Contributions of the fronto-striatal network to executive functions: Transcranial magnetic stimulation - positron emission tomography studies

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ABSTRACT

One of the important processes involved in working memory is the monitoring of information held in memory. Monitoring refers to the tracking of different events that may have occurred at different times or places in order to make a decision or perform an action. It is required at times when executive tasks are involved, such as set-shifting tests. Indeed, in order to perform a set-shift, one often needs to keep track of the remaining available rules. Recently, fMRI studies have demonstrated that the dorsolateral prefrontal cortex (DLPFC) plays an important role in the monitoring of information held in working memory. However, imaging studies can only provide neuronal correlates of cognitive performance, without establishing their causal relations.

Here we assessed the role of the right DLPFC in monitoring using repetitive transcranial magnetic stimulation (rTMS) to disrupt on-going processes within a given cortical region. When rTMS was applied to the right DLPFC during feedback reception on their previous response, the subjects' WCST performance deteriorated. This was not the case when rTMS was applied during other stages of executive processing. This result is consistent with the proposed role of the right DLPFC in the monitoring of events in working memory.

Second, we investigated the functional role of the left DLPFC during set-shifting, and its modulatory effect on the striatal dopaminergic system. We

applied continuous theta burst stimulation, a newly proposed rTMS methodology, to the left and right DLPFC while subjects underwent positron emission tomography (PET) with [^{11}C]raclopride. Stimulation of the left DLPFC, which transiently disrupted its function, impaired Montreal-Card-Sorting-Task (MCST) performance and affected dopamine release in the striatum. In contrast, right DLPFC stimulation had no significant effect on behaviour and striatal dopamine release.

Lastly, in order to investigate cortical dopamine transmission during executive function, we used PET with [^{11}C]FLB 457. We observed significantly more dopamine release in the right anterior cingulate cortex (ACC) when subjects performed the MCST than during the control task. These findings are consistent with previous fMRI studies which demonstrate ACC activation in similar tasks involving conflict of monitoring.

In summary, these studies provide important insights on the mechanisms of executive functions of the human brain *in vivo*, and shed some light on the origin of executive deficits underlying certain neurological disorders associated with prefrontal and/or dopamine dysfunction, such as Parkinson's disease or schizophrenia.

ABRÉGÉ

Il a récemment été démontré par l'IRMf que le cortex préfrontal dorsolatéral (CPFDL) droit voyait son activité augmenter autant lors de la présentation de feedbacks négatifs que positifs dans une tâche classique d'appariement de cartes (Wisconsin-Card-Sorting-Task –WCST-). Il a également été montré que le CPFDL gauche, en conjonction avec le striatum, voyait quant à lui son activité augmenter uniquement lors de la présentation de feedbacks négatifs. Ces patrons d'activation sont compatibles avec leur présumé rôle respectif dans le monitoring des informations maintenues en mémoire et dans le changement de règle (set-shifting). Cependant, les études d'imagerie procurent uniquement les corrélats neuronaux de la performance cognitive, pas leurs relations de causalité.

Dans ce travail nous avons testé le rôle du CPFDL droit dans le monitoring au moyen de la stimulation magnétique transcrânienne par trains de potentiels (rTMS), une méthode permettant d'altérer de façon transitoire les traitements d'une région corticale ciblée. Lorsque la rTMS a été appliquée au CPFDL droit alors que les sujets recevaient des feedbacks associés aux réponses qu'ils venaient de donner, leur performance au WCST détériorait par rapport à une condition de contrôle (stimulation du vertex). Par contraste, l'application de la rTMS lors d'une tâche simple de couplage n'affectait pas les

performances. Ce résultat est compatible avec le rôle présumé du CPFDL droit dans le monitoring des événements en mémoire de travail.

Dans un deuxième temps, nous avons étudié le rôle du CPFDL gauche lors du set-shifting et sa relation avec le système dopaminergique striatal. Nous avons appliqué une nouvelle méthode de stimulation rTMS (theta burst) au CPFDL gauche et droit en conjonction avec une analyse de l'activité cérébrale par tomographie par émission de positrons (TEP) utilisant le radioligand dopaminergique [^{11}C]raclopride. Nous avons observé que la stimulation du CPFDL gauche, tout en affectant de façon transitoire la performance dans une tâche d'appariement nommée Montreal-Card-Sorting-Task (MCST), était accompagnée d'une libération de dopamine dans le striatum alors que la stimulation du CPFDL droit ne générait aucun effet significatif.

