al., 2010; Verbruggen & Logan, 2008, 2009a). Yet, it now appears that inhibition is multifaceted and can take different forms combining also 1') reflexive, 2') non-selective and 3') proactive mechanisms (e.g., Albares et al., 2014; Aron, 2011; Bari & Robbins, 2013; Bissett & Logan, 2014; Boy, Husain, & Sumner, 2010; Braver, 2012; Chiu, Aron, & Verbruggen, 2012; Coxon, Stinear, & Byblow, 2006, 2007; Jaffard et al., 2008; Jaffard, Benraiss, Longcamp, Velay, & Boulinguez, 2007; Jahfari et al., 2012; Lavalley, Meemken, Herrmann, & Huster, 2014; MacDonald, Coxon, Stinear, & Byblow, 2014; Majid, Cai, George, Verbruggen, & Aron, 2012; Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2011; Stinear, Coxon, & Byblow, 2009; van Belle, Vink, Durston, & Zandbelt, 2014; Verbruggen & Logan, 2009b; Verbruggen, Stevens, & Chambers, 2014; Wessel & Aron, 2014; van Belle, Vink, Durston, & Zandbelt, 2014; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013; Zandbelt & Vink, 2010). This major source of ambiguity has been illustrated in an influential review from Aron (2011), in which it was convincingly argued that classical reactive paradigms are limited as models of inhibitory control. Aron's call for a reassessment of the theoretical framework of response inhibition including proactive inhibitory control has been popular. However, following studies have mostly focused on how a subject prepares to stop an upcoming response tendency by means

1 of Stop Signal Tasks (SST)¹. Yet, SST is not a unique and unambiguous measure of response
2 inhibition (Boehler, Appelbaum, Krebs, Hopf, & Woldorff, 2012; Erika-Florence, Leech, &
3 Hampshire, 2014; Swick et al., 2011). It is likely that other classical inhibitory paradigms do
4 not assay common, or at least closely related, inhibitory mechanisms as is generally assumed
5 (Chambers et al., 2009). In particular, the equally popular go/nogo task (GNG)², which puts
6 more emphasis on action restraint, could also involve proactive control. Yet, this control may
7 not rely on the same mechanisms as those inferred from the SST.
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17 It is particularly difficult to assess brain-behavior relationships in GNG studies
18 because the neural inhibitory function under scrutiny is precisely intended to suppress overt
19 measurable behavior. Usually, the behavioral index of inhibitory control in GNG studies is no
20 more than the number of errors a subject makes on no-go trials. Standard chronometric
21 paradigms do not provide behavioral markers for successfully inhibited responses. In other
22 words, it is a substantial challenge to discriminate conflicting models of response inhibition
23 on the sole basis of behavioural results. Conversely, the different models currently debated in
24 the literature make specific and testable predictions about the dynamics of inhibition-related
25 activations (Fig. 1). However, these predictions have never been properly tested, either
26 because classical designs introduce confounds between response inhibition and parallel
27 processes involved in more general aspects of cognitive control or because the most recent
28 models have never been assessed with whole-brain event-related fMRI.
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49 *1.1 Model of reactive, selective inhibition of response*

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51 The basic theoretical assumption of the most popular model is that inhibitory
52 processes are phasic reactive mechanisms that are selectively triggered by the external
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57 ¹ In the SST, participants must respond as quickly as possible to a particular stimulus (go) and withhold the
58 ongoing response when, on a minority of the trials, the go stimulus is followed by an additional stop signal.

59 ² In the GNG, participants must respond as quickly as possible to a particular stimulus (go) and withhold their
60 response when, on some trials, the go stimulus is substituted by a nogo signal.
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1 stimulus one must refrain to react to (Logan & Cowan, 1984; Logan, Van Zandt, Verbruggen,
2 & Wagenmakers, 2014; van den Wildenberg, van der Molen, & Logan, 2002; Verbruggen &
3 Logan, 2008, 2009a). Here, selectivity refers to the perceptual decision mechanisms that
4 involve the detection, discrimination, or identification of sensory stimuli (Gold and Ding,
5 2013). We do not consider the decision mechanisms that involve the selection between
6 alternative responses, which are critical for performance but confound response inhibition
7 processes in choice reaction time tasks (Criaud & Boulinguez, 2013). Within this framework,
8 several psychological processes would be specifically launched by information derived from
9 nogo stimuli: error detection, inhibition *per se*, and behavioral correction (e.g., Cohen et al.,
10 2009; Fassbender et al., 2004; Garavan, Ross, Murphy, Roche, & Stein, 2002; Garavan et al.,
11 1999; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Hester, Murphy, & Garavan, 2004;
12 Kelly et al., 2004). Yet, the typical format of the go/nogo task likely does not allow for
13 examination of these processes under conditions in which other cognitive processes are
14 minimized (e.g., Chambers et al., 2009; Simmonds, Pekar, & Mostofsky, 2008; Swick et al.,
15 2011). Indeed, most published go/nogo studies use complex designs with burdensome
16 cognitive requirements in several dimensions³ that blur the interpretation of both behavioural
17 and brain activity measures. Most neuroimaging studies are therefore of limited help for
18 disentangling the actual psychological mechanisms that directly contribute to reactive,
19 selective inhibition of response. A recent meta-analysis controlling for these potentially
20 confounding effects shows that the cascade of neural events specifically induced by
21 information derived from nogo stimuli with respect to go stimuli within a large right
22 lateralized parieto-frontal network is actually driven by the engagement of high attentional or
23 working memory resources, not by inhibitory processes *per se* (Criaud & Boulinguez, 2013).

24 ³ i.e., the difficulty in identifying nogo signals, the frequency of nogo signals among all signals, the working
25 memory load (variable stimulus-response associations). The justification for the use of complex designs in
26 go/nogo studies relies on the disputed assumption that this strategy increases the inhibitory effort necessary to
27 successfully withhold responses to no-go stimuli, i.e., that this strategy enhances the inhibitory brain activity
28 elicited by no-go stimuli.

1 To which extent nogo response inhibition engages reactive and selective mechanisms that
2 actually suppress the ongoing motor response requires further investigation. GNG using two
3 simple stimuli and a single prepotent motor response pose a limited risk to introduce
4 confounds (ibid). Only then can the nogo BOLD response predicted by the psychological
5 model be circumscribed to the brain regions which actually play a direct role in response
6 inhibition. This will be assessed here.
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17 *1.2 Model of reactive, non-selective inhibition of response*

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19 Recent researches have suggested that non-selective inhibitory mechanisms may
20 operate to prevent actions from being emitted prematurely (Duque & Ivry, 2009; Duque,
21 Labruna, Verset, Olivier, & Ivry, 2012; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010;
22 Frank, 2006; Frank, Samanta, Moustafa, & Sherman, 2007). These studies used different
23 behavioural protocols based on complex choice RT tasks involving concurrent responses (i.e.,
24 decision about which choice to make or which action to execute) and lack brain imaging
25 assessment. To which extent the mechanisms inferred from these investigations also apply to
26 response control in GNG studies might be worth considering. It is indeed possible that
27 inhibition of response applies early on to any stimulus (both go or nogo) rather than
28 specifically to the inappropriate stimulus after it has been identified (nogo only). This
29 assumption cannot be evaluated with standard GNG designs which do not allow to distinguish
30 between the hypothesis of an early, nonselective, inhibition of all possible responses, and the
31 hypothesis of a late, selective, inhibition of the erroneous response. To this aim, a control
32 condition for which there is no need to refrain from reacting is mandatory (Fig. 1, Fig. 2). One
33 recent study from Albares and colleagues used a GNG design which meets these constraints.
34 It provided electrophysiological clues as to the involvement of automatic, non-selective,
35 inhibitory activity. This form of reactive control would rely on an executive setting
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1 implemented when the situation is unpredictable, and released as soon as the context is no
2 longer conflicting (see also Chiu & Aron, 2014). However, no whole-brain analysis of fMRI
3 data was performed that could have identified a functional network supporting the hypothesis.
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5 This will be assessed here.
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10 11 *1.3 Model of proactive, non-selective inhibition of response*

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14 Because of the very nature of the task, SST undoubtedly probe online control of
15 ongoing responses (Logan et al., 2014). This is more questionable for GNG. In these tasks,
16 behavioural inhibition can be accounted for without postulating the intervention of reactive
17 and selective feedback-based mechanisms. Rather, action restraint can be achieved by
18 proactive mechanisms implemented in anticipation of stimulation (Forstmann, Brown, Dutilh,
19 Neumann, & Wagenmakers, 2010; Forstmann, van den Wildenberg, & Ridderinkhof, 2008).
20 Yet, in GNG, proactive inhibitory control may not only involve a form of preparation to stop
21 –i.e., a pre-activation of the reactive control network when the need to inhibit can be
22 anticipated- as inferred in SST. Proactive inhibitory control could also operate as a gating
23 mechanism acting on movement initiation processes when the context is uncertain, as initially
24 inferred from a cue-target detection task by Jaffard and colleagues (Jaffard et al., 2008, 2007).
25 According to the model, response inhibition is non-selective because reaction to any stimulus
26 is prevented in anticipation of stimulation. This locking state would operate by means of tonic
27 modulation of the baseline activity of cortico-striatal connections (Forstmann et al., 2010,
28 2008; Jaffard et al., 2008, 2007). This mechanism has been assumed to be the default mode of
29 executive control (Criaud, Wardak, Ben Hamed, Ballanger, & Boulinguez, 2012). The release
30 of proactive inhibitory control would be triggered by the identification of the go signal,
31 allowing a slow but controlled response. Incidentally, the locking state could also be released
32 at any time depending on subjects' expectations of upcoming events (context-dependent
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1 control). However, proactive inhibitory control has been studied mainly by means of cue-
2 target tasks, and direct neural based evidence of the major involvement of the function in
3 GNG is still missing. To comply with the explicit dynamics the model, though, behavioural
4 and neuroimaging investigations of proactive inhibitory control require the amendment of
5 standard GNG procedures by 1) setting-up a control condition in which there is no need to
6 refrain from reacting, 2) analyzing pre-stimulus activity. This will be assessed here.
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17 **2. Materials and Methods**

18 *2.1 Research participants*

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21 Twenty naïve, healthy, right-handed subjects (aged from 20 to 42 years, 10 males) with
22 normal or corrected-to-normal vision, and without history of psychiatric or neurological
23 disease, participated in the study. The experiment was performed in compliance with the code
24 of ethics of the World Medical Association (Declaration of Helsinki) and the protocol was
25 preapproved by the appropriate ethical committee in Biomedical Research (Comité de
26 protection des personnes sud-est IV, N°11/025). All subjects gave written informed consent
27 and were paid 50€ for their participation.
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41 *2.2 Go/nogo task, apparatus and fMRI design*

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43 We implemented a simple equiprobable GNG task inspired from early seminal
44 investigations (e.g., Eimer, 1993; Menon, Adleman, White, Glover, & Reiss, 2001) and
45 reproduced from preliminary work from our group (e.g., Criaud et al., 2012; Jaffard et al.,
46 2007). This refined version of the standard GNG task is based on the methodological
47 amendments that were deemed necessary to characterize both reactive and proactive
48 inhibitory processes with event-related fMRI (Criaud & Boulinguez, 2013). The procedure is
49 substantially different from other influential studies (e.g., Bokura, Yamaguchi, & Kobayashi,
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1 2001; Falkenstein, Hoormann, & Hohnsbein, 1999; Garavan et al., 2002, 1999) which used
2 highly complex designs that engage high attentional or working memory resources. Here, we
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4 set-up stable stimulus–response associations, reduced to one bit of information the complexity
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6 of identification of go and nogo signals, and used equiprobable go and no-go signals to limit
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8 potential confounds. With respect to the last point, it must be noticed that our approach does
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10 not prevent prepotent automaticity (i.e., fast automatic responses that take precedence over
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12 any other potential response, Isoda & Hikosaka, 2011). Indeed, although biasing go/nogo
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14 probabilities in favour of go stimuli might appear necessary to build-up an automatic response
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16 to one or several stimuli when there is high uncertainty about the type of response, the nature
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18 or the identity of the stimuli, it is not necessary when the design involves a simple speeded
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20 reaction time task with a single response and only one bit of information (e.g., Eimer, 1993).
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22 In these conditions, it has repeatedly been observed that a stimulus that does not require a
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24 response elicits covert motor activations of the single prepotent response. Most often, these
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26 automatic activations do not produce overt responses precisely because they are counteracted
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28 at some point by inhibitory mechanisms (McBride, Boy, Husain, & Sumner, 2012; Sumner &
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30 Husain, 2008). Yet, they can be observed both peripherally in the muscles of the responding
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32 hand (Boulinguez, Jaffard, Granjon, & Benraiss, 2008) or centrally over the motor cortex
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34 (Boulinguez, Ballanger, Granjon, & Benraiss, 2009; Jaffard et al., 2007).
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43 Subjects were asked to react as fast as possible to visual go stimuli by pressing a button
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45 with the right thumb while refraining from reacting to visual nogo stimuli, complying with a
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47 maximum error rate (false alarms and omissions) of 10% of all trials. At the beginning of a
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49 trial, the visual fixation point could turn either red or green. In the main condition, the red cue
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51 indicated that a go stimulus (go_trials), a nogo stimulus (nogo_trials) or no stimulus at all
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53 (catch trials) could occur, inviting subjects to implement proactive inhibitory control to avoid
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55 erroneous automatic responses to nogo stimuli. In the control condition, no inhibition was
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1 required since the green cue indicated that no nogo stimulus would be presented
2 (go_control_trials only). This condition enabled subjects to react automatically to any
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5 upcoming event.
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7 Subjects were holding an amagnetic handle mounted with a highly sensitive button in the
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9 right hand positioned below the sternum. A panel equipped with light-emitting diodes
10 (LEDs – Ø5mm, 8800mcd) was used to present the visual stimuli (the visual display was
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12 viewed through a mirror). One LED was placed in the centre of the panel and set at the
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14 subject's eye level. It served as a fixation point for the eyes, and as a cue indicating the
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16 experimental condition. The target stimulus (go) was composed of eight other LEDs
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18 surrounding the central fixation point and forming a diamond (3.44° of visual angle). The
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20 nogo stimulus was composed of eight similar LEDs surrounding the central fixation point
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22 and forming an X (3.44° of visual angle) (Fig.2). Stimuli were presented and behavioural data
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24 were acquired using a real-time acquisition system (Labview™). The appearance of the
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26 fixation point indicated the beginning of a trial and lasted until the end of the trial. Pre-
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28 stimulus delays (time between the beginning of a trial and stimulus presentation) varied
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30 randomly from two to six seconds in steps of 1sec to avoid the predictability of stimulus
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32 occurrence. In order to optimize the discriminative power of the contrast intended to reveal
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34 proactive control related activity, we used only the longest pre-stimulus delays (four to six
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36 seconds) (see Criaud et al., 2012).
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46 The experiment was divided into four acquisition sessions. Each session was composed
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48 of 20 go trials, 20 nogo trials, 20 go_control trials and 20 catch trials (no stimulus), randomly
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50 presented, for a sum of 80 trials/condition of interest, giving a total of 320 trials for the
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52 experiment.
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58 *2.3 Data acquisition*

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2 Images were acquired on a 3-T MEDSPEC 30/80 AVANCE whole-body imager (Bruker,
3 Ettlingen, Germany), equipped with a circular polarized head coil. For each participant, we
4 acquired a high-resolution structural T1-weighted image (MPRAGE sequence, resolution
5 $1 \times 0.75 \times 1.22$ mm) in sagittal orientation, covering the whole brain. For functional imaging,
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7 we used a T2*- weighted echoplanar sequence, covering the whole brain with 28 interleaved
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9 3-mm- thick/0-mm-gap axial slices (repetition time=1867 ms, echo time=30 ms, flip
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11 angle=77°, field of view=19.2×19.2 cm, 64×64 matrix of 3×3 mm voxels). We acquired 337
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13 functional volumes per session during four sessions, for a total of 1348 volumes per subject.
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22 *2.4 Data analysis*

23 *2.4.1 Behavioural analysis*

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25 Non-selective inhibitory control would not only account for the ability to counteract
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27 inappropriate responses to nogo stimuli, it would also strongly account for the latency of
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29 initiation of responses to go stimuli (Jaffard et al. 2007; Criaud et al. 2012; Albares et al.,
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31 2014; Chiu and Aron, 2014). Indeed, the model predicts that late volitional responses to
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33 appropriate go stimuli are provided after automatic response to any kind of visual stimulus
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35 has been prevented. Conversely, when the situation is predictable, the model assumes fast
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37 automatic responses to go stimuli. Accordingly, the lengthening of reaction time (RT, the time
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39 between a go stimulus presentation and the button press response) in the red cue condition
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41 with respect to the green cue condition provides a convenient marker of the involvement of
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43 non-selective inhibitory control (Criaud et al. 2012). We then assessed RT differences
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51 between the go and go_control conditions by means of a paired-t-test.
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53 *2.4.2 fMRI preprocessing*

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55 Data were processed using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/>), according
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57 to the general linear model (Friston et al. 1995). The first six functional volumes of each
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1 session were removed to eliminate non-equilibrium effects of magnetization. The remaining
2 331 images were corrected for differences in slice acquisition time. The images were then
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4 corrected for head movements by realigning all the images with the first image using rigid
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6 body transformations, and unwrapped according to the fieldmap recording. Spatial
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8 normalization was improved using the DARTEL toolbox on an MNI template. Data were
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10 spatially smoothed with an isotropic Gaussian filter (8mm full width at half maximum).
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13 *2.4.3 Event-related analyses of BOLD signal changes*

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16 In the statistical analysis, 16 event types were defined at the first level, including
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18 10 effects of interest (2 periods -pre-stimulus and post-stimulus- for 5 types of trial -
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20 go_control, go, nogo, catch_control, catch_nogo-) and 6 effects of no interest (inter-trial
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22 interval and short pre- stimulus delays -2 to 3 sec- for each trial type). The events were time-
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24 locked to the onset of the stimulus or to the onset of the cue depending on the analysis,
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26 modeled according to their onset and their duration, and convolved with a canonical
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28 hemodynamic response function (HRF). Data were high pass-filtered at 128s and summarized
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30 into two contrasts per subject. We successively assessed (Fig.2):
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36 - The activity specifically triggered by nogo stimuli with respect to go stimuli, in
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38 order to identify reactive selective inhibitory mechanisms. For each participant, the difference
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40 in stimulus evoked activity between the nogo and go conditions was assessed by a one
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42 sample t-test applied to the contrast [(nogo) - (go)].
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46 - The activity triggered by any stimulus when the context is uncertain with respect to
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48 when the context is predictable, in order to identify reactive non-selective inhibitory
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50 mechanisms. The activity between the two conditions of uncertainty was assessed by a one
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52 sample t-test applied to the contrast [(nogo+go) - (go_control)]. The contrast was balanced by
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54 weighting the go_control condition (x2) in order to compensate for the unequal number of
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56 trials in the red fixation point and green fixation point conditions.
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- The activity preceding any stimulus when the context is uncertain with respect to when the context is predictable, in order to identify proactive non-selective inhibitory mechanisms. The activity specifically implemented in the pre-stimulus period when proactive control was required was assessed by a one sample t-test applied to the contrast [(red cue) - (green cue)]. Go and catch trials were included within each condition. The events of interest were modelled according to their onset and their duration (defining the pre-stimulus period). The analysis focused on the longest pre-stimulus delays (4 to 6 seconds, including two thirds of the trials) in order to optimize the signal to noise ratio.

3. Results

3.1 Behaviour

The false alarm rate was low ($10.4 \pm 5.8\%$ of nogo trials) indicating good overall inhibitory performance, an essential prerequisite for proper analysis of RT data. RT were significantly shorter in the go_control condition ($305 \pm 55\text{ms}$) than in the go condition ($384 \pm 48\text{ms}$), $t=11.95$; $p<0.001$.

3.2 Event-related analyses of BOLD signal changes

3.2.1 Reactive, selective brain activity

The analyses returned no significant BOLD changes (supplementary Table 1).

3.2.2 Reactive, non-selective (context dependent) brain activity

Seven brain regions were more activated by any stimulus when the context was uncertain than by the go_control stimulus when the context was predictable (ie., did not require response inhibition) (Table 1): 1) the fusiform gyrus, extending to the cuneus and the superior parietal cortex, 2) the left insula, extending to the inferior frontal gyrus and the anterior part of the medial temporal lobe, 3) the postcentral gyrus, extending to the posterior cingulate

gyrus, 4) the pre-supplementary motor area (pre-SMA), 5 and 6) the left premotor cortex, and 7) the inferior parietal cortex (Fig.3).

3.2.3 Proactive, non-selective (context dependent) brain activity

BOLD increase was observed in a large network during the pre-stimulus period when the context required refraining from reacting (Table 2 and Fig.3). This proactive network is composed of 1) the dorsomedial frontal cortex (dmFC), the posterior part of the superior temporal gyrus, the postcentral gyrus, the middle temporal gyrus (MTG), the precuneus, the supplementary motor area (SMA) and the angular gyrus.

4. Discussion

The objective of this study was to assess the physiological plausibility of the three main conflicting psychological models of GNG response inhibition. This was achieved by testing their respective predictions regarding event-related BOLD modulations by means of an experimental design which was intended to limit the confounds between response inhibition and parallel processes involved in more general aspects of cognitive control.

4.1 Model of reactive, selective inhibition of response

The present work reports no significant activation evoked by the stimuli that have to be withheld (nogo) with respect to the stimuli that require a motor response (go) (see supplementary Table 1). This is clearly in contradiction with most previous studies which reported strong activation of a large network (including especially dorsolateral pre-frontal cortex (DLPFC), right inferior frontal gyrus (IFG), SMA, insula, inferior parietal lobule (IPL); see Banich & Depue, 2015; Chambers et al., 2009; Mostofsky & Simmonds, 2008; Simmonds et al., 2008; Swick et al., 2011 for reviews) on the basis of intricate experimental designs (low frequency of nogo signals, complexity of stimuli identification, instability of

1 stimulus-response associations). Obviously, a main limitation of our research is that it is
2 difficult to differentiate a null effect from a very small effect on the basis of the measure
3 derived from this kind of study (Frick, 1995). However, the null hypothesis which was not
4 rejected by the present results is strongly supported by more powerful meta-analyses of
5 patterns of brain activation controlling for the complexity of experimental designs across
6 studies (Criaud & Boulinguez, 2013). Indeed, it comes out from these meta-analyses that
7 classical complex designs introduce important confounds because they engage multiple
8 control systems to a varying extent, including for instance attention (Chikazoe et al., 2009),
9 learning of stimulus-response associations (Liljeholm & O’Doherty, 2012), response
10 selection (Mostofsky & Simmonds, 2008), or prediction processing (Volz, Schubotz, & von
11 Cramon, 2003). When minimizing the recruitment of such additional cognitive processes, as
12 the present experimental design does, nogo-induced activations vanish. Taken together,
13 meta-analytical and empirical data suggest that the critical inhibitory process in the go/nogo
14 task is likely not reactive and selective. This conclusion feeds into wider debate on the
15 reliability of dominant inhibitory models of frontal lobe function (e.g., Banich & Depue,
16 2015; Erika-Florence et al., 2014; Hampshire, 2015; Hampshire, Chamberlain, Monti,
17 Duncan, & Owen, 2010; Hampshire & Sharp, 2015; Swick & Chatham, 2014).

4.2 *Model of reactive, non-selective inhibition of response*

46 The present results report increased activation evoked by all stimuli (go and nogo)
47 associated with increased RT to target stimuli when the situation is unpredictable with
48 respect to when the situation is predictable (Fig.3). Broadly, this pattern of results is
49 consistent with the different models assuming non-selective, context-dependent, inhibitory
50 control (Albares et al., 2014; Brass & Haggard, 2008; Duque & Ivry, 2009; Duque et al.,
51 2012, 2010; Frank, 2006; Frank et al., 2007). The “hold your horses” computational model

1 of decision making (Frank, 2006; Frank et al., 2007) assumes that preventing premature
2 responding is achieved by the implementation of a “global nogo” signal in the cortico-basal
3 ganglia loops, acting on suppression of all responses rather than modulating the execution
4 of any particular response. Given the specific design used in the present experiment, we
5 assume that this model does not only apply to complex choice tasks involving concurrent
6 responses -i.e., high-conflict decision about which action to execute- as initially proposed
7 by Frank and colleagues (Frank, 2006; Frank et al., 2007). The present data strongly suggest
8 that a global nogo signal is also generated in simple situations for which only the decision
9 whether to execute an action or not is concerned. This conclusion also supports the
10 hypothesis derived from TMS studies according to which non-selective inhibitory
11 mechanism can be directed at an already selected response in order to control when this
12 response is executed (the impulse control model of movement preparation: Duque & Ivry,
13 2009; Duque et al., 2012, 2010). Finally, by applying whole-brain analyses, the present
14 study supplements the recent investigations from Albares and colleagues who used
15 combined fMRI and EEG recordings during a similar paradigm (the model of automatic
16 motor inhibition: Albares et al., 2014, 2015). The BOLD activity reported here reminds that
17 response control in uncertain contexts involves more than just automatic motor inhibition.
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41 A key result is that we found activity predicted by the model of non-selective,
42 context-dependent, inhibitory control in the supplementary motor complex and the premotor
43 cortex, the key regions described in the above-mentioned studies. We also found significant
44 activation in the insula, coherent with the idea that this structure plays a direct role in
45 response suppression (e.g., Nakata et al., 2008; Sharp et al., 2010; Swick et al., 2011). Yet,
46 stimulus-related BOLD responses fitting the predictions of the reactive non-selective model
47 were also found in several other regions whose involvement in response control is broadly
48 accepted but whose exact role is still unclear. This is the case of the inferior parietal cortex,
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1 which likely plays a critical role in the decision to act (Desmurget et al., 2009; Desmurget
2 & Sirigu, 2009). As such, its activation was associated with decreased activity within the
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4 motor circuitry -SMA, Putamen and M1- when prepotent responses must be withheld
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6 (Jaffard et al., 2008). The somatosensory cortex and the superior temporal gyrus (STG)
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8 were also repeatedly found to be involved in action control (e.g., Karch et al., 2009;
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10 Wijeakumar et al., 2015). Notably, the activity of the STG was more closely associated with
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12 the activity of the insula and the activity of the inferior parietal cortex in detecting
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14 infrequent/salient events (Corbetta, Shulman, & others, 2002; Wijeakumar et al., 2015; see
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16 also Andersen, 2011 for evidence of anatomical connectivity). A generally accepted
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18 interpretation is that the temporo-parietal junction (TPJ) serves as an alerting system
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20 directing attention away from the current set of task rules. In the present study/contrast,
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22 there is precisely no infrequent/salient event, and stimulus-induced activation of the
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24 Insula/STG/IPL network is related to the uncertainty of the context rather than the alerting
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26 properties of the stimulus. We therefore suggest that the role of IPL in associative memory
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28 and stimulus-response mapping (see Wijeakumar et al., 2015) is related to a more general
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30 function consisting in breaking automatic stimulus-response associations. Finally, although
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32 methodological precautions were taken to minimise the biases inherent in classical go/nogo
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34 studies, some activations still reflect perceptual and attentional processes that are inevitably
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36 involved in the task when the context is uncertain (Sharp et al., 2010). In particular, the
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38 involvement of the occipito-temporal visual stream is not surprising given that, when the
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40 context is uncertain, visual identification of the stimulus is required to trigger the long
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42 latency response to the go signal after automatic activations have been automatically
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58 *4.3 Model of proactive, non-selective inhibition of response*

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1 Here, we report increased activation in the prestimulus period combined with
2 increased RT to target stimuli when the situation is unpredictable, with respect to when the
3 situation is predictable (Fig.3). Broadly, this pattern of results is consistent with the
4 predictions of the model of proactive inhibitory control. The ensemble of regions more
5 active in anticipation of stimulus occurrence when the situation requires action restraint
6 is consistent with the proactive network formerly evidenced with a different cue-target task
7 (Jaffard et al., 2008, 2007). This network includes the medial parieto-frontal areas -dmFC
8 and precuneus- and the left inferior parietal cortex. Of particular interest is the dmFC which
9 has been proposed as the source of the ‘neural brake’ mechanism that blocks specific
10 ongoing motor activity (e.g., Brass & Haggard, 2007, 2008; Cho et al., 2012; Filevich,
11 Kühn, & Haggard, 2012; Kühn, Haggard, & Brass, 2009; Narayanan & Laubach, 2006).
12 Since this region was not found in the contrasts revealing reactive inhibitory activity, this
13 top-down function cannot be confounded here with a simple form of preparation to stop
14 (Aron, 2011; Chikazoe et al., 2009; Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010;
15 Jahfari et al., 2012; Swann et al., 2011; Zandbelt, van Buuren, Kahn, & Vink, 2011;
16 Zandbelt & Vink, 2010). Several other brain regions that were previously identified as
17 playing a role in reactive non-selective inhibition of response also showed proactive
18 modulations in uncertain contexts: the SMA, the TPJ, the insula and the somatomotor
19 cortex. However, we found no or very little overlap (only in the MTG, Fig.4) between
20 proactive and reactive clusters. It is therefore unlikely that proactive modulations are related
21 to a pre-activation of the reactive control network when the need to inhibit can be
22 anticipated. Rather, it seems that neighboring but distinct functional modules operate to
23 implement proactive control and to support reactive inhibition: Proactive control would
24 engage pre-SMA while reactive inhibition would be mainly supported by SMA-proper;
25 Proactive control would engage a posterior part of the insula while reactive inhibition would

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rely on the middle/ventral portion; Proactive control would be supported by a more anterior cluster within the TPJ than reactive inhibition. These observations remind how complex the functional attributes of these regions can be (Geng & Vossel, 2013; Nachev, Kennard, & Husain, 2008; Nieuwenhuys, 2012; Rushworth, Kennerley, & Walton, 2005).

Whether proactive inhibitory control directly operates as a gating mechanism acting on movement initiation processes when the context is uncertain (Criaud et al., 2012; Jaffard et al., 2008, 2007) or operates by modulating in anticipation the sensitivity of reactive self-inhibitory networks within the motor system (Albares et al., 2014) cannot be inferred from the present results. The most recent of these two hypotheses –setting automatic inhibition of automatic responses- clearly assumes that proactive control and reactive non-selective inhibition of response are the two sides of the same coin. This issue remains to be further explored.

5. Limitations of the study

One potential limitation to the imaging part of our study is that fMRI investigations that rely on BOLD signals are unable to distinguish between neural excitation and inhibition (Buzsáki, Kaila, & Raichle, 2007; Logothetis, 2008). In addition, the technique is not very powerful at unraveling the time course of the different cognitive and sensorimotor mechanisms that operate during the small time-window during which response inhibition must occur. In consequence, the exact role of the different brain regions recruited in this GNG task and the nature of their interactions cannot be inferred from the present results. This is all the more important given that, despite the different methodological precautions that were taken to minimise the biases inherent in classical go/nogo studies, we are not immune to remaining confounds between inhibitory processes and other parallel functions in this study

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Another obvious limitation of the study is related to the lack of significant effect in the [nogo – go] contrast which is supposed to reveal the involvement of selective reactive inhibitory processes. Since we complied with most recommended criteria, it is tempting to accept the null hypothesis (Frick, 1995). Yet, we acknowledge that we just did not obtain significant effect.

6. Conclusion

As a whole, these results validate the physiological plausibility of two out of the three main models of GNG response inhibition. We report no hemodynamic evidence for the involvement of control processes operating specifically in reaction to nogo stimuli. Conversely, we provide strong support for the involvement of non-selective mechanisms that allow refraining from reacting to any stimulus when the situation is unpredictable. Both behavioural and neuroimaging data suggest that this control is context-dependent, and is achieved through the interplay of proactive and reactive mechanisms. The identification of functionally distinct sub-regions respectively involved in proactive and reactive control indicates that proactive control does not simply consist in pre-activating the functional modules of the reactive control network when the need to inhibit can be anticipated. In conclusion, this work strongly supports the synthetic view that proactive and reactive inhibition interact to allow switching between action restraint and automatic reactivity, a basic function of behavioral control (Hikosaka & Isoda, 2008, 2010; Isoda & Hikosaka, 2007, 2011; van Belle et al., 2014).

These results open-up new clinical issues. Indeed, impairments in the ability to implement or release this form of non-selective, context-dependent, executive setting would be devastating in different neurologic and psychiatric conditions. Although impulsivity is

1 classically considered as the main outcome of inhibitory dysfunction (Bari & Robbins,
2 2013), impairment of the inhibitory control mechanisms highlighted in the present study
3
4 would account for much more disorders than usually admitted. While hypoactivity of the
5
6 proactive network likely contributes to impulsivity (e.g., Ballanger et al., 2009),
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8 hyperactivity of the proactive network predicts opposing symptoms like for instance akinesia
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10 (e.g., Favre, Ballanger, Thobois, Broussolle, & Boulinguez, 2013).
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Figure legends

1
2 Figure 1: Schematic event-related hemodynamic responses respectively predicted by the
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4 different models of response inhibition. In classical go/nogo tasks, nogo (red line) and go
5
6 (green line) signals are scrambled within the same block of trials (standard mixed-block
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8 design), assuming that inhibition is triggered by the nogo stimulus but not by the go stimulus
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10 (*reactive, selective mechanisms*). The *reactive selective* model mostly derived from this kind
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12 of design predicts that BOLD modulations related to response inhibition should take the form
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14 of a typical canonical hemodynamic response function (HRF) to impulse stimulation elicited
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16 by the nogo stimulus but not by the go stimulus. By contrast, an alternative view assuming a
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18 *reactive and non-selective* form of inhibition suggests that both go and nogo stimuli induce
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20 inhibition of automatic response in order to prevent false alarms when the situation is
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22 unpredictable. The BOLD activity induced by this possible form of inhibitory control cannot
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24 survive the standard [(nogo) – (go)] contrast, given that the function is systematically
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26 involved in both conditions. A control condition in which there is no need to refrain from
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28 reacting (i.e., no uncertainty about the identity of the upcoming stimulus) is required to
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30 pinpoint these reactive non-selective mechanisms. Finally, a third model assumes that
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32 response inhibition can be achieved by *proactive, non-selective* mechanisms gating movement
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34 initiation before any stimulus occurs. The model predicts BOLD responses that differ with
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36 respect to two main features. First, relevant activity is assumed to take place in the pre-
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38 stimulus period. Experimentally, this can be achieved by using a cue informing about the
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40 context. The event-related BOLD modulations that must be considered are those triggered by
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42 the cue and released by the go signal. Second, the duration of the period during which
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44 inhibitory activity is sustained must be modelled in the convolution process in order to
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46 generate an appropriate BOLD response waveform. The control condition in which there is no
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need to refrain from reacting is also required to pinpoint these proactive non-selective mechanisms.

Figure 2: Illustration of the GNG experimental design and the statistical contrasts used to assess the three different possible forms of inhibitory control. Subjects were asked to react to a go stimulus (diamond) by means of a button press, and to withhold responses to an equiprobable nogo stimulus (X). The colour of the fixation point indicated the level of uncertainty. The red fixation point could be followed by either the nogo or the go stimulus (uncertainty condition) while the green fixation point was always followed by a go stimulus (go_control, certainty condition).

Figure 3: Event-related fMRI results. When the GNG design limits the confounds between response inhibition and parallel processes involved in more general aspects of cognitive control, only the reactive non-selective and the proactive non-selective models of inhibitory control provide activations consistent with their own predictions.

Figure 4: Proactive (red) and reactive non-selective (green) activations show very little overlap (yellow). This suggests that distinct functional modules within the same key brain regions operate to implement proactive control and to support reactive inhibition.

Table legends

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Table 1: Regions more activated by a stimulus when the context is uncertain with respect to when the context is predictable, as assessed by the contrast [(nogo+go) - (go_control)]. (*reactive, non-selective inhibitory network*).

Table 2: Regions more activated during the pre-stimulus period when the context is uncertain with respect to when the context is predictable, as assessed by the contrast [(red cue) - (green cue)]. (*proactive, non-selective inhibitory network*).