Enfin, de façon à analyser la transmission dopaminergique corticale dans cette fonction exécutive, nous avons mis en œuvre une nouvelle étude en TEP utilisant le ligand [^{11}C]FLB 457. Nous avons observé une libération significative de dopamine dans le cortex cingulaire antérieur droit (CCA) lors de la réalisation de la MCST par rapport à une condition de contrôle. Ce résultat, pris ensemble avec d'autres travaux utilisant l'IRMf, confirme que l'activation du CCA dans ce type de tâche est liée au monitoring de conflit.

En résumé, nos résultats apportent un nouvel aperçu des mécanismes cérébraux mis en jeu dans les fonctions exécutives. Ils offrent en outre de nouvelles perspectives concernant l'origine des déficits exécutifs sous-tendant les affections neurologiques associéés aux dysfonctions préfrontales et/ou dopaminergiques comme la schizophrénie ou la maladie de Parkinson.

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Encouraged by my mentors and family, I decided to study abroad, and therefore applied to the graduate program in neurological science at McGill University. Dr. Antonio P. Strafella reviewed my application and accepted to be my supervisor despite my lack of neuroscience background. He kindly answered all my beginner's questions and guided me to form the fundamental concepts of cognitive neuroscience. He gave me many opportunities to participate in other on-going projects and to collaborate with visiting researchers Dr. Igor Sibon and Dr. Takuya Hayashi, who gave me important insights on other fields of cognitive neuroscience.

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CONTRIBUTIONS OF AUTHORS

In accordance with McGill Faculty of Graduate Studies and Research guideline for manuscript-based thesis, the contributions of each author need to be explicitly stated, and are hence summarized below.

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TABLE OF CONTENTS

LIST OF FIGURES

Chapter 1

Introduction

On a daily basis, we are constantly faced with changing circumstances that require planning and generation of novel actions. The abilities we call upon in order to respond accurately to new situations are often referred to as 'executive functions' and are frequently used for managing conditions where routine activation of behavior would not be sufficient for optimal performance and in which top-down control is needed to modify behavior. Executive processes are cognitive mechanisms by which performance is optimized in situations requiring the simultaneous operation of a number of different processes (Baddeley, 1986). However, due to the complex nature of executive networks (Gazzaniga et al., 1998), it is unclear how different cortical and subcortical neural systems interact with each other and contribute to executive function. Several aspects of executive function have been described, including among others planning and initiating sequences of responses, cognitive flexibility, abstract thinking, rule based regulation of behavior, inhibiting inappropriate actions and selecting relevant sensory information.

"Patients are the greatest teachers of the cognitive neuroscience."

Dr. Brenda Milner, 1918 -

As often emphasized by Dr. Brenda Milner through extensive lesion studies in patients and non-human primates in the past several decades, we now know that the prefrontal cortex and the striatum form the key anatomical structures necessary for executive functions (Hazy et al., 2007; Petrides, 2005; Stuss and Alexander, 2007). Due to significant evolutionary differences, however, such as the unavailability of verbal instructions, critical controversies arise when one extrapolates findings from animal to human studies. Because there are large non-homogeneities and compensatory mechanisms after lesions, there is also great difficulty in depicting how exactly executive functions "reside" in the human brain.

Thanks to the recent development of human brain mapping techniques, it is now possible to investigate the human brain with a very high spatial and temporal resolution, all the while with minimally invasive procedures. One of the most popular and widely available methods is functional magnetic resonance imaging (fMRI). With this technique, one can observe changes in blood oxygen level dependency (BOLD), which are correlated with blood flow in response to

manipulative stimuli or to the subject's responses, with an approximate resolution of 3 mm^3 and 2-3 seconds.

For example, Monchi et al. (2001) previously showed how sub-structures of the prefronto-striatal network contribute to sub-processes of executive functions during the Wisconsin Card Sorting Task (WCST), a widely used neuropsychological test that assesses executive performance. The right dorsolateral prefrontal cortex (DLPFC, Brodmann area (BA) 9/46) was shown to be involved with monitoring information held in working memory during the feedback period of the WCST, whether the feedback was positive or negative, while the left DLPFC was only engaged in the processing of negative feedback, i.e., the planning of a set-shift. This was in accord with other fMRI-WCST studies (Konishi et al., 2002; Lie et al., 2006) and human lesion studies (Stuss and Alexander, 2007). Results show bilateral caudate nucleus activation in conjunction with the left DLPFC only when the subject received negative feedback. The involvement of the caudate nucleus during executive performance follows nicely with the well-described cortico-striato-pallido-thalamo-cortical loop proposed by Alexander et al., (1986). According to this hypothesis, the DLPFC-caudate circuitry plays an important role in cognitive processes.