- Hemodynamic responses predicted by disputing models of response inhibition are gauged
- no evidence found for processes operating selectively in reaction to nogo stimuli
- evidence found for non-selective but context-dependent mechanisms
- proactive and reactive control support global action restraint in uncertain context

Inhibition of prepotent response

Stim/condition	Inhibition of prepotent response		
	REACTIVE SELECTIVE	REACTIVE NON-SELECTIVE	PROACTIVE NON-SELECTIVE
NoGo	yes	yes	yes
Go	no	yes	yes
Go_control	no	no	no

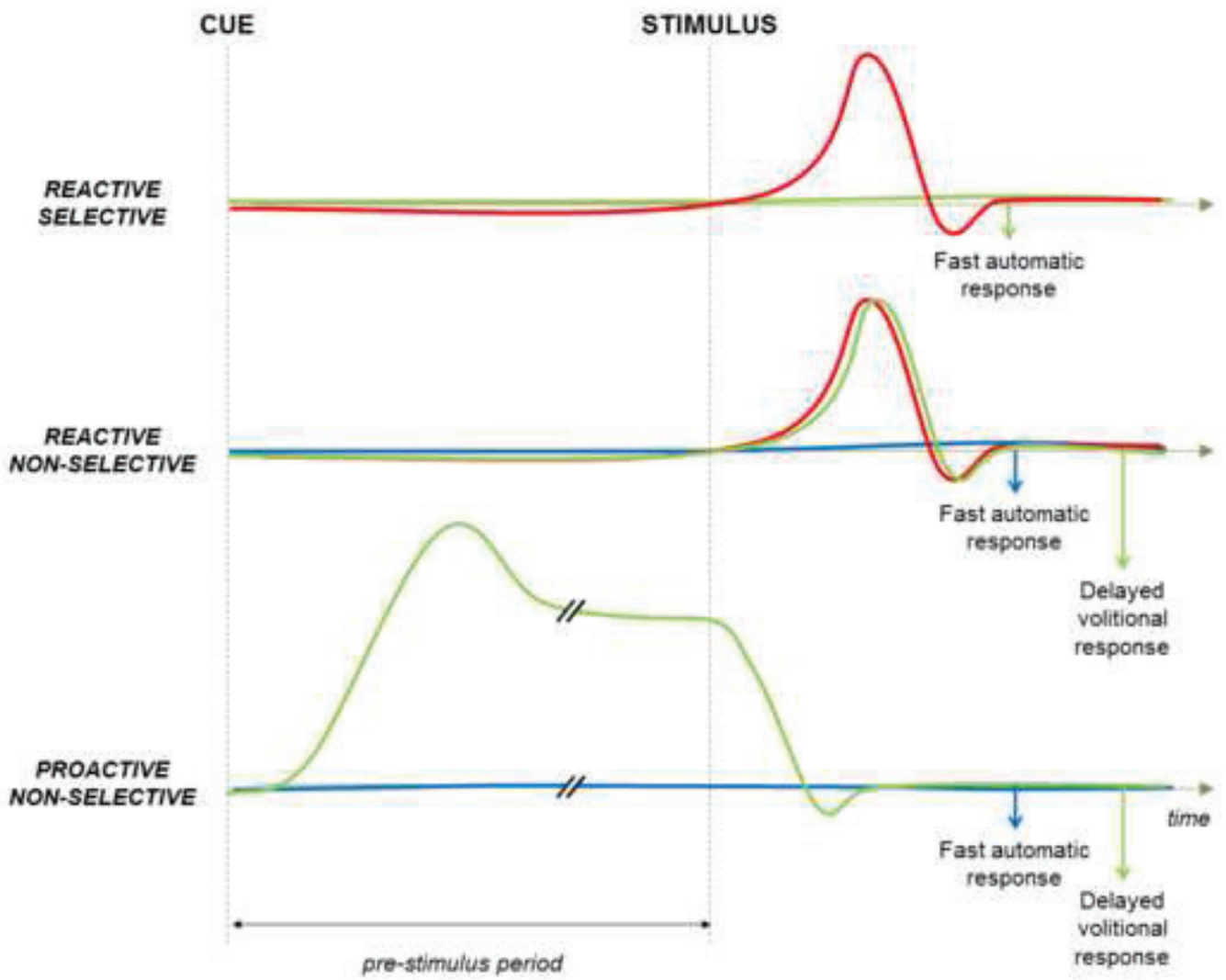


Figure2
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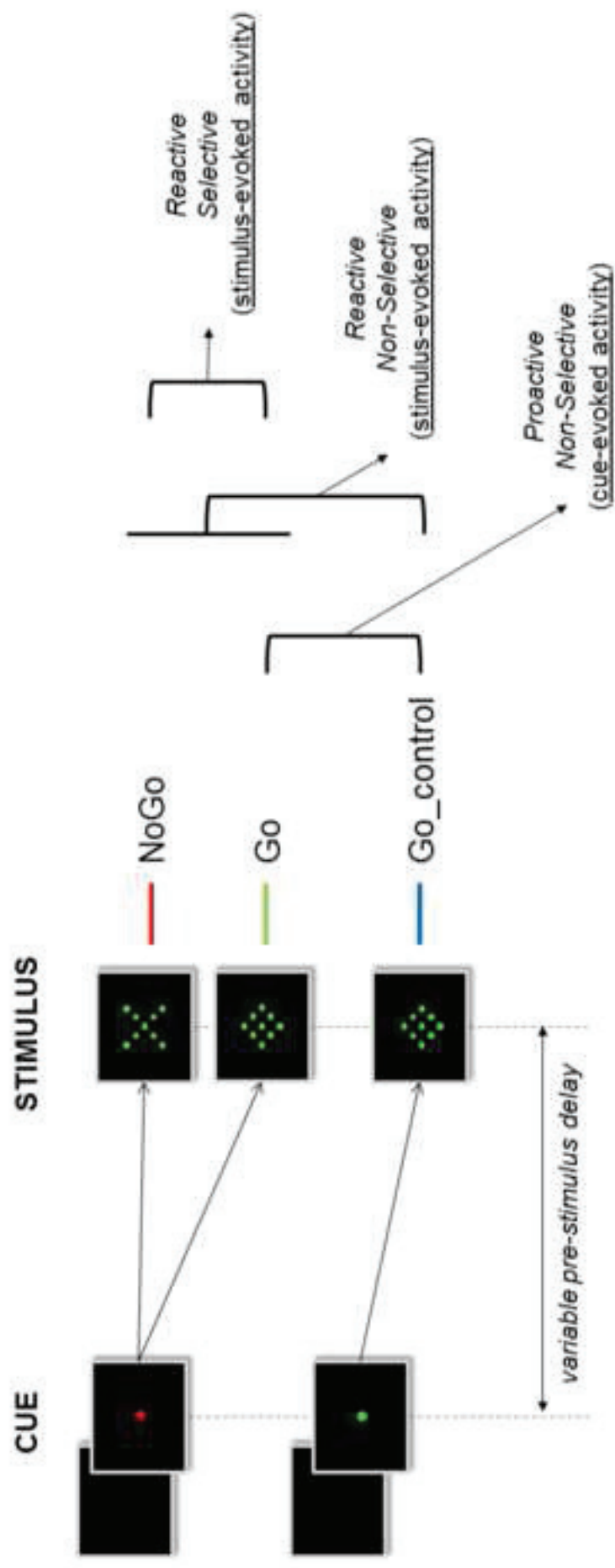
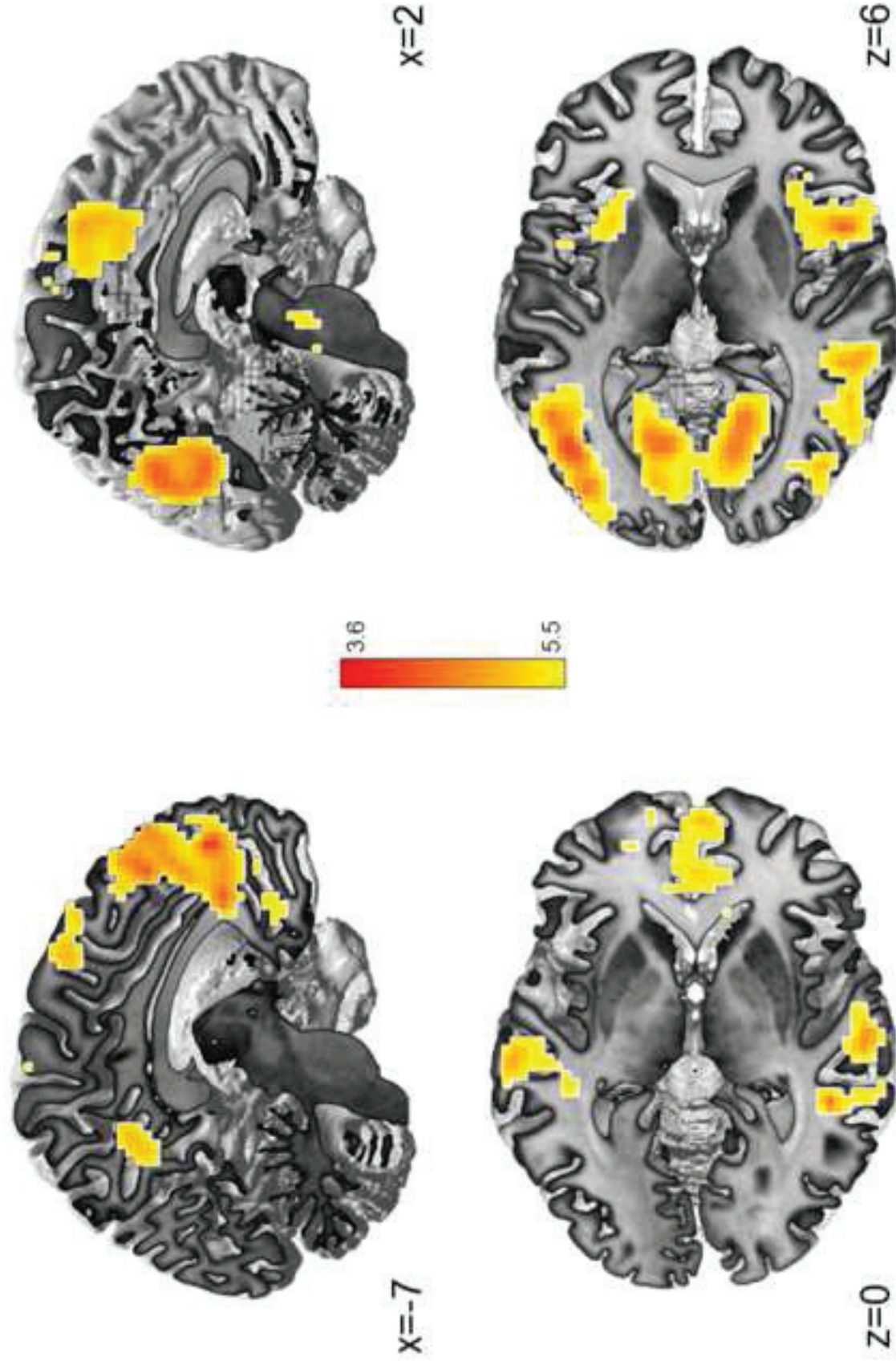


Figure3
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**PROACTIVE
NON-SELECTIVE**

**REACTIVE
NON-SELECTIVE**

Figure4
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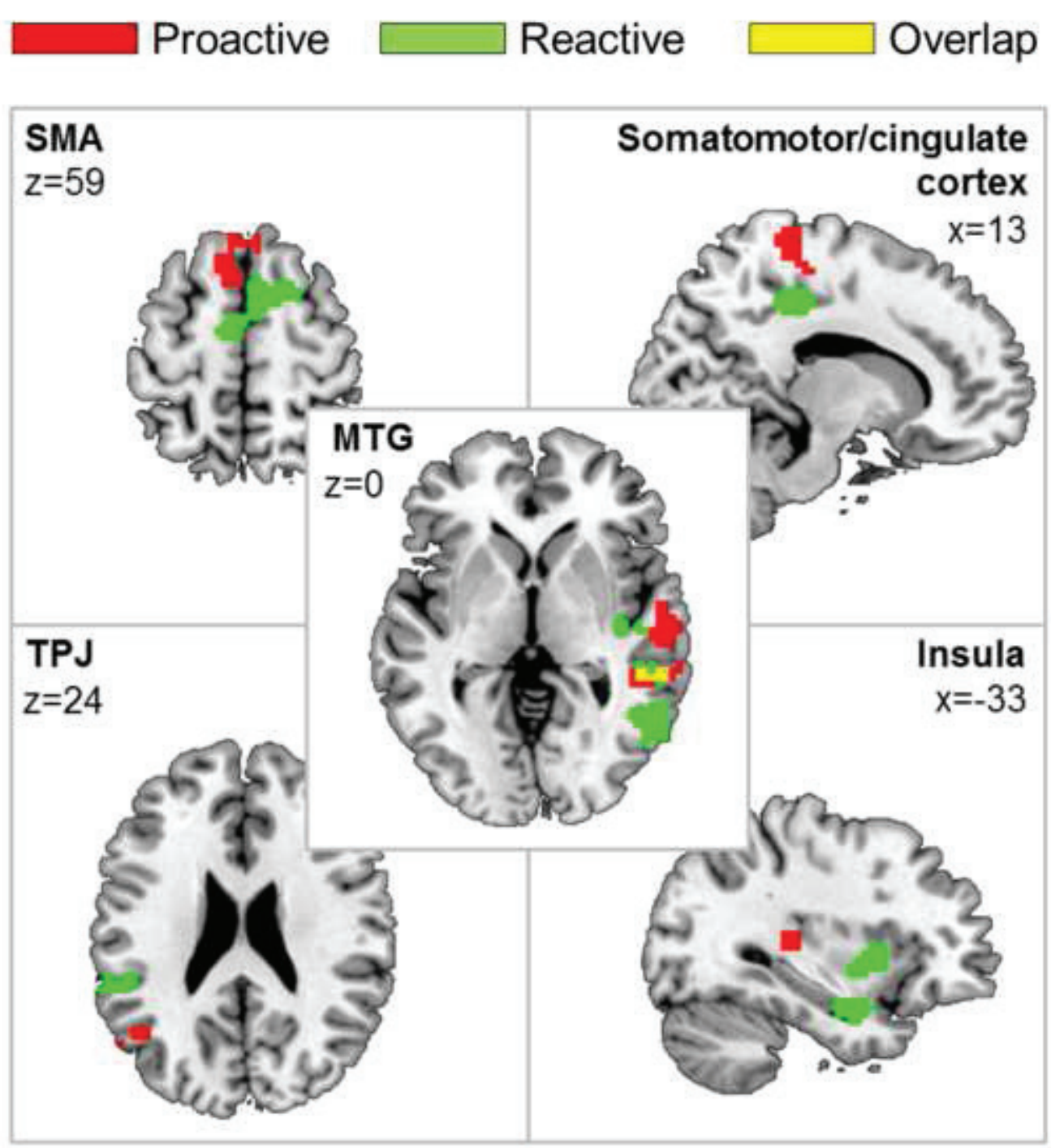


Table 1: Regions significantly more activated by a stimulus when the context is uncertain with respect to when the context is predictable, as assessed by the contrast [(nogo+go) - (go_control)]. Increases of activation are assumed to be related to reactive, non-selective –context- dependent- inhibitory mechanisms.

Region	BA	Side	p_{FWE}	k	z-score	x	y	z
Fusiform Gyrus	37	R	0.000	6376	5.63	33	-48	-18
Cuneus	18	R			5.60	12	-75	30
Superior Parietal Gyrus	7	L			5.53	-15	-72	30
Insula	48	L	0.000	222	5.30	-33	9	3
Inferior Frontal Gyrus	48	L			4.46	-45	9	-15
Medial Temporal Lobe	36	L			4.36	-36	0	-24
Postcentral Gyrus	*	R	0.000	172	4.83	12	-30	45
Gyrus Cingulate, Posterior Part		R			4.39	12	-9	33
Superior Frontal Gyrus	32	R	0.000	519	4.78	12	12	42
SMA	6	R			4.61	15	6	60
SMA	6	R			4.59	6	9	57
Postcentral Gyrus	3	L	0.000	338	4.74	-57	-18	21
Precentral Gyrus	6	L			4.68	-30	-18	60
Postcentral Gyrus	3/39	L			4.64	-51	-24	48
Inferior Parietal Gyrus	7	L	0.000	207	4.51	-24	-42	54
Inferior Parietal Gyrus	40	L			4.47	-39	-42	48
Postcentral Gyrus	3	L			3.85	-36	-33	51
Precentral Gyrus	4/48	L	0.001	76	4.49	-54	3	15
Precentral Gyrus	4	L			4.36	-54	6	36
Supramarginal Gyrus	39	L	0.003	52	4.47	-60	-39	27
Inferior part of the Parietal Lobe	39	L			4.02	-48	-36	21

Cortical areas are based on the Brodmann, theaal and the Hammers atlas (Gousias et al., 2008; Hammers et al., 2003; Tzourio-Mazoyer et al., 2002). Activations are reported at level of significance of $P < 0.001$, uncorrected for multiple comparisons, and a cluster extend of more than 50 voxels. P_{FWE} is the value corrected at the cluster level. k_E is the number of voxel in the cluster. z-score is the value of the z score of the voxel. L = left; R = right; BA = Brodmann's area; x, y and z are the MNI coordinates.

Table 2: Regions significantly more activated during the pre-stimulus period when the context is uncertain with respect to when the context is predictable, as assessed by the contrast [(red cue) - (green cue)]. Increases of activation are assumed to be related to proactive, non-selective - context-dependent- inhibitory mechanisms.

Region	BA	Side	p_{FWE}	k_E	z-score	x	y	z
Superior Frontal Gyrus (medial part)	10	L	0.000	1039	5.10	-3	54	9
Superior Frontal Gyrus (medial part)	9	L			4.68	-9	57	33
Superior Frontal Gyrus (medial part)	9	L			4.56	-6	45	33
Superior Temporal Gyrus (posterior part)	48	R	0.000	466	4.99	36	-27	12
Middle Temporal Gyrus	21	R			4.85	48	-36	3
Postcentral Gyrus	3/48	R			4.81	51	-9	15
Postcentral Gyrus	3	R	0.004	91	4.73	12	-33	69
Precentral Gyrus	4	L			3.68	-3	-24	72
Postcentral Gyrus	3	R			3.58	3	-30	57
Middle Temporal Gyrus	20	L	0.000	212	4.42	-51	-21	-9
Superior Temporal Gyrus (posterior part)	21	L			4.12	-63	-24	-3
Insula	48	L			4.06	-30	-30	12
Precuneus	31	R	0.001	121	4.19	15	-51	33
Posterior Cingulate Gyrus	23	L			3.68	-6	-51	36
SMA	8	L	0.014	72	4.00	-9	21	60
Superior Frontal Gyrus (medial part)	8	L			3.54	-3	30	57
Superior Frontal Gyrus (medial part)	8	R			3.42	6	33	60
Angular Gyrus	39	L	0.046	53	3.88	-42	-72	39
Middle Temporal Gyrus	39	L			3.52	-45	-60	24

Cortical areas are based on the Brodmann, the aal and the Hammers atlas (Gousias et al., 2008; Hammers et al., 2003; Tzourio-Mazoyer et al., 2002). Activations are reported at level of significance of $P < 0.001$, uncorrected for multiple comparisons, and a cluster extend of more than 50 voxels. P_{FWE} is the value corrected at the cluster level. k_E is the number of voxel in the cluster. z-score is the value of the z score of the voxel. L = left; R = right; BA = Brodmann's area; x, y and z are the MNI coordinates.

2.2.5 Conclusion

En ligne avec les conclusions de la méta-analyse du premier chapitre, nos données hémodynamiques ne correspondent pas aux prédictions du modèle standard réactif et sélectif d'inhibition de réponse. Par contre, nous rapportons des données parfaitement compatibles avec les prédictions des modèles contextuels non-sélectifs de contrôle (proactif et réactif).

Ces données généralisent le modèle originel de Frank (Frank, 2006, 2011; Franck et al., 2007 ; Wiecki et Frank, 2013) et élargissent son application au-delà des seules situations de choix complexes. Si l'inhibition automatique des activations automatiques (modèle réactif non-sélectif) semble bien engager le complexe moteur supplémentaire (voir Albares et al., 2014 en Annexe pour des évidences supplémentaires issues de travaux de notre groupe combinant IRMf et EEG), elle engagerait également d'autres régions dont le rôle n'a pas été envisagé par Frank. C'est le cas de l'insula, pourtant souvent mis en évidence dans des tâches d'inhibition (Brass et Haggard, 2007 ; Garavan et al., 1999 ; Swick et al., 2011 ; Tamm et al., 2002 ; Wager et al., 2005), et du cortex pariétal inférieur/gyrus temporal supérieur connus pour jouer un rôle dans la détection d'événements saillants (Corbetta et al., 2002; Wijeakumar et al., 2015).

Ces données appuient également le modèle proactif élaboré dans la partie expérimentale comportementale (Criaud et al., 2012) et inspiré des travaux utilisant une tâche attentionnelle d'amorçage (Jaffard et al., 2007, 2008). Les données anatomo-fonctionnelles sont très similaires à celles de Jaffard et collègues. Elles mettent en particulier en évidence le rôle du cortex frontal dorsomédian, le gyrus temporal supérieur, le gyrus postcentral, le gyrus temporal moyen, le précunéus, la SMA et le gyrus angulaire. Ces données rejettent l'idée selon laquelle le contrôle inhibiteur proactif consisterait simplement à préactiver les mécanismes réactifs. En effet, il

n'existe pas de recouvrement entre les régions supportant l'activité et celles supportant l'activité proactive.

Néanmoins, plusieurs questions restent posées:

La première question concerne les relations entre processus proactifs et processus réactifs. Nous ne pouvons pas déterminer si les deux constituent des mécanismes indépendants concourant à la même fonction, ou si les premiers représentent la fonction de contrôle des seconds. Le modèle proactif de Jaffard et collègues suppose l'existence d'une fonction indépendante de gating des mécanismes d'initiation de l'action. Le modèle d'inhibition automatique des activations automatiques (Albares et al., 2014) inspiré du modèle de Frank (2006) suppose quant à lui la mise en œuvre d'un setting exécutif permettant de moduler par anticipation la sensibilité des populations d'interneurones inhibiteurs réglant le niveau d'auto-inhibition du complexe moteur supplémentaire. Ces deux interprétations de l'activité proactive sont possibles.

La seconde concerne le rôle des ganglions de la base. Nous n'avons pas mis en évidence d'activité en leur sein. Ce résultat est incompatible avec les nombreuses données cliniques (Baglio et al., 2008 ; Riegel et al., 2003) ou de stimulation cérébrale profonde (Albares et al., 2015b ; Ballanger et al., 2009 ; Favre et al., 2013 ; Jahanshahi et al., 2015). Nous attribuons cette absence d'effet à la difficulté d'observation de d'activité sous-corticale très circonscrite lors d'analyses cerveau entier en IRMf. Des analyses en régions d'intérêt, non présentées dans l'article original car non indispensables à la démonstration, confirment le rôle des ganglions de la base dans le contrôle inhibiteur, et plus précisément du striatum dorsal, STN et GPi dans l'activité réactive, et du striatum ventral dans l'activité proactive (Figure 8).

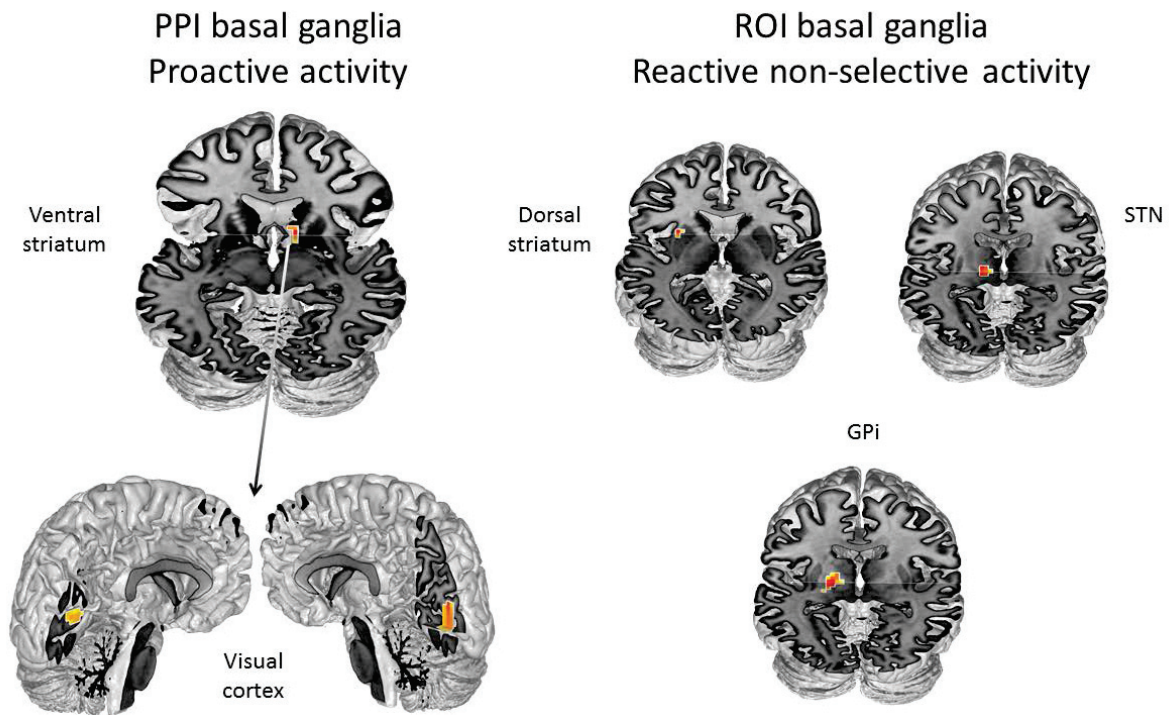


Figure 8 : Activité des ganglions de la base. Pendant la période pré-stimulus, l'activité du striatum ventral est corrélée à celle du cortex visuel. Ce couplage prédit le temps de réaction (analyses d'interaction psychophysologique –PPI-) et confirme le rôle de l'attention dans la performance dans une tâche de Go/Nogo. Une analyse en régions d'intérêts (ROI) de l'activité réactive non-sélective révèle le rôle du striatum dorsal, du noyau sous-thalamique (STN) et du pallidum interne (Gpi).

Chapitre 3

Le dysfonctionnement du contrôle inhibiteur : un rôle paradoxal dans les troubles de la maladie de Parkinson ?

Le second chapitre a permis de renforcer les hypothèses émergentes de l'inhibition non-sélective, et de révéler une partie de leurs supports anatomo-fonctionnels. La révélation de ce modèle alternatif est susceptible d'alimenter le domaine clinique dans la mesure où un dysfonctionnement prédit un spectre de troubles qui déborde largement les conséquences attendues d'un dysfonctionnement des seuls mécanismes inhibiteurs réactifs et sélectifs. C'est cette idée que nous allons tester ici en nous intéressant à la maladie de Parkinson, pathologie caractérisée par des troubles du contrôle de l'action prenant leur origine dans un dérèglement des boucles cortico-ganglio-thalamo-corticales (Kalia et Lang, 2015 ; Lees et al., 2009).

3.1 La maladie de Parkinson

La maladie de Parkinson est une dégénérescence des neurones dopaminergiques de la substance noire. C'est la seconde maladie neurodégénérative la plus fréquente après la maladie d'Alzheimer. Elle est diagnostiquée dans environ 1,5% de la population après 65 ans (de Lau et Breteler, 2006 ; Lees et al., 2009). La compréhension et la prise en charge de la maladie sont rendues compliquées par un ensemble de facteurs comme, entre autres, 1) son étiologie inconnue, même si plusieurs facteurs génétiques et environnementaux sont à l'étude (Broussolle et Thobois, 2002 ; Kalia et Lang, 2015), 2) sa phase prodromique prolongée pendant laquelle la progression de la maladie ne peut être formellement diagnostiquée malgré une perte de neurones

dopaminergiques dépassant 60% (Agid, 1991 ; Braak et al., 2006 ; Kalia et Lang, 2015), 3) l'absence de biomarqueur clair de la maladie (Miller et O'Callaghan, 2015).

Les symptômes cardinaux de la maladie sont le tremblement de repos, l'akinésie/bradykinésie/hypokinésie et la rigidité (Fahn, 2003 ; Thobois et Broussolle, 2005). Les tremblements de repos sont présents lors d'un état de relâchement musculaire alors que la rigidité est liée à une augmentation du tonus des muscles (Dujardin et Defebvre, 2007; Rodriguez-Oroz et al., 2009). L'akinésie est certainement le symptôme le plus mal compris et le plus difficile dans sa prise en charge thérapeutique. Elle est classiquement définie comme une réduction de la motricité volontaire et automatique (en l'absence de toute paralysie) et qui se traduit en particulier par un ralentissement à l'initiation du mouvement (Hallett, 1990). Si cette triade parkinsonienne est classiquement associée à la déplétion dopaminergique et à une nature motrice des dysfonctionnements, il convient de souligner que la dégénérescence est en fait beaucoup plus étendue. Elle implique les neurones cholinergiques du noyau de Meynert, les neurones sérotoninergiques du noyau du Raphé, les neurones noradrénergiques du locus coeruleus, les cellules du système olfactif, le tronc cérébral, la moëlle épinière, le système autonome... (Del Tredici et Braak, 2012 ; Jellinger, 2012 ; Olanow et Obeso, 2012). Il apparaît désormais que cette pathologie non-dopaminergique peut être associée à une variété de caractéristiques cliniques comme les troubles de l'équilibre, le freezing de la marche, la dysphagie, les dérèglements du système autonome, les troubles du sommeil, les altérations de l'humeur, la démence, et des troubles cognitifs plus généraux (Figure 9; Arnulf et al., 2002 ; Grabli et al., 2012 ; Pagonabarraga et al., 2015 ; Christopher et al., 2013 ; Antonelli et Strafella, 2014 ; Antonelli et al., 2010 ; Broussolle, 2014). Ces symptômes sont résistants à la médication dopaminergique classique qui vise en particulier les symptômes moteurs. Notons également que cette dopa-

résistance concerne aussi une partie des symptômes dits moteurs. C'est le cas de l'akinésie, qui nous intéresse plus particulièrement ici (Favre et al., 2013; Fox, 2013; Schubert et al., 2002).

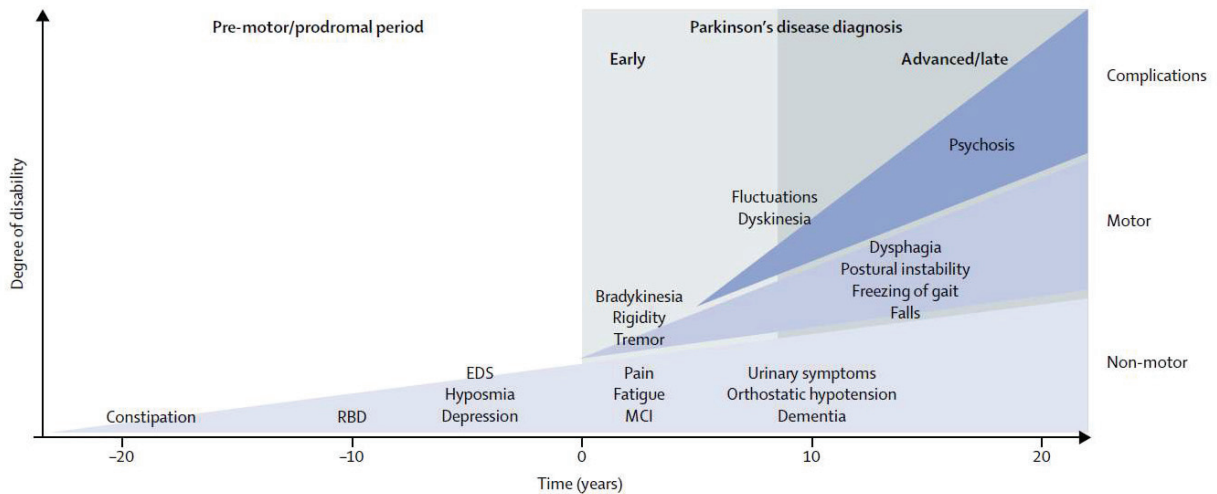


Figure 9 : Symptômes cliniques et déroulement temporel de la maladie de Parkinson. Illustration tirée de Kalia et Lang (2015).

La maladie de Parkinson est une pathologie caractérisée par un dysfonctionnement des ganglions de la base. Les troubles associés nous intéressent plus particulièrement dans la mesure où ces structures profondes sont au cœur du contrôle de l'action (Mink, 1996). Deux noyaux ont notamment été impliqués dans l'inhibition de réponse : les structures d'entrée que sont le striatum et le STN (Figure 10 ; Aron et Poldrack, 2006 ; Duann et al., 2009 ; van den Wildenberg et al., 2006 ; Zandbelt et Vink, 2010). Néanmoins, s'il est clair que la physiopathologie de la maladie prend son origine dans une dégénérescence sous-corticale, il est également clair que les dysfonctionnements engagent l'ensemble de la circuiterie cortico-ganglio-thalamo-corticale (Haegelen et al., 2008 ; Demetriades et al., 2011). Dans la droite ligne de la démarche présentée aux chapitres précédents, l'imagerie fonctionnelle représente un également un outil privilégié

pour tenter de mieux comprendre l'articulation entre fonctions, architecture cérébrale et comportement dans le cadre pathologique (Stoessl et al., 2014).

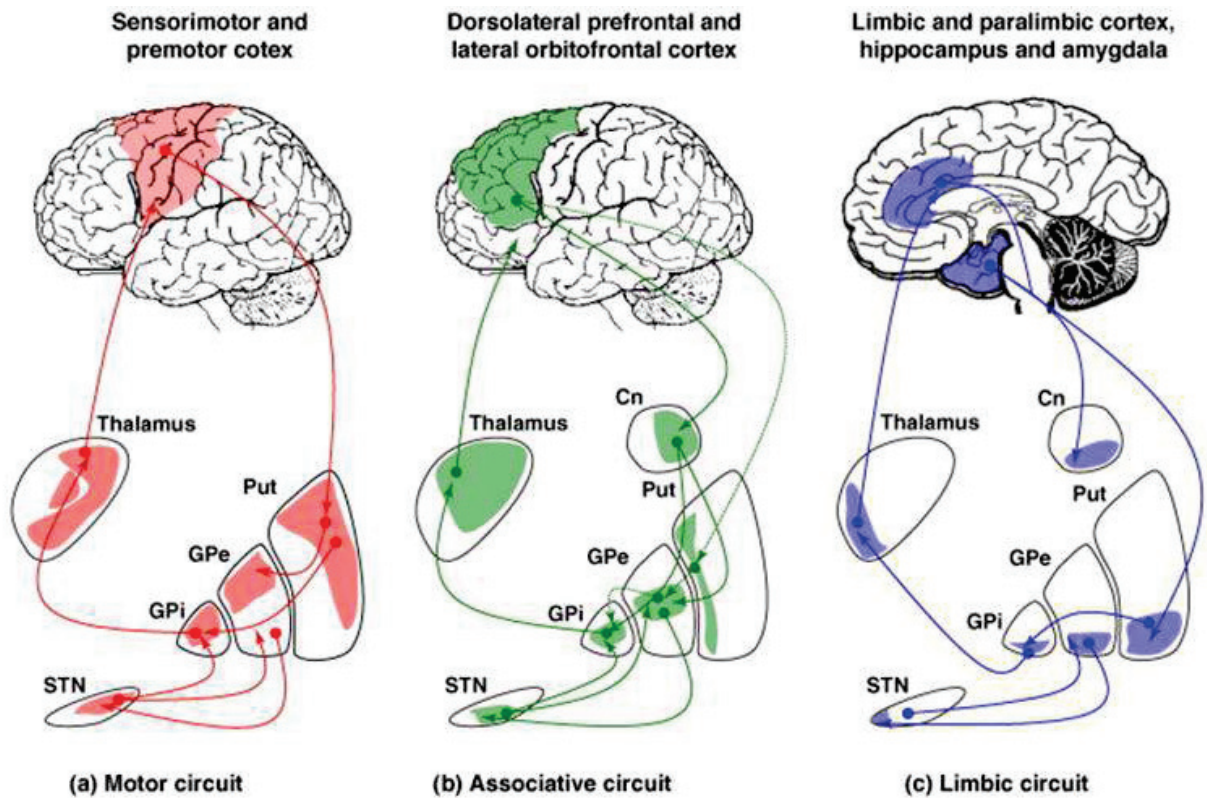


Figure 10 : Schéma illustrant les circuits cortico-ganglio-thalamo-corticales principaux du cerveau humain. Cette figure représente l'organisation pseudo-anatomique des boucles motrices, associative et limbique. (a) Boucle motrice. Les neurones du cortex sensorimoteur projettent vers le putamen posterolatéral (Put). Deux projections principales partent du putamen organisés topographiquement jusqu'aux régions posterolatérales des noyaux cibles : (i) la voie directe vers le GPi et (ii) la voie indirecte qui connecte le putamen postérieur au GPe, au STN et au GPi. Le GPi est le noyau de sortie principal du signal des ganglions de la base vers le cortex via le thalamus. (b) Boucle associative. Cette boucle prend sa source dans les cortex préfrontal dorsolatéral et orbitofrontal, qui projettent vers le noyau caudé (Cn) et dans la région antéromédiane du putamen. Depuis le striatum (Cn + Put) projette vers la région dorsomédiane du GPi et la région antéromédiane du GPe et le STN convergent vers le GPi et à nouveau vers le cortex via the noyau ventral antérieur du thalamus. (c) Boucle limbique. Cette boucle part de l'hippocampe, de l'amygdale et des cortex limbique et paralimbique et projette vers le striatum ventral (ventral région du noyau caudé et du putamen, ainsi que le NAcc). Le striatum ventral projette vers la région limbique du GPe, la regions ventromédiane du STN, le GPi ventral et vers le cortex via le noyau dorsomédian du thalamus. La physiopathologie de la maladie de Parkinson implique clairement des régions identifiées dans les chapitres précédents comme jouant un rôle clef dans le contrôle de l'action et l'inhibition, au niveau cortical (e.g., cortex moteur, cortex cingulaire) ou sous-cortical (e.g., striatum dorsal, striatum ventral, thalamus). *Figure tirée de Obeso et al., (2008) et Krak et al., (2010).*

3.2 Les dysfonctionnements du contrôle inhibiteur

3.2.1 Les troubles généralement liés à un déficit du contrôle inhibiteur

Le trouble classiquement attribué au dysfonctionnement du contrôle inhibiteur est l'impulsivité (Bari et Robbins, 2013 ; Billieux et al., 2014). Elle est définie comme l'impossibilité de retenir une action spontanée, sans réflexion, ou sans contrôle volontaire (Bari and Robbins, 2013). De la même façon que l'inhibition est multifacette et au centre d'interactions multisystémiques, l'impulsivité se présente sous plusieurs formes (Bari et Robbins, 2013). C'est un symptôme important de pathologies neurologiques ou psychiatriques comme par exemple le syndrome de Gilles de la Tourette (Houeto et al., 2005), la schizophrénie (Kaladjian et al., 2011), les troubles de l'attention avec hyperactivité (attention deficit/hyperactivity disorder -ADHD, Biederman et Faraone, 2005), etc.

Malheureusement, les études qui se sont intéressées à ces troubles présentent des biais ou insuffisances:

Premièrement, souvent élaborés via des questionnaires neuropsychologiques, les scores d'impulsivité sont plus basés sur une description des signes comportementaux superficiels et des rapports verbaux des patients que sur de véritables fondements biologiques (Voir Robbins et al., 2012 pour une revue et une critique du DSM-IV -Diagnostic and Statistical Manual of Mental Health Disorders- toujours valable pour le DSM-V). Comme le suggèrent Robbins et collaborateurs, les avancées récentes et rapides dans les domaines de la neurobiologie (incluant les neurosciences cognitives) et la génétique devraient contribuer à mieux identifier et comprendre ces troubles cliniques en permettant d'établir des « endophénotypes neurocognitifs » dérivées de mesures comportementales et cérébrales.

Deuxièmement, les études qui tentent d'identifier l'endophénotype « impulsivité » utilisent évidemment les paradigmes classiques d'inhibition de réponse sur la base du modèle standard (e.g., Cho et al., 2013 ; Cilia et al., 2010, 2011 ; Cilia et van Eimeren, 2011 ; Horn et al., 2003; Jahanshahi et al., 2015 ; Kaladjian et al., 2007, 2011 ; Mazzola-Pomietto et al., 2009; Obeso et al., 2011 ; Rodriguez-Oroz et al., 2011 ; van Eimeren et al., 2010). Les connaissances issues de ces travaux doivent impérativement être revisitées à la lumière des amendements théoriques et méthodologiques que nous avons présentés dans le chapitre précédent.

3.2.2 Hypo- vs. hyper- activité du contrôle inhibiteur proactif

L'hypo-activité du contrôle inhibiteur proactif est susceptible d'engendrer des symptômes d'hyper-réactivité caractéristiques de l'impulsivité (Ballanger et al., 2009). Dans cet état, les patients sont soumis à leurs automatismes, habitudes ou impulsions. Mais le modèle du contrôle inhibiteur proactif ne prédit pas uniquement la survenue de comportements impulsifs comme conséquence d'un dysfonctionnement de l'inhibition de réponse. Un excès de contrôle est susceptible d'engendrer à l'inverse des symptômes d'hypo-réactivité, qui peuvent se traduire par un déficit ou un retard à l'initiation motrice, d'émotions ou d'actions/pensées volontaires dirigées vers un but. Les patients seraient en quelque sorte verrouillés dans un état de contrôle par défaut. Des troubles à expression motrice comme l'akinésie pourraient ainsi avoir une origine strictement exécutive. Mais pour l'instant, seuls quelques travaux comportementaux accréditent cette thèse (Albares et al., 2015b ; Favre et al., 2013).

3.3 L'akinésie dans la maladie de Parkinson revisitée

Bien que des études récentes de notre groupe aient déjà suggéré que la difficulté à initier une action (qui constitue une partie des symptômes akinétiques du patient parkinsonien) pourrait être liée à un déficit de contrôle inhibiteur proactif (Albares et al., 2015b ; Favre et al., 2013), l'hypothèse est toujours très spéculative dans la mesure où elle n'est toujours supportée par aucune évidence neurofonctionnelle. C'est précisément à la recherche de cette évidence que nous proposons de partir maintenant, en respectant la ligne de conduite construite dans les premiers chapitres.

3.3.1 Données de neuroimagerie

Article 4: Criaud M et al. (Submitted). Proactive inhibitory network dysfunction in parkinsonian akinesia. Parkinsonism & Related Disorders

Proactive inhibitory network dysfunction in parkinsonian akinesia

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Running title: Impaired control over motor initiation in PD

Key words: response inhibition; fMRI; proactive control; reaction time; Parkinson's disease

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Abstract

INTRODUCTION: Impairment in initiating movements in PD might be related to executive dysfunction associated with abnormally increased level of proactive inhibitory control, a pivotal mechanism consisting in gating movement initiation in uncertain contexts. However, there is currently no direct neural-based evidence supporting this hypothesis.

METHODS: Twelve PD patients on antiparkinsonian medication and fifteen matched healthy controls performed a simple reaction time task during event-related functional MRI scanning.

RESULTS: The increase in movement initiation latency observed in PD patients with regard to controls was associated with pre-stimulus BOLD increases within several nodes of the proactive inhibitory network (caudate nucleus, precuneus, thalamus, SMA).

CONCLUSIONS: These data provide physiological evidence consistent with impaired control of proactive inhibition over motor initiation in PD. Patients would be locked into a default mode of control maintaining anticipated inhibition over willed movements even when the situation does not require action restraint. The functional and neurochemical bases of brain activity associated with executive settings need to be addressed thoroughly in future studies to better understand disabling symptoms that have few therapeutic options like akinesia.

Introduction

Slowness or failure in movement initiation in Parkinson's disease (PD) is particularly disabling and still poorly understood [1–3]. This disorder, referring to one aspect of akinesia [1], is classically associated with the cardinal motor features of the disease. However, it was recently suggested on the basis of behavioral and pharmacological studies that akinesia might not be of purely motor nature. Indeed, neither dysfunction of the motor circuit nor dopaminergic depletion can account on their own for akinesia [4]. It has been suggested that difficulties in initiating movements in PD could rather have an executive origin [4]. These troubles could indeed be due to dysfunctions of unheralded mechanisms of inhibitory control of action.

It is widely accepted that response inhibition is impaired in PD [4,5-10]. Yet, much more emphasis has been placed on the impairment of the reactive mechanisms that countermand an initiated action when instructed by a specific signal [6]. Very little is known about the possible dysfunctions of the proactive mechanisms that prepare a subject to refrain from reacting before he has been exposed to any stimulation [11-15] (Fig.1). Still, impairments of proactive inhibitory control predict difficulties in initiating movements [4]. Akinesia could be due to the fact that PD patients are locked into a default mode of control, by which they maintain inappropriate response inhibition over willed movements even when the context does not require action restraint. However, there is currently no direct neural-based evidence supporting this hypothesis. Here, we use event-related fMRI to assess the changes in pre-stimulus brain activity within the proactive inhibitory network that are associated with delayed movement initiation in PD.

Material and methods

Participants

Two groups participated in the study. Twelve non-demented (MATTIS > 130), non-depressed (BDI <13) parkinsonian patients, with no history of neurological disorder other than PD, were enrolled. Since dopaminergic medication was not found to improve proactive inhibitory control of movement initiation in PD [4], all patients were tested on regular parkinsonian medication. Fifteen matched healthy control participants, with no history of neurologic or psychiatric disorder, were also recruited. All participants were right handed with normal or corrected-to-normal vision. Demographic and clinical characteristics of the PD patients are presented in Table 1. The protocol was approved by the local Ethical Committee in Biomedical Research (N° CPP 11/094) and participant consent was obtained according to the code of ethics of the World Medical Association.

Experimental design and apparatus

The original data presented in this paper are part of a larger pharmacological study testing the noradrenergic modulation of motor control in PD. Here, we focus only on a subset of the conditions used in this larger study (simple go reaction time task, placebo). The whole experiment was based on a modified version of the classical go/nogo task inspired by a critical meta-analysis of the literature [12,13]. Subjects were asked to react as fast as possible to visual go stimuli by pressing a nonmagnetic handgrip with the right hand (go trials) while refraining from reacting to unpredictable visual no-go stimuli (no-go trials). In a control condition in which only go stimuli were presented (go_control trials), subjects were not required to refrain from reacting.

A panel equipped with light-emitting diodes (LEDs–Ø5 mm, 8800 mcd) was used to present the visual stimuli. One LED was placed in the centre of the panel and set at the subject's eye level. It served as a fixation point for the eyes. The target stimulus (go) was composed of

eight other LEDs surrounding the central fixation point and forming a diamond (3.44° of visual angle). Stimuli were presented and behavioural data were acquired using a real-time acquisition system and the software Presentation™.

The appearance of the fixation point indicated the beginning of a trial and lasted until the end of the trial. Pre-stimulus delays (time between the beginning of a trial and stimulus presentation) varied randomly from two to six seconds in steps of 1s. The inter-trial interval varied randomly and exponentially from two to six seconds. The target was presented for 100 ms. In a control condition (the condition of interest of the present study), the visual fixation point was green indicating that only targets could be presented. Subjects were then able to react automatically to any upcoming event. In another condition, the fixation point turned red, indicating that a go stimulus or a no-go stimulus could occur with equal probability, inducing subjects to refrain from reacting to any signal. Catch trials (no stimulus after the appearance of the fixation point) were added (25% of all trials). Subjects were instructed to comply with a maximum error rate (false alarms and omissions) of 10% of all trials.

The whole experiment was composed of four runs of 20 go trials, 20 no-go trials, 20 go_control trials and 20 catch trials (no stimulus) randomly presented, giving a total of 320 trials and 80 trials/condition of interest. We were interested only in the go_control condition in the present study because earlier investigations showed that PD patients are not impaired in their ability to react and to refrain from reacting in uncertain contexts, but rather have difficulties for initiating responses when they are supposed to release voluntarily and anticipatorily proactive inhibition over motor initiation [4].

Images were acquired on a 1.5-T Siemens MRI scanner, equipped with a circular polarized head coil. For each participant, we acquired a high-resolution structural T1-weighted image (EPI sequence, resolution $1\times 1\times 1$ mm) in sagittal orientation, covering the whole brain. For functional imaging, we used a T2*- weighted echoplanar sequence, covering the whole

brain with 28 interleaved 3.44-mm-thick/0-mm-gap axial slices (repetition time=2620 ms, echo time=60 ms, flip angle=90°, field of view=220 cm, 64×64 matrix of 3.44×3.44×4.4 mm voxels).

Data processing

We assessed RT and error rates (after ArcSin transform) differences between the two groups by means of Mann-Whitney U tests. Correlations were calculated between the experimental data (RT) and clinical data (UPDRS, akinesia score, MATTIS, BDI, disease duration) in order to control for the effects of disease severity, clinical symptoms, and dopaminergic medication.

Neuroimaging data were processed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>), according to the general linear model. The first five functional volumes of each run were removed to account for magnetic saturation effects. The remaining 240 images were corrected for differences in slice acquisition time and realigned to correct for head movement. Outlier scans (>1.5% variation in global intensity or >0.5 mm/time repetition scan-to-scan motion) were detected and repaired using the ArtRepair SPM toolbox (<http://spnl.stanford.edu/tools/ArtRepair/ArtRepair.html>). Spatial normalization was improved using the DARTEL toolbox on an MNI template. Data were spatially smoothed with an isotropic Gaussian filter (8 mm full width at half maximum).

Ten events (2 periods -pre- and post-stimulus- for 5 types of trial –go_control, go, no-go, catch_control, catch_no-go-) were time-locked to the onset of the cue, modeled according to their onset and their duration, and convolved with a canonical hemodynamic response function. We focused our analysis on the pre-stimulus period of the go_control condition, all other events being considered as events of non interest in the statistical analysis. The hypothesis of an inappropriate implementation of proactive inhibitory control predicts overactivation during the pre-stimulus period in PD patients with respect to controls in the network known to support this executive function. Since functional studies in healthy subjects have shown that

proactive inhibition may elicit activity in the striatum, the subthalamic nucleus, the supplementary motor area (SMA), the dorsal premotor cortex (PMd), the angular gyrus, the dorsomedial prefrontal cortex, the thalamus, the insula and the right inferior frontal gyrus (rIFG) [11,14,13], we used a mask encompassing only these regions, based on the aal atlas [16]. Data were high pass-filtered at 128s and summarized into one contrast pooling the pre-stimulus period of the go_condition per subject. The statistical parametric group maps were generated with a random-effects model. The resulting individual statistical maps were entered into a two-sample t-test PD vs. controls.

In order to further assess the relationship between the level of pre-stimulus activity within the proactive network and the latency of movement initiation, we performed a complementary regression analysis. To better characterize the variability seen in behavior, we pooled the two groups and used individual normalized RT (RT/mean) as a parametric regressor of the pre-stimulus BOLD. The regressor effect was summarized into one contrast per subject. We applied a one sample t-test on the 27 individual statistical maps. All maps were thresholded at $p < 0.001$ uncorrected for display purposes, and all results were reported after peak-level cluster-wise family wise error (FWE) correction for multiple comparisons.

Results

Behavioral data: On average, the error rate was low ($2.3 \pm 5.8\%$ of premature responses to go trials) indicating a good inhibitory performance, but no significant difference between the two groups was observed ($p > 0.7$). However, RT was significantly longer for PD patients than healthy controls (474 ± 91 vs. 400 ± 72 ms, $p < 0.05$). The changes in RT were not correlated with disease severity, levodopa equivalent daily dose (LEDD) and the UPDRS score. This is probably due to the fact that standard clinical measures hardly assess the specific kind of akinesia we are studying.

fMRI data: Several regions included in two different clusters showed greater BOLD signal in PD patients compared to matched controls: the precuneus (BA 7; x: -16, y: -66, z: 60; z-score: 4.91; cluster size: 1600; pcor < 0.001), and the caudate nucleus (body, x: 20, y: -24, z: 16; z-score: 3.87) extending to the thalamus (pulvinar, x: 16, y: -16, z: 20; z-score: 4.09) (a 134 voxels cluster which closely approached the conventional statistical threshold after conservative FWE correction; pcor = 0.055) (Fig.2). The trial-by-trial regression analysis shows that the increase in RT correlates with an increase of BOLD signal in the SMA (x: 8, y: 2, z: 60; z-score: 4.85; cluster size: 382; pcor < 0.01) (Fig.2).

Discussion

Although it is one of the cardinal symptoms of PD, akinesia still needs a narrowed and consensual definition [1-5,17], as this term often includes both bradykinesia (slowing of movement), hypokinesia (decreased amplitude of movement) and failure to initiate movement. Here, we focus only on movement initiation disorders. This aspect has certainly been overlooked in standard clinical assessments. At least, the lengthening of RT observed for PD patients in the present study does not correlate with the clinical scores.

The issue of inhibitory control dysfunctions in PD is a central matter for understanding motor and non-motor disorders [5-9,18,19]. Recent conceptual and methodological insights from healthy subjects have significantly challenged our understanding of response inhibition [13], and now offer the opportunity to test unexplored aspects of inhibitory control in PD [6]. In particular, proactive inhibitory control mechanisms have been revealed, that gate movement initiation in anticipation of external stimulation to prevent premature or erroneous responses to upcoming events when the context is uncertain [4,11,12]. Here, we report evidence that BOLD increase within the proactive inhibitory network (precuneus, caudate nucleus, thalamus, SMA) during the pre-stimulus period predicts movement initiation lengthening in PD patients with

respect to controls (Fig.2). This observation provides some further insights into how dysfunction of the thalamocortical route produces akinesia through its action upon motor cortical regions [20]. It also highlights the pivotal role of the precuneus in executive control through its engagement under a variety of processing states and its strong interconnections with the striatum and the SMC [21].

The pattern of differential brain activity between patients and controls is consistent with the hypothesis that parkinsonian subjects maintain inappropriate response inhibition although the situation does not require action restraint. More generally, the stronger the activation within the proactive inhibitory network, the longer the delay to initiate a motor response (Fig.2). Given that PD patients are not impaired in their ability to release proactive inhibitory control when externally triggered by a cue [4], the present results further support the view that the difficulty to initiate action is related to dysfunctional endogenous control of proactive inhibition.

Our findings might provide new lines of inquiry for future studies of parkinsonian akinesia. First, further clarification of its pathophysiological and neurochemical features could rely on the systematic analysis of the critical pre-stimulus brain activity related to response control. The non-dopaminergic origin of akinesia [4,17], which is emphasized in the present results by the fact that RT is not related to the LEDD, calls for comprehensive pharmacological neuroimaging research targeting non-levodopa-responsive motor symptoms [22-24]. This includes gait disorders, which might represent an extreme form of this non-specific executive dysfunction [25-28]. Second, akinesia needs to be considered along with other symptoms because it may not be the single outcome of proactive inhibitory control disorders. While impulsivity is usually viewed as the main consequence of disorders of response inhibition [17,29], the present data show that dysfunctional inhibitory control may lead to a wider range of symptoms including difficulties initiating actions. This is especially consistent with the reverse observation that hypoactivation within the proactive inhibitory network is associated

with impulsive action in PD [10,30], suggesting that akinesia and impulsivity are the two sides of the same coin.

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Figure legend

Figure 1: Behavioural procedure, model of context-dependent proactive inhibitory control, and clinical hypotheses. A) When there is uncertainty about an upcoming stimulus, subjects must refrain from reacting automatically to any stimulation to prevent erroneous responses [23]. This can be achieved by implementing inhibitory control during the pre-stimulus period [11,12]. In most stimulus-response protocols as in the simple go/no-go task illustrated here, proactive inhibitory control can induce an anticipated locking of neural processes underlying movement execution/initiation. The identification of the target stimulus (go) is necessary to release proactive inhibition and allow movement initiation. Importantly, PD patients are neither impaired for implementing proactive inhibitory control in uncertain contexts nor for releasing control on the basis of an external cue [4]. B) When there is no uncertainty about the upcoming stimulus in a simple target detection task, no proactive inhibitory setting is required. Healthy subjects can trigger fast automatic responses. This is likely not the case for PD patients, who might be locked into an inappropriate mode of executive control leading to the implementation of proactive inhibition even when the situation does not require action restraint (see [4]). The identification of the target stimulus (go) would act as an external cue to trigger the release of proactive inhibition, accounting for delayed response latency in PD [4]. In the present study, we focus on this simple experimental condition and track the differences in pre-stimulus brain activity between PD patients and matched controls in order to test this hypothesis.

Figure 2: fMRI results. A) Regions more activated in patients than controls during the pre-stimulus period. B) Region whose activity during the pre-stimulus period predicts RT.

Table 1 Demographic and clinical characteristics of the participants

	Participants	Age (years)	Gender	MATTIS	BDI	UPDRS-III	Duration (years)	LEDD (mg/day)	RT (ms)
Controls	1001	41	M		1				262
	1002	45	F	144	4				390
	1003	43	M	132	0				335
	1004	64	F	141	6				345
	1005	42	F	141	0				377
	1007	62	M	141	1				286
	1008	44	F	142	5				454
	1009	67	F	142	2				519
	1010	42	M	141	10				455
	1011	41	F	143	2				436
	1012	60	F	142	4				446
	1014	56	F	141	10				386
	1015	45	M	144	1				421
	1016	66	M	142	6				495
	1017	70	F	138	6				387
Patients	2001	66	F	137	21		4	750	554
	2002	57	M	140	6	9	7	1125	426
	2004	45	M	141	13	23	8	1325	287
	2005	58	F	131	11	13	9	1770	386
	2007	56	M	139	8	12	6	1425	537
	2008	45	F	141	13	16	19	450	451
	2009	69	F	133	19	13	6	800	551
	2011	70	M	140	7	11	2	380	597
	2012	60	M	134	0	13	9	1225	530
	2013	46	M	138	8	17	7	560	439
	2014	50	M	139	19	7	2	420	536
	2015	52	M	134	8	6	5	550	400

BDI: Beck Depression Inventory, UPDRS: Unified Parkinson's Disease Rating Scale, RT: Reaction Time, LEDD: Levodopa Equivalent Daily Dose, M: male, F: female.

Figure 1

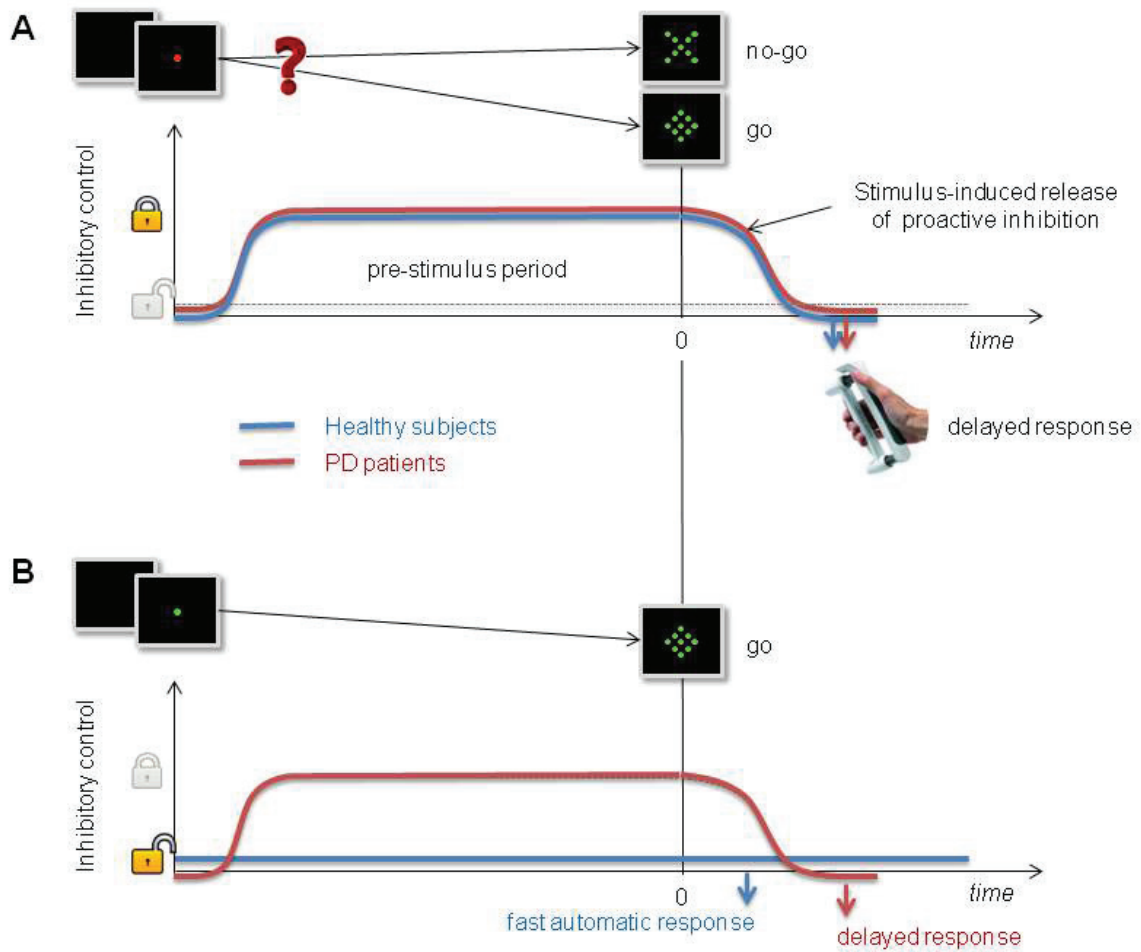
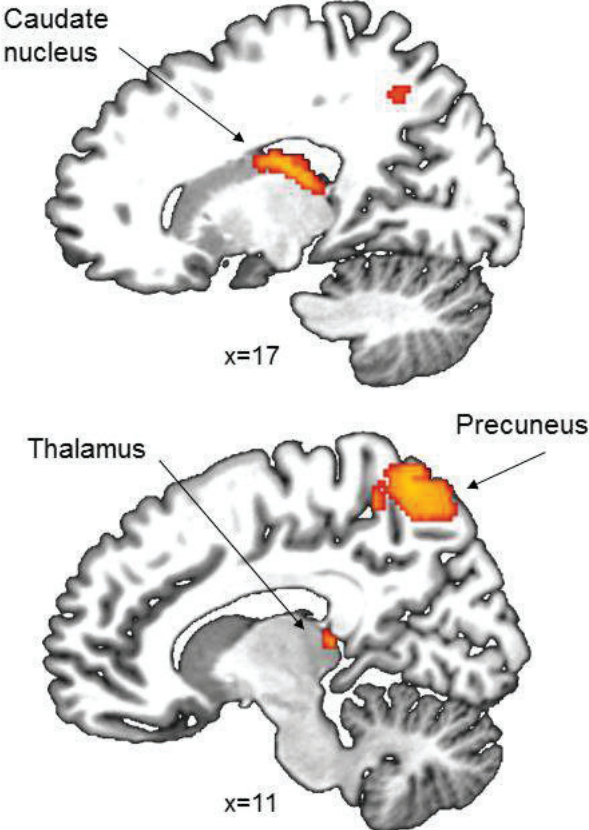
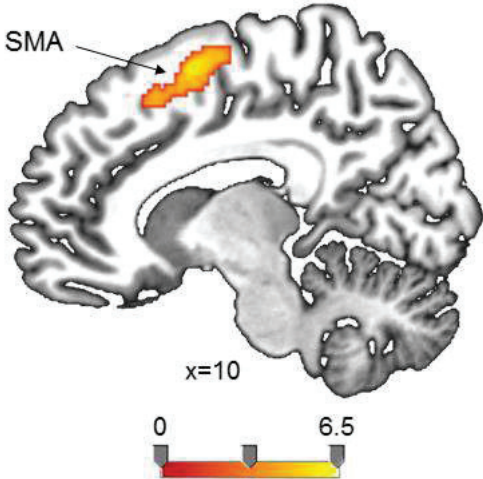


Figure2

A- Between-group differences



B- RT regression analysis



3.3.2 Conclusion

L'akinésie du patient parkinsonien semble bien avoir une origine exécutive conforme à nos prédictions. En effet, nos résultats mettent en évidence une hyper-activité du réseau proactif qui explique le retard à l'initiation du mouvement. Cette hyper-activité sous-tendant l'état de « verrouillage » supposé est particulièrement pénalisante dans les conditions dans lesquelles les patients sont censés laisser libre cours à leurs automatismes sensorimoteurs. Il reste à savoir si ce dysfonctionnement est susceptible de rendre compte de symptômes possiblement associés et extrêmement pénalisants comme le freezing de la marche (Welter et al., 2010).

Si les modulations d'activité observées sont, de par leur nature et leur localisation, suffisantes pour valider l'hypothèse du verrouillage exécutif, les résultats posent quand même question. Il semble en effet tout à fait étonnant de ne pas observer de modulation d'activité dans certains nœuds du réseau, en particulier les ganglions de la base et l'insula (Figure 10). En ce qui concerne les ganglions de la base, l'absence de modulation est incompatible avec les nombreuses données cliniques (Baglio et al., 2008 ; Riegel et al., 2003) ou de stimulation cérébrale profonde (Ballanger et al., 2009 ; Favre et al., 2013 ; Albares et al., 2015b ; Jahanshahi et al. 2015). Comme pour les travaux chez les sujets sains présentés dans au chapitre 2, nous attribuerons cette absence d'effet à la difficulté d'observation d'activité sous-corticale très circonscrite lors d'analyses en cerveau entier. En ce qui concerne le silence de l'insula chez les patients parkinsoniens, nous ne sommes pas enclins à accepter l'idée que son dysfonctionnement ne joue pas de rôle clef dans les troubles de l'initiation du mouvement d'origine inhibitrice sur la foi de cette seule absence d'effet. Un manque de puissance statistique de nos données est susceptible de l'expliquer. Aussi, nous proposons d'approfondir et d'élargir notre analyse du rôle de l'insula

dans la symptomatologie parkinsonienne en utilisant les méthodes adaptées vues au premier chapitre.

3.4 Focus sur le rôle de l'insula

3.4.1 Le rôle de l'insula dans l'inhibition de réponse

L'insula est une structure essentielle dans l'inhibition de réponse (Swick et al., 2011). Située derrière les lobes frontaux, pariétaux et temporaux, de nombreuses fonctions lui ont été attribuées. Il s'agit en effet d'un nœud (hub) intégratif entre plusieurs systèmes fonctionnels (Kurth et al., 2010). En forme de triangle, l'insula peut être divisée en trois parties: dorso-postérieure, ventro-antérieure et intermédiaire. Ces zones diffèrent par leur cytoarchitecture (passant de granulaire dans sa partie postérieure à agrulaire dans sa partie antérieure, Mesulam and Mufson 1985 ; Mufson et al., 1997 ; Bonthuis et al., 2005), mais aussi par les fonctions qu'elles supportent (Kurth et al., 2010). La partie postérieure est impliquée dans les tâches somatomotrices alors que la partie centrale est associée à l'olfaction et au goût. La partie antérieure est divisible en deux régions dont la partie la plus ventrale est associée aux aspects socio-émotionnels tandis que la partie dorsale participe aux fonctions cognitives de plus haut niveau. Cette répartition se retrouve au niveau de la connectivité (Nieuwenhuys, 2012). En particulier, on retrouve une interconnection striato-insulaire organisée dans un gradient antéro-postérieur (Chikama et al., 1997).

Le rôle de l'insula dans l'inhibition de réponse a été mis en évidence de nombreuses fois dans la littérature (Brass et Haggard, 2007 ; Garavan et al., 1999 ; Swick et al., 2011 ; Tamm et al., 2002 ; Wager et al., 2005), et nous le retrouvons dans nos données (page 99). En effet, l'insula postérieure est impliquée dans le contrôle proactif non-sélectif, et l'insula dorsale dans le contrôle réactif non-sélectif. Cependant, son rôle exact reste à déterminer (intégration des

informations motrices primaires ? contrôle top-down de l'action ? rôle de switch d'un mode d'action contrôlé à un mode automatique ?).

3.4.2 L'insula dans la maladie de Parkinson

L'insula est devenue, ces dernières années, un enjeu clé dans la compréhension de la maladie de Parkinson. On la retrouve en effet impliquée dans un grand nombre de symptômes de la maladie, en particulier des symptômes non-moteurs (Christopher et al., 2014a, Annexe 3). Dans notre étude chez les patients parkinsoniens, nous n'avons, de façon très surprenante, pas mis en évidence de dysfonctionnement de l'insula. En effet, les dysfonctionnements de l'insula ont été associés aussi bien à des symptômes hypo-réactif comme l'apathie (Pluck et Brown, 2002 ; Robert et al., 2012 ; Reijnders et al., 2010 ; Spiegel et al., 2009 ; Weller et al., 2009) qu'à des symptômes hyper-réactifs comme l'impulsivité (Belin-Rauscent et al., 2015).

Pour essayer de mieux comprendre le rôle de l'insula dans les troubles exécutifs de la maladie de Parkinson, forts de l'expérience du chapitre 1 nous avons réalisé une méta-analyse plutôt qu'une simple revue de questions. Dans un souci d'approche systémique des dysfonctionnements de la maladie, nous avons examiné un large spectre de symptômes.

3.4.3 Méta-analyse

Article 5: Criaud M et al. (In revision). The contribution of the insula in Parkinson's disease: a quantitative meta-analysis study. Human Brain Mapping

The contribution of the insula in Parkinson's disease: a quantitative meta-analysis study.

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Abstract

The insula region is known to be an integrating hub interacting with multiple brain networks involved in cognitive, affective, sensory and autonomic processes. There is growing evidence suggesting that this region may have an important role in Parkinson's disease (PD). Thus, to investigate the functional organization of the insular cortex and its potential role in parkinsonian features, we used a coordinate-based quantitative meta-analysis approach, like the activation likelihood estimation (ALE). A total of 132 insular foci were selected from 96 published experiments comprising the five functional categories: cognition, affective/behavioural symptoms, bodily awareness/autonomic function, sensorimotor function and non-specific resting functional changes associated with the disease. We found a significant convergence of activation maxima related to PD in different insular regions including anterior and posterior regions bilaterally. This study provided evidence of an important functional distribution of different domains within the insular cortex in PD, particularly in relation to non-motor aspects, with an influence of medication effect.

Keywords: Parkinson's Disease, insula, non-motor symptoms, dopamine, cognition, behavior

Introduction

In the last few years, the insula region has generated a great deal of interest, and while generally being considered a limbic region, it is now known to be involved in numerous other functions. In fact, the insula is considered to be an integrating hub linking several functional systems, each with a set of anatomically and functionally different regions involved in cognitive, affective, sensory and autonomic processes (Kurth et al. 2010, Christopher et al. 2014a). This triangle-shaped area located beneath the frontal, parietal and temporal lobes is divided into four functional integrative nodes (Kurth et al. 2010). The mid-posterior insula is implicated in somatomotor functions while the central insula participates in olfactory and gustatory tasks. The ventral anterior insula is linked to social and emotional functions whereas the dorsal anterior insula is mainly involved in cognition.

To date, no studies have directly investigated the contribution of the insula to symptoms of PD. While PD is primarily considered a movement disorder, these patients are also afflicted by a number of non-motor symptoms, i.e. behavioural, cognitive changes as well as sensory and autonomic complications (Chaudhuri and Schapira, 2009; Park and Stacy, 2009). In general, imaging and neurophysiological studies investigating brain abnormalities in PD have focused on different cortical and subcortical regions but have never addressed the role of the insula, despite substantial evidence supporting its potential contribution to non-motor symptoms in PD. Deposition of alpha-synuclein in the insula (Braak et al. 2006) could impair directly receptor function and synaptic activity in this region. The degeneration of dopaminergic, cholinergic and serotonergic projecting neurons to the insula (Halliday et al. 1990) could also affect significantly its functional integrity. The loss of neurotransmitters modulation in the insula could affect information processing through heavy interconnections between the insula and different cortical regions (i.e. frontal, temporal, parietal, cingulate cortex) (Cauda et al. 2011; Nieuwenhuys, 2012) as well the basal ganglia (Chikama et al. 1997) .

Recent review from Christopher et al. 2014a pinpointed the possible role of the insula in non-motor symptoms of PD To further investigate the functional organization of the insular cortex and its potential role in parkinsonian features, we applied a quantitative meta-analysis method on published neuroimaging studies to identify in the core features of PD associated with the insula which are consistently manifested across patient cohorts and range of tasks. We used

a coordinate-based quantitative meta-analysis approach, like the activation likelihood estimation (ALE) (Eickhoff et al. 2009; Wager et al. 2009) to overcome the classical limitations of neuroimaging studies such as heterogeneity of patient population and small sample sizes. This approach has been used consistently and successfully in a number of recent studies (Arsalidou et al. 2013; Criaud and Boulinguez, 2013; Herz et al. 2014; Kurth et al. 2010; Mutschler et al. 2009; Pan et al. 2012; Shao et al. 2014; Uddin et al. 2013).

Methods

Literature Search

To review all imaging studies possibly involving the insula in Parkinson's disease, the Web of Science and Pubmed databases were examined from 1993 to 2015 using the following keyword combinations: “ ‘Parkinson's disease' AND ‘Insula' ”, “ ‘Parkinson's disease' AND ‘fMRI or functional magnetic resonance' ”, “ ‘Parkinson's disease' AND ‘PET or positron emission tomography' ”. This search resulted in 96 studies (Table1). Only fMRI and PET (receptor ligands and H₂O¹⁵) studies were considered. All articles were screened for eligibility with the following inclusion criteria:

- English articles including original data
- Idiopathic PD patients
- No comparison with other brain pathologies
- No pharmacological trials
- 3D coordinates reported in stereotactic space (MNI or Talairach)
- Level of significance reported (p value, cluster or voxel level, correction)

For each study included, the coordinates located in the insular cortex were collected.

Meta-analysis Based on Activation Likelihood Estimation

To assess the functional role of the insular cortex in parkinsonian features, all imaging studies included in the meta-analysis were sorted into five functional categories. A total of 132 insular foci were selected from 96 published experiments (Table 1, appendix) comprising the five functional categories: cognition (30 studies), affective/behavioural symptoms (24 studies), bodily awareness/autonomic function (8 studies), sensorimotor function (21 studies) and non-specific resting functional changes associated with disease (13 studies). All Talairach coordinates were converted to MNI space using the Lancaster transform (Lancaster et al. 2007).

The activation likelihood estimation (ALE) is a coordinate-based meta-analysis method. Activation maxima reported in studies (i.e. foci) are modelled as spatial 3D Gaussian

probability distributions (Laird et al. 2005). The distribution is centered at the reported coordinates and its size is directly related to the sample size (number of participants) (Eickhoff et al. 2009). Once all the distributions of a study have been generated, a modelled activation map is created for the study (Turkeltaub et al. 2012). The union of the modelled activation maps describing the convergence of results across studies at each voxel represents the ALE map. To identify true congruence from noise, permutation tests were performed. The ALE map was compared to the null distribution, a randomly distributed map, and tested for significance for each voxel (Eickhoff et al. 2012). The meta-analysis was performed with Ginger ALE software (<http://brainmap.org/ale>). Statistical significance was set at a family-wise error (FWE) corrected threshold of $p < 0.05$ with a cluster extent of 10 voxels. The ALE value, cluster volume (in voxels) and the MNI coordinates are reported for each analysis. The maps of the ALE values were superimposed on a colin.nii atlas (Laird et al. 2005) using the Mango software (<http://ric.uthscsa.edu/mango//mango.html>).

A meta-analysis was first conducted on all of the imaging studies combined together to assess the contribution of all experiments in the insular activity, then separate meta-analyses were conducted on specific functional sub-categories (cognition, sensorimotor, affective/behavioural symptoms) to evaluate the contribution of different experiments in the insular sub-regions. Finally, another set of analyses was conducted to estimate the effect of the medication on studies with patients ON and OFF medication.

Results

Table 1 (appendix) summarizes the demographics and experimental conditions of the 96 imaging reports included in the meta-analysis. Briefly, these included 20 PET studies with receptor imaging, 25 PET with H₂O¹⁵ or TC99m, and 51 fMRI. The total number of experiments (96) included 1852 patients (age 63 y/o +/- 5 SD) and 801 controls (age 61 y/o +/- 7 SD) (Table 1, appendix). 30 studies (31 %) reported experiments related to cognition (executive function, memory, language, MCI, dementia, etc.), 24 studies (25 %) reported experiments with affective/behavioural symptoms, 8 studies (8 %) were related to bodily awareness/autonomic function, 21 studies (22 %) were associated with sensorimotor function, and 13 studies (14 %) reported non-specific changes associated with disease.

The whole group ALE meta-analysis across the 96 published experiments revealed significant convergence of activation maxima related to PD in different insular regions (Table 2, Fig. 1). These clusters were located in the right ventral anterior insula (MNI: x = 38, y = 16, z = -2; ALE value=0.050), left ventral anterior insula (-36, 18, -8; ALE value=0.039), and left dorsal posterior insula (-42, -12, 4; ALE value=0.040) (Fig.1A). When looking at the effect of the medication, a significant convergence of activation maxima was observed for the different medication states (ON or OFF) (Fig. 1B). The ON medication studies (30 experiments) showed a significant convergence of activation maxima in the left and right ventral anterior insula (-38, 18 -8; ALE value=0.022; 32, 26, -4; ALE value=0.019), whereas in the OFF medication studies (57 experiments), convergence was localized more posteriorly, in the left and right dorsal posterior insula (-42, -12, 4; ALE value=0.036; 38, -16, 4; ALE value=0.037).

A significant convergence of activation maxima was also observed for the different functional subcategories (Table 3). In fact, combining cognitive and behavioural/affective domains (54 studies) showed a significant convergence of activation maxima in the left and right ventral anterior insula (-34, 20 -8; ALE value=0.030; 38, 14, -4; ALE value=0.027) and in the left and right dorsal posterior insula (-42, -12, 4; ALE value=0.039; 38, -16, 4; ALE value=0.037) (Fig. 2A). Instead, the analysis limited only to the cognitive domain identified smaller overlapping clusters (Fig. 3A) in the left and right ventral anterior insula (-36, 20, -8; ALE value=0.025; 38,

12, -4; ALE value=0.022) and in the left and right dorsal posterior insula (-42, -12, 2; ALE value=0.030; 36, -18, 6; ALE value=0.025). The behavioural/affective symptoms also showed an overlapping cluster in the right ventral mid-insula (44, 2, -4; ALE value=0.018) (Fig. 3B). When focusing on the effect of the medication, a significant convergence of activation maxima was observed for the different medication state (ON or OFF). The ON medication studies (21 experiments) showed a significant convergence of activation maxima in the left and right ventral anterior insula (-36, 18 -8; ALE value=0.019; 32, 26, -4; ALE value=0.019), whereas in the OFF medication studies (28 experiments), convergence was localized more posteriorly, in the left and right dorsal posterior insula (-42, -12, 4; ALE value=0.035; 38, -16, 4; ALE value=0.035) (Fig. 2B).

A significant convergence of activation maxima related to the sensorimotor function (21 studies) was seen instead in the left mid-insula (-42, 6, -8; ALE value=0.018) and the right anterior insula (44, 18, -2; ALE value=0.014), which did not overlap with other domain-related clusters (Table 3).

Discussion

Despite strong presumption, no neuroimaging studies have directly addressed the contribution of the insula as a critical region in PD pathology. The current study confirmed the importance of the insula in PD in acting as a hub for processing critical information related to the body state and for integrating cognitive-affective, sensorimotor and autonomic information (Fig.1). This report provides evidence of an important functional distribution of different domains within the insular cortex in PD, particularly in relation to non-motor aspects, with changes related to the effect of disease and medication state.

When focusing on the cognitive and behavioural/affective domains of the disease, the insula show a bilateral involvement of both anterior and posterior regions (Fig. 2, 3). The anterior involvement is quite consistent with accumulating research in healthy subjects showing that this region plays a central role in directing cognitive processes and implementing/maintaining task set (Dosenbach et al. 2006, 2007). In conjunction with the anterior cingulate cortex (i.e. salience network), the anterior insula allows switching between neural networks required for executive functions (Seeley et al. 2007; Menon and Uddin, 2010; Swick et al. 2011). It has also a well established contribution in processing affect and emotion and it is critically involved in social interactions requiring self-awareness, interoception and integration of both affective/emotional and environmental stimuli (Craig, 2009). In other words, it is very likely that neurodegenerative processes affecting this region could disrupt both cognitive and socio/affective functions in PD (Christopher et al. 2014a; Nieuwenhuys, 2012).

An interesting finding was the observation in these PD patients (performing cognitive and behavioural/affective tasks) of a significant convergence of activation maxima in the posterior regions of the insula (Fig. 2B). While the biological explanation of this finding is not entirely clear, it is likely that this may be the result of the dopaminergic changes described before (Christopher et al. 2014b). Indeed, when focusing on the effect of medication, we found some evidence supporting the role of dopamine depletion. We reported that while PD patients OFF medication presented with a significant convergence of activation maxima mainly in dorsal posterior regions of the insula, PD patients ON medication showed, in contrast, a more physiological involvement of bilateral anterior insula (Fig. 2B).

It is possible that in those patients OFF medication, the bodily sensations generated by the motor symptoms (i.e. bradykinesia and rigidity) may lead to an abnormal activation of the posterior insula, generally implicated in the processing of position, movement and sensation of the body (Chang et al. 2013; Cerasa et al. 2006). This abnormal interoceptive information of how the body ‘feels’ may lead to an abnormal salience processing in the anterior insula affecting how affective/emotional sensations are perceived in patients with PD, which is partially restored by dopaminergic medication. In alternative, the more posterior activation in the OFF medication state (during cognitive and behavioural/affective tasks) may simply be related to a compensatory activation due to inadequate recruitment of the anterior insula. In contrast, when ON dopaminergic medication, patients may be better able to recruit the anterior insula during cognitive processing.

A significant convergence of activation maxima related specifically to sensorimotor tasks was seen in the mid-insula confirming the role of this region in processing bodily awareness in relation to somatosensory information and coordination of movement.

Although the Activation Likelihood Estimation technique overcomes the classical limitations of neuroimaging studies, it only reveals convergences of activity from different studies, not the actual activations. Thus, interpretations of the results should be made taking into consideration the limitation inherent to this technique. However, it offers a valuable approach to investigate an under-recognized region involved in the pathogenesis of Parkinson’s disease. The insula is substantially affected by alpha-synuclein deposition in PD and the insular abnormalities found in neuroimaging studies highly point toward its contribution to a wide range of non-motor symptoms, including somatosensory disturbances. Thus, as an important hub involved in integrating diverse information, the insula should be considered as a region of interest when investigating cognitive and behavioural changes, as well as disruptions in viscerosensory or somatosensory processes in Parkinson’s disease.