The involvement of the caudate nucleus in set-shifting processes was confirmed later by a fMRI study in which the authors used a variant of the WCST

that emphasizes the set-shifting component (i.e. the Montreal Card Sorting Task (MCST)) (Monchi et al., 2006b). However, while very informative, BOLD signal changes only estimate the oxygen consumption level in a given area; they do not elucidate the underlying neurochemical mechanisms of the set-shifting process. Using [^{11}C]raclopride, a dopamine D_2-receptor antagonist, during positron emission tomography (PET), Monchi et al., (2006a) showed that performing the MCST increased synaptic dopamine transmission in the bilateral caudate nucleus. This provided unique evidence of striatal dopaminergic involvement in the set-shifting process.

Functional neuroimaging studies (PET and fMRI) have provided great insights into the role of the DLPFC and striatum during the WCST and MCST. However, PET and fMRI studies can only provide neuronal correlates of a cognitive performance, not their causal relations (Rushworth et al., 2002; Walsh and Cowey, 2000). The specific functional relevance of the DLPFC and striatal dopamine release during card sorting tasks, then, remains to be established. With the available technology today, it is possible to modulate the activation of a given cortical area by using repetitive transcranial magnetic stimulation (rTMS) (Wassermann and Lisanby, 2001), and combining it with functional imaging techniques such as [^{11}C]raclopride PET. This provides us with a valuable probe

of brain function that is unparalleled in its ability to investigate and “dissect“ the prefrontal-striatal loops in awake, behaving, healthy human subjects.

However, while [^{11}C]raclopride offers important insight on the striatal dopamine neurotransmission during executive functions (Monchi et al., 2006a), its low affinity limits its application to extrastriatal low receptor concentration regions such as the prefrontal cortex (Goldman-Rakic et al., 2000). As revealed by studies in primates, despite a lower density of dopamine receptors in the cortex relative to the striatum, cortical dopamine also plays a critical role in executive functions (Murphy et al., 1996; Watanabe et al., 1997). In humans, converging evidence suggests that cortical dopamine is involved with high-level cognition. For example, it has been shown that the prefrontal function in executive processes is strongly influenced by the COMT-genotype, which plays an important role in regulating the prefrontal dopaminergic system (Foltynie et al., 2004; Goldberg et al., 2003; Winterer et al., 2006). In addition, while performing working memory tasks has provided evidence of increased dopamine release in the frontal cortex (Aalto et al., 2005a; Sawamoto et al., 2008), anterior cingulate cortex (ACC, BA 32/24) dopamine receptor density has been shown to be significantly correlated with healthy adults' performance level on the WCST as well (Lumme et al., 2007).

In order to elucidate the contribution of different prefrontal / subcortical regions and underlying neurochemical mechanisms associated with executive functions, this doctoral thesis will describe three studies. The specific objects are:

1) To confirm the role of the right DLPFC in the monitoring of information held in working memory during the performance of the WCST
2) To confirm the role of the left DLPFC-caudate network in set-shifting during the performance of the MCST
3) To demonstrate increased dopamine release in the prefrontal cortex during the performance of the MCST

The next chapter of this thesis gives a critical review of background literature, followed by three manuscripts that addressed the above-mentioned objectives. The final chapter provides a summary and an overall conclusion of this doctoral work.

Chapter 2

Background

2.1. Localizing executive functions

The prefrontal-striatal network has long been known to play an important role in executive functions (Alexander et al., 1986). To date, while the involvement of the prefrontal cortex and the striatum in these functions is well established, much less is clear on how the different structures (e.g. DLPFC, ACC, caudate nucleus, etc.) of the fronto-striatal circuitry contribute to executive functions in healthy subjects.

In the past, while human lesion studies provided useful insights on the functional role of a given brain area (Owen et al., 1990; Petrides and Milner, 1982; Stuss and Alexander, 2007), the fact that these lesions are generally quite extensive and rarely involve only one specific cytoarchitectonic area cannot be disregarded. Functional neuroimaging studies give us the opportunity to delineate the contributions of the prefrontal-striatal circuits to executive functions. A growing body of neuroimaging literature has emphasized the important contribution of the DLPFC and ACC to executive functions through their reciprocal connections (Botvinick et al., 2001; Cohen et al., 2000; D'Esposito et

al., 1995; Heyder et al., 2004; Kondo et al., 2004; Koski and Paus, 2000; Ridderinkhof et al., 2004), while the caudate nucleus, described as the input structure of the basal ganglia from the PFC (Alexander et al., 1986), has been shown to play a critical role in cognitive function (Grahn et al., 2008).