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First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
Ballanger <i>Rest</i>	2010	PD with visual hallucination vs. CPD (ON)	Affective & Behavioural symptoms (Visual Hallucination)	7 PD with visual hallucinations (7 CPD)	69 PD (67 CPD)	24 vs. 15 (ON)	PET (¹⁸ F Setoperone)
Ballanger <i>Rest</i>	2012	PD vs. NC (OFF)	Other	8 PD (7 NC)	63 PD	27 (OFF)	PET (¹⁸ F MPPF)
Ballanger <i>Rest</i>	2012	PD with depression vs. NC (OFF)	Affective & Behavioural symptoms (Depression)	4 PD with depression (7 NC)	54 PD with depression	26 (OFF)	PET (¹⁸ F MPPF)
Ballanger <i>Rest</i>	2012	PD with depression vs. CPD (OFF)	Affective & Behavioural symptoms (Depression)	4 PD with depression (8 CPD)	54 with depression	26 (OFF)	PET (¹⁸ F MPPF)
Beyer <i>Rest</i>	2008	PD with early dementia vs. PD with late dementia (ON)	Cognition (Dementia)	9 PD with early dementia (6 PD with late dementia)	74 PD with early dementia (70 PD with late dementia)	40 vs. 40 (ON)	fMRI
Bohhalter <i>Task: somatosensory discrimination</i>	2009	Correlation between somatosensory discrimination and working memory scale (OFF)	Cognition (Working Memory and Somatosensory Discrimination)	12 PD (12 NC)	59 PD (47 NC)	17 (ON)	PET (H ¹⁵ O)
Borghammer <i>Rest</i>	2012	PD vs. NC (OFF)	Other	21 PD (11 NC)	64 PD (60 NC)	16 (ON)	PET (¹⁸ F FDG)
Brefel-Courbon <i>Task: cold water stimulation inducing painful or non-painful sensation on the hand</i>	2005	Pain induced activity, PD vs. NC (OFF)	Bodily Awareness (Pain)	9 PD (9 NC)	65 PD	25 (OFF)	PET (H ¹⁵ O)
Brefel-Courbon <i>Task: cold water stimulation inducing painful or non-painful sensation on the hand</i>	2005	Pain induced activity, PD vs. NC (ON)	Bodily Awareness (Pain)	9 PD (9 NC)	65 PD	15 (ON)	PET (H ¹⁵ O)
Brefel-Courbon <i>Task: cold water stimulation inducing painful or non-painful sensation on the hand</i>	2005	Pain induced activity, PD OFF vs. PD ON	Bodily Awareness (Pain)	9 PD	65 PD	25 OFF vs. 15 ON	PET (H ¹⁵ O)
Brefel-Courbon <i>Task: cold water stimulation inducing painful or non-painful sensation on the hand</i>	2013	Pain induced activity, CPD vs. PD with neuropathic pain (OFF)	Bodily Awareness (Pain)	9 PD with neuropathic pain (9CPD)	61 PD with neuropathic pain (65 CPD)	28 vs. 25 (OFF)	PET (H ¹⁵ O)
Caproni <i>Task: finger tapping sequences executed with the right hand, conditions: 1 finger sequence, simple 5 fingers sequences, complex 5 fingers sequence.</i>	2013	1 finger sequence, PD vs. NC (OFF)	Motor	11 PD (11 NC)	65 PD (65 NC)	20 (OFF)	fMRI
Caproni <i>Task: finger tapping sequences executed with the right hand, conditions: 1 finger sequence, simple 5 fingers sequences, complex 5 fingers sequence.</i>	2013	Simple 5 fingers sequence, PD vs. NC (OFF)	Motor	11 PD (11 NC)	65 PD (65 NC)	20 (OFF)	fMRI
Caproni <i>Task: finger tapping sequences executed with the right hand, conditions: 1 finger sequence, simple 5 fingers sequences, complex 5 fingers sequence.</i>	2013	Complex 5 fingers sequence, NC vs. PD (OFF)	Motor	11 PD (11 NC)	65 PD (65 NC)	20 (OFF)	fMRI
Cerasa <i>Task: Synchronized tapping with right index</i>	2006	Synchronized tapping vs. rest, PD vs. NC (OFF)	Motor	10 PD (11 NC)	64 PD (63 NC)	28 (OFF)	fMRI
Ceravolo <i>Rest</i>	2011	PD PPTg stimulation ON vs. OFF (OFF)	Other	6 PD	65 PD	74 PPTg ON vs. 38 PPTg OFF (OFF)	PET (¹⁸ F FDG)
Christopher	2013	NC vs. PD with MCI (OFF)	Cognition (MCI)	11 PD with MCI (14 NC)	71 PD with MCI (68 NC)	31 (ON)	PET (¹¹ C FLB 457)

<i>Rest</i>									
Christopher	2013	CPD vs. PD with MCI (OFF)	Cognition (MCI)	11 PD with MCI (11 CPD)	71 PD with MCI (69 CPD)	31 vs. 23 (ON)	PET (¹¹ C FLB 457)		
<i>Rest</i>									
Christopher	2014	NC vs. PD with amnesic MCI (OFF)	Cognition (amnesic MCI)	9 PD with amnesic MCI (14 NC)	68 PD with amnesic MCI (68 NC)	36 (ON)	PET (¹¹ C FLB 457)		
<i>Rest</i>									
Christopher	2014	NC vs. PD with MCI (OFF)	Cognition (MCI)	10 PD with MCI (14 NC)	70 PD with MCI (68 NC)	21 (ON)	PET (¹¹ C FLB 457)		
<i>Rest</i>									
Christopher	2014	CPD vs. PD with amnesic MCI (OFF)	Cognition (amnesic MCI)	9 PD with amnesic MCI (11 CPD)	68 PD with amnesic MCI (69 CPD)	36 vs. 23 (ON)	PET (¹¹ C FLB 457)		
<i>Rest</i>									
Christopher	2014	CPD vs. PD with MCI (OFF)	Cognition (MCI)	10 PD with MCI (11 CPD)	70 PD with MCI (69 CPD)	21 vs. 23 (ON)	PET (¹¹ C FLB 457)		
<i>Rest</i>									
Christopher	2014	PD with MCI vs. PD with amnesic MCI (OFF)	Cognition (amnesic MCI)	9 PD with amnesic MCI (10 PD with MCI)	68 PD with amnesic MCI (70 PD with MCI)	36 vs. 21 (ON)	PET (¹¹ C FLB 457)		
<i>Rest</i>									
Christopher	2014	Correlation between brain activity and memory score (OFF)	Cognition (amnesic MCI)	9 PD with amnesic MCI	68 PD with amnesic MCI	36 (ON)	PET (¹¹ C FLB 457)		
<i>Rest</i>									
Cilia	2008	Gambling PD vs. CPD (OFF)	Affective & Behavioural symptoms (Gambling)	11 gambling PD (40 CPD)	57 gambling PD (55 CPD)	18 vs. 19 (ON)	SPECT (TC99m)		
<i>Rest</i>									
Cilia	2011	Correlation activity change and gambling score (OFF)	Affective & Behavioural symptoms (Gambling)	15 gambling PD	60 gambling PD	17 (ON)	SPECT (TC99m)		
<i>Rest</i>									
Cools	2006	Error vs. correct responses	Cognition (Learning)	14 PD	66 PD	39 OFF vs. 16 ON	fMRI		
<i>Task: probabilistic reversal learning task</i>									
Delaveau	2009	Placebo vs. Levodopa during task recognition (OFF)	Affective & Behavioural symptoms (Emotion recognition)	14 PD	61 PD		fMRI		
<i>Task: emotional/face matching</i>									
Delaveau	2010	NC vs. PD (OFF)	Affective & Behavioural symptoms (Emotion recognition)	14 PD (13 NC)	61 PD (56 NC)		fMRI		
<i>Task: emotional/face matching</i>									
Delaveau	2010	PD placebo vs. l-dopa	Affective & Behavioural symptoms (Emotion recognition)	14 PD (13 NC)	61 PD (56 NC)		fMRI		
<i>Task: emotional/face matching</i>									
Delapina	2012	Anti-correlation between brain activity and pain threshold (OFF)	Bodily Awareness (Pain)	8 PD with pain (8 CPD)	65 PD with pain (62 CPD)	16 vs. 12 (OFF)	PET (H ¹⁵ O)		
<i>Task: cold water stimulation inducing painful or non-painful sensation on the hand</i>									
Elsinger	2003	Synchronized tapping vs. rest (OFF)	Motor	10 PD	67 PD	24 (OFF)	fMRI		
<i>Task: Synchronized tapping with right index</i>									
Fregni	2006	NC vs. PD with depression (OFF)	Affective & Behavioural symptoms (Depression)	26 PD with depression (29 NC)	66 PD with depression (65 NC)	35 (ON)	SPECT (TC99m)		

<i>Rest</i>									
Gamma	2014	PD with visual hallucination vs. PD with visual hallucination and cognitive dysfunction (ON)	Cognition (Cognitive Dysfunction in Visual Hallucinations)	6 PD with visual hallucination and cognitive dysfunction (5 PD with visual hallucination)	71 PD	23 (ON)	fMRI		
<i>Rest</i>									
Goldman	2014	CPD vs. PD with visual hallucination (ON)	Affective & Behavioural symptoms (Visual Hallucination)	25 PD with visual hallucination (25 CPD)	75 PD with visual hallucination (75 CPD)	44 vs. 39 (ON)	fMRI		
<i>Rest</i>									
Hanakawa	1999	Walk vs. rest, PD vs. NC (OFF)	Motor	10 PD (10 NC)	67 PD (67 NC)	35 (OFF)	SPECT (TC99m)		
<i>Task: Walking or resting just before the scan</i>									
Helmich	2010	Connectivity from the anterior putamen, NC vs. PD (OFF)	Other	41 PD (36 NC)	57 PD (57 NC)	28 (OFF)	fMRI		
<i>Rest</i>									
Helmich	2010	Connectivity from the posterior putamen, PD vs. NC (OFF)	Other	41 PD (36 NC)	57 PD (57 NC)	28 (OFF)	fMRI		
<i>Rest</i>									
Hsu	2007	PD vs. NC (OFF)	Other	27 PD (24 NC)	66 (62 NC)	26 (ON)	SPECT (TC99m)		
<i>Rest</i>									
Hyoung	2010	CPD vs. PD with MCI (OFF)	Cognition (MCI)	18 PD with MCI (20 CPD)	66 PD with MCI (62 CPD)	25 vs. 22 (ON)	PET (¹⁸ F FDG)		
<i>Rest</i>									
Imon	1999	PD Hoehn and Yahr stage 3 or 4 vs. NC (ON)	Other	12 PD Hoehn and Yahr stage 3 or 4 (48 NC)	63 PD Hoehn and Yahr stage 3 or 4 (58 NC)		SPECT (TC99m)		
<i>Rest</i>									
Jeoh	2012	PD before vs. after STN-DBS surgery (OFF)	Motor	12 PD	56 PD	34 vs. 23 (OFF)	fMRI		
<i>Task: Tapping with left or right hand</i>									
Kaasinen	2004	Anti-correlation novelty seeking scale and brain activity (OFF)	Cognition (Executive)	28 PD	62 PD	39 (ON)	PET (¹¹ C FLB 457)		
<i>Rest</i>									
Kahan	2012	Interaction movement and STN stimulation (ON/OFF), (OFF)	Motor	10 PD	58 PD	21 (OFF)	fMRI		
<i>Task: voluntary hand movement</i>									
Kikuchi	2001	NC vs. PD Hoehn and Yahr stage 3/4 (ON)	Other	11 PD Hoehn and Yahr stage 3 or 4 (11 NC)	59 PD Hoehn and Yahr stage 3/4 (62 NC)	28 (ON)	SPECT (TC99m)		
<i>Rest</i>									
Kikuchi	2001	PD Hoehn and Yahr stage 1/2 vs. PD Hoehn and Yahr stage 3/4 (ON)	Other	11 PD Hoehn and Yahr stage 3 or 4 (7 PD Hoehn and Yahr stage 1 or 2)	59 PD Hoehn and Yahr stage 3/4 (60 PD Hoehn and Yahr stage 1/2)	19 vs. 28 (ON)	SPECT (TC99m)		
<i>Rest</i>									
Kostic	2010	PD vs. NC (ON)	Other	24 PD (26 NC)	65 PD (63 NC)	19 (ON)	fMRI		
<i>Rest</i>									
Kostic	2010	PD with depression vs. CPD (ON)	Affective & Behavioural symptoms (Depression)	16 PD (24 CPD)	66 PD (65 CPD)	23 vs. 19 (ON)	fMRI		
<i>Rest</i>									

Lee <i>Rest</i>	2014a	PD with MCI vs. PD with MCI and dementia (ON)	Cognition (MCI and Dementia)	15 PD with MCI and dementia (36 PD with MCI)	73 PD with MCI and dementia (71 PD with MCI)	17 vs. 20 (ON)	fMRI
Lee <i>Rest</i>	2014a	NC vs. PD with MCI and dementia (ON)	Cognition (MCI and Dementia)	15 PD with MCI and dementia (25 NC)	73 PD with MCI and dementia (70 NC)	17 (ON)	fMRI
Lee	2014b	PD with ICD vs. CPD (OFF)	Affective & Behavioural symptoms (ICD)	11 PD with ICD (11 CPD)	57 PD with ICD (59 CPD)	14 vs. 15 (ON)	PET (¹⁸ F-FP-CIT)
Lee <i>Rest</i>	2014c	PD with high olfaction score vs. NC (ON)	Autonomic symptoms (Olfaction)	38 PD with high olfaction score (50 NC)	69 PD with high olfaction score (69 NC)	18 (ON)	fMRI
Liotti	2003	Phonation, before vs. after voice therapy	Motor	5 PD with hypophonia	61 PD with hypophonia		PET (H ¹⁵ O)
<i>Task: speech task including phonation, reading and conversation</i>							
Loize	2009	Correlation with error in recognition (OFF)	Affective & Behavioural symptoms (Emotion recognition)	9 PD	66 PD	38 (OFF)	fMRI
<i>Task: emotional and non-emotional gesture recognition</i>							
Luo <i>Rest</i>	2014	PD with depression vs. NC (OFF)	Affective & Behavioural symptoms (Depression)	29 PD with depression (30 NC)	51 PD with depression (54 NC)	28 (OFF)	fMRI
Maillet	2012	Hand movement, PD OFF vs. PD ON	Motor	12 PD	60 PD	40 OFF vs. 10 ON	fMRI
<i>Task: Hand movement and/or speech production</i>							
Mak <i>Rest</i>	2014	PD with MCI vs. CPD (ON)	Cognition (MCI)	24 PD with MCI (66 CPD)	69 PD with MCI (63 CPD)	20 vs. 17 (ON)	fMRI
Mallol	2007	NC vs. PD (OFF)	Motor	13 PD (11 NC)	65 PD (62 NC)	23 (OFF)	fMRI
<i>Task: finger to thumb and hand rotation movements</i>							
Mattay	2002	PD OFF vs. PD ON	Cognition (Working Memory)	10 PD	55 PD	9 OFF vs. 5 ON	fMRI
<i>Task: N-back</i>							
Monchi	2004	Negative vs. control feedback (OFF)	Cognition (Executive)	8 PD	57 PD	12 (OFF)	fMRI
<i>Task: Wisconsin Card Sorting Task with negative, positive and control feedback</i>							
Oishi <i>Rest</i>	2004	Correlation verbal IQ score	Cognition (Executive)	44 PD	66 PD		SPECT (TC99m)
Oishi <i>Rest</i>	2004	Correlation full IQ score	Cognition (Executive)	44 PD	66 PD	(ON)	SPECT (TC99m)
Pavese <i>Rest</i>	2010	CPD vs. PD with Fatigue (OFF)	Affective & Behavioural symptoms (Fatigue)	10 PD with fatigue (9 CPD)	65 PD with fatigue (63 CPD)	35 vs. 33 (OFF)	PET (¹⁸ F-FDOPA)
Pavese <i>Rest</i>	2010	CPD vs. PD with Fatigue (OFF)	Affective & Behavioural symptoms (Fatigue)	8 PD with fatigue (8 CPD)	65 PD with fatigue (64 CPD)	35 vs. 34 (OFF)	PET (¹¹ C-DASB)

Payoux	2009	Interaction movement and GP stimulation (OFF)	Motor	5 PD	58 PD	PET (H ¹⁵ O)
<i>Task: Opening and clenching fist</i>						
Peran	2009	Generation of action verbs (ON)	Cognition (Language)	14 PD	64 PD	fMRI
<i>Task: object naming and generation of action verbs related to man-made or manipulable biological objects</i>						
Peran	2009	Generation of action verbs vs. objects naming (man-man objects) (ON)	Cognition (Language)	14 PD	64 PD	fMRI
<i>Task: object naming and generation of action verbs related to man-made or manipulable biological objects</i>						
Peran	2009	Generation of action verbs with biological objects vs. naming man-man objects) (ON)	Cognition (Language)	14 PD	64 PD	fMRI
<i>Task: object naming and generation of action verbs related to man-made or manipulable biological objects</i>						
Peran	2009	Naming biological objects (ON)	Cognition (Language)	14 PD	64 PD	fMRI
<i>Task: object naming and generation of action verbs related to man-made or manipulable biological objects</i>						
Pinto	2004	Silent articulation, OFF STN DBS (OFF)	Motor	10 PD with STN DBS and dysarthria	54 PD with STN DBS and dysarthria	PET (H ¹⁵ O)
<i>Task: Speech, silent articulation or silence production</i>						
Pinto	2011	Hand movement, NC vs. PD (OFF)	Motor	9 PD (15 NC)	59 PD (55 NC)	fMRI
<i>Task: Hand movement and/or speech production</i>						
Pinto	2011	Hand movement and speech production NC vs. PD (OFF)	Motor	9 PD (15 NC)	59 PD (55 NC)	fMRI
<i>Task: Hand movement and/or speech production</i>						
Poisson	2013	PD with mirror movements vs. CPD (OFF)	Motor	8 PD with mirror movements (6 CPD)	59 PD with mirror movements (65 CPD)	fMRI
<i>Task: index to thumb opposition movement</i>						
Politis	2013	Sexual vs. neutral cue, PD with hypersexuality vs. CPD (OFF)	Affective & Behavioural symptoms (Hypersexuality)	12 PD with hypersexuality (12 CPD)	55 PD with hypersexuality (62 CPD)	fMRI
<i>Task: Rating the follow cues: dopaminergic drugs, appetizing food, money and gambling, sexual and neutral</i>						
Reijnders	2010	Anti-correlation apathy scale (ON)	Affective & Behavioural symptoms (Apathy)	55 PD	62 PD	fMRI
<i>Rest</i>						
Robert	2012	Correlation apathy scale (ON)	Affective & Behavioural symptoms (Apathy)	45 PD	61 PD	PET (18F FDG)
<i>Rest</i>						
Rottschy	2013	Memory load, PD vs. NC (ON)	Motor	23 PD (23 NC)	67 PD (65 NC)	fMRI
<i>Task: memorize and retype variably long visuo-spatial stimulus sequences after short or long delays (immediate or delayed serial recall)</i>						
Sawamoto	2007	PD vs. NC (OFF)	Cognition (Executive)	7 PD (9 NC)	59 PD (61 NC)	PET (H ¹⁵ O)
<i>Task: mental calculation of the day of the week depending on clues and instruction.</i>						
Schwingschuh	2013	Ankle movement, PD vs. NC (ON)	Other	20 PD (10 NC)	67 PD (35 NC)	fMRI
<i>Task: Cued ankle movement</i>						
Sheng	2014	PD with depression vs. NC (ON)	Affective & Behavioural symptoms (Depression)	20 PD (25 NC)	56 PD (57 NC)	fMRI

<i>Rest</i>									
Sheng	2014	PD with depression vs. CPD (ON)	Affective & Behavioural symptoms (Depression)	20 PD (21 CPD)	56 PD (57 CPD)				fMRI
<i>Rest</i>									
Shine	2013a	PD with visual hallucination vs. CPD (ON)	Affective & Behavioural symptoms (Visual Hallucination)	9 PD (13 CPD)	66 PD (62 CPD)	27 vs. 21 (ON)			fMRI
<i>Task: Bistable percept paradigm</i>									
Shine	2013a	PD with visual hallucination vs. CPD (ON)	Affective & Behavioural symptoms (Visual Hallucination)	9 PD (13 CPD)	66 PD (62 CPD)	27 vs. 21 (ON)			fMRI
<i>Rest</i>									
Shine	2013b	Complex vs. simple cues, CPD vs. PD with freezing gait (OFF)	Motor	14 PD with freezing gait (15 CPD)	63 PD with freezing gait (63 CPD)	32 vs. 29 (OFF)			fMRI
<i>Task: Walk based stop signal task with simple or complex (Stoop based) cues.</i>									
Shine	2013c	Walk vs. freezing (OFF)	Motor	18 PD	67 PD	39 (OFF)			fMRI
<i>Task: Walk based stop signal task with simple or complex (Stoop based) cues.</i>									
Song	2014	NC vs. PD	Other	33 PD (33 NC)	71 PD (67 NC)	14			SPECT (TC99m)
<i>Rest</i>									
Subramanian	2011	Feedback vs. no feedback group (ON)	Cognition (Executive)	10 PD	64 PD	15 (ON)			fMRI
<i>Task: Hand movement guided with or without neurofeedback</i>									
Tan	2015	NC vs. PD (OFF)	Bodily Awareness (Pain)	14 PD (17 NC)	63 PD (61 NC)	22 (OFF)			fMRI
<i>Task: Heat-induced pain</i>									
Toxopeus	2012	Inhibition, NC vs. PD (OFF)	Motor	13 PD (19 NC)	59 PD	22 (OFF)			fMRI
<i>Task: wrist movement divided in initiation, inhibition and gradual movement modulation.</i>									
Turner	2013	Movement-related activity, NC vs. PD (OFF)	Motor	12 PD (12 NC)	57 PD (58 NC)	42 (OFF)			PET (H ¹⁵ O)
<i>Task: predictive visuomotor tracking task</i>									
Ulla	2010	Manic vs. euthymic induced by STN DBS (ON)	Affective & Behavioural symptoms (Hypomania)	5 PD with hypomania	62 PD with hypomania	36 (OFF)			PET (H ¹⁵ O)
<i>Rest</i>									
Ventre-Dominey	2014	Spatial working memory, STN-DBS ON vs. OFF (OFF)	Cognition (Working Memory)	13 PD	55 PD	9 DBS ON vs. 39 DSB OFF (OFF)			PET (H ¹⁵ O)
<i>Task: spatial and non-spatial working color and movement association</i>									
Weder	2000	NC vs. PD (OFF)	Cognition (Somatosensory discrimination)	12 PD (12 NC)		17 (ON)			PET (H ¹⁵ O)
<i>Task: finger exploratory discrimination</i>									
Weige-Lussen	2009	Olfactory stimulation (ON)	Autonomic symptoms (Olfaction)	18 PD	59 PD	28 (ON)			fMRI
<i>Task: Olfactory stimulation</i>									
Wu	2011	PD vs. NC (OFF)	Other	18 PD (18 NC)	62 PD (62 NC)	22 (OFF)			fMRI
<i>Rest</i>									
Ye	2012	PD vs. NC	Cognition	16 PD	62 PD	16			fMRI

(ON)	(16 NC)	(64 NC)	(ON)
(Language)			
<i>Task: Temporal connective comprehension</i>			

Table 1: List of studies including first author, year of publication, the contrast used and the medication state during the task, the sub-category, the number of patients and controls, the age of each group, the UPDRS and the state of medication during the evaluation and the modality. PD: Parkinson's Disease patient, NC: normal control, CPD: control group of PD patients, MCI: mild cognitive impairment, STN: sub-thalamic nucleus, DBS: deep-brain stimulation, PPTg: nucleus tegmenti pedunculopontini, ON: ON medication (normal intake of medication), OFF: OFF medication (withdraw of medication over night).

Tables

Table 2: Activation-likelihood-estimation: Clusters from the whole group meta-analysis

Cluster	Side	k	ALE value	x	y	z
# 1	R	477	0.050	38	16	-2
	R		0.039	38	-16	4
# 2	L	143	0.039	-36	18	-8
	L		0.024	-32	24	4
	L		0.021	-42	6	-8
# 3	L	119	0.040	-42	-12	4

Location of significant convergence of activation maxima from the whole group meta-analysis, thresholded at $p < 0.05$ (FWE-corrected), the side (R: right, L: left), the number of voxels (k), the ALE value and the MNI coordinates.

Table 3: Activation-likelihood-estimation from different functional subcategories

Cluster	Side	k	ALE value	x	y	z
<i>Cognition and Affective/Behavioural symptoms</i>						
# 1	R	115	0.027	38	14	-4
	R		0.024	42	4	-2
	R		0.022	32	26	-4
# 2	L	115	0.039	-42	-12	4
# 3	R	104	0.037	38	-16	4
# 4	L	54	0.030	-34	20	-8
<i>Cognition</i>						
# 1	L	85	0.030	-42	-12	2
# 2	R	62	0.025	36	-18	6
# 3	R	52	0.022	38	12	-4
	R		0.022	30	26	-4
# 4	L	37	0.025	-36	20	-8
<i>Affective/Behavioural symptoms</i>						
# 1	R	15	0.018	44	2	-4
<i>Motor</i>						
# 1	L	32	0.018	-42	6	-8
# 2	R	11	0.014	44	18	-2

Location of significant convergence of activation maxima from the sub-category meta-analyses, thresholded at $p < 0.05$ (FWE-corrected), the side (R: right, L: left), the number of voxels (k), the ALE value and the MNI coordinates.

Figures

Figure 1:

ALE map of clusters showing changes in PD ($p < 0.05$). A: Whole group analysis. B: Effect of the medication.

Figure 2:

ALE map of clusters showing changes in PD ($p < 0.05$). A: Cognitive and Affective/Behavioural symptoms analysis. B: Effect of the medication on Cognitive and Affective/Behavioural symptoms.

Figure 3:

ALE map of clusters showing changes in PD ($p < 0.05$). A: Cognitive analysis. B: Affective/Behavioural symptoms.

Figure 1

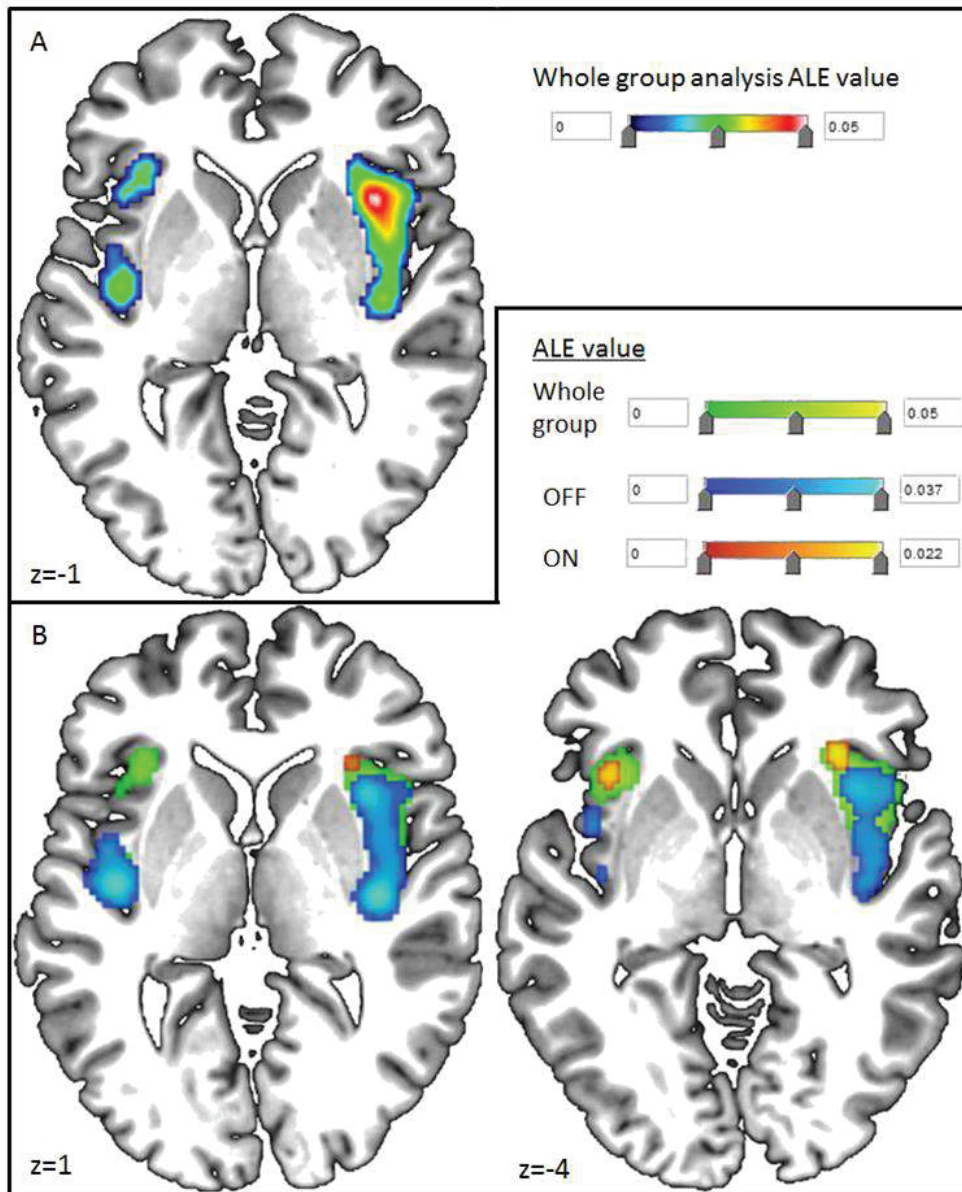


Figure 2

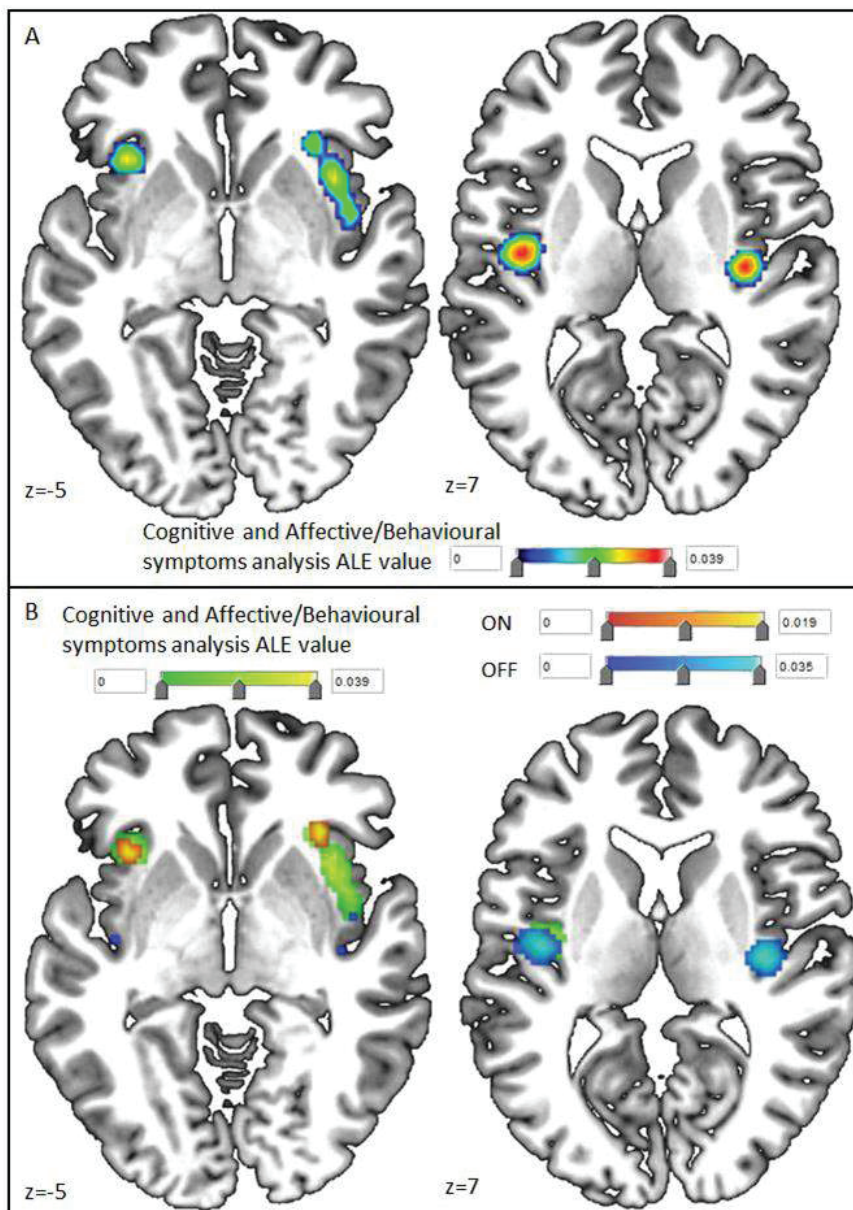
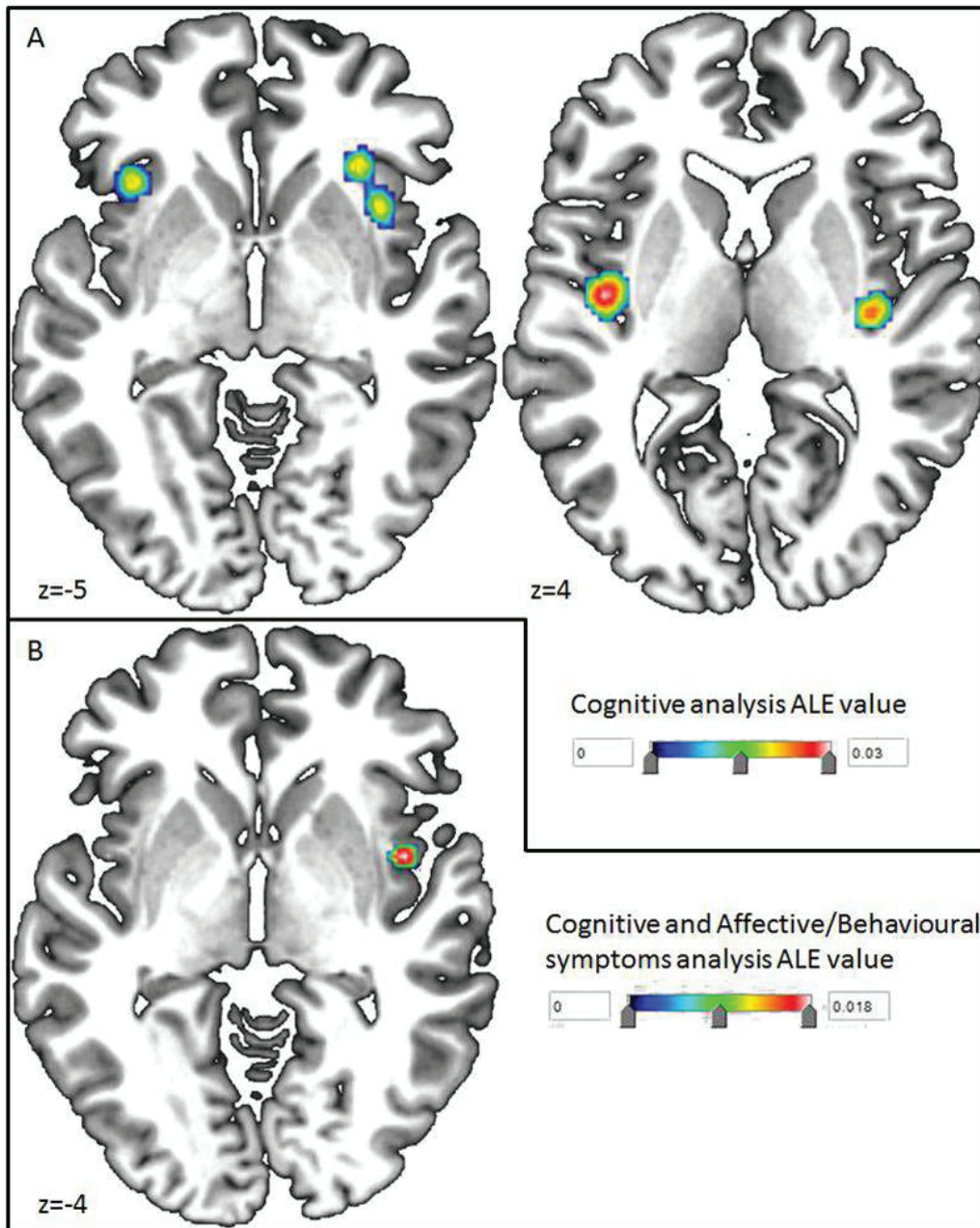


Figure3



3.4.4 Conclusion

Cette étude révèle que l'insula est une région qui joue un rôle central dans le contrôle cognitif. En particulier, l'insula antérieure est impliquée en conjonction avec le cortex cingulaire antérieur et le réseau de détection de saillance dans la permutation entre états de contrôle, et plus généralement dans les fonctions exécutives qui reposent sur ce mécanisme (Christopher et al. 2014b; Seeley et al. 2007; Menon and Uddin, 2010). De ce point de vue, les données empiriques collectées en IRMf présentées dans la partie précédente s'accordent mal avec 1) les résultats de cette méta-analyse, mais également avec 2) les résultats de méta-analyses de la fonction d'inhibition de réponse chez les sujets sains (Swick et al., 2011 ; Criaud et Boulinguez, 2013). En effet, nous possédons maintenant un ensemble d'évidences indiquant que l'insula joue un rôle clef dans l'inhibition active de réponse chez le sujet sain et dans les troubles exécutifs du patient parkinsonien, mais les troubles du contrôle de l'action sondés empiriquement dans nos travaux de semblent pas liés à des modulations d'activité de l'insula. Plusieurs pistes peuvent être avancées. Nous sommes peut-être simplement en face d'une erreur de type II liée au manque de puissance statistique de nos protocoles IRMf. Si tel n'est pas le cas, alors la réflexion doit être portée sur la nature exacte de l'activité de l'insula. Il est envisageable que celle-ci ne soit pas directement liée à la suppression active et anticipée de l'excitation motrice, mais qu'elle ait un rôle dans des fonctions plus générales (attention, saillance, intégration d'évidence...) et/ou réactives. Son dysfonctionnement serait alors susceptible d'expliquer de nombreux troubles du contrôle cognitif et exécutif, possiblement avec expression motrice, mais les mécanismes d'inhibition à proprement parler, à l'instar du controversé gyrus frontal inférieur droit (Chatham et al., 2012 ; Hampshire et al., 2010 ; Duann et al., 2008 ; Swick et al., 2011). Cette interprétation théorique est la seule cohérente à nos yeux avec l'absence d'effet dans une tâche épurée de contrôle inhibiteur

limitant les confusions potentielles entre fonctions cognitives corolaires comme celle que nous avons élaborée.

Notre étude met également en évidence des dysfonctionnements multiples de l'insula avec un spectre très large de troubles non moteurs associés dans la maladie de Parkinson. Cela nous ouvre de nouveaux horizons dans la compréhension de la pathologie. L'insula antérieure dont nous venons de discuter l'implication dans le contrôle exécutif est également impliquée dans le traitement des affects et de l'émotion, ainsi que dans les interactions sociales. La mise en évidence de cet overlap anatomo-fonctionnel pourrait expliquer comment le processus neurodégénératif est susceptible de rendre compte de troubles aussi variables que des dysfonctionnements exécutifs et des troubles socio-affectifs (Christopher et al. 2014a; Nieuwenhuys, 2012). Par extension, ils suggèrent que les mécanismes de verrouillage qui nous intéressent sont susceptibles de ne pas s'appliquer au seul domaine moteur, mais qu'ils concernent aussi possiblement le contrôle des émotions et des affects.

Il nous semble nécessaire d'aller plus loin dans l'investigation des déficits corticaux dans cette maladie des noyaux gris centraux. Pour ce faire, après avoir exploré les symptômes spécifiques d'hypo-réactivité (akinésie), puis le large spectre des symptômes non-moteurs, il conviendrait à l'avenir de se focaliser sur l'autre face de la pièce que représentent les symptômes d'hyper-réactivité induits par les traitements (stimulation cérébrale profonde du noyau sous-thalamique –Albares et al., 2015b ; Ballanger et al., 2009 ; Favre et al., 2013- ou dopathérapie – Antonelli et al., 2013 ; Antonelli et Strafella, 2014 ; Antonini et Cilia, 2009 ; Cilia et van Eimeren, 2011 ; Probst et van Eimeren, 2013).

3. 5 Conclusion

Le dysfonctionnement du contrôle inhibiteur dans la maladie de Parkinson a un effet paradoxal. Il ne génère pas d'impulsivité à l'état symptomatique mais tend au contraire à maintenir le patient de façon inappropriée dans un état de verrouillage exécutif qui annihile sa réactivité automatique. Les données empiriques d'imagerie fonctionnelles affirment que ce verrouillage repose sur l'hyperactivation d'une partie du réseau d'inhibition proactive incluant le striatum, le thalamus, le précuneus et la SMA. Les données méta-analytiques suggèrent quant à elles que l'insula est susceptible de jouer également un rôle important dans ce contrôle, mais qu'il n'est soit pas proactif soit pas directement centré sur la suppression d'activation motrice.

Chapitre 4

Conclusions et perspectives

Dans cette recherche doctorale, la conception traditionnelle sélective et réactive du contrôle inhibiteur est clairement remise en cause. Ce type de processus ne correspondrait, au mieux, qu'à une partie des mécanismes engagés dans le contrôle de l'action. Nous avons mis en évidence l'importance des processus non-sélectifs, qu'ils soient proactifs ou réactifs, que ce soit au moyen de méta-analyses (*Chapitre 1*) ou de travaux de psychophysique et de neuroimagerie (*Chapitre 2*) chez le sujet sain. En particulier, les mécanismes proactifs mis en évidence permettent d'éclairer l'articulation entre les différents niveaux de contrôle (sensorimoteur, exécutif et cognitif), trop peu souvent considérés conjointement dans la littérature. Enfin, dans le *Chapitre 3*, nous mettons en évidence le potentiel d'exploitation de ces nouveaux modèles dans le domaine clinique. En effet, les travaux visant à expliquer la symptomatologie dysexécutive, et en premier lieu ceux centrés sur l'impulsivité, s'appuient quasi exclusivement sur des modèles incomplets, voire erronés du contrôle de l'action. Ici, nous montrons que la prise en compte du modèle d'inhibition proactive permet de revisiter certains dysfonctionnements exécutifs dans la maladie de Parkinson. Mieux, ces modèles revisités permettent d'interpréter un plus large éventail de troubles, incluant notamment des troubles de nature hypoproductive comme l'akinésie. En guidant les investigations d'imagerie fonctionnelle vers d'autres régions d'intérêt et surtout une autre dynamique cérébrale d'intérêt, le nouveau modèle psychologique que nous proposons permet de révéler les bases neurales de troubles invalidants restant à ce jour mal compris et sans solution thérapeutique satisfaisante.

4.1 L'inhibition de réponse : une fonction aux multiples facettes

Comme l'ont récemment affirmé des auteurs majeurs du champ, l'inhibition est une fonction aux multiples facettes (Bari et Robbins, 2013). Et il est probable qu'elle le soit plus encore qu'ils ne l'ont envisagé dans leur revue puisqu'ils n'y intègrent pas les fonctions que nous venons de mettre en exergue. D'ailleurs, bien que la thèse défendue dans cette revue de questions soit que la variété des formes d'impulsivité serait due à la variété des mécanismes d'inhibition susceptibles d'être dysfonctionnels, l'association troubles de l'inhibition/impulsivité reste une constante.

Evidemment, nous voudrions insister ici sur le fait que nos conclusions se limitent aux tâches de la même nature que celle que nous avons utilisée (Go/NoGo). Bien que cette tâche soit censée solliciter plus de mécanismes inhibiteurs que d'autres puisqu'elle met potentiellement en jeu à la fois des mécanismes de verrouillage et des boucles de rétroaction, nous reconnaissons sans ambiguïté qu'elle n'intègre pas tous les mécanismes d'inhibition. En particulier, nous pouvons affirmer, a posteriori, que les mécanismes de suppression de l'action en cours mis en jeu dans les tâches de Stop n'ont pas été sondés dans nos travaux. En affirmant qu'ils ne sont pas impliqués dans une tâche de Go/Nogo, nous ne concluons pas que ces mécanismes ne sont pas impliqués non plus dans une tâche de Stop. De par la nature même de la tâche, il ne peut en être autrement, des mécanismes réactifs que nous n'avons pas testés ici sont impliqués dans la tâche de Stop. Ceci met en exergue le fait que nos travaux ne dressent pas un tableau exhaustif du caractère multifacettes de l'inhibition de réponse. Ils apportent toutefois des arguments en faveur des opposants au modèle anatomo-fonctionnel d'Aron (Chatham et al., 2012 ; Hampshire et al., 2010 ; Sharp et al., 2010 ; Swick et al., 2011), en démontrant que l'implication du gyrus frontal inférieur est liée à la sollicitation de fonctions cognitives corolaires requises par la complexité de la tâche. Bien sûr, la même rigueur dans le réductionnisme devra être appliquée pour revisiter la

tâche de Stop et lever dans un futur proche les ambiguïtés qui pèsent encore sur ses interprétations.

Une autre limite de la portée de nos travaux tient à l'absence de données de connectivité fonctionnelle. Si la méthode que nous avons choisie a permis de répondre spécifiquement à nos questions de modélisation psychologique de la fonction d'inhibition et de revisiter la cartographie cérébrale associée, elle ne permet pas d'entrevoir la façon dont ces régions interagissent pour former ces réseaux fonctionnels. Nous n'avons pas présenté ces données de connectivité dans le document principal pour plusieurs raisons. Premièrement, elles n'apportent pas d'arguments supplémentaires à la question de la plausibilité physiologique des mécanismes d'inhibition testés, et étaient donc susceptibles de brouiller le message. Deuxièmement, d'autres travaux au sein de l'équipe s'appuient sur une méthode permettant de sonder cette connectivité fonctionnelle avec plus de précision. Ils utilisent l'EEG et la séparation de sources pour sonder la connectivité fonctionnelle entre les sources d'activité significatives (Figure 11). Cette technique, en plus de mesurer directement une activité neurale, a l'avantage d'une résolution temporelle optimale. Ce critère est essentiel pour démêler les processus s'opérant dans la fenêtre temporelle extrêmement courte qui nous intéresse (de l'ordre d'un TR, 300 ms). Cet atout s'ajoute au pouvoir de discrimination spectrale des processus psychologiques de l'EEG, qui s'oppose à la mesure indirecte de l'activité neurale que représente l'adaptation physiologique associée au BOLD. Ces travaux (Lio, 2014 ; Lio et al., soumis) renforcent en particulier l'hypothèse selon laquelle le contrôle proactif consisterait à moduler la sensibilité des réseaux locaux auto-inhibiteurs de la SMA. En d'autres termes, le contrôle proactif permettrait le verrouillage de l'action en prédisposant à l'inhibition automatique des activations automatiques, et permettrait

paradoxalement l'expression des automatismes sensorimoteurs en inhibant temporairement les réseaux locaux d'inhibition automatique (voir également Albares et al., 2014, Annexe 2).

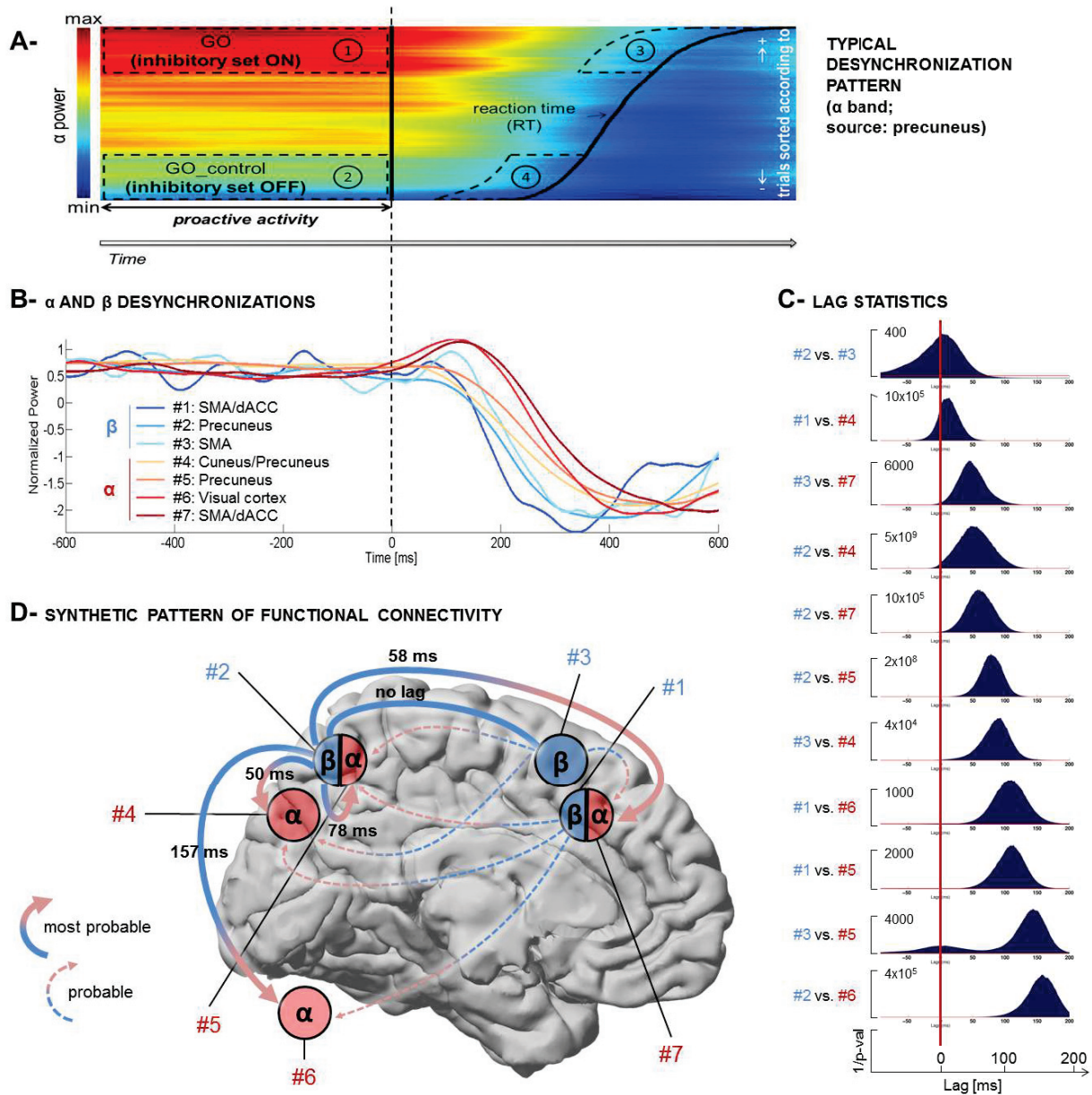


Figure 11 : Complémentarité des investigations EEG pour l'étude des réseaux fonctionnels de l'inhibition de réponse. A) Illustration d'une désynchronisation induite par un stimulus cible. Chaque ligne de l'axe Y représente un essai individuel. Les essais sont triés en fonction du temps de réaction. La dynamique de la puissance du signal d'une source (dans le précunéus), dans une bande de fréquence particulière (ici la bande alpha caractérisant une activité inhibitrice) montre ici un pattern consistant avec les prédictions du modèle de contrôle proactif : une activité soutenue dans la période pré-stimulus en condition d'incertitude contextuelle (essais GO) mais pas en condition de contrôle (GO_control, dont la désynchronisation est induite par le signal GO et dont la puissance prédit le temps de réaction de la réponse). B) Déroulé temporel des sources montrant un pattern d'activité compatible avec les prédictions du modèle proactif (parmi l'ensemble des sources obtenues après séparation et pour toutes les bandes de fréquences). C) Direction de la connectivité fonctionnelle entre les sources significatives obtenue par corrélations croisées avec décalages des amplitudes instantanées. D) Synthèse de la connectivité fonctionnelle. L'activité beta est censée indexer un signal de contrôle qui gouverne les modulations alpha. Notons la cohérence avec nos propres données en ce qui concerne le rôle supposé du précunéus, de la SMA et de l'ACC. Tiré de Lio et al. (soumis).

Beaucoup d'aspects de cette fonction multifacettes restent donc à explorer. Cette perspective est d'autant plus intéressante que nos résultats suggèrent l'existence d'un processus de contrôle global, susceptible de s'appliquer à tous les domaines qui mettent en jeu des interactions sensorimotrices : prise de décision, régulation des affects, mémoire, attention, (la première formulation d'inhibition proactive provient d'ailleurs de travaux dans ce domaine) etc... L'enjeu est donc considérable, et nous allons consacrer une bonne partie de nos prochains projets à mettre à nouveau ce modèle à l'épreuve pour tenter de le consolider et de le populariser... ou l'abandonner.

4.2 Vers de nouvelles perspectives thérapeutiques ?

Le modèle du contrôle proactif offre de nouvelles perspectives dans l'étude des dysfonctionnements de l'inhibition de réponse et la recherche de solutions potentielles de remédiation. Tout d'abord, les amendements méthodologiques que nous proposons sont susceptibles de fournir des méthodes de test des troubles de l'inhibition plus performantes, et de compléter en ce sens la palette d'outils diagnostiques conformément à la démarche de recherche d'endophénotypes neurocognitifs que Robbins et ses collaborateurs ont récemment appelée de leurs vœux (Robbins et al., 2012). Ensuite, l'utilisation de notre modèle doit guider les investigations neurofonctionnelles vers d'autres cibles. De trop nombreuses études ont certainement cherché des marqueurs de dysfonctionnement cérébral au mauvais endroit au mauvais moment, comme par exemple tous les travaux ayant emboité le pas des résultats d'Aron concluant au rôle central du gyrus frontal inférieur droit dans l'inhibition sélective de réponse, en opérant systématiquement des analyses en régions d'intérêt de l'activité évoquée par le signal à inhiber. L'adoption des amendements méthodologiques que nous proposons pour les protocoles

comportementaux et les analyses de l'activité cérébrale représentent une concession à faible coût pour les chercheurs en neurosciences cliniques qui ne seraient pas convaincus par notre modèle. En effet, ce que nous proposons (ajout d'une simple condition de contrôle) n'empêche pas de tester les prédictions des modèles concurrents (et réciproquement), et il nous semblerait regrettable à l'avenir de se priver de considérer l'ensemble des dysfonctionnements possibles lors de l'investigation des troubles du contrôle.

Notre nouveau modèle psychologique et neurofonctionnel de contrôle rend compte des troubles de l'initiation de l'action du patient parkinsonien. Une perspective très importante de ce résultat essentiel est maintenant de déterminer les bases neurochimiques de la fonction, pour peut-être entrevoir de nouvelles solutions pharmacologiques aux troubles akinétiques qui ne sont pas remédiés de façon satisfaisante par la médication dopaminergique. De façon consistante d'ailleurs, d'autres travaux récents de notre groupe ont confirmé que la médication dopaminergique ne restaurait pas les capacités de contrôle de l'inhibition proactive des patients (Favre et al., 2013). Nous privilégions actuellement la piste noradrénergique. Plusieurs arguments provenant de travaux chez l'animal (Belujon et al., 2007; Delaville et al., 2011; Parent et Hazrati, 1995), mais également de travaux cliniques dans d'autres pathologies faisant le lien entre NA et impulsivité (Chamberlain et Shakian, 2007), nous ont orientés vers ce neurotransmetteur. Des travaux comportementaux récents renforcent l'hypothèse dans le cas précis de la maladie de Parkinson (Albares et al., 2015b). Nous avons également pris part au sein du groupe aux premières investigations en imagerie chez le patient akinétique au moyen d'un protocole pharmacologique en IRMf. Les résultats montrent que la prise de clonidine (agoniste des récepteurs adrénérgiques de type α_2) augmente chez les patients l'activité de la région du cortex medial préfrontal dont nous avons montré au chapitre 2 qu'elle jouait un rôle clef dans le contrôle

inhibiteur proactif. Ces résultats préliminaires (Figure 12) vont dans le sens d'un dysfonctionnement du contrôle inhibiteur accru pour les patients sous clonidine par rapport aux sujets de contrôle (i.e., plus d'inhibition proactive, plus de retard à l'initiation du mouvement sous clonidine). Ils vont également dans le sens des travaux de Braak suggérant que l'atteinte du système noradrénergique jouerait un rôle important, voire précurseur, dans la progression de la maladie de Parkinson (Braak et al., 2004; Marien et al., 2004). Cette piste nous semble importante à suivre car les enjeux liés au développement de traitements pharmacologiques non-dopaminergiques complémentaires ou alternatifs sont importants (voir Fox, 2013 pour revue). Bien que l'étude du système noradrénergique soit particulièrement difficile, une opportunité s'est récemment offerte à nous avec la mise au point d'un traceur TEP chez l'homme (Nahimi et al., 2015). A ce titre, ma formation à l'outil est un objectif essentiel de mon stage post-doctoral à Toronto.

Enfin, puisque notre modèle psychologique de contrôle suggère que l'inhibition proactive est l'état par défaut du système exécutif, son dysfonctionnement pourrait expliquer de nombreux troubles du comportement. Nous n'en sommes toutefois pas encore à ce stade de généralisation. En effet, malgré d'évidents points communs avec des troubles comportementaux observés dans d'autres pathologies (ADHD, schizophrénie, Tourettes par exemple : Biederman et Faraone, 2005 ; Houeto et al., 2005 ; Kaladjian et al., 2011), certaines contradictions restent à résoudre au sein de la symptomatologie parkinsonienne avant d'envisager l'extension des domaines d'application à d'autres fonctions et d'autres pathologies. Les incohérences proviennent essentiellement des troubles du comportement impulsif (ICDs) que l'on observe fréquemment chez le patient parkinsonien (environ 15% des patients, Weintraub et al., 2010). Les ICDs recouvrent un ensemble relativement vaste de symptômes (jeu pathologique, hypersexualité,

addiction, achats compulsifs) considérés à la fois comme des déficits du contrôle inhibiteur et comme des effets secondaires des traitements dopaminergiques (Antonini and Cilia, 2009 ; Averbeck et al., 2014 ; Cilia et al., 2010, 2011 ; Cilia and van Eimeren, 2011 ; van Eimeren et al., 2010). Ce constat s'objecte à notre hypothèse noradrénergique. On peut néanmoins lui opposer une question encore en suspens : Les ICDs sont-ils vraiment un trouble de l'inhibition (ou plutôt un dysfonctionnement des processus de prise de décision ou de motivation sous dépendance dopaminergique)? Nous tenterons de répondre à cette question avant d'envisager l'élargissement des domaines d'application de notre modèle.

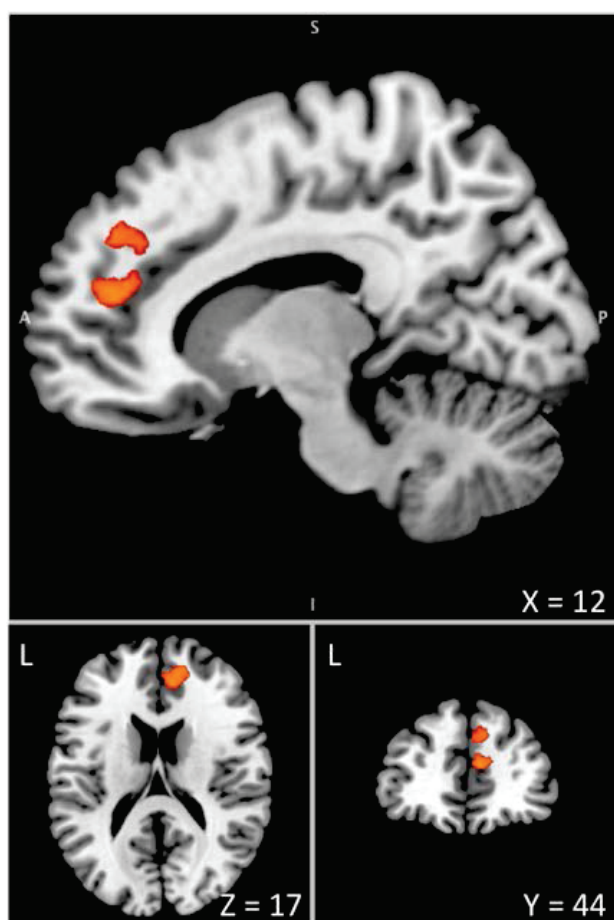


Figure 12 : Effet de la prise de clonidine chez les patients parkinsoniens par rapport à des sujets de contrôle : L'augmentation de l'activité du cortex médial préfrontal explique un ralentissement à l'initiation du mouvement accru chez les patients. Cette région est impliquée dans le contrôle inhibiteur proactif, comme nous le montrons au chapitre 2, et comme l'ont suggéré également de précédents travaux (Jaffard et al., 2008 ; Kuhn et al., 2009 ; Filevich et al., 2012). *Illustration tirée de Ballanger et al. (2014).*

4.3 Conclusion générale

Ce travail pose certainement plus de questions qu'il n'apporte de réponses. Mais il m'aura apporté beaucoup plus que ces quelques réponses. Il met en exergue l'intérêt de combiner les méthodes et théories issues de différentes disciplines, des sciences humaines à la neurologie en passant par le traitement du signal. C'est précisément ce que j'étais venu chercher à l'Université Claude Bernard et au Centre de Neurosciences Cognitives, depuis ma formation initiale en Psychologie. Ce travail doctoral m'a renforcée dans ma conviction, et je suis ravie aujourd'hui de continuer mon parcours dans un autre environnement, qui me permettra de poursuivre cette quête...

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Annexes

Annexe 1 : Albares M, **Criaud M***, Wardak C, Nguyen SC, Ben Hamed S, Boulinguez P. (2011). Attention to baseline: does orienting visuospatial attention really facilitate target detection? Journal of Neurophysiology, 106(2):809-16.*

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Attention to baseline: does orienting visuospatial attention really facilitate target detection?

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Albares M, Criaud M, Wardak C, Nguyen SC, Ben Hamed S, Boulinguez P. Attention to baseline: does orienting visuospatial attention really facilitate target detection? *J Neurophysiol* 106: 809–816, 2011. First published May 25, 2011; doi:10.1152/jn.00206.2011.—Standard protocols testing the orientation of visuospatial attention usually present spatial cues before targets and compare valid-cue trials with invalid-cue trials. The valid/invalid contrast results in a relative behavioral or physiological difference that is generally interpreted as a benefit of attention orientation. However, growing evidence suggests that inhibitory control of response is closely involved in this kind of protocol that requires the subjects to withhold automatic responses to cues, probably biasing behavioral and physiological baselines. Here, we used two experiments to disentangle the inhibitory control of automatic responses from orienting of visuospatial attention in a saccadic reaction time task in humans, a variant of the classical cue-target detection task and a sustained visuospatial attentional task. Surprisingly, when referring to a simple target detection task in which there is no need to refrain from reacting to avoid inappropriate responses, we found no consistent evidence of facilitation of target detection at the attended location. Instead, we observed a cost at the unattended location. Departing from the classical view, our results suggest that reaction time measures of visuospatial attention probably rely on the attenuation of elementary processes involved in visual target detection and saccade initiation away from the attended location rather than on facilitation at the attended location. This highlights the need to use proper control conditions in experimental designs to disambiguate relative from absolute cueing benefits on target detection reaction times, both in psychophysical and neurophysiological studies.

saccades; electrooculography; inhibition; human

ONE ATTRIBUTE of the selective attention system is its capacity to select a part of the environment over which an impending signal is to occur. Orienting visuospatial attention is known to facilitate information processing of stimuli at attended locations. A consistent behavioral outcome of this effect is a reduction of response latency [reaction time (RT)] to salient stimuli presented at the attended location (Posner 1980; Jonides 1981). The underlying neural mechanisms involve the modulation of neural processing in the visual cortex (e.g., Kastner and Ungerleider 2000; Corbetta and Shulman 2002). Such a modulation can theoretically take multiple forms. It has been suggested that it involves the variation of baseline activity in the absence of visual stimulation, the enhancement of visual

responses to targets at attended locations, and possibly the suppression of unwanted information at the unattended location (e.g., Kastner and Ungerleider 2000; Luck et al. 1997; Sylvester et al. 2007, 2009). However, the hypothesis that orienting visuospatial attention improves single-target detection by facilitating visual processing appears questionable (Fecteau and Munoz 2005; Kahn et al. 2010). In the present report, we propose that methodological refinements of the standard experimental design used to measure the effects of visuospatial orienting (the cueing method) may help to resolve this issue.

An attention shift that is elicited by the presentation of a visual cue reduces RT to a target presented shortly afterward at the same location. The pioneering and seminal work of Posner and colleagues (1980) popularized this cueing method. This work had the virtue of using various means to orient visuospatial attention and of referring cue and no-cue trials to a neutral control condition. What is often forgotten, however, is the fact that the authors did not obtain consistent combined benefits and costs of visuospatial orienting with respect to this neutral control condition (supposed to index facilitation of visual processing for attended stimuli at the expense of unattended stimuli) across all experimental designs. Whereas the costs were systematic, the benefits were, on the other hand, inconsistent. It remains unclear from these data why benefits are more labile than costs. The authors (Posner et al. 1980) overlooked this aspect and stated the following:

“since both costs and benefits are aspects of our knowledge of the position of an expected signal, it is clear that the difference between the benefit trials and the cost trials is a legitimate way of asking whether expectancy changes the efficiency of performance of signals arriving from expected versus unexpected conditions.”

Most subsequent studies accordingly restricted their experimental conditions to valid and invalid trials to estimate the net effect of orienting, thus describing a relative benefit of attention orienting. Most of them assumed, however, explicitly or not, that behavioral enhancements and neural increases for attended locations are necessarily coupled with behavioral decrements and neural decreases for unattended locations. In the present report, we directly address the question of the behavioral gains of orienting using a different control condition in a saccadic RT task, namely, a simple target detection.

Indeed, while the neutral cue condition is intended to provide a control condition in which RT is supposed to be a reliable measure of target detection time, we assumed that RT

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is likely not an uncompromising measure of overt visuospatial attention. RT, as measured in standard cued target detection tasks, involves many more mechanisms than are assumed by simplistic interpretations of attentional modulation, i.e., more than just orienting of attention and target detection (e.g., Doricchi et al. 2010; Van Der Lubbe et al. 2005). In particular, predictive cues elicit automatic motor activations, which, in turn, call for response inhibition to prevent false alarms, i.e., to withhold automatic responses to cues (Boulinguez et al. 2008; Sumner and Husain 2008; see also Allport 1993 for an early discussion). Such cue-related response inhibition probably involves multiple executive and motor mechanisms (Duque et al. 2010; Stinear et al. 2009; Van Der Lubbe et al. 2005). Importantly, this inhibitory control relies not only on postcue responsive mechanisms but also on precue proactive mechanisms that depend on the subject's expectations of the trial structure (Jaffard et al. 2007, 2008; Boulinguez et al. 2008, 2009; Boy et al. 2010; Chen et al. 2010). A major consequence of this is that these proactive mechanisms influence the neutral cue condi-

tion, whenever one is set up to measure attentional effects, leading to possible misinterpretations of classical behavioral outcomes (Fig. 1) (Jaffard et al. 2007). The extent to which disregarding the proactive inhibitory control of response affects our current interpretation of orienting effects in spatial cueing paradigms remains unknown. To infer whether target detection as such is improved by attentional orienting, cued RTs need to be compared with RTs obtained in a simple target detection task, i.e., in the absence of any cue presentation.

Here, we report the results of two experiments in which we tested whether orienting attention leads to faster target detection compared with a simple target detection task. In *experiment 1*, the effect of visuospatial attention orientation was assessed in a saccadic RT task using spatially predictive cues and visual targets. In the control experiment (*experiment 2*), visuospatial attention was oriented in a sustained fashion free from potential confounds by the effects of proactive inhibitory control over automatic responses to cues. In both experiments, cues and targets were purposefully highly salient to avoid

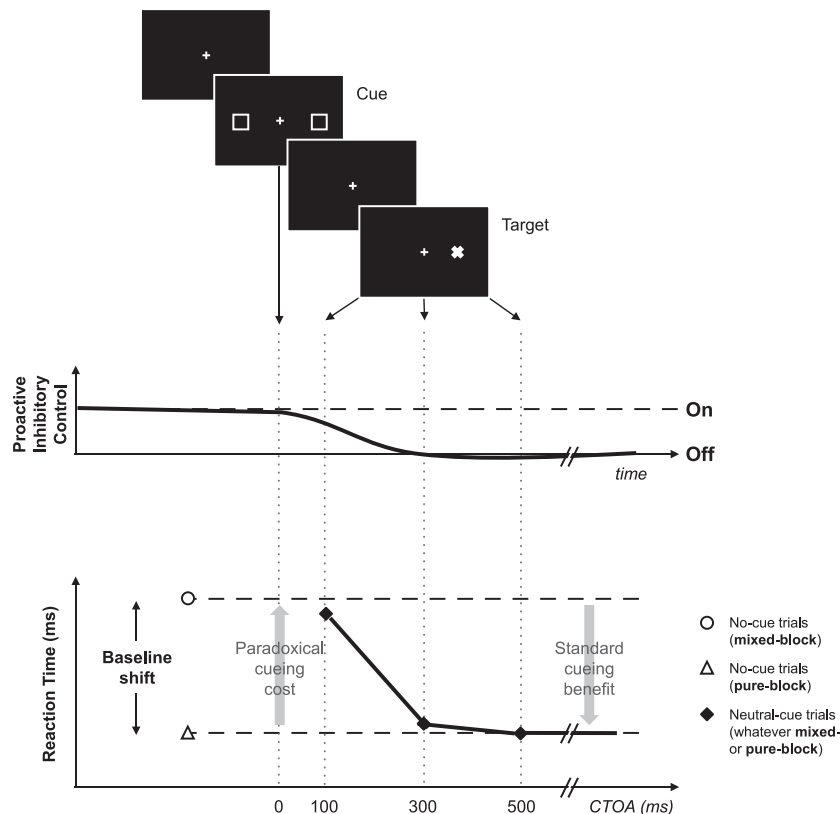


Fig. 1. Proactive inhibitory control in cue-target paradigms. *Top*: time course of a cued-target detection trial. While subjects are required to fixate on a central point (+), a neutral cue is briefly presented (bilateral squares). At variable intervals from the cue, a target is presented (×), and subjects are required to respond to it as quickly as possible by a button press or an eye movement. *Middle*: schema of the hypothetical progressive release of inhibitory control triggered by cue presentation. When no-cue trials are intermixed with cued trials in the same block (as in standard mixed block designs), tonic inhibition of movement-triggering processes is required to prevent false alarms and cannot be lifted until the first stimulus has been identified. Cue identification triggers the rapid release of proactive inhibitory control and, hence, allows automatic responses to subsequent stimuli. Conversely, when the target is not preceded by a warning signal, proactive inhibitory control is maximum at target occurrence (no-cue trials, mixed block design). The time required to identify the target and then release inhibition accounts for the dramatic increase in reaction times (RTs) observed in this condition with respect to pure block, no-cue trials, a condition in which only targets are presented and for which no proactive inhibitory control is required. *Bottom*: effect of block structure on RTs as a function of cue-target onset asynchrony (CTOA). Cueing methods typically use a standard mixed block design, in which cue and no-cue trials are intermixed in the same block. Such a paradigm provides shorter RTs in cue trials than in no-cue trials at cue-target delays of ≥ 300 ms. This behavioral difference is classically attributed to an attentional benefit taking the form of a brief surge of arousal triggered by the neutral cue. This temporal benefit defines the so-called “warning” or “alerting” effect (solid black curve). However, this effect vanishes when referring cued trials to a control condition that does not require the prevention of automatic responses to cues (no-cue trials performed in a pure block design). Proactive inhibitory control fully accounts for the significant difference observed between the RT baselines of the two designs (no-cue trials in a mixed block design vs. no-cue trials in a pure block design).

confounding contrast sensitivity or visual acuity effects known to take place under more stringent saliency conditions. Departing from previous interpretations, we found no consistent evidence of facilitation by a spatial cue or after sustained attentional orienting at the attended location with respect to a proper control condition (simple target detection task) in which there was no need to refrain from reacting to avoid inappropriate responses. Instead, we describe a consistent cost at the unattended location.

EXPERIMENT 1: ORIENTING VISUOSPATIAL ATTENTION WITH A SPATIAL CUE

In *experiment 1*, we used a saccadic cued target detection task. We favored saccadic eye movements over other behavioral tasks because they are known to tightly index the displacements of visual attention when overt responses to stimuli are allowed (Posner 1980). In addition, they are also very likely to involve the inhibitory control of automatic responses to cues (e.g., Ballanger 2009; Lo et al. 2009; Stuphorn et al. 2010) compared with manual response tasks, for example.

Materials and Methods

Subjects. Eighteen naive subjects (age: 19–59 yr old, 12 women and 6 men) with normal vision participated in the experiment. The experimental protocol was preapproved by the local ethical committee in compliance with the Commission for the Protection of Human Subjects in Biomedical Research.

Apparatus. Subjects were seated in a darkened room in front of a panel set 50 cm from their eyes. Their heads were fixed using a chinrest to maintain the viewing distance and stabilize the head. The panel was equipped with white light-emitting diodes (LEDs; 0.5 mm, 8800 mcd). One LED was placed at the center of the panel and set at the subject's eye level (fixation point). Two other LEDs, located at 14.6° of the visual angle to the left and right of the central fixation point, served as targets. Each of these targets was surrounded by four LEDs forming squares (5.7°) and serving as cues. Horizontal eye movements were monitored with an electrooculographic (EOG) method using Ag-AgCl electrodes of low impedance disposed near the outer canthi of the eyes (BM623, Biomedica Mangoni) and sampled at 1,000 Hz (12-bit analog-to-digital converter).

Procedures. Stimuli were presented and data were acquired using a real-time data-acquisition system (ADwin-Pro, Keithley Instruments, Cleveland, OH) controlled by laboratory-made software (Docometre) by courtesy of Franck Buloup (Institut des Sciences du Mouvement, Marseille, France). Figure 2 shows the experimental design. Eye positions were monitored online so that inappropriate

movements could be detected automatically on the basis of real-time derived signals (thresholds were set individually). These would result in the interruption of the ongoing trial. Each trial began with the participant maintaining gaze at the central fixation point for at least 1 s. After a variable delay of gaze stabilization (1,000–2,000 ms), a cue would appear for 50 ms. The cue was either a neutral cue (two squares around the possible locations of the target) or a spatial cue (one square around the most probable location of the target with an 80% predictability) followed 100, 300, or 500 ms later by a left or right target lit for 1,000 ms [the cue-target delay defines the cue-target onset asynchrony (CTOA)]. Subjects were asked to react as quickly as possible by making an eye movement toward the target. The next trial was triggered after a variable (1,300–3,000 ms) intertrial interval.

We used CTOA as a variable to analyze no-cue trials. CTOA in this case is obviously virtual but allows a comparison of conditions that differ only with regard to the presence or absence of the cue, with all other events of the experimental procedure being strictly identical, including the timing of the target presentation from trial onset (see Jaffard et al. 2007 for empirical data and an extended discussion¹).

After a training session of 30 trials, subjects performed 7 blocks of trials as follows: 1 pure block, 5 mixed blocks, and 1 pure block (Fig. 2). The pure blocks contained only uncued trials (a control condition for which no proactive inhibitory control was required, 100 trials). The mixed blocks (120 trials each) contained spatial cue trials (50% of all trials), neutral cue trials (20% of all trials), no-cue trials (15% of all trials), and catch trials (without targets, 15% of all trials). Trials preceded by spatial cues were divided into valid (80%) and invalid (20%) trials. Left and right target trials were equally distributed for each condition. Trials were randomized within each block. All in all, subjects performed 810 trials, including 200 no-cue trials (pure block design), 90 no-cue trials (mixed block design), 120 neutral cue trials, and 300 spatial cue trials (240 valid and 60 invalid).

Data analysis. All data were analyzed using Matlab (MathWorks) and Analyse open source software (<http://sourceforge.net/projects/analyse/>). Offline EOG signals were filtered using a second-order Butterworth filter (10-Hz low-pass cutoff frequency with dual pass to remove phase shift). Eye velocity was obtained by differentiating eye position signals. The variability of eye velocity during fixation was

¹ In this report, the time elapsed before target presentation was manipulated for no-cue trials presented both in pure block and mixed block designs. No effect was observed (Jaffard et al. 2007; Fig. 2B): RT was very stable across foreperiods in these control conditions. In other words, this means that 1) CTOA in trials with cues can be appropriately compared with trials with no cues, and 2) all conditions of CTOA can be collapsed in the latter condition. Nevertheless, to ensure that there was no effect of the time elapsed between fixation onset and target onset in the present data, we analyzed RT as a function of time from fixation onset to target onset for no-cue trials. None of the 18 subjects showed significant correlation between the duration of the foreperiod and saccadic RT.

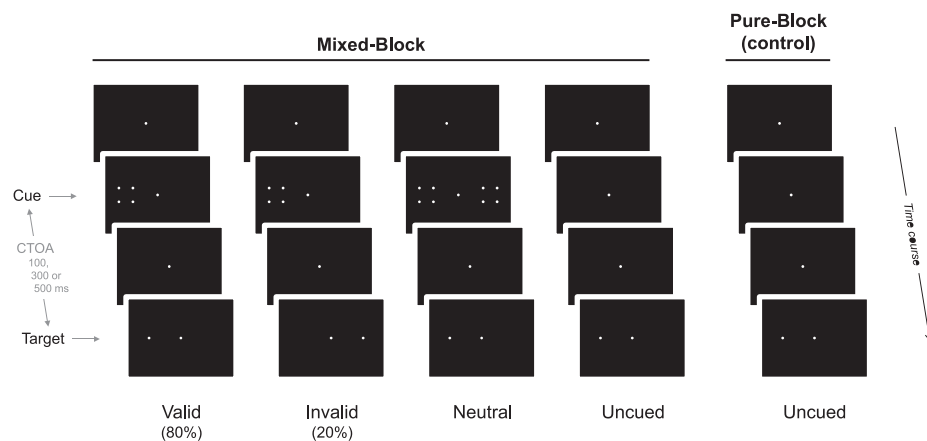


Fig. 2. Overview of the experimental design of *experiment 1*.

calculated during the first second of each recording and served as a baseline to identify movement initiation. Saccadic RT was determined when the velocity signal reached 1 mean + 3 SDs of the baseline epoch, providing that the velocity of the eye exceeded 10°/s, remained continuously above that value for at least 10 ms, and subsequently exceeded 35°/s (e.g., Boulinguez et al. 2001). Only trials with saccades in the desired direction and latencies over 130 ms were included in the latency analyses (0–4.6% were excluded, ensuring reliable RT analysis).

In accordance with our previous studies, we found that saccadic RT distributions were not suitable for using the means as a measure of the distribution's central tendency because they were not found to be Gaussian. Not surprisingly, the best fit was obtained with the ex-Gaussian density function (Ratcliff 1979; Farrel and Ludwig 2008). Therefore, we characterized the shape of saccadic RT distributions for each subject/condition by fitting an ex-Gaussian function by means of a maximum likelihood estimation. Because the Gaussian component is usually taken to reflect encoding and motor processes, we used the parameter μ , which characterizes the central tendency of the Gaussian distribution for statistical analyses. In other words, we removed from the analysis the non-Gaussian part of the saccadic RT distribution, which has the effect of adding noise to the well-characterized Gaussian process in which we were interested. In a minority of conditions (5.5%), the fitting returned no significant Gaussian component. We then used the mode of these exponential distributions. A 5 cue condition (no-cue mixed block vs. no-cue pure block vs. neutral vs. valid vs. invalid) \times 3 CTOA (100 vs. 300 vs. 500 ms) ANOVA with repeated measures was applied to these RT data as well as to the error rate. Post hoc comparisons were performed using Duncan's test.

Results

Typical response profiles are shown for a representative subject in Fig. 3.

Errors. Target detection performance was high across all conditions of interest (correct response rate > 95.4%, mean: 98.8%). Errors were exclusively composed of anticipations (missed target rate: 0%). As previously observed with electromyographic recordings in a manual button press task (Boulinguez et al. 2008), these anticipations were time locked to cue onset (false alarms). A significant interaction of cue condition and CTOA was observed ($F_{8,136} = 9.4$, $P < 0.001$). It revealed that three conditions provided a larger amount of false alarms than all others (mean: 0.54%). Not surprisingly, these conditions corresponded to spatially cued trials in which the single cue could be mistaken for a target: valid cue, CTOA 300 (4.6%, $P < 0.001$); valid cue, CTOA 500 (2.42%, $P < 0.05$); and invalid cue, CTOA 500 (4.28%, $P < 0.001$).

Saccadic RTs. Group results showed a significant interaction of cue condition and CTOA ($F_{8,136} = 16.5$, $P < 0.001$), revealing several major outcomes. First, we observed a strong baseline shift effect: the saccadic RT for no-cue trials was much larger in the mixed block design (Fig. 4, black circles) than in the pure block design (Fig. 4, black squares) regardless of CTOA (respective means: 325 vs. 215 ms, $P < 0.001$). We also reproduced the paradoxical and controversial “warning” or “alerting” effect: at CTOA 100, saccadic RTs for neutral cue trials (Fig. 4, blue circles) were larger than saccadic RTs for no-cue trials in the pure block design (315 vs. 217 ms, $P < 0.001$; Fig. 4, black squares) but were not different from saccadic RTs for no-cue trials in the mixed block design (319 vs. 320 ms, $P > 0.6$; Fig. 4, black circles). The reverse pattern was observed for CTOA 300 and CTOA 500, where saccadic RTs for neutral cue trials were not different from saccadic RTs for no-cue trials in the pure block design (CTOA 300: 222 vs. 212 ms, $P > 0.36$, and CTOA 500: 221 vs. 213 ms, $P > 0.43$) but were shorter than saccadic RTs for no-cue trials in the mixed block design (CTOA 300: 222 vs. 322 ms, $P < 0.001$, and CTOA 500: 221 vs. 334 ms, $P < 0.001$).

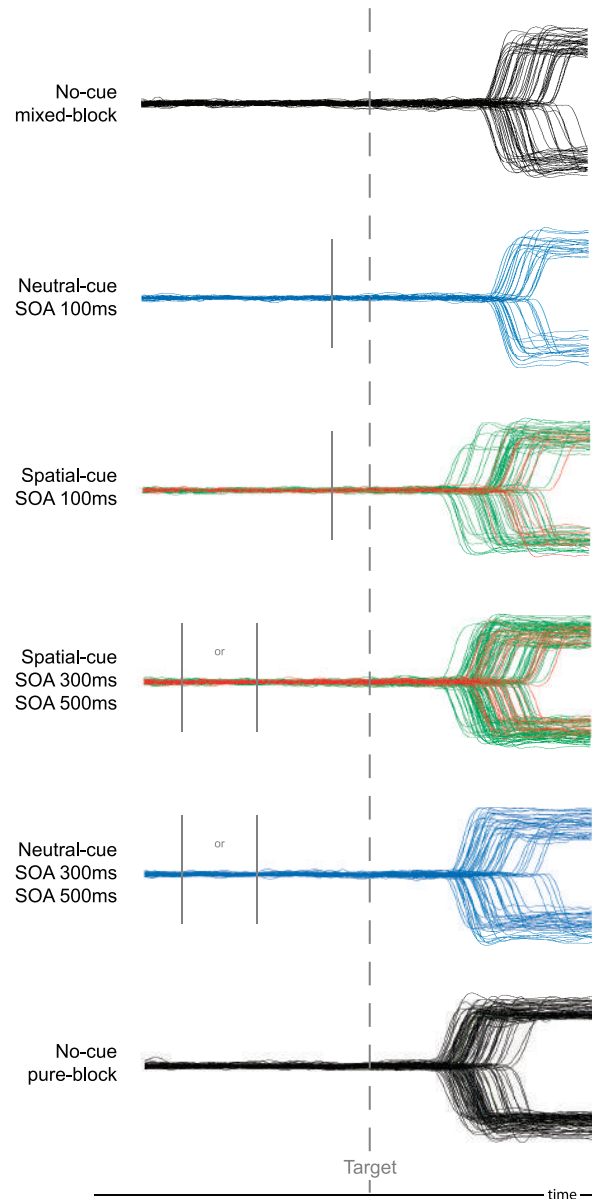


Fig. 3. Horizontal eye positions (*subject RP*) plotted for each condition of interest as a function of time (*experiment 1*). Time series are synchronized with respect to target occurrence. Vertical bars indicate cue presentation time. Black line, no cue; blue line, neutral cue; green line, valid cue; red line, invalid cue.

Second, we found consistent shorter saccadic RTs for valid trials (Fig. 4, green circles) than for invalid trials (Fig. 4, red circles), both at short (CTOA 100: 263 vs. 308 ms, $P < 0.01$) and long (CTOA 300: 220 vs. 240 ms, $P < 0.05$, and CTOA 500: 220 vs. 242 ms, $P < 0.05$) cue-target delays.

Third, we found that invalid trials revealed longer saccadic RTs (Fig. 4, red circles) than neutral cue (Fig. 4, blue circles) and no-cue pure block (Fig. 4, black squares) trials at long cue-target delays (CTOA 300: 240 vs. 222 and 212 ms, respectively, $P < 0.05$, and CTOA 500: 242 vs. 221 and 213 ms, respectively, $P < 0.05$), whereas in valid trials, saccadic RTs (Fig. 4, green circles) were not different from neutral cue and no-cue pure block trials (CTOA 300: 220 vs. 222 and 212 ms, respectively, $P > 0.43$, and CTOA 500: 220 vs. 221 and 213 ms, respectively, $P > 0.44$). A different pattern was observed at short cue-target delay (CTOA 100): valid trials generated shorter

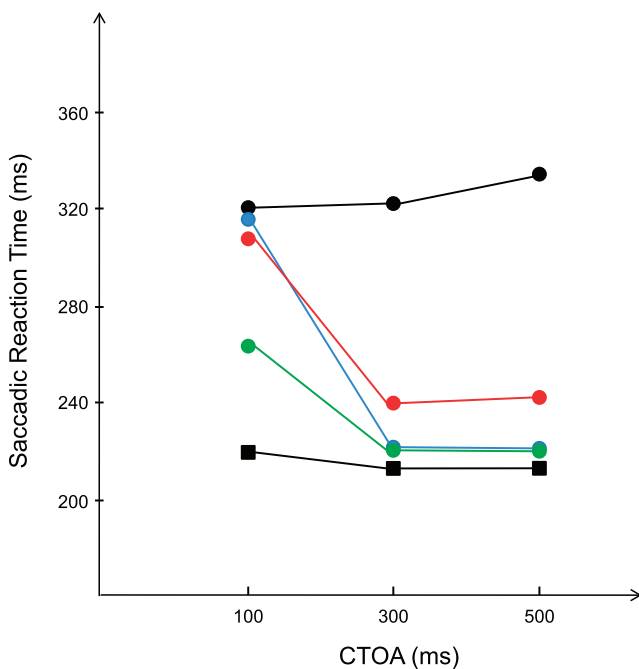


Fig. 4. Mean saccadic RTs plotted as a function of CTOA (*experiment 1*). Black line, no cue; blue line, neutral cue; green line, valid cue; red line, invalid cue. Circles, mixed block; squares, pure block.

saccadic RTs than invalid, neutral cue, and no-cue mixed block trials (263 vs. 308, 315, and 320 ms, $P < 0.001$), yet paying a significant cost with respect to no-cue pure block trials (263 vs. 220 ms, $P < 0.001$).

Discussion

Here, we reproduce the classical observation that a spatial cue induces a consistent orienting effect as saccadic RTs are shorter for valid trials than for invalid trials. However, and departing from commonly accepted interpretations of this effect, we found that the presentation of a valid spatial cue never shortened saccadic RTs to subsequent targets with respect to a pure target detection condition in which no information was provided in advance (no-cue pure block, Figs. 1 and 4). As a result, it seems unlikely that the mechanisms of attentional modulation subserving visuospatial orienting, as assessed with RT, act exclusively by facilitating the elementary processes involved in visual target detection and saccade initiation at the attended location.

Rather, our interpretation is that the main effect of a cue is to release the proactive inhibitory control and, hence, cancel the “upward” RT biases for cue-target delay beyond 300 ms (Fig. 1). Interestingly, for such cue-target delays, we found identical RTs for both valid cue trials, neutral cue trials, and no-cue pure block trials. This pattern of results strongly suggests that cue presentation, whether it is predictive of target location or not, allows switching from controlled inhibition of eye movement initiation to automatic reactive saccadic behavior, in the absence of any additional gain specifically attributable to attentional orientation. As a result, and most interestingly, the longer RTs observed for invalid cue trials at cue target delays beyond 300 ms probably correspond to an attenuation of the elementary processes involved in visual target detection and/or saccade replanning toward the unattended location. In other words, orienting visuospatial attention would generate no benefit at attended locations lasting >100 ms, at either sensory or motor levels. Whether costs at the unattended location more likely result from sensory or oculomotor processes cannot be determined on the basis of these data.

Alternatively, it could be that the release of proactive inhibition is a spatial function that gets facilitated at the cued location.

Nevertheless, transient relative facilitation was observed after cue presentation at the shortest CTOA (100 ms): the valid cue reduced saccadic RTs with respect to both neutral cue and invalid cue conditions, indicating that, while the inhibitory executive control is not yet released (same RTs for neutral cue and invalid cue conditions but different from the RTs for pure block no-cue condition), the valid cue elicits a relative facilitation of target processing. Several independent and mutually nonexclusive processes can account for this early visuospatial facilitation. The standard exogenous orienting view asserts that an automatic enhanced attentional processing of visual space is triggered by the cue (Jonides 1981). Alternatively, this effect may also be due to an early release of the proactive inhibitory control imposed by the mixed design: the presentation of the spatial cue may help release the inhibition of the superior colliculus on the ocular motoneurons that help to keep the eyes stationary on a visual target (Lo et al. 2009). This hypothesis assumes, however, that proactive inhibitory control may be spatially selective (see Duque et al. 2010 for an extended discussion about the selectivity of inhibitory mechanisms during response preparation). Such an interpretation is in line with studies suggesting that exogenous visuospatial attention specifically facilitates saccade planning rather than visual target processing (Khan et al. 2010). In any case, the relative facilitation of saccadic RTs by visuospatial attention was actually restricted to very short (100 ms) cue-target delays in the present experiment, and the potential interplay between the respective effects of releasing proactive inhibitory control and orienting visuospatial attention within this short period of time makes interpretation difficult.

Experiment 2 was precisely intended to test visuospatial attention without involving the confounding effects of the proactive inhibitory control of response. Visuospatial attention was thus oriented in a sustained fashion in different blocks of trials, and results were compared with a control condition corresponding to the pure target detection condition of *experiment 1*.

EXPERIMENT 2: ORIENTING VISUOSPATIAL ATTENTION IN A SUSTAINED FASHION

Materials and Methods

Subjects. Ten different naive subjects (age: 19–38 yr old, 5 women and 5 men) with normal vision participated in *experiment 2*. The experimental protocol was preapproved by the local ethical committee in compliance with the Commission for the Protection of Human Subjects in Biomedical Research.

Apparatus and procedures. The apparatus and general methods were identical to those used in *experiment 1* with the exception of the following details. No visual cues were used. Attention was biased toward left or right by instructing the subjects beforehand that the target would appear 80% of the time to the corresponding side. Subjects were instructed to take into account this information to react as fast as possible by making an eye movement toward the target. Three overt attention conditions were performed: 1) attention divided equally to left and right hemifield locations, 2) attention biased toward the left location, and 3) attention biased toward the right location.

The control condition (divided attention) was composed of two pure blocks, as in *experiment 1* (100 trials each). In two other blocks (oriented attention), trials were more frequent on one side (attended condition, 120 trials) than on the other side (unattended condition, 40 trials). After a training session of 30 trials, subjects performed one control block (divided attention) followed by either a left- or right-oriented attention block. Another control block was performed at the end of the session. The order of presentation of left- and right-oriented attention blocks was counterbalanced across subjects. All in all, each subject performed 520 trials.

Results

Errors. Target detection performance was high across all conditions of interest (correct response rate: >97.1%, mean: 98.4%). Errors were exclusively composed of anticipations or saccades in the wrong direction (missed target rate: 0%). No significant differences were observed between blocks.

Saccadic RTs. No significant differences were observed between the two divided attention blocks for any of the 10 subjects. Thus, data were pooled for further analysis. A three-condition (divided, attended, and unattended) ANOVA with repeated measures (Duncan's test) was applied to the data (the central tendency μ of the ex-Gaussian distribution of each condition). A significant effect was observed ($F_{2,18} = 6.9, P < 0.01$). Saccadic RTs were longer when reacting to unattended locations than when attention was not previously oriented (228 vs. 193 ms, respectively, $P < 0.01$). However, no significant benefits were observed for attended locations over the divided attention condition (187 vs. 193 ms, respectively, $P > 0.6$; Fig. 5).

Discussion

While previous studies using manual RTs tended to find modest significant benefits during sustained visuospatial attention (4–12 ms; Mangun and Buck 1998; Tassinari et al. 1987), the present results are more in accordance with what has been described in most reports (e.g., Bisiacchi et al. 1991; Proverbio and Mangun 1994; Mertens 1956; Mowrer 1941; Posner et al. 1980): Large significant costs have usually been observed without significant benefits when sustaining attention to a restricted location of the visual field. It can be argued that cue-induced shifts of spatial attention and sustained attention rely on partly segregated networks and cannot be directly compared. Nevertheless, we interpret the results of both experiments as evidence that orienting visuospatial attention, as assessed with RT, has no or little effect on early visual processing at the attended location, never mind how attention is biased.

GENERAL DISCUSSION

The dominant view is that attentional modulation in spatial vision systems takes the form of an enhancement of neuronal responsiveness

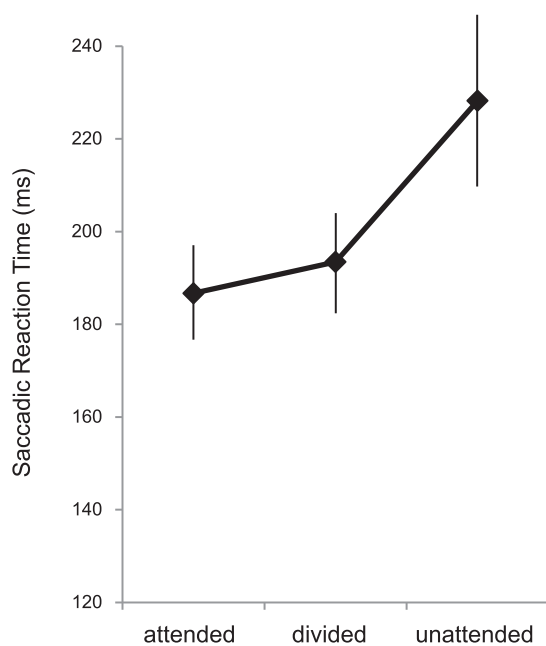


Fig. 5. Mean saccadic RTs (*experiment 2*). Vertical bars indicate SDs.

and expectation-related signals in visual and oculomotor structures at the attended location rather than an attenuation of these processes at the unattended location (e.g., Muller et al. 2003). The RT results presented here provide evidence that challenges this view. Visuospatial attention would attenuate processing away from its locus rather than facilitate target detection and saccadic response at its locus, irrespective of how attention is shifted. While this has already been suggested when the visuospatial bias is induced by sustained attention (e.g., Bisiacchi et al. 1991; Proverbio and Mangun 1994), this possibility is usually not considered when attention is oriented by means of cues. This result highlights the need to use proper control conditions in experimental designs to disambiguate relative from absolute attention orientation benefits on target detection RTs, both in psychophysical and neurophysiological studies.

Attention to Baselines

Behavioral baselines. Our results show that understanding the mechanisms by which attention modulates spatial perception or motor programming (as measured by target detection behavioral benefits and/or costs), and their corresponding neuronal substrates (neuronal enhancement and attenuation), requires the use of a proper control condition in which information processing abilities remain strictly unbiased up to target occurrence. Unfortunately, most available studies do not fulfil this requirement. These considerations revive some forgotten as well as current controversies on which our data may shed light. For example, early behavioral investigations have tested top-down spatial orienting by manipulating the probability of the spatial position of a target within pure block designs (Mertens 1956; Mowrer 1941). In agreement with the present results, they failed to obtain orienting benefits.

Physiological baselines. As a correlate, our observations also highlight the importance of referring neurophysiological or imaging neuronal modulations to a baseline that is free from potential confounds, such as proactive inhibition of action, and call for the reassessment of the theoretical framework used to interpret attentional modulation of visual processing. Consistent with our proposal, Corbetta et al. (2005) previously failed to report expectation-related increases of signals in the visual cortex when a spatial cue directed the subjects' attention to a given location in the visual field. As discussed by the authors, when attempting to account for this surprising result, only two conditions seemed to elicit consistently spatially selective preparatory signals: 1) when early sensory mechanisms are needed to separate a weak signal from noise and 2) when nearby distracters must be filtered out (Moran and Desimone 1985; Serences et al. 2004; Sylvester et al. 2008). In fact, even in electrophysiological studies, the most striking effects of visuospatial attention are generally reported in studies using multiple competitive stimuli (for a review, see Bisley et al. 2010). Yet most empirical evidence, when there is no competition between multiple stimuli, has been interpreted to mean that location cueing generates activation at the attended location rather than inhibition at the unattended location (Kastner and Ungerleider 2000). Here, we propose an alternative reading of similar results in that orienting, as measured by RTs, may act by attenuating visual, executive, or motor processing in/toward the unattended location rather than enhancing it in/toward the attended location. Hence, the mechanism of sensory suppression may not be limited to the interaction between two visual items within the same receptive field but may extend even beyond a given hemifield. Future neurophysiological work using appropriate control conditions is needed to test this hypothesis.

Does Attention Really Facilitate Visual Processing?

Our main finding is that, when referred to simple target detection RTs, valid cueing benefits are inexistent, whereas invalid cueing induces systematic costs. The exact functional significance of this cost

cannot be directly addressed by the present work as attentional orienting effects cannot be dissociated from executive control release or motor reprogramming costs. Motor reprogramming seems to have a minor contribution to this overall cost as paradigms using nonoriented manual responses have also described a difference in RTs between valid and invalid orienting conditions similar to those reported here (e.g., Posner et al. 1980). Additional experiments will need to specifically address this question. However, our purpose is not to deny the well-documented effects of spatial attention on other aspects of visual perception. For example, contrast sensitivity (e.g., Reynolds and Chelazzi 2004) and visual acuity (e.g., Carrasco et al. 2004) are unambiguously enhanced by focused attention. A major aspect of the two tasks that has been used here is that both the cue and target are highly salient stimuli. In such a context, it seems quite plausible that sensory attentional effects become negligible in the face of other cognitive processes, such as proactive inhibition control or motor replanning. This observation does not preclude the fact that specific attentional benefits have been observed in different experimental situations.

Conclusions

Our results are important in several respects. First, they demonstrate that the standard cueing method used to study visuospatial orienting does not allow satisfactory disentangling of attentional from executive control mechanisms. As a consequence, we propose a refinement of behavioral assessment of visuospatial orienting to disambiguate the topology of attentional and executive networks in future neuroimaging and neurophysiological studies. We suggest the systematic introduction in experimental designs of a control condition that does not require subjects to withhold automatic responses to upcoming stimuli (i.e., no-cue trials performed in a pure block design). Second, our results call for a reassessment of the theoretical framework used to interpret cueing effects, suggesting that visuospatial facilitation of target detection at the attended location may only account for transient cue-related effects. In contrast with the classical view, the results strongly suggest that attention orienting, as measured by RTs, relies on the attenuation of the elementary processes involved in visual target detection or motor programming at the unattended location. Finally, this new theoretical approach may provide novel insights into top-down and bottom-up interactions in cognitive and motor control as well as related clinical disorders. Indeed, numerous symptoms that have been attributed to impaired attention or motor functions in standard cueing studies may be reinterpreted in terms of executive and inhibitory dysfunction (Ballanger et al. 2009; Boulinguez et al. 2009).

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DISCLOSURES

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The Dorsal Medial Frontal Cortex Mediates Automatic Motor Inhibition in Uncertain Contexts: Evidence from Combined fMRI and EEG Studies

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Abstract: Response inhibition is commonly thought to rely on voluntary, reactive, selective, and relatively slow prefrontal mechanisms. In contrast, we suggest here that response inhibition is achieved automatically, nonselectively, within very short delays in uncertain environments. We modified a classical go/nogo protocol to probe context-dependent inhibitory mechanisms. Because no single neuroimaging method can definitely disentangle neural excitation and inhibition, we combined fMRI and EEG recordings in healthy humans. Any stimulus (go or nogo) presented in an uncertain context requiring action restraint was found to evoke activity changes in the supplementary motor complex (SMC) with respect to a control condition in which no response inhibition was required. These changes included: (1) An increase in event-related BOLD activity, (2) an attenuation of the early (170 ms) event related potential generated by a single, consistent source isolated by advanced blind source separation, and (3) an increase in the evoked-EEG Alpha power of this source. Considered together, these results suggest that the BOLD signal evoked by any stimulus in the SMC when the situation is unpredictable can be driven by automatic, nonselective, context-dependent inhibitory activities. This finding reveals the paradoxical mechanisms by which voluntary control of action may be achieved. The ability to provide controlled responses in unpredictable environments would require setting-up the automatic self-inhibitory circuitry within the SMC. Conversely, enabling automatic behavior when the environment becomes predictable would require top-down control to deactivate anticipatorily and temporarily the inhibitory set. *Hum Brain Mapp* 00:000–000, 2014. © 2014 Wiley Periodicals, Inc.

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Marion Albares and Guillaume Lio contributed equally to this work.

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INTRODUCTION

Inhibition of prepotent behavioral impulses is a key component of executive functions [Hofmann et al., 2012]. However, it is a significant challenge to assess brain-behavior relationships when the function under scrutiny is precisely intended to suppress overt measurable behaviors. The challenge is all the more complex that brain imaging techniques are not very powerful at unravelling the time course of concurrent excitatory and inhibitory mechanisms. This limitation relates to the physiological nature of the signal [e.g., Logothetis, 2008], the necessary compromise for spatio-temporal resolution [e.g., Babiloni et al., 2009], and the technical aspects of data processing [e.g., Lio and Boulinguez, 2013].

Response inhibition is usually tested by means of reaction time (RT) tasks in which subjects are asked to provide a motor response to one stimulus and to withhold their response to another, like in the classical go/nogo paradigm [Chambers et al., 2009]. Although standard chronometric paradigms do not provide behavioral markers for identifying successfully inhibited responses, functional neuroimaging studies have reported a large distributed network of cortical and subcortical regions activated by nogo stimuli [Swick et al., 2011]. However, these nogo activations are by no means direct markers of response inhibition mechanisms. As recently demonstrated in a series of meta-analyses, most of the regions forming the “nogo” network are inconsistently activated across studies and most of the BOLD modulations typically elicited by nogo signals are actually driven by the engagement of high attentional resources, not by inhibitory processes *per se* [Criaud and Boulinguez, 2013]. Based on the high temporal resolution of electroencephalography (EEG), numerous studies [recently reviewed by Huster et al., 2013] used psychophysiological measures to try to identify the specific processes underlying behavioral inhibition. Unfortunately, it seems that none of the standard EEG-derived measures can be considered an unambiguous indicator of a proper inhibitory process either [Huster et al., 2013].

From a theoretical point of view, this high level of inconclusiveness is not totally surprising for at least two reasons. First, neuroimaging studies that rely on blood oxygenation level-dependant (BOLD) signals are unable to distinguish between neural excitation and inhibition [Buzsáki et al., 2007; Logothetis, 2008], whereas most EEG studies on behavioral inhibition have not convincingly solved the problem of source signal mixing at scalp electrodes to identify unequivocally the EEG components contributing to the averaged event-related potentials (ERPs)

[Huster et al., 2013]. Second, the psychological models that have guided neuroimaging protocols and analyses rely on the disputed assumption that inhibitory processes are selectively¹ triggered by the external stimulus one must refrain from reacting to [see Criaud and Boulinguez, 2013 for critical review]. Converging evidence now indicates that: (1) nonselective inhibitory mechanisms may operate to prevent actions from being emitted prematurely [Duque and Ivry, 2009; Duque et al., 2010, 2012; Frank, 2006; Frank et al., 2007; Jaffard et al., 2007], and (2) action restraint may apply by default, before any stimulus is presented in an uncertain environment. This type of processing is commonly designated “proactive control” [Boulinguez et al., 2008, 2009; Boy et al., 2010c; Chen et al., 2010; Criaud et al., 2012; Forstmann et al., 2008, 2010; Jaffard et al., 2007, 2008; Lo et al., 2009; Stuphorn et al., 2010; Zandbelt et al., 2013]. It is thus possible that, when facing potential conflict, inhibition of response applies early on to any stimulus rather than specifically to the inappropriate stimulus after it has been identified. Evaluating this possibility cannot be done with standard go/nogo protocols which do not allow to disentangle between the hypothesis of a late, selective, inhibition of the erroneous response and the existence of an early, nonselective, inhibition of all possible responses (Fig. 1).

Two elements would be necessary to address the shortcomings above. (i) The inclusion in the experimental design of a control condition for which response inhibition is definitely absent. In this case, for instance, on some trials, the subjects would be provided with advance information that there will be no conflict for the upcoming stimulation and hence no need to refrain from reacting (Fig. 1). This idea is reminiscent of recent behavioral findings suggesting that an executive setting is required for the manifestation of automatic response inhibition [Chiu and Aron, 2014]. (ii) The use, in addition of fMRI, of EEG techniques able to probe inhibitory neural response with high temporal resolution. Indeed, provided that proper separation of the different sources of interest from a set of mixed signals contributing to the overall electrical activity recorded on the scalp has been performed [Makeig and

¹Here, selectivity does not refer to the selection between alternative movements (as it often does in studies using choice RT tasks). It rather refers to the perceptual decision mechanisms that involve the detection, discrimination, or identification of sensory stimuli [Gold and Ding, 2013]. This point is central because studies interested in response inhibition have, in compliance with the implicit dynamics of the dominant models assuming selective, reactive processing, focused on the cascade of events specifically launched by information derived from nogo stimuli with respect to go stimuli.

Onton, 2009; Lio and Boulinguez, 2013], EEG frequency-specific signals may generate more detailed information than corresponding measures based on the BOLD fMRI signal [Huster et al., 2013; Siegel et al., 2012]. In particular, it has been suggested that Alpha and Beta oscillations might play a substantial role in response inhibition. Starting with Alpha oscillations, it has been hypothesized that they would partly stem from rhythmic fluctuations of GABAergic inhibitory interneurons [see Jones et al., 2000 and Lorincz et al., 2009 for physiological and computa-

tional accounts] and would drive neuronal spike timing and firing rate [see Haegens et al., 2011 for demonstration that Alpha power is negatively correlated with spiking rate in the monkey premotor and motor cortex during sensorimotor tasks]. As a consequence, it has been proposed that Alpha oscillations might index an active inhibitory mechanism that modulates cortical excitability or contributes to information gating within a given region [Hindriks and Van Putten, 2013; Jensen and Mazaheri, 2010; Klimesch et al., 2007; Klimesch, 2012; Mathewson et al., 2011].

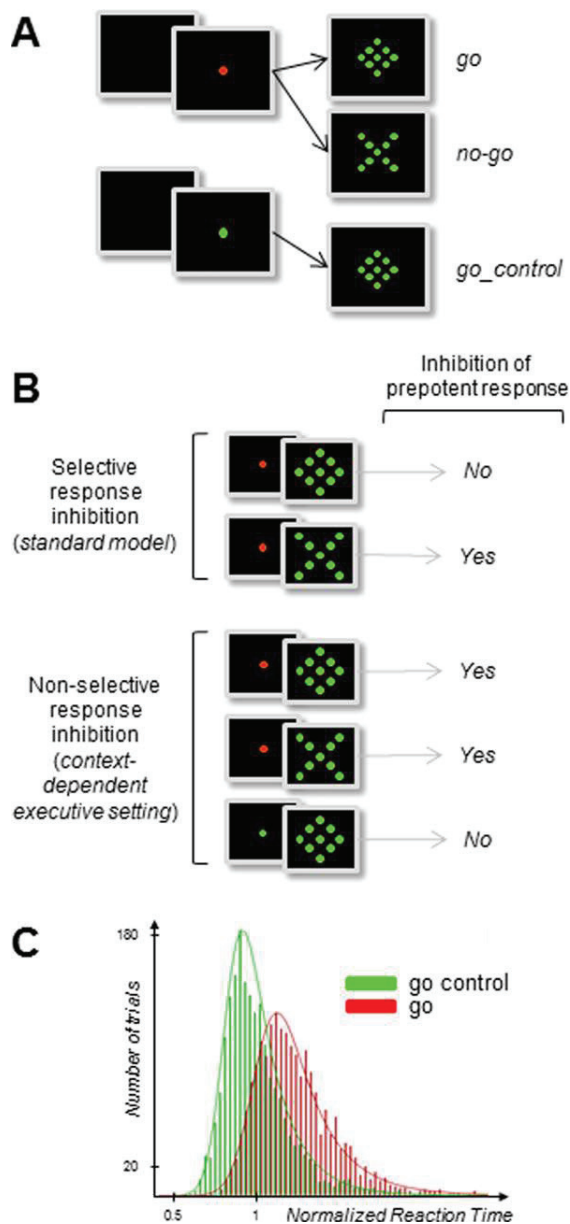


Figure 1.

Protocol (A), models' predictions (B), and behavioral results (C). (A) Subjects were asked to react as fast as possible to a go stimulus (diamond) by means of a button press with the right thumb, and to withhold responses to an equiprobable nogo stimulus (X). In a control condition requiring no hypothetical inhibitory setting, only go stimuli were presented (go_control). In classical go/nogo tasks, go and nogo signals are scrambled within the same block of trials (standard mixed block design), assuming classically that inhibition is triggered by the nogo but not by the go stimulus. In contrast, an alternative view suggests that both stimuli induce automatic response inhibition in order to prevent premature responding. In other words, the usual nogo vs. go contrast would be incomplete to evidence all response inhibition mechanisms. To this aim, a control condition in which response inhibition is definitely not involved would be necessary (go trials for which subjects know in advance that there is no need to refrain from reacting). In the present experiment, this control condition was set by manipulating the color of the central fixation point (FP) of the display. A green FP indicated that not any nogo stimulus would be presented, enabling subjects to react automatically to any upcoming event (go_control condition). Conversely, a red FP was not informative of the identity of the upcoming target. (B) Strong, specific, predictions are attached to each hypothesis. The late, selective, account predicts that stimuli that have to be withheld (nogo) should induce specific brain activations with respect to stimuli that require a motor response (go). Conversely, the early, nonselective, account predicts that all stimuli presented in a context of uncertainty (both nogo and go) should induce inhibition-related brain activations with respect to stimuli presented in a predictable environment (go_control). At the behavioral level, the standard model does not predict RT differences between go and go_control conditions. Conversely, the alternative model predicts that inhibition of automatic responses to any visual stimulus should lengthen RT in the red FP with respect to the green FP condition [e.g., Criaud et al., 2012]. (C) Normalized RT for go and go_control trials, pooled for all subjects. Distributions are best fitted by ex-Gaussian functions. The RT difference between go and go_control trials reflects the effect of fast automatic response inhibition, a prerequisite for giving appropriate slow volitional response. Consistent with recent investigations using comparable methods and providing similar data and conclusions [Chiu and Aron, 2014], this major behavioral result fits the predictions of the automatic, nonselective, account of response inhibition.

Figure 1.

(See legend on the following page.)

Beta band oscillations have also been associated with GABAergic activity and sensorimotor processing, and with the idea that these oscillations could be associated with the functional inhibition of sensorimotor cortical regions [Jensen et al., 2005; Gaetz et al., 2011]. However, the exact role of Beta oscillations in sensorimotor transmission still needs to be specified. It is assumed to relate to the maintenance of the current sensorimotor state [Engel and Fries, 2010] and, more generally, to large-scale communication between sensorimotor and nonsensorimotor areas [Kilavik et al., 2013].

In the present study, we combined fMRI and high-resolution EEG recordings (with spectral analyses performed at the source level) in a go/nogo paradigm that was amended in accordance with the methodological principles described above (Fig. 1).

MATERIALS AND METHODS

Subjects

fMRI experiment

Twenty naïve right-handed subjects (ages: 25 ± 5.1 , 7 females) with normal or corrected-to-normal vision, and without history of psychiatric or neurological disease, participated in the experiment.

EEG experiment

Twenty naïve right-handed subjects (whole group mean age: 26 ± 5.3 , 12 females) with normal or corrected-to-normal vision and without history of psychiatric or neurological disease, participated in the EEG experiment. Thirteen of the twenty subjects who participated in the fMRI experiment also participated in the EEG experiment. For these subjects, the two experiments were performed within a single day. Seven subjects participated in the fMRI experiment in the morning while the EEG experiment was performed in the afternoon, and vice versa for the other six subjects. Both experiments were performed in compliance with the code of ethics of the World Medical Association (Declaration of Helsinki) and the protocol was preapproved by the appropriate ethics committee in Biomedical Research (CPP sud-est IV, N°11/025). All subjects gave written informed consent and were paid 50€ for their participation in each experiment.

Behavioral Testing Procedures

We used a go/nogo task inspired by our recent work [Criaud et al., 2012] (Fig. 1A). Subjects were asked to react as fast as possible to go stimuli by pressing a button with the right thumb while refraining from reacting to nogo stimuli. At the beginning of a trial, the visual fixation point could turn either red or green, randomly. A red fixation point indicated that a go stimulus, a nogo stimulus or

no stimulus at all could occur, go and nogo events being equiprobable. In a control condition, no inhibition was required: A green fixation point indicated that no nogo stimulus would be presented. This condition enabled subjects to react automatically to any upcoming event.

Apparatus

A panel equipped with light-emitting diodes (LEDs – $\varnothing 5$ mm, 8,800 mcd) was used to present the visual stimuli. One LED was placed in the centre of the panel and set at the subject's eye level. It served as a fixation point for the eyes. The target stimulus (go) was composed of eight other LEDs surrounding the central fixation point and forming a diamond (3.44° of visual angle). Stimuli were presented and behavioral data were acquired using a real-time acquisition system (ADwin-Pro, Keithley Instruments, Cleveland, OH) controlled by laboratory-made software (Docometre) by courtesy of Franck Buloup (Institut des Sciences du Mouvement, Marseille).

The appearance of the fixation point indicated the beginning of a trial and lasted until the end of the trial. Prestimulus delays (time between the beginning of a trial and stimulus presentation) varied randomly from 2 to 6 s in steps of 500 ms. The inter-trial interval was fixed to 1 s in the EEG experiment, but varied randomly and exponentially from two to six seconds in the fMRI experiment. Subjects were asked to react as fast as possible to target presentation (100 ms duration) by pressing a button with their right thumb. In a control condition (go_control trials), the visual fixation point was green indicating that only targets could be presented. Subjects were then able to react automatically to any upcoming event. In another condition (go and nogo trials), the fixation point turned red, indicating that a go stimulus or a nogo stimulus could occur with equal probability. The nogo stimulus was composed of eight LEDs forming a X of 3.44° of visual angle centered on the fixation point (100 ms duration). Subjects were asked to refrain from reacting to these nogo signals. Catch trials (no stimulus after the appearance of the fixation point) were added (25% of all trials). Subjects were instructed to comply with a maximum error rate (false alarms and omissions) of 10% of all trials.

Procedure

In the fMRI experiment, the visual display was projected onto a screen located 56 cm from the subject's eyes (the screen was viewed through a mirror). Subjects were holding an amagnetic handle mounted with a highly sensitive button in the right hand positioned below the sternum. The experiment was divided into four acquisition sessions. Each session was composed of 20 go trials, 20 nogo trials, 20 go_control trials, and 20 catch trials, randomly presented, for a total of 80 trials/condition of interest.

The EEG experiment took place in a dedicated room within the fMRI center. Subjects were seated in a

darkened, shielded room in front of the panel set at 50 cm from their eyes. Ten blocks of forty trials each were performed by each subject. Each block was composed of 10 go trials, 10 nogo trials, 10 go_control trials and 10 catch trials, randomly presented, for a total of 100 trials/condition of interest.

Behavioral analyses

Typically, inhibitory performance in go/nogo tasks is estimated using the percent of responses to nogo stimuli. However, provided that suitable executive setting conditions are controlled in the experimental design, RT of trials for which an appropriate motor response was given might offer a reliable dependent variable indexing the involvement of response inhibition mechanisms [e.g., Boulinguez et al., 2008; Criaud et al., 2012; Jaffard et al., 2007; see Fig. 1 legend for detailed description]. Indeed, although RT differences between go trials in the uncertain versus the control conditions are multifactorial (involving especially different requirements with respect to visual identification mechanisms), they are conditioned on the implementation of an inhibitory setting [Chiu and Aron, 2014; Marini et al., 2013]. For each subject and each trial, RT was normalized with respect to the subject's mean value of the control condition (go_control) [Boulinguez et al., 2008]. Through this computation, all individual RTs are distributed around the value 1, which represents the individual mean RT of the control condition. The mode of each individual distribution was used for group statistical analysis. This was intended to avoid potential biases due to interindividual variability and non-Gaussian distributions of individual RT. A Wilcoxon's test was applied to compare go and go_control conditions.

Event-Related fMRI

Data acquisition

Images were acquired on a 3-T MEDSPEC 30/80 AVANCE whole-body imager (Bruker, Ettlingen, Germany), equipped with a circular polarized head coil. For each participant, we acquired a high-resolution structural T1-weighted image (MPRAGE sequence, resolution $1 \times 0.75 \times 1.22$ mm) in sagittal orientation, covering the whole brain. For functional imaging, we used a T2*-weighted echoplanar sequence, covering the whole brain with 36 interleaved 3-mm-thick/0-mm-gap axial slices (repetition time = 1,867 ms, echo time = 30 ms, flip angle = 77° , field of view = 19.2×19.2 cm, 64×64 matrix of 3×3 mm voxels). We acquired 337 functional volumes per session during four sessions, for a total of 1,348 volumes per subject.

fMRI preprocessing

Data were processed using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/>), according to the general

linear model [Friston et al., 1995]. The first six functional volumes of each session were removed to eliminate nonequilibrium effects of magnetization. The remaining 331 images were corrected for differences in slice acquisition time. The images were then corrected for head movements by realigning all the images with the first image using rigid body transformations, and unwrapped according to the fieldmap recording. Spatial normalization was improved using the DARTEL toolbox on an MNI template. Data were spatially smoothed with an isotropic Gaussian filter (8 mm full width at half maximum).

Event-related analysis of BOLD signal changes

In the statistical analysis, 12 event types were defined at the first level, including 10 effects of interest (2 periods—Prestimulus and poststimulus—For 5 types of trial - go_control, go, nogo, catch_control, catch) and two effects of no interest (intertrial interval, short prestimulus delays). The events were time-locked to the onset of the target, modeled according to their onset and their duration, and convolved with a canonical hemodynamic response function (HRF). Poststimulus regressors were built on the basis of the onset of the stimulus convolved with the standard canonical HRF. Prestimulus regressors were built on the basis of the onset of the cue, and the variable duration of the cue-stimulus period was used to define the duration of the event for convolution with the HRF. Since pre- and poststimulus were disjointed by a jittered delay comprised between 2 and 6 s, the different regressors were easily defined and separated. Data were highpass filtered at 128 s and summarized into one contrast per subject.

We performed two contrasts to assess, respectively, the activity specifically triggered by nogo stimuli with respect to go stimuli, and the activity evoked by any stimulus when the context is uncertain with respect to when the context is predictable. For each participant, the difference in stimulus evoked activity between the nogo and go conditions was assessed by a one sample *t* test applied to the contrast [(nogo)-(go)]. The difference in stimulus evoked activity between the two conditions of uncertainty was assessed by a one sample *t* test applied to the contrast [(nogo + go) - go_control]. The contrast was balanced by weighting the go_control condition ($\times 2$) to compensate for the unequal number of trials in the red fixation point and green fixation point conditions. The SPM group maps were generated with a random-effects model. The resulting individual statistical maps were entered into one sample *t* tests. Clusters displayed on statistical parametric maps were thresholded at a corrected cluster level of $P < 0.05$ using a voxel level threshold of $P < 0.0001$ uncorrected for multiple comparisons (and a cluster extent of more than 30 contiguous voxels).

We used a region of interest (ROI)-based analysis approach, with the label function of the WFU pickAtlas program [Maldjian et al., 2003, 2004] to include all the regions which might play a role in response inhibition in

go/nogo tasks [according to the review and meta-analysis from Swick et al. 2011]. The selected regions were the Anterior Cingulate Cortex, the Inferior Frontal Gyrus, the Superior Frontal Gyrus, the Medial Frontal Gyrus, the Middle Frontal Gyrus, the Inferior Parietal Lobule, and the Insula.

EEG

Data acquisition

The BiosemiTM ActiveTwo Mk2 system (31.25 nV resolution) was used to record EEG data from 128 electrodes mounted in an elastic cap at BiosemiTM ABC system standard locations. Six additional external electrodes were added: Four temporal electrodes (Biosemi spherical coordinates: Phi -103.5 Theta $-18 -36$, and Phi 103.5 Theta $18 36$), and two electrodes attached to the outer canthi of the left and right eyes (Phi $103.5 -103.5$ Theta $81 -81$). The CMS active electrode and the DRL passive electrode of the ActiveTwo system were used instead of classical ground electrodes of conventional systems (these two electrodes form a feedback loop driving the average potential of the subject—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 2,048 Hz. Offline, data were high-pass filtered above 1 Hz, low-pass filtered at 95 Hz, notch filtered at 50 Hz, and downsampled to 1,024 Hz. Then, data were epoched from 200 ms before stimulus onset to 1,000 ms after stimulus onset.

EEG preprocessing

For each subject, corrupted epochs and artifacts (blinks, eye movements, ballistocardiac noise, and other electrical noises) were automatically detected and rejected using a first ICA dedicated only to EEG preprocessing. We used an higher order statistics (HOS)-based blind source separation (BSS) algorithm [Infomax ICA; Bell and Sejnowski, 1995] with EEGLAB [Delorme and Makeig, 2004] and the FASTER toolbox [Nolan et al., 2010]. A total of 5,834 trials (corresponding to the concatenation of individual trials obtained from our 20 participants) were acquired after trials rejection. Only trials with RT distant from no more than the distribution mode ± 2 standard deviations were included in the group independent component analysis (gICA) (4,251 trials).

Advanced processing was performed on the basis of recent methodological developments. First, we applied BSS. Indeed, as recently reviewed by Huster et al. [2013], classical ERPs (N2/P3) are not reliable markers of inhibitory processes because they likely involve several mechanisms confounded with proper inhibitory processes, like conflict-related and evaluative processing stages. One likely reason is that the overall electrical activity recorded on the scalp is composed of a set of mixed signals. To

address this problem, we first used a robust second-order statistics (SOS)-based algorithm to unmix this set of signals. To optimize separation, UW-SOBI [Belouchrani et al., 1997; Yeredor, 2000] was privileged over more popular but less robust higher order statistics-based algorithms [Lio and Boulinguez, 2013]. Then, in a second step, we applied group independent component analysis (gICA). This approach offers a straightforward and computationally tractable solution to the problem of multisubject analysis by creating aggregate data containing observations from all subjects. By providing a single estimation of the mixing and the demixing matrices for the whole group, gICA allows direct estimation of the components that are consistently expressed in the population [see Eichele et al., 2011 for discussion of the broad interest of using this method] and, hence, more efficient source separation and localization of these components [Lio and Boulinguez, 2013].

The UW-SOBI algorithm is an adaptation of the well known SOBI algorithm [Tang et al., 2005] reformulated as an uniformly weighted nonlinear least squares problem to avoid the common “whitening” phase which is known to limit the performance of BSS/ICA algorithms in noisy conditions [Cardoso, 1994, 1998]. One hundred time-delayed covariance matrices, with time delays from 1/1,024s to 100/1,024s were calculated on each of the 4,251 remaining epochs. Then the 100 averaged time-delayed covariance matrices were approximately joint diagonalized with the UWEDGE algorithm [Tichavsky and Yeredor, 2009], leading to the identification of 134 independent components (ICs).

Methodological principals of event-related analyses of EEG signal changes

We took advantage of our unique design offering a psychophysical marker of the motor output (RT) both in the condition requiring inhibition of automatic responses and in the control condition. Indeed, the introduction of a go_control condition not only allows comparison of inhibition-related brain activations generated in nogo and go trials with an appropriate reference condition, it also gives the opportunity to assess quantitative behavioral markers of automatic response inhibition by contrasting go with go_control RTs (Fig. 1C). This alternate approach is based on the following rationale: The more powerful the inhibitory activity, the more the response to go with respect to go_control trials should be delayed, bearing in mind that attentional modulations are also likely to contribute to the overall effect [Marini et al., 2013]. Primarily, we selected the relevant sources among the 134 ICs for further analysis by tracking over time, for each component, the significant activity changes between the go and go_control conditions. The critical (i.e., earliest) sources coming out from this blind test were further submitted to a first coarse-grained analysis consisting in the comparison of the ERPs evoked within each single source by the nogo, the go and the go_control stimuli, respectively. Then, a

more fine-grained assay was performed, based on supplementary analyses guided by the behavioral data on a single-trial basis.

Selection of relevant sources/detection of the earliest electrophysiological indices of response inhibition

In order to track the earliest activity evoked by reactive inhibitory processes, a multiple hypothesis testing procedure was designed. For each IC, the mean evoked activity was estimated both for the go and the go_control conditions in height time-periods of 25 ms, from 50 to 250 ms after stimulus onset. A Wilcoxon's test ($P < 0.05$, Bonferoni's corrected) was used to test differences between go and the go_control conditions for each IC and each time period. Since we found only one IC showing significant early differences (Supporting Information Fig. S1), the next processing steps were applied only to this component (Fig. 2).

Analyses of relevant sources activity

IC source localization. The 3D distribution of the selected source current densities was estimated by means of the sLoreta software [Pascual-Marqui, 2002]. The head model used for this analysis was obtained by applying the BEM method to the MNI152 template [Mazziotta et al., 2001]. The 3D solution space was restricted to cortical gray matter and was partitioned into 6,239 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. Four sets of analyses were performed.

Coarse-grained analysis: Event-related potentials. The ERPs respectively evoked by the nogo, the go and the go_control stimuli were assessed. For each trial the voltage at peak amplitude ($t = 168$ ms) was recorded. Comparisons between the three conditions were performed by means of Wilcoxon's tests.

Fine-grained analysis: Psychophysiological correlations. In order to assess the relation between the behavioral and electrophysiological markers of response inhibition at a more detailed level, all trials for which an appropriate motor response was provided (go and go_control distributions) were merged for refined single-trial analyses. The relation between RT and the amplitude of the evoked component of the selected source was assessed by means of Pearson correlations. These calculations were applied after Vincentization of RT data. The 3,926 artifact free trials were partitioned in 9 classes: $RT < 5th < 10th < 20th < 40th < 60th < 80th < 90th < 95th < 100th$ percentile of the RT distribution.

Fine-grained analysis: Event-related spectral power analysis. We assessed how the different frequency bands contribute to the ERPs by means of fast Fourier transforms. Then, we calculated stimulus-induced (time locked) power changes of ongoing oscillations of the selected source [see Nikulin

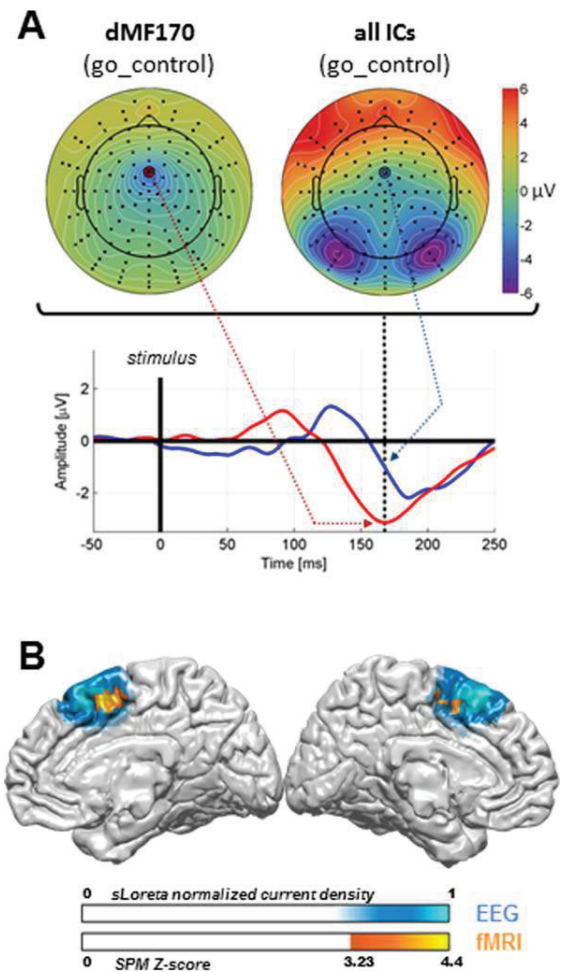


Figure 2.

(A) Topographic mapping of dMF170 activity at peak time, back-projected on the scalp after source separation (upper left side), as compared with topographic mapping of all mixed components before source separation (upper right side). Time-series of the net activity at C23 are presented for each condition (lower part; red: dMF170; blue: overall activity). The whole topography is strongly influenced by powerful visual activity around 170 ms to the extent that the dMF170 component remains invisible without filtering all interferent sources by means of advanced source separation. (B) Source localization of the dMF170 component with sLoreta. The probability map is presented on the MNI atlas. It extends across the SMC. Combined fMRI results are superimposed. BOLD imaging reveals an overlapping region that is more activated by the stimulus when the situation requires response inhibition (go and nogo conditions pooled together for analysis) than when it does not (go_control condition).

et al., 2007; Van Dijk et al., 2010 for discussion] in order to estimate how these changes modulate the evoked response. These modulations were assessed by means of

single-trial analyses. Further data preprocessing was performed in order to get optimal time/frequency resolution within 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), low Gamma (30.5–44.5 Hz), and high Gamma (57.5–77.5) band activities. Six elliptic infinite impulse response (IIR) bandpass filters were designed with the Matlab™ signal processing toolbox. Relatively large pass band widths were set to get optimal time resolution, i.e., optimal estimation of the temporal dynamics of the frequency bands of interest at the single-trial level. The filters used the following specifications:

- Filter 1 (Delta/Theta power): High pass frequency: 1.5 Hz; Low pass frequency: 7.5 Hz; Transition band width: 1 Hz; Attenuation: 80 dB; Order: 18; sections: 9.
- Filter 2 (Alpha power): High pass frequency: 7.5 Hz; Low pass frequency: 13.5 Hz; Transition band width: 1 Hz; Attenuation: 80 dB; Order: 16; sections: 8.
- Filter 3 (Beta 1–2 power): High pass frequency: 13.5 Hz; Low pass frequency : 19.5 Hz; Transition band width: 1 Hz; Attenuation: 80 dB; Order: 16; sections: 8.
- Filter 4 (Beta 3 power): High pass frequency: 19.5 Hz; Low pass frequency: 30.5 Hz; Transition band width: 1 Hz; Attenuation: 80 dB; Order: 20; sections: 10.
- Filter 5 (Low Gamma power): High pass frequency: 30.5 Hz; Low pass frequency: 44.5 Hz; Transition band width: 1 Hz; Attenuation: 80 dB; Order: 20; sections: 10.
- Filter 6 (High Gamma power): high pass frequency: 57.5 Hz ; low pass frequency: 77.5 Hz ; transition band width: 5 Hz ; attenuation: 80 dB; order: 14; sections: 7.

Then, the activity of the selected component was extracted from the recorded scalp activity of the 3,926 artifact free trials (re-epoching from 1,500 ms before to 1,000 ms after the stimulus onset). In order to quantify the power (the scalp contribution) of the component, the source activity was back transformed to the electrode space, and displayed on the electrode that mostly contributes to the source variance (C23/Fcz for the dm170 component). Then, to analyze the temporal dynamics of the signal within each frequency band of interest, the following method was implemented: First, each trial was filtered with the corresponding filter in both forward and reverse directions to insure zero-phase distortion. Second, the complex analytic signal of each filtered trial was derived by the Hilbert transform (Matlab™ Hilbert function). Third, the instantaneous amplitude envelopes of the filtered trials were computed by taking the absolute magnitude of the complex waveform. Then, the studied time range was restricted to 200 ms pre- to 800 ms post-stimulus in order to avoid edge effects/transient responses of digital filters. Finally, for visualization only, a trial moving average smoothing was applied (windows length: 400).

Fine-grained analysis: ERP/evoked power correlations. The relationship between the amplitude of the evoked component and the power within each frequency band at component peak time was assessed by means of Pearson's correlations, as described above (psychophysiological correlations).

RESULTS

Behavioral Data

The false alarm rate (number of responses to nogo signals/number of nogo signals) was low both in the EEG (0.082 ± 0.076) and in the fMRI (0.12 ± 0.089) experiments, indicating good inhibitory performance.

Go RT normalized with respect to the mean go_control RT was found to be significantly longer than go_control normalized RT in both the EEG (1.24 vs. 1, $P < 0.001$) and the fMRI (1.3 vs. 1, $P < 0.001$) experiments. Considering that the go_control condition involves no inhibitory control, this result is consistent with the hypothesis that a certain level of inhibitory control is involved in the go condition (Fig. 1).

fMRI Data

We first contrasted the nogo and go conditions to assess the specificity of response inhibition activations in uncertain environments. We found no significant difference, suggesting that response inhibition is not triggered differently by nogo and go signals. Thus, both conditions were collapsed for further analysis.

We then contrasted the condition with uncertainty (red fixation point condition, nogo and go conditions merged) with the condition without uncertainty (green fixation point condition, go_control condition). This contrast is prone to reveal the brain regions supporting nonselective response inhibition that are more activated by any stimulus when the context is uncertain. Only one region (cluster size: 99 voxels) returned a significant difference. This area was localized in the medial frontal gyrus (BA 6). Response peaks were observed both in the SMA-proper ($[-6, -6, 63]$, z score: 4.45; $[3, -3, 54]$, z score: 4.65) and in the pre-SMA ($[6, 9, 57]$, z score: 4.97).

EEG Data

Selection of relevant sources/detection of the earliest electrophysiological indices of response inhibition

We searched for the components that significantly accounted for the RT difference between the conditions with and without uncertainty. In order to focus on relevant inhibitory activity, we performed this analysis within an early 0–250 ms poststimulus time window. We found only one component showing early significant difference in activity between the conditions with and without

uncertainty (within an early 125–175 ms time window with respect to stimulus onset, Supporting Information Fig. S1). Consistent with the fMRI data, this component was localized in the dorsal medial frontal cortex (Fig. 2), with a probability map covering the supplementary and presupplementary motor areas (supplementary motor complex, SMC). The other EEG components for which significant differences were found between the conditions with and without uncertainty reported late, nonoverlapping changes in activity, starting around 200 ms and lasting beyond 250 ms (Supporting Information Fig. S1). These late components were generated within the cuneus, the precuneus and the anterior cingulate cortex (ACC), whose combined activities more likely account for the classical ERPs N2 and P3 (Supporting Information Fig. S2). As a consequence, only the relevant early dorsomedial frontal component was selected for further analysis.

Coarse-grained analysis

The corresponding event-related potential peaked negatively at 168 ms. Its amplitude was not different between go and nogo trials ($P > 0.82$). Yet, it was greater in the condition without uncertainty (go_control) than in the conditions with uncertainty (go or nogo trials) (-3.12 vs. -2.58 and -2.63 μV , respectively, $P_s < 0.01$, Fig. 3).

Fine-grained analyses

Refined analyses showed that the amplitude of the event-related potential is a linear function of RT (Pearson's correlation = 0.99; $P < 0.001$). Spectral analyses performed at the source level revealed that delta/theta and Alpha bands show a burst of activity evoked by the stimulus. However, only the Alpha band power evoked modulations are consistent with the BOLD increase observed within the same region (more powerful evoked activity for longer RT) (Fig. 4A). Consistently, the amplitude of the ERP is negatively correlated with Alpha power measured at ERP peak time (Pearson's correlation = 0.90; $P < 0.01$) (Fig. 4B).

Theoretically, groupBSS estimates sources that are group/task related and maximally similar across space/time and subjects [Lio and Boulinguez, 2013]. As a consequence, to observe the full effect size across the whole group RT distribution, the ERPs for each class of RT have been calculated directly from the single trial analysis. In this case it cannot be precisely determined whether each subject contributes equally to each class. To control for this possible source of inaccuracy, we performed complementary, more conventional group level (second level) analyses on the basis of single subject (first level) analyses. These supplementary analyses are presented in the Supporting information file (2. Supplementary analyses). They provide similar results than the groupBSS analyses, strengthening the validity of our initial approach and demonstrating the contribution of most subjects to the overall group result.

DISCUSSION

It is problematical to distinguish critical brain activity from redundant brain activity in inhibitory tasks on the basis of BOLD analyses [e.g., Chambers et al., 2009], especially when the methods rely on complex designs [Criaud and Boulinguez, 2013]. Consequently, while fMRI studies have repeatedly found a large number of structures, the interpretation of brain activations in go/nogo tasks is often questionable. In the present fMRI study, we found no evidence for specific activations induced by the stimuli that had to be withheld with respect to those requiring a motor response. In other words, we found no evidence for the involvement of selective response inhibition in the present go/nogo task. The difference between the classical reports and ours likely relies on the fact that we used a simple, refined, task design preventing from potential confounds with the numerous cognitive processes involved in the complex tasks typically used to probe response inhibition. Consistent with this interpretation, a critical review of fMRI investigations of response inhibition based on repeated meta-analyses of typical go/nogo experiments has recently suggested that most of the activity specifically elicited by stimuli requiring action restraint is actually driven by the engagement of high attentional or working memory resources, not by inhibitory processes *per se* [Criaud and Boulinguez, 2013]. Obviously, there is too much evidence from clinical [e.g., Nachev et al., 2008; Picton et al., 2007; Sumner et al., 2007], stimulation [e.g., Chen et al., 2009; Duque et al., 2013; Juan and Muggleton, 2012; Obeso et al., 2013], and animal [e.g., Chen et al., 2010; Isoda and Hikosaka, 2007] studies to infer from this result that the most expected brain region, the SMC, does not play a direct role in response inhibition. This result rather suggests that, in this type of task which does not require selection between alternative responses, the critical inhibitory process is not selective, i.e., is not specific to the processing of nogo signals. As discussed below, the critical inhibitory process would rather be context-dependent. It would consist in blindly suppressing *any* automatic response when the situation is potentially conflicting in order to allow deliberate, long latency responses.

Bursts in Alpha Power Evoked by Unpredictable Stimuli are Related to Increases in BOLD and Suppression of Early ERP in the SMA

Using an approach that manipulated stimulus uncertainty, we show that, in unpredictable contexts, any stimulus triggers an increase in BOLD activity in the supplementary motor complex (SMC) (Fig. 2B). Theoretically, this enhancement is not straightforward to interpret. It can reflect early inhibition of automatic responses, preparation of long latency volitional responses, conflict resolution or action selection, reminding how complex the functional attributes of this region can be [Nachev et al.,

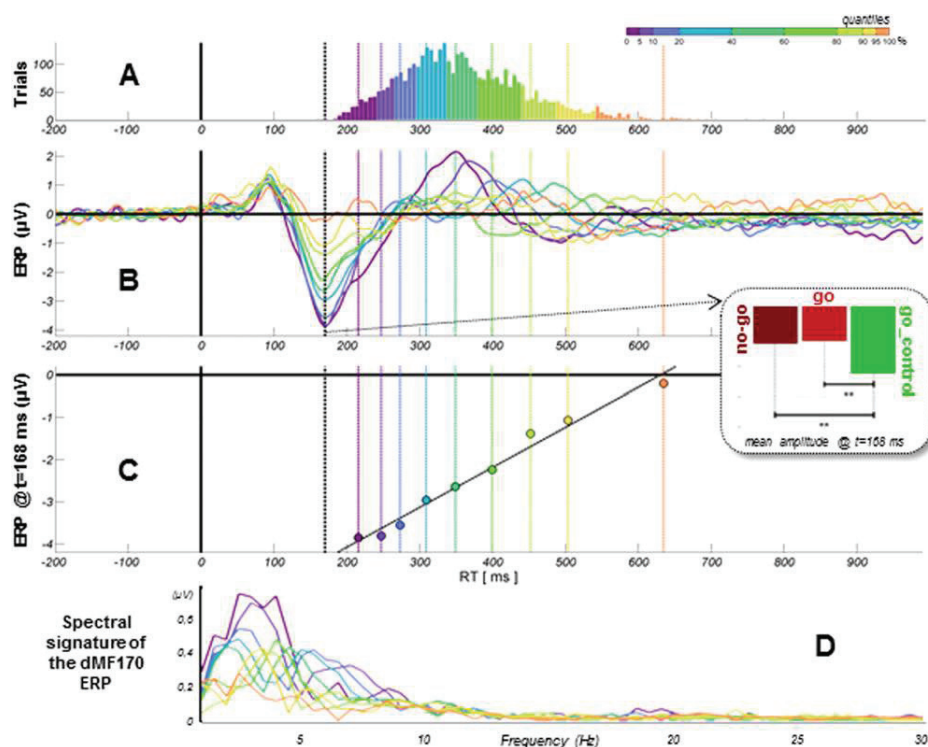


Figure 3.

Psychophysiological characteristics of the dMF170 component. **(A)** Cumulated distributions of RT (go and go_control trials merged for analysis). Data are Vincenzated with unequal-sized subsets to compensate for RT distribution inhomogeneity in order to better assess what accounts for these differences in RT (quantiles are displayed with color code). **(B)** Time series of dMF170 activity (back-projected on electrode C23/Fcz) (t_0 = target presenta-

tion). The component peaks negatively approximately 170 ms after stimulus presentation, identically for go and nogo trials (means), but shows larger amplitude for the go_control condition. The mean evoked potential is displayed for each quantile. **(C)** The mean evoked potential for each quantile is referred to the corresponding mean RT. The amplitude of the dMF170 closely predicts RT. **(D)** Fast Fourier transform of the dMF170 ERP.

2008; Rushworth et al., 2005]. EEG signals provide relevant data to evaluate the validity of each of these possibilities. As reported in the results, advanced blind source separation revealed that the only source showing early amplitude differences between the conditions with and without uncertainty was consistently located in the SMC (Fig. 2).²

²Longer latency effects were found in the ACC and the visual system, starting about 200 ms (Supporting Information Fig. S1), which is also the timing of the fastest automatic responses of the control condition (Fig. 3). These activity changes are consistent with a different level of involvement of visual attention in the two conditions, but do not seem critical for response inhibition with regard to their timing since inhibitory processes are expected to be active before the temporal window during which fast automatic motor responses are triggered (Supporting Information Fig. S1). This activity of the cingulate/visual regions might rather be associated with subsequent processes critical for producing long latency responses (Supporting Information Fig. S2), like mismatch and conflict detection, perceptual decision or response program updating (e.g., Gonzalez-Rosa et al., 2013; Huster et al., 2011, 2013; Kropotov et al., 2011).

Consistent with the model assuming context dependent executive setting, the amplitude of this single source (hereinafter referred to as the “dMF170”) was identical for the nogo and go trials, but different in the go_control condition (Fig. 3). Interestingly, spectral analyses of the dMF170 uncovered only one frequency band showing power evoked modulations consistent with the BOLD increase observed within the same region (Fig. 4). The fact that this activity was observed in the Alpha band strongly suggests, according to recent studies, that the BOLD signal evoked by any stimulus when the situation was unpredictable was driven by inhibitory activity [Haegens et al., 2011; Hindriks and Van Putten, 2013; Jensen and Bonnefond, 2013; Jensen and Mazaheri, 2010; Klimesch et al., 2007; Klimesch, 2012; Mazaheri et al., 2009; Mathewson et al., 2011]. Supporting this interpretation, the efficiency of automatic inhibitory mechanisms has been related to GABA concentration in the SMA as measured with magnetic resonance spectroscopy, and attributed to the involvement of local inhibitory interneurons [Boy et al., 2010a].

The DMF170 Component as a Physiological Marker of Both Automatic Response Activation and Concurrent Automatic Inhibition

The evoked potential of the dMF170 component was found to peak around 170 ms poststimulus (Figs. 2–4), well before the standard N2/P3 ERP markers of response

inhibition (Supporting Information Fig. S1 and Fig. S2). This supports the idea that early, automatic, inhibitory mechanisms within the SMC are involved in action control [Boy et al., 2010a–c; Sumner et al., 2007]. Importantly, the amplitude of the dMF170 was predictive of RT in trials for which a response was required: large negative amplitudes were observed for fast responses in predictable situations, but peak amplitude was gradually suppressed as RT increased (Fig. 3). In other words, the amplitude of the evoked potential of the dMF170 was attenuated when the response had to be withheld. Importantly, this attenuation of the ERP is unequivocally attributable to the burst in Alpha power. Indeed, the burst of Alpha power is time locked to the ERP but evolves in the opposite direction (Fig. 4). Thus, the burst of Alpha power cannot be just the spectral representation of the ERP, which is rather accounted for by delta/theta activity (Fig. 3D; see also Supporting Information analyses). In this respect, the pattern of activity observed within the lowest frequency band in the present study (Fig. 4) is partly reminiscent of previous reports associating the low-theta burst preceding rapid motor responses to the disinhibition of impulsive motor responses [Delorme et al., 2007]. Taken together, these findings suggest that: (i) automatic inhibition is self-generated within the supplementary motor system and (ii) automatic inhibition develops concurrently with any automatic motor activation, not selectively in response to undesired automatic motor activation.

These findings could not have been derived from standard psychophysical, fMRI, or ERP approaches. Although some clues about the involvement of nonselective inhibitory mechanisms have been provided separately by former fMRI [Jaffard et al., 2008] and EEG [Boulinguez et al., 2009] studies, only the use of advanced methods allowing proper separation of the numerous sources mixed in the EEG signal allowed identification of the involvement of the early dMF170 component (Fig. 2). This masked component likely provides the missing link in the framework of

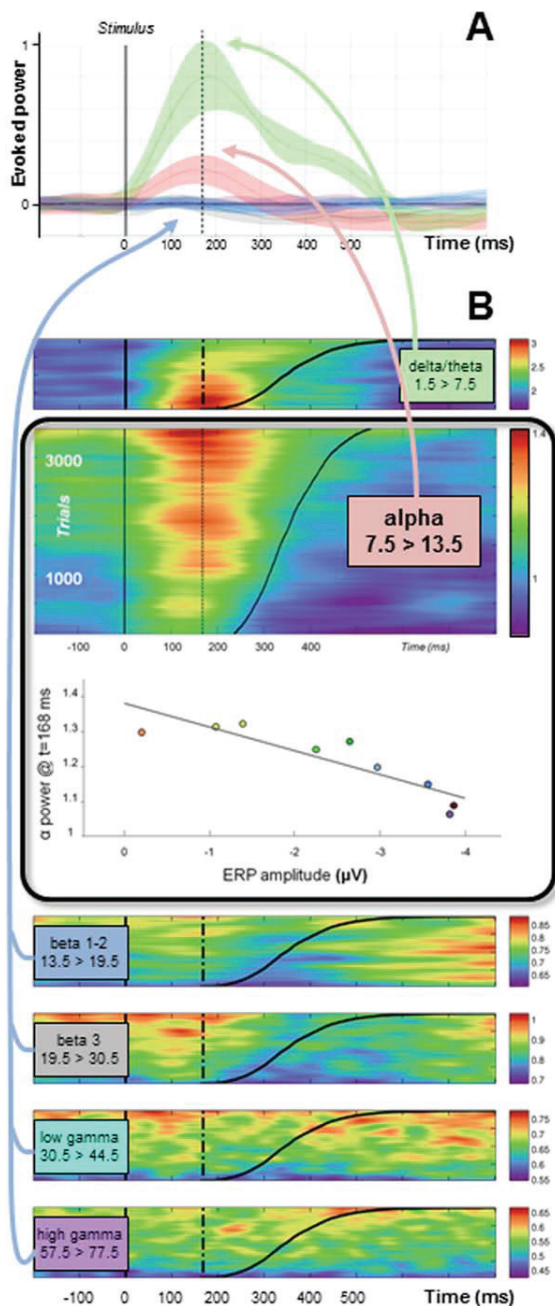


Figure 4.

(See legend on the following page.)

Figure 4.

Spectral analyses of the “dMF170” component. (A) Mean evoked activity within each frequency band of interest (power is normalized with respect to the prestimulus period). Only delta/theta and Alpha bands show evoked activity. (B) Single-trial modulations in spectral power within each frequency band of interest. Trials are sorted according to RT (black line). Only the Alpha band shows power evoked modulations consistent with the BOLD increase observed within the same region (more powerful evoked activity for longer RT). Correlation analysis shows that the higher the Alpha power at peak time, the smaller the amplitude of the dMF170. In contrast, the delta/theta band shows less powerful evoked activity for longer RT, reflecting possibly the evoked excitatory activity driving SMC efference (more powerful evoked activity for shorter RT, i.e., for noninhibited responses). No activity evoked by the stimulus is observed in upper frequency bands.

the electroencephalography of response inhibition, supporting the idea that none of the standard EEG-derived measures (see Supporting Information Fig. S2) can provide an unambiguous indicator of functional inhibition [Huster et al., 2013]. Nevertheless, due to the intimate nature of the EEG signal, some caution should be exerted when interpreting these data. Indeed, the basis of the EEG signal is formed of spatiotemporally summed postsynaptic potentials, and strongly relates to the input a region generates, not necessarily to its output. As a consequence, if the dMF170 ERP evoked by any stimulus likely reflects transient automatic activation of motor processes, it does not necessarily reflect the output of the SMC. Assuming, in light of the existing literature (see “Introduction”), that Alpha oscillations actually index an active inhibitory mechanism that gates information processing within a given region [Hindriks and Van Putten, 2013; Jensen and Mazaheri, 2010; Klimesch et al., 2007; Klimesch, 2012; Mathewson et al., 2011], what can be inferred from the present data is that integrative processes in the SMC are likely suppressed when action restraint is required, with consequent suppression of short latency responses at the behavioral level. Yet, recent evidence that Alpha power is negatively correlated with spiking rate in monkeys premotor cortex [Haegens et al., 2011] makes it tempting to further speculate about the possible role of Alpha oscillations in driving neuronal spiking in human SMC as well.

Based on these observations, we propose that the dMF170 component likely provides a reliable biomarker of both automatic response activation and concurrent automatic inhibition. While the ERP would index the strength of automatic motor activations, the burst of Alpha power time-locked to the stimulus might provide a direct, real time, physiological correlate of activation of local, automatic, self-inhibitory networks that gates information within the SMC.

Controlling Automatic Inhibition of Automatic Responses as a Basic Executive Mechanism?

As suggested by its flexible functioning (whether or not the situation is potentially conflicting), the SMC appears to play a central role in task setting [Forstmann et al., 2008, 2010; Nachev et al., 2008; Rushworth et al., 2004; Vallesi et al., 2009]. Yet, dissociating the nearly indistinguishable roles of the SMC in response inhibition and switching during executive control is far from trivial [e.g., Kenner et al., 2010]. Previous findings support the hypothesis that a contextual activation of inhibitory networks within the SMC via proactive control might play a critical role in executive functions [e.g., Obeso et al., 2013]. Depending on their expectations of upcoming events, subjects could switch anticipatorily from one mode of control to another, i.e., from automatic inhibition of response to automatic processing of sensorimotor information, and reciprocally. This mechanism could be achieved by activating/deactivating

local inhibitory circuitry within SMC with consequent attenuation/enhancement of SMC early, reactive, automatic activity. These findings are partly reminiscent of pioneer electrophysiological studies in monkeys [Isoda and Hikosaka, 2007]. They reveal, in humans, the complex, flexible, and paradoxical mechanisms by which voluntary control of action may be achieved [Braver et al., 2009; Haggard, 2008; McBride et al., 2012; Verbruggen and Logan, 2008, 2009]. Yet controversy remains regarding which part of the SMC precisely supports this elementary form of functional inhibition [Wardak, 2011], and which brain regions provide the control signals for the generation of the inhibitory set within the SMC [Brass and Haggard, 2007; Braver et al., 2009; Filevich et al., 2012; Jaffard et al., 2007, 2008; Kuhn et al., 2009]. The concept of proactive control [effects of foreknowledge on inhibition-related neurocognitive processes: Aron, 2011; Braver et al., 2009; Chen et al., 2010; Criaud et al., 2012; Criaud and Boulinguez, 2013; Jaffard et al., 2007, 2008; Jahfari et al., 2010, 2012; Lo et al., 2009; Zandbelt and Vink, 2010; Zandbelt et al., 2013] combined with the methodological advances provided by EEG-based spectral analyses [e.g., Bengson et al., 2012; Mazaheri et al., 2009] provide a powerful framework for further investigation.

Relevance to More General Models of Action Control

The control mechanism proposed above is reminiscent of some processes described in former models. Our model resembles the “dual-route” model of interference [e.g., Forstmann et al., 2008; Eimer, 1995; Kornblum et al., 1990; Ridderinkhof, 2002] in the sense that the controlled process of response activation is paralleled by a direct response capture route that requires inhibition to prevent erroneous responses. Yet, the dual route model assumes a selective inhibition of inappropriate automatic activations, while our model assumes inhibition of any automatic response whether inappropriate or not. In this respect, our model resembles more closely the “hold your horses” model of decision making [Franck, 2006; Franck et al., 2007] which assumes that preventing premature responding is achieved by the generation of a “global nogo” signal in the cortico-basal ganglia loops, acting on suppression of all responses rather than modulating the execution of any particular response. Yet, the “hold your horses” model is assumed to apply to high-conflict win/win decisions in complex choice tasks involving concurrent responses (i.e., decision about which action to execute). The present data do not only identify a physiological marker of the “global nogo” signal, they also extend the concept to simple situations for which only the decision whether to execute an action or not is concerned. At a more general level, the basic control mechanism inferred from the present results is also partly reminiscent of some processes described in the impulse control model of movement preparation

[Duque and Ivry, 2009; Duque et al., 2010, 2012], in the sense that a nonselective inhibitory mechanism can be directed at an already selected response in order to control when this response is executed. Of particular interest for that purpose is certainly the integrative “What, When, Whether” model of intentional action proposed by Brass and Haggard [2008]. This model clearly separates the mechanisms related to the decision about which action to execute from the mechanisms related to the decision about whether to execute an action or not, and when to initiate it. Although this issue remains to be further explored, the elementary inhibitory mechanism inferred from the present findings might represent a basic function common to all these actions whether simple or complex.

CONCLUSION

In summary, the present data provide empirical support for the claim that response inhibition is not necessarily a control process intended to override a prepotent response tendency, but can also be itself a prepotent response tendency which has to be temporarily controlled [Jasinska, 2013]. We suggest that an early, automatic, nonselective self-inhibitory mechanism of the SMC is involved in response control when the context is uncertain, and is released when the situation becomes predictable. It is not too speculative to suggest that automatic inhibition of automatic motor responses probably has a pivotal role in the numerous functions supported by the SMC [Nachev et al., 2008]. These results open-up new clinical perspectives since impairments in the ability to implement or release this form of inhibitory setting would be devastating in different psychiatric and neurologic conditions. Such executive dysfunctions may account for various motor and cognitive disorders, as might obviously be the case for impulsivity [Ballanger et al., 2009] but also for opposing symptoms like akinesia [e.g., Favre et al., 2013].

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*Annexe 3 : Christopher L, Koshimori Y, Lang AE, **Criaud M**, Strafella AP. (2014) Uncovering the role of the insula in non-motor symptoms of Parkinson's disease. Brain, 137(Pt 8): 2143-54.*

REVIEW ARTICLE

Uncovering the role of the insula in non-motor symptoms of Parkinson's disease

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Patients with Parkinson's disease experience a range of non-motor symptoms, including cognitive impairment, behavioural changes, somatosensory and autonomic disturbances. The insula, which was once thought to be primarily a limbic cortical structure, is now known to be highly involved in integrating somatosensory, autonomic and cognitive-affective information to guide behaviour. Thus, it acts as a central hub for processing relevant information related to the state of the body as well as cognitive and mood states. Despite these crucial functions, the insula has been largely overlooked as a potential key region in contributing to non-motor symptoms of Parkinson's disease. The insula is affected in Parkinson's disease by alpha-synuclein deposition, disruptions in normal neurotransmitter function, alterations in connectivity as well as metabolic and structural changes. Although research focusing on the role of the insula in Parkinson's disease is scarce, there is evidence from neuroimaging studies linking the insula to cognitive decline, behavioural abnormalities and somatosensory disturbances. Here, we review imaging studies that provide insight into the potential role of the insula in Parkinson's disease non-motor symptoms.

Keywords: Parkinson's disease; neuroimaging; insula; cognition; behaviour

Introduction

The insula is a cortical region 'hidden' beneath the frontal, temporal and parietal lobes. Until recently its functional roles have remained largely unknown and often overlooked. The insula has long been considered part of the limbic cortical system (Mesulam and Mufson, 1982a), however, recent research suggests its involvement in a wide variety of functions. In fact, it seems that the insula may be a crucial brain region in humans, because of its role in processing subjective awareness, and integrating important

homeostatic information from the body with higher level cognitive processes (Craig, 2009). In particular, the anterior division of the insula is expanded in humans compared to other closely related species, alluding to its role in higher-order awareness and social cognition (Bauernfeind *et al.*, 2013). The insula is also thought to process visceral feelings or signals from the body, and these signals can assist in rapid decision-making processes involving risk, uncertainty or social interactions (Craig, 2002; Singer *et al.*, 2009). This has also been described as the somatic marker hypothesis, which proposes that visceral and emotional information guide decisions

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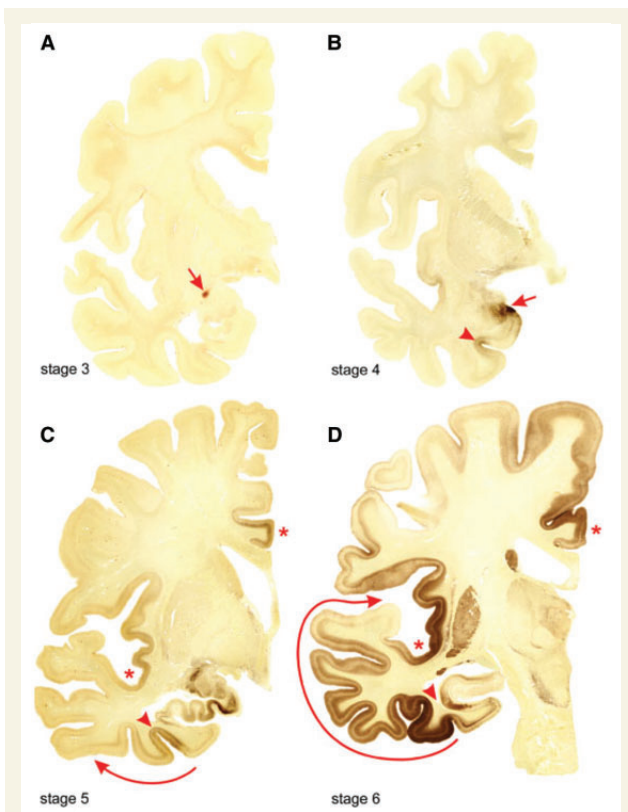


Figure 1 (A–D) Stages 3–6 according to Braak's staging demonstrating immunolabelling of alpha-synuclein adapted from Braak *et al.* (2006). (D) The alpha-synuclein deposition affecting the insular cortex. Arrows indicate regions of alpha-synuclein deposition and direction of spread. Asterisks indicate alpha-synuclein deposition in the insular and anterior cingulate cortices.

in uncertain situations, rather than purely cognitive processes (Damasio, 1996). Recent research has suggested separate functional roles for the anterior and posterior insula in more cognitive/affective and viscerosensory/somatosensory awareness, respectively (Chang *et al.*, 2013).

How does the insula relate to Parkinson's disease? Although once thought to be primarily a motor disorder, Parkinson's disease is now well characterized by an array of non-motor symptoms. These non-motor symptoms range from behavioural and cognitive changes, to autonomic and sensory changes (Chaudhuri and Schapira, 2009; Park and Stacy, 2009). Cortico-striatal circuitry has been the primary anatomical focus of many of the symptoms of Parkinson's disease. However, the insula is also highly interconnected with the basal ganglia (Chikama *et al.*, 1997; Fudge *et al.*, 2005), and many other cortical regions including the frontal, temporal, parietal, and cingulate cortices (Cauda *et al.*, 2011; Nieuwenhuys, 2012). Thus, the insula is able to interact with multiple brain networks, and is multifaceted in its involvement in a wide range of cognitive, affective, sensory and autonomic processes. Studies investigating brain abnormalities in Parkinson's disease underlying non-motor symptoms have focused on many of

these brain regions, however, the insula is rarely a central focus despite its potential importance in contributing to these symptoms.

According to Braak's staging hypothesis of Parkinson's disease progression, alpha-synuclein is highly deposited throughout the insula by stage 5 (Braak *et al.*, 2006) (Fig. 1). Thus, it would not be surprising, that alpha-synuclein could cause alteration in receptor function and thus synaptic activity in these neurons. This could in part, contribute to a number of non-motor symptoms experienced by patients with Parkinson's disease. Additionally, the degeneration of neurotransmitter systems in Parkinson's disease could affect the normal modulation of cortical activity in the insula. Degeneration of dopaminergic, cholinergic and serotonergic pathways projecting to the insula in patients with Parkinson's disease (Halliday *et al.*, 1990) could have drastic effects on the functional integrity of this region. The insula, like other cortical regions, relies on neuromodulation from these neurotransmitter systems for normal function. For example, levels of excitatory glutamate in the insula have been shown to correlate with the awareness of one's own emotions (Ernst *et al.*, 2013), demonstrating the relationship between levels of neurotransmitter release and function. Finally, this area may be susceptible to structural changes such as grey matter loss in more advanced disease stages, either due to direct involvement of alpha-synuclein pathology or secondary to loss of synaptic input.

Although Parkinson's disease affects the whole brain, more special attention should be paid to the insula as a region underlying non-motor symptoms in Parkinson's disease. Here, we will review the potential role of the insula as revealed by neuroimaging studies evaluating various non-motor symptoms of Parkinson's disease. First, we will review insular involvement in cognitive impairment in Parkinson's disease. This will lead to a discussion of the role of the insula in behavioural and affective symptoms of Parkinson's disease, followed by a review of the contribution of the insula to somatosensory symptoms in Parkinson's disease. Lastly, the potential role of the insula in autonomic dysfunction in Parkinson's disease will be discussed.

A brief overview of insular anatomy

The insula is tucked beneath the frontal and temporal lobes bilaterally within the brain. The anatomical organization of the insula corresponds to its functional roles and can be divided into anterior and posterior divisions, separated by the central insular sulcus. It is highly interconnected with the basal ganglia in a connectivity gradient from posterior to anterior, with posterior insula projecting to the dorsal/posterior striatum, and anterior insula progressively towards anterior and ventral regions of the striatum (Fig. 2). This organization is highly consistent with the functional roles of both dorsal/posterior insula and striatum in sensorimotor processes, and anterior/ventral regions in cognitive and affective processing (Chikama *et al.*, 1997; Flynn *et al.*, 1999). The insula is also divided into posterior granular and anterior agranular sections with a large transitional dysgranular mid-section (Fig. 3). The posterior division receives convergent spinal, humoral and vagal nerve

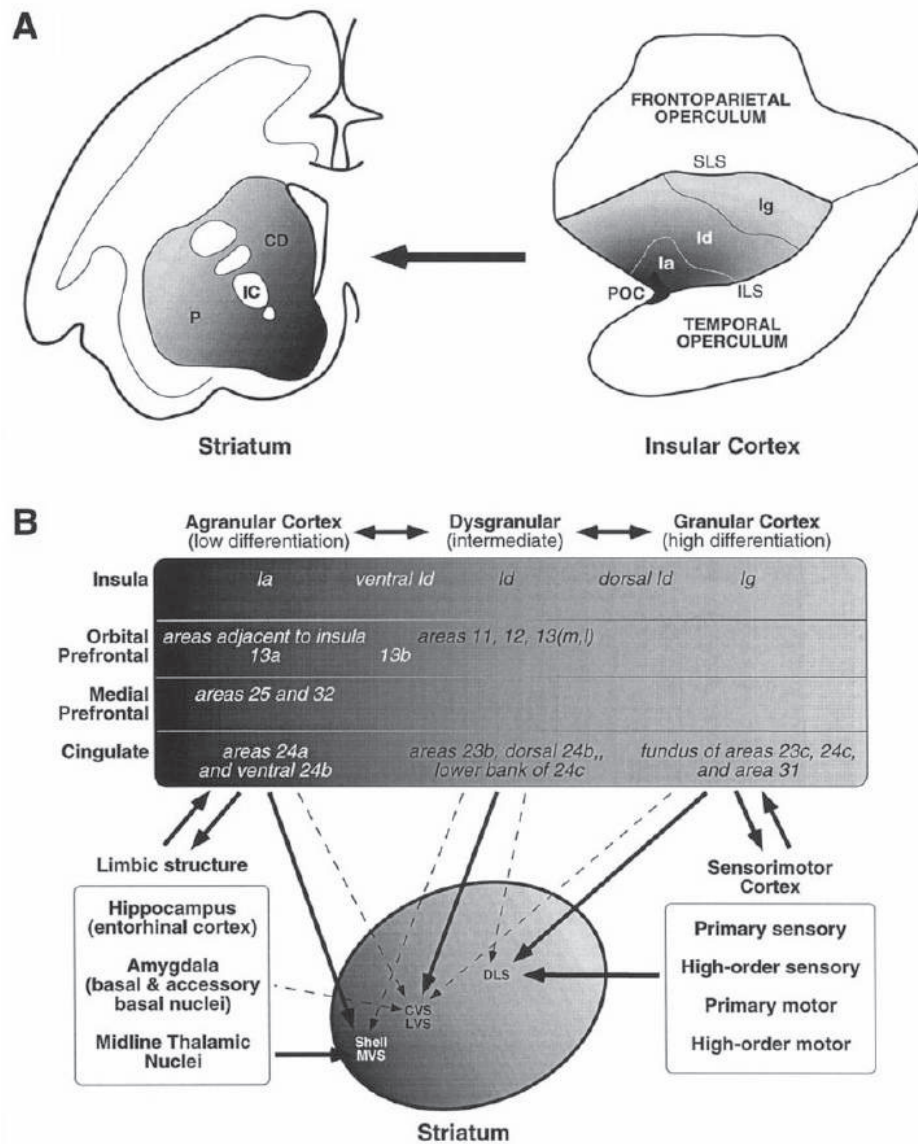


Figure 2 Diagram from Chikama *et al.* (1997) illustrating the progressive continuum of interconnections between regions of the striatum and insular cortex. The posterior granular insula projects to the dorsolateral striatum which both govern sensorimotor function. The intermediate dysgranular insula projects to both dorsolateral and more ventral striatal subdivisions involved in cognitive processes. The anterior agranular insula projects primarily to the ventral striatum, both of which are involved in affective and limbic functions. P, putamen; IC, internal capsule; CD, caudate nucleus; CVS, central ventral striatum; LVS, lateral ventral striatum; DLS, dorsolateral striatum; SLS, superior limiting sulcus; Ia, agranular insula; Id, dysgranular insula; Ig, granular insula; POC, piriform olfactory cortex; ILS, inferior limiting sulcus.

projections carrying visceral and interoceptive information. The connections in the posterior insula to posterior and dorsal basal ganglia, as well as the thalamus support its role in sensorimotor processing. The anterior agranular insula is highly interconnected with a number of cortical regions involved in cognition, decision-making and emotion. It has bidirectional interconnections with the orbitofrontal cortex, amygdala, hippocampus, dorsolateral prefrontal cortex and anterior cingulate cortex (Mesulam and Mufson, 1982a, b; Flynn *et al.*, 1999).

Cognition and the insula in Parkinson's disease

Accumulating research suggests that the anterior insula plays a central role in directing cognitive processes. It has been shown, often in conjunction with the anterior cingulate cortex, to allow for switching between brain networks required for executive functioning (Seeley *et al.*, 2007; Menon and Uddin, 2010). Additionally, the anterior

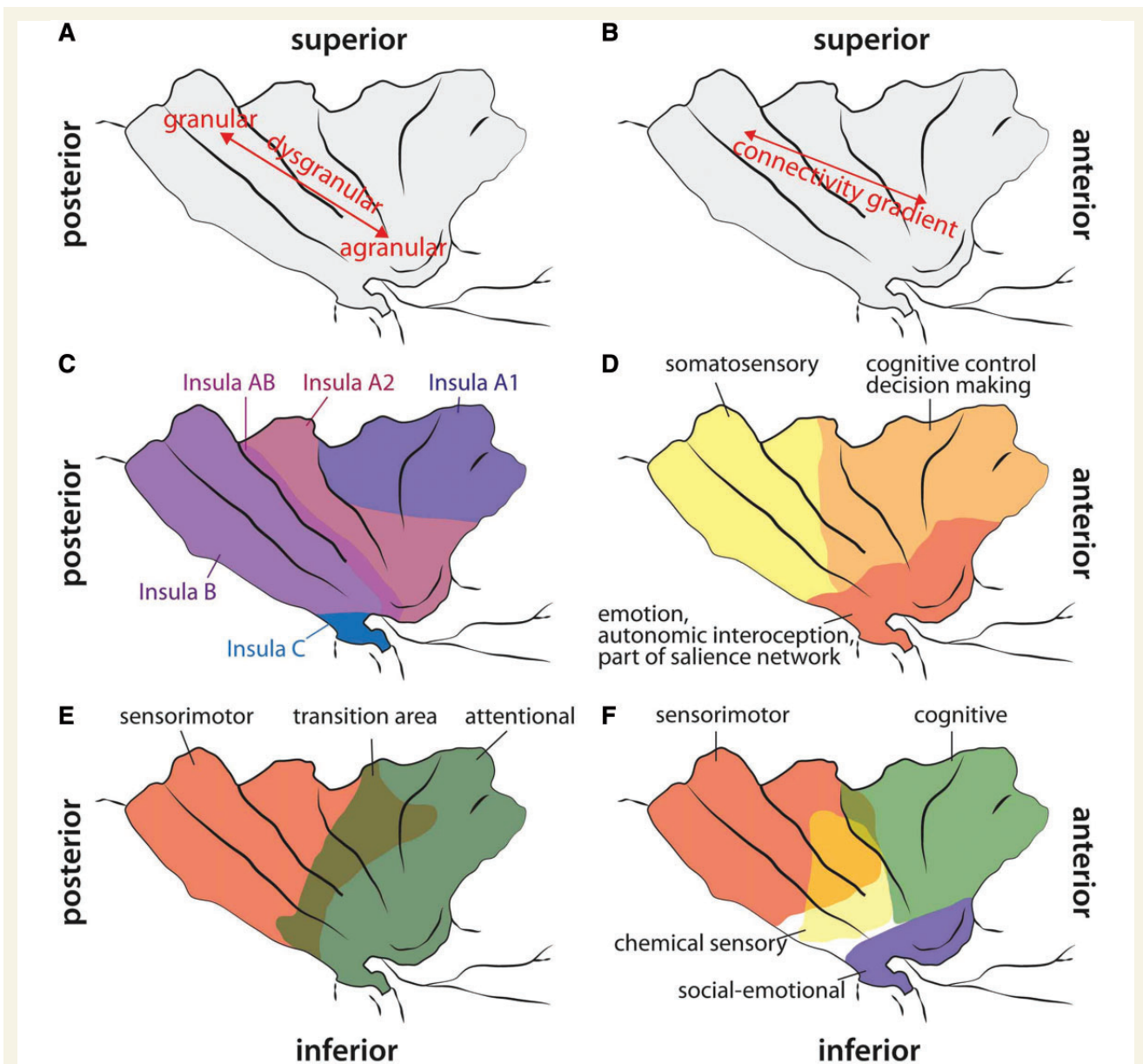


Figure 3 Illustration of various classifications of insular subdivisions. (A and C) Cytoarchitectonic maps of the insula; (B) the connectivity gradient in the insula. (D–F) Different functional subdivisions of the insula. The anterior subdivision is involved in cognition, affective and chemosensory processing, whereas the posterior division is involved in somatosensory and autonomic processing. Image from Klein *et al.* (2013).

insula is highly involved in complex social interactions that require interoception, self-awareness and the incorporation of both emotional and environmental stimuli (Craig, 2009) (Fig. 4). Patients with Parkinson's disease experience a wide range of cognitive difficulties that may progress to full-blown dementia (Litvan *et al.*, 2012). Cortical regions including the dorsolateral prefrontal cortex, anterior cingulate cortex and ventrolateral prefrontal cortex show abnormal activation in patients with Parkinson's disease related to executive functioning, and thus are of interest in potentially underlying cognitive changes (Monchi *et al.*, 2004, 2007). In patients with

Parkinson's disease, the insula has been found to have abnormal activation patterns during cognitive tasks (Monchi *et al.*, 2004; Shine *et al.*, 2013), and its dorso-anterior portion is functionally connected with the anterior cingulate cortex and dorsolateral prefrontal cortex, which are consistently involved in cognitive processes (Chang *et al.*, 2013). Few studies have set out to investigate the insula, and its role has not been discussed in the context of contributing to cognitive decline in Parkinson's disease. Thus, abnormalities in the insula are likely under-reported. It has recently been shown that those patients with mild cognitive impairment also have

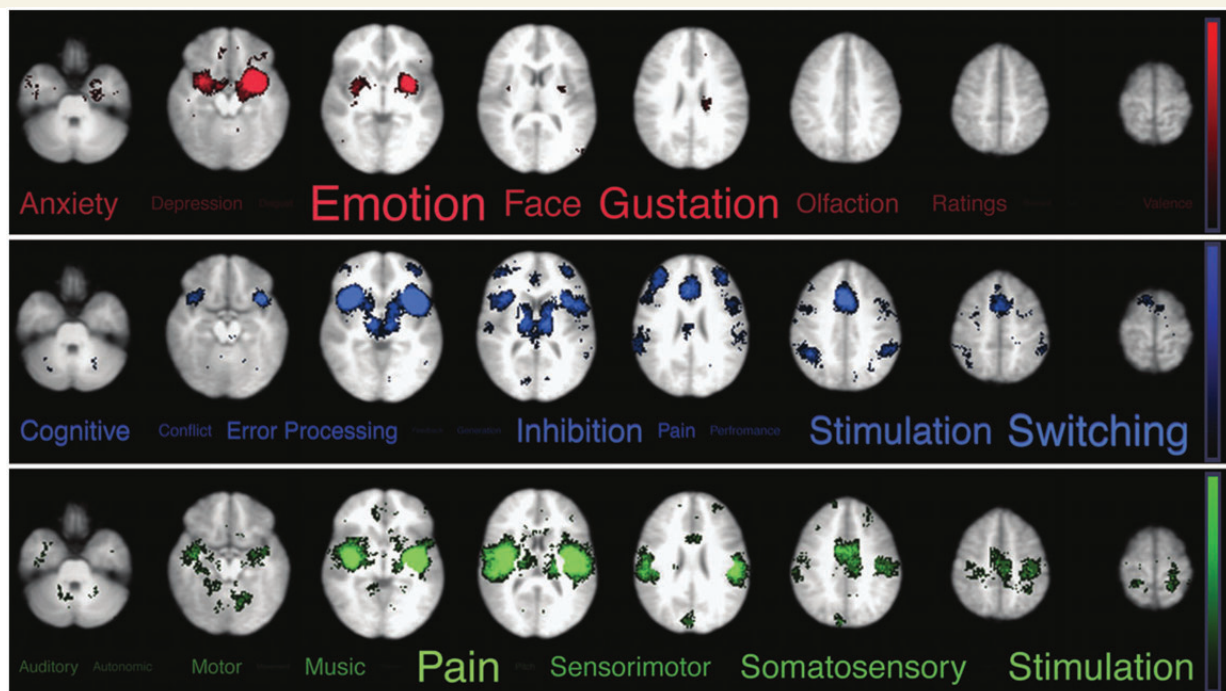


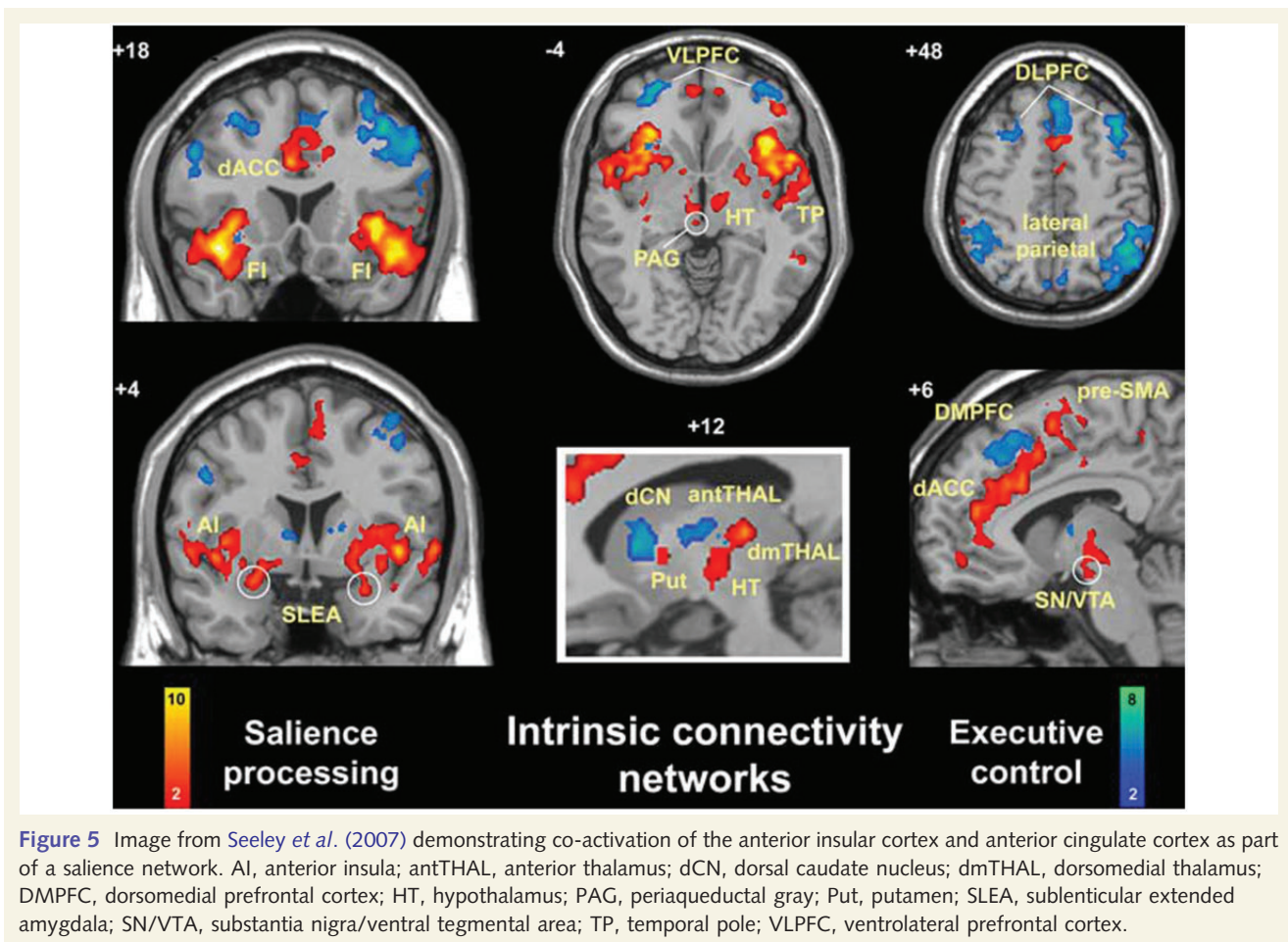
Figure 4 Image adapted from [Chang et al. \(2013\)](#) demonstrating terms most strongly associated with activation in various insular subdivisions (strength of association represented by size and opacity of the word). The dorsal anterior (blue) and ventral anterior (red) insula are most strongly associated with cognitive flexibility and emotion, respectively, whereas the posterior division is involved in pain and somatosensation.

deficits in social cognition, whereas those without cognitive impairment, do not ([Anderson et al., 2013](#)). Due to the close proximity in anatomical location of cognitive and socio-emotional regions in the anterior insula, it is reasonable that pathological processes affecting the anterior insula could disrupt both cognitive and social function. Now that the cognitive role of the insula is becoming more prevalent in the literature, it will be important to investigate its role in Parkinson's disease and how its dysfunction could lead to disruptions in cognition and eventually dementia.

The anterior cingulate cortex and insula are functionally and structurally connected, and have recently been described as part of a 'salience network,' due to their consistent activation during cognitively demanding tasks, and the ability of this network to switch between brain networks involved in cognition, including the central executive and default-mode networks ([Seeley et al., 2007](#)) ([Fig. 5](#)). Thus, it is crucial to consider the role of the insula as part of a network interacting with other brain regions. The strong connectivity of these regions in humans is reflected by the presence of unique von Economo neurons, which are large bipolar neurons interconnecting the anterior cingulate cortex and anterior insula in humans and chimpanzees, thought to rapidly transmit information related to cognition and awareness ([Allman et al., 2010](#)). Patients with Parkinson's disease with cognitive deficits not meeting criteria for dementia, are described as having Parkinson's disease with mild cognitive impairment and are at an increased risk for developing dementia ([Caviness et al., 2007](#)). A recent study conducted by our group investigating

dopaminergic contributions to Parkinson's disease with mild cognitive impairment using PET imaging ([Christopher et al., 2013](#)), found that these patients have more severe striatal dopamine depletion than both healthy control subjects and cognitively normal patients with Parkinson's disease. The level of dopamine depletion was correlated with loss of D2 receptor availability in the right anterior insula. Patients with Parkinson's disease with mild cognitive impairment also showed reduced D2 receptor availability in the bilateral insula compared to healthy controls and cognitively normal patients. Furthermore, the D2 receptor availability in the right anterior insula was directly proportional to executive performance in a neuropsychological test battery ([Fig. 6](#)). These findings demonstrate that striatal dopamine depletion, which is a hallmark of Parkinson's disease, is associated with a loss of dopaminergic modulation in the insula in Parkinson's disease with mild cognitive impairment, and in turn that insular dopamine modulation is directly related to executive abilities. We concluded that both striatal and insular dopamine dysfunction underlie executive impairment, and that such a loss likely disrupts normal function of the insula as a cognitive hub, and as a key region of the salience network in patients with Parkinson's disease and mild cognitive impairment.

A recent study investigating potential mechanisms underlying visual misperceptions in Parkinson's disease found that the inability to activate the anterior insula was related to impaired viewing of bistable images ([Shine et al., 2013](#)). The authors concluded that dysfunctional attentional networks involving the insula could



underlie visual misperceptions or hallucinations, which are common problems in Parkinson's disease, especially but not exclusively related to antiparkinsonian medications. The insula is also highly involved in social behaviour, and thus it seems appropriate that it possesses both cognitive and emotional processing abilities. For example, it is involved in emotional processes such as disgust, which may emanate from social encounters. One study investigating the ability of patients with Parkinson's disease to recognize facial emotions, found that patients had an impaired ability to recognize disgust on the faces of others (*Suzuki et al., 2006*). The authors claimed that dysfunction of the insula is a likely reason for this impairment based on previous findings demonstrating that insular lesions do in fact impair the recognition of facial emotions (*Calder et al., 2000*). This is also in agreement with evidence for dysfunction of the anterior insula in disorders such as autism and schizophrenia, where the ability to perceive and relate to the emotions of others is significantly impaired (*Uddin and Menon, 2009; White et al., 2010*).

The mid-to-dorsal anterior insula is normally highly functionally connected to the pre-supplementary motor area in healthy people (*Chang et al., 2013*), which is a brain region crucial for integrating information for the preparation of movements. Thus, relevant information obtained from cognitive processes is made available for selecting actions. The right mid-anterior insula has reduced functional

connectivity to the pre-supplementary motor area in patients with Parkinson's disease compared with healthy controls (*Wu et al., 2011*). Although this region is involved in motor control, such a loss of connectivity could impact the effective incorporation of higher order cognitive information into the selection of behaviours. Resting state functional connectivity analysis of the anterior insula shows high connectivity with the inferior temporal and anterior cingulate cortex (*Cauda et al., 2011*), which are also crucial regions for cognitive function. Interestingly, these are some of the first and most affected cortical regions by alpha-synuclein deposition according to Braak's staging hypothesis (*Braak et al., 2006*). The insula is not only one of the first cortical regions to be pathologically affected in Parkinson's disease, but also in other neurodegenerative diseases, including Alzheimer's disease and frontotemporal dementia (*Chu et al., 1997; Braak et al., 2006; Seeley, 2010*). In non-parkinsonian patients with amnesic mild cognitive impairment, it was shown that anterior insular connectivity to brain regions, including the inferior frontal gyrus, pre-supplementary motor area, anterior cingulate cortex, inferior parietal cortex, caudate, putamen, thalamus, and hippocampus, was significantly reduced compared to healthy control levels (*Xie et al., 2012*). Thus cognitive function, including memory, may be reliant on intact functional brain networks including the insula. A more severe loss of insular function may have a profound effect on self-awareness and thus appropriate

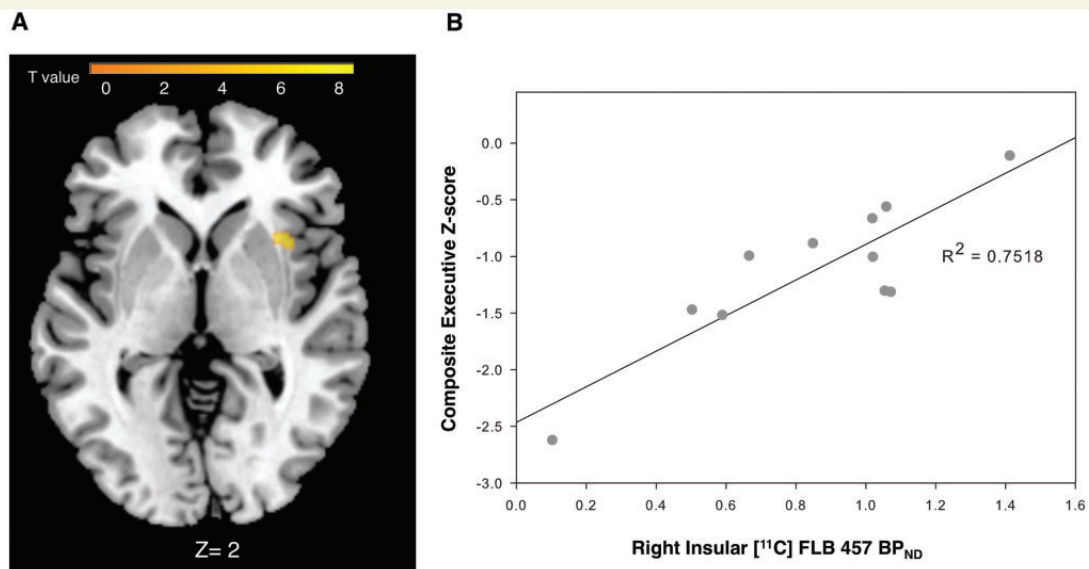


Figure 6 Image from Christopher *et al.* (2013) showing a direct linear relationship between D2 receptor availability and executive performance in the right anterior insula of patients with Parkinson's disease with mild cognitive impairment.

behaviour, which is often severely impaired in neurodegenerative disease. Although not specifically investigated in Parkinson's disease, patients with frontotemporal dementia have a loss of von Economo neurons; the large bipolar neurons interconnecting the anterior cingulate cortex and insula in humans (Seeley *et al.*, 2006). Pathological changes in the insula affecting these neurons may have an impact on self-awareness and cognitive function in Parkinson's disease. Further investigation into insular pathology and its impact on cognition in Parkinson's disease is clearly needed.

The insula and affective and behavioural symptoms

The insula was originally thought of as a limbic cortical structure, and has a well-established role in processing affect and emotion. The ventro-anterior portion of the insula is functionally connected to limbic areas including the amygdala, superior temporal sulcus, postero-lateral orbitofrontal cortex and the ventral tegmental area (Chang *et al.*, 2013). It also becomes engaged in situations involving the evaluation of risk and uncertainty (Paulus *et al.*, 2003; Rudolf *et al.*, 2012). The insula has been reportedly involved in contributing to depression, and insular activity may aid in predicting outcomes of depression treatment (Sprengelmeyer *et al.*, 2011; McGrath *et al.*, 2013). Patients with Parkinson's disease experience a wide range of non-motor behavioural symptoms such as depression, anxiety and fatigue, which could in part be related to dysfunction of the insular cortex. In a PET imaging study investigating depression in patients with Parkinson's disease, it was found that serotonin 1A receptor availability was reduced in depressed patients with Parkinson's disease in the right insula compared to non-depressed patients with Parkinson's disease

(Ballanger *et al.*, 2012). Receptor availability was also reduced in the left hippocampus, left superior temporal cortex and orbitofrontal cortex compared with non-depressed patients with Parkinson's disease. These changes in depressed patients with Parkinson's disease could potentially contribute to limbic dysfunction. Although not well explored in Parkinson's disease, the insula is known to be interconnected with the amygdala, and the level of connectivity is directly related to trait anxiety (Baur *et al.*, 2013). The amygdala is also a limbic region highly affected by alpha-synuclein deposition in Parkinson's disease (Braak *et al.*, 1994). Thus, the symptoms of anxiety frequently seen in patients with Parkinson's disease could be related to dysfunction of this amygdala-insula pathway. More research investigating the neural correlates of anxiety in Parkinson's disease is needed to determine key brain regions associated with this psychiatric symptom.

Central fatigue, another common non-motor symptom in Parkinson's disease, affects patients' ability to sustain mental and physical tasks. Fatigue is difficult to study in patients with Parkinson's disease as its symptoms can overlap with psychiatric disturbances such as depression (Friedman *et al.*, 2007). However, it is clear that fatigue occurs in patients with no evidence of psychiatric illness as well. Additionally, mental fatigue, which is characterized by deficits in sustaining attention and vigilance, may be associated with cognitive impairment (Friedman *et al.*, 2007). A PET imaging study investigating serotonergic and dopaminergic function in relation to fatigue in Parkinson's disease found that serotonin transporter availability was reduced in the insula (left and right, whole insula), anterior cingulate cortex, striatum and thalamus in patients with fatigue (Pavese *et al.*, 2010). The authors also reported reduced ^{18}F -DOPA uptake in the left caudate and insula (mid-posterior) of patients with Parkinson's disease with fatigue versus those without fatigue. They concluded that insular

dopaminergic and serotonergic dysfunction could contribute to symptoms of fatigue in Parkinson's disease.

The anterior insula is a key region involved in the experience of empathy. This can be considered an affective function, however 'perspective-taking' must also be involved which may require cognitive functions such as attention, working memory and cognitive flexibility in social situations (Leigh *et al.*, 2013). It is well known that patients with Parkinson's disease have an apathetic disposition, characterized by a dulled sense of emotion, which can have a significant impact on daily life (Pluck and Brown, 2002). In a recent study examining the metabolic basis of apathy in non-demented and non-depressed patients with Parkinson's disease, it was found that cerebral metabolism measured with PET in the right anterior insula as well as right inferior frontal gyrus, right middle frontal gyrus, and right cuneus, was positively correlated with apathy scores (Robert *et al.*, 2012). A loss of normal metabolic activity in insular neurons in Parkinson's disease could contribute to the blunting of emotion frequently observed in patients with Parkinson's disease. High apathy scores have also been shown to correlate with lower grey matter density in the bilateral insula of patients with Parkinson's disease, as well as the bilateral inferior parietal gyrus, the bilateral inferior frontal gyrus, the right (posterior) cingulate gyrus and the right precuneus (Reijnders *et al.*, 2010). Considering the insula as a central hub for emotional awareness, it is likely that dysfunction of this region would be associated with a lack of motivation in patients with Parkinson's disease. This is in agreement with studies showing that damage or atrophy in the insula can result in apathy, blunted emotional responses during risky decision-making (Case *et al.*, 2009; Weller *et al.*, 2009), or the finding that patients with Parkinson's disease have a reduced ability to recognize facial emotions of others (Suzuki *et al.*, 2006).

In addition to experiencing depression or apathy, anywhere from 6–15.5% of patients with Parkinson's disease develop impulse control disorders and related compulsive disorders such as hobbyism, punding and dopamine dysregulation syndrome, which are typically due to dopaminergic medication (Callesen *et al.*, 2013). Impulse control disorders in Parkinson's disease have been suggested to be attributable to altered activity of the mesocorticolimbic dopamine system (Steeves *et al.*, 2009; van Eimeren *et al.*, 2009; Ray *et al.*, 2012). In a PET imaging study using a high affinity D2 receptor antagonist radioligand to measure cortical D2 receptor availability, it was found that novelty seeking, a trait associated with impulsive behaviour, was negatively correlated with D2 receptor availability in the insula (Kaasinen *et al.*, 2004). Thus, baseline dopaminergic modulation in the insula may affect the propensity of patients with Parkinson's disease to behave impulsively in response to medication. In another study investigating impulsivity, patients with Parkinson's disease with pathological gambling showed significant negative correlations between gambling severity and regional cerebral blood flow in prefrontal, limbic, temporal, and striatal regions as well as the bilateral anterior insular cortices (Cilia *et al.*, 2011). Although a major finding of this study was disconnectivity of the striatum from the anterior cingulate cortex in Parkinson's disease gamblers, patients with Parkinson's disease both with and without pathological gambling also showed a diminished connectivity of the insula to the

posterior cingulate gyrus and parahippocampal gyrus, respectively, compared with healthy controls (Cilia *et al.*, 2011). Thus, diminished connectivity in the insula with other key regions involved in evaluating risk and executing behaviours could affect impulse control in Parkinson's disease. As previously mentioned, patients with Parkinson's disease often show a blunted emotional response. Consistent with this, is the observation that patients with Parkinson's disease have increased levels of alexithymia, a condition characterized by difficulty expressing emotions, compared with healthy control subjects (Costa *et al.*, 2010). Interestingly, alexithymia in Parkinson's disease was recently found to significantly correlate with self-reported impulse control disorders, and patients with alexithymia had significantly higher levels of impulse control disorders than non-alexithymic patients (Goerlich-Dobre *et al.*, 2014). Thus, dysfunction in the insula affecting emotional processing may also increase the likelihood of problems with impulse control in Parkinson's disease. The normal role of the insula in processing mood states and impulsive behaviours in healthy individuals is not well understood, and therefore more research is needed to better disentangle the role of the insula in affective processes.

Posterior insula and disruptions in bodily awareness

Experimental studies in non-human primates have shown that the insular cortex receives afferents from the dorsal thalamus, which processes information from the brainstem and spinal cord (Mufson and Mesulam, 1984; Mesulam and Mufson, 1985). This information is related to conscious awareness of head motion, balance, perception, pain, temperature, gustatory and viscerosensory information. The insula receives afferents from several sensory cortical areas, including somatosensory cortex, somatosensory association areas, primary vestibular areas and auditory association areas (Nieuwenhuys, 2012). The mid to posterior insula has been frequently implicated in the processing of awareness with relation to the position, movement and sensation of the body, and is functionally connected to the supplementary motor area and somatosensory cortex (Chang *et al.*, 2013). This interoceptive information of how the body 'feels' is constantly incorporated into cognitive, social and emotional processes in order to execute behaviour (Craig, 2002). Thus, awareness of bodily sensations and cognitive functions are not distinct, but rather are integrated into behaviour through the insula. For example, the posterior insula is thought to play an integral role in distinguishing one's own body from the bodies of others (Heydrich and Blanke, 2013).

Patients with Parkinson's disease often experience disturbances in sensory perceptions of the body (Koller, 1984). One crucial function of the posterior insula related to bodily sensation is its involvement in the processing of pain. Awareness of pain is critical, as it allows for rapid action in response to threatening situations. In a study examining pain thresholds in patients with Parkinson's disease with H₂O PET, it was found that patients with Parkinson's disease OFF medication experience lower pain thresholds,

associated with increased activation in the right insular cortex, as well as prefrontal cortex and anterior cingulate cortex (Brefel-Courbon *et al.*, 2005). However, when ON L-DOPA medication this activation was within the normal range. This established that in patients with Parkinson's disease, dopamine has a modulating effect on insular activation in response to pain. This may hold true not only for painful stimuli, but the processing of other sensory stimuli that have an impact on behaviour. Additionally, the anterior insula may use contextual information combined with somatosensory information from the posterior insula, producing a subjective experience or perception of events. For example, one study examining how the insula is involved in pain perception, found that anterior insular activity correlated with the significance of a stimulus (i.e. highly threatening versus low threat), and that this was related to the subject's perception of how painful the stimulus was (Wiech *et al.*, 2010). Abnormal salience processing in the anterior insula could also affect how sensations are perceived in patients with Parkinson's disease.

Patients with Parkinson's disease have considerable difficulty in executing coordinated movement. They also have reduced performance on tests of kinaesthesia, which is the ability to perceive the motion and position of the body in space (Jobst *et al.*, 1997). The mid and posterior insula are essential for awareness of bodily movements and thus for coordinated motion. For example, the mid-insula becomes activated during the experience of agency or control over one's actions (Farrer and Frith, 2002). Patients with Parkinson's disease show increased gait-induced activation in the right posterior insula (as well as left cingulate and temporal cortices) when walking on a treadmill compared to healthy control subjects (Hanakawa *et al.*, 1999). This increased activation could be due to dysfunctional regulation of cortical activity, or the result of compensatory activation. Activation in the insula associated with bodily awareness may be necessary for coordinating movements effectively. The insula is also thought to be involved in the perception of time, and timing of movements. Patients with Parkinson's disease required to synchronize movements show increased activation in the right insula among other regions compared with healthy control subjects (Cerasa *et al.*, 2006). This increased activation could be related to the greater difficulty they experience in effectively timing synchronized movement, or compensatory activation. Thus, mid and posterior insular cortex serve a crucial role in interoceptive sensation and behaviour, and should be further considered in understanding the complex neurobehavioural disturbances of Parkinson's disease.

The insula and autonomic dysfunction

In particular, the posterior part of the insula processes visceral and autonomic information. As mentioned previously, this autonomic information from the body is incorporated into cognitive, social and emotional processes, to aid in effective decision-making and behaviour (Beissner *et al.*, 2013). For example, patients with peripheral autonomic denervation have reduced insula activity related to fear conditioning (Critchley *et al.*, 2002). This demonstrates

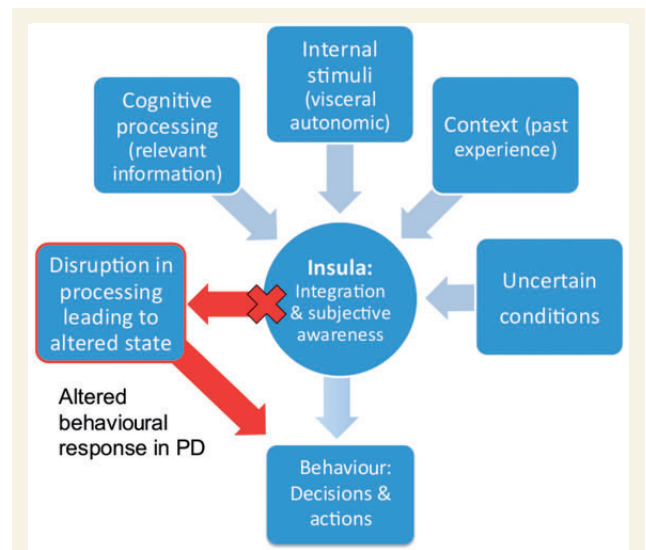


Figure 7 Chart demonstrating integration of information in the insula for adaptive behaviour. The insula processes cognitive, affective and interoceptive information in uncertain conditions, while taking past experiences into context to generate a subjective feeling or state of awareness. A disruption of input to the insula or integration of these components may alter the subjective state and ultimately behaviour in patients with Parkinson's disease (PD).

how the insula integrates autonomic information relevant to the current state of the body with environmental cues to guide behaviour. Such autonomic input is crucial for preparation to act in various situations whether they are threatening, challenging or emotionally salient. Thus, the seemingly disparate functions of the insula can be unified into a framework that describes its overall purpose as integration of cognitive, affective and interoceptive information in various environmental conditions to create a state of subjective awareness (Fig. 7). Autonomic functions have been shown to directly relate to emotional states and subjective experience. The constriction of the gut in response to stress or the increase in heart rate when anxious, among other bodily states of arousal, are examples of how autonomic changes in the body directly relate to emotional states, and how these enter conscious awareness (Critchley, 2005). These 'somatic markers' as proposed by Damasio and colleagues (1996), are thought to act as 'gut feelings' that guide adaptive behaviour. The loss of awareness, or dampening of these feelings that enter subjective awareness could negatively affect behaviour in neurodegenerative disease, such as Parkinson's disease (Fig. 7). However, there is little evidence from neuroimaging studies of dysfunctional autonomic processing at the cortical level in patients with Parkinson's disease.

In Parkinson's disease, the autonomic nervous system is severely affected by Lewy pathology throughout the sympathetic ganglia and parasympathetic nuclei (Wakabayashi and Takahashi, 1997). Pathological changes in the insula could also play a role in autonomic dysfunction, or 'dysautonomia' in Parkinson's disease (Siddiqui *et al.*, 2002). Dysautonomia in Parkinson's disease can

include bladder disturbances, sweating abnormalities, and orthostatic hypotension. Autonomic dysfunction is typically associated with advanced stages of the disease, although it may also occur in the early disease stages (Bonnet *et al.*, 2012), and has a significant impact on daily life (Magerkurth *et al.*, 2005). The insula is known to be involved in autonomic arousal, including cardiovascular arousal. For example, insula (right in particular) activation correlates with mean arterial blood pressure and heart rate during mental stressor tasks or exercise (Critchley *et al.*, 2000). A post-mortem study in Parkinson's disease showed that Lewy body densities in the left posterior insular cortex were significantly higher in patients with Parkinson's disease with orthostatic hypotension than those without orthostatic hypotension. This group difference was not observable in other cortical areas such as the temporal or parietal cortex (Papapetropoulos and Mash, 2007). However, the pathogenesis of orthostatic hypotension is also associated with degeneration of the peripheral autonomic nervous system (Jain and Goldstein, 2012), which may even precede the classical motor symptoms of Parkinson's disease (Goldstein *et al.*, 2012). Studies investigating the neural correlates of autonomic dysfunction in Parkinson's disease are scarce, and thus there is little evidence at the moment for a clear link between dysautonomia and aberrant insula function in Parkinson's disease. More research is needed to determine the potential contribution of the insula to autonomic symptoms in Parkinson's disease.

The somatosensory regions for processing olfaction and taste reside in the ventro-anterior insula adjacent to somatosensory and viscerosensory cortex from other areas of the body (De Araujo *et al.*, 2003; Ogawa *et al.*, 2005). Although there is little neuroimaging evidence of insular involvement in olfaction or gustation in Parkinson's disease, it should be noted that a loss of smell and taste, in particular the loss of smell is one of the first and even presymptomatic signs of Parkinson's disease (Doty *et al.*, 1992). This is likely due to the olfactory bulb being affected by alpha-synuclein deposition early in the disease process (Hawkes *et al.*, 1997); however, the loss of input to the olfactory and gustatory areas in the insula may also propagate these symptoms and affect chemosensory function in Parkinson's disease. More work will be needed to elucidate the role of the insular cortex in association with chemosensation in patients with Parkinson's disease.

Conclusions and future directions

The insula has been under-recognized as a key region involved in the pathogenesis of non-motor symptoms in Parkinson's disease. There is accumulating evidence that the insula plays a crucial role in cognitive, affective, somatosensory and autonomic processes, and thus abnormalities in the insula found in neuroimaging studies of patients with Parkinson's disease should be considered and explored in greater detail. The insula is substantially affected by alpha-synuclein deposition in Parkinson's disease, and shows altered functional connectivity as well as abnormalities in dopaminergic and serotonergic function related to cognitive and

affective symptoms. There is evidence that abnormal insular activity may be related to a range of non-motor symptoms, including somatosensory disturbances. Now that the insula is known to be a central hub involved in integrating diverse information for behavioural processes, it should be considered as a region of interest when investigating cognitive and behavioural changes, as well as disruptions in viscerosensory or somatosensory processes in Parkinson's disease.

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