2.1.1. Lateral prefrontal cortex and executive function

Lesion studies in primates have provided a large amount of information regarding the role of the lateral PFC in working memory (Curtis and D'Esposito, 2004; Petrides, 2005). There are two main models depicting the functional organization of the lateral PFC. In the domain–specific model, it was proposed that while the DLPFC is engaged in processing spatial information, the ventrolateral PFC (VLPFC, BA 47/12) is involved with non-spatial information such as faces or objects (Levy and Goldman-Rakic, 2000). This hypothesis is well suited for the dorsal-ventral stream of the visual pathways originating from the posterior regions of the brain (Ungerleider and Mishkin, 1982). The process-specific model, on the other hand, suggests that the DLPFC is engaged in high-level executive control of monitoring and manipulation in working memory, while the VLPFC is involved with active encoding and retrieval of information (Petrides, 1994, 1995, 2000, 2005).

In humans, meta-analyses of neuroimaging studies with spatial and non-spatial working memory failed to observe the dorsal-ventral specificity for the domain-specific model (Owen et al., 1998), favoring the process-specific model of the prefrontal organization (c.f., McIntosh et al., 1994; Stephan et al., 2003). It is hypothesized, then, that the VLPFC interacts with the posterior regions of the brain for behaviours such as the retrieval of information, while the DLPFC provides higher-level executive processes such as manipulation and monitoring (Owen, 2000).

Hemispheric lateralization within the PFC is also an important issue in executive function (Aron et al., 2004a; 2004b; Johnson et al., 2003; Tulving et al., 1994), and an extensive review exists on human lesion studies that claim that the left frontal lobe is accountable for task-setting while the right frontal lobe is more involved with monitoring (Stuss and Alexander, 2007).

Several neuroimaging studies support the task-specific lateralization of the PFC in humans. During the performance of the WCST, left DLPFC activation has been reported when set-shifting is required (Monchi et al., 2001; Nagahama et al., 2001), while right DLPFC activation is more involved in monitoring the feedback of the subject's previous response (Lie et al., 2006; Monchi et al., 2001; Nagahama et al., 2001). It has also been proposed that the left DLPFC is a key structure for the implementation of top-down cognitive control, based on its

constant activation during color naming in the Stroop task (MacDonald et al., 2000), as well as when difficult planning is required during the Tower of London task (Owen et al., 1996a). On the other hand, it has been proposed that the role of the right DLPFC is to monitor information held in working memory, since it was actively recruited during the time-monitoring process (Vallesi et al., 2008), the judgement of item-familiarity task (Dobbins et al., 2004), the active manipulation and monitoring of spatial information (Owen et al., 1996b) and the verbal item recognition task (Cabeza et al., 2003).

2.1.2. Anterior cingulate cortex and executive function

Lesions of the medial frontal area have been known to impair a wide range of behaviours (Krainik et al., 2001; Nachev, 2006). Stuss and Alexander (2007) reported that lesions of the medial frontal cortex comprising the ACC impaired several cognitive task performances including the simple and choice reaction time task, the feature integration, the verbal fluency, the Stroop task (naming color patches and incongruent interference) as well as some tasks measuring sustained attention.

Neuroimaging studies with fMRI and PET also put forth the argument that the ACC is one of the core components associated with executive function, but its precise role is still a matter of debate (Bush et al., 2000). In a meta-analysis of

neuroimaging studies of executive function, the ACC was activated during task-switching, response suppression, and the WCST (Buchsbaum et al., 2005). Botvinick et al. (2004) also argued that the ACC is involved in several cognitive tasks that engage response override, underdetermined responding, and error commission. Other authors have emphasized the role of the ACC in detecting and processing error signals (Debener et al., 2005; Luu et al., 2000) and attention (Bush et al., 1999; Nobre et al., 1997).

Due to its multiple associations to various executive tasks, the exact role of the ACC has been difficult to determine. In fact, in terms of cytoarchitecture, the ACC is heterogeneous in its functions and connections. In humans, this brain structure can be divided into dorsal (i.e. supracallosal) and rostral (i.e. subcallosal) regions (Devinsky et al., 1995; Koski and Paus, 2000; Mayberg, 1997; Vogt et al., 1995). It has been proposed that the dorsal regions of the ACC are involved in cognition, especially during conflict monitoring (Kerns et al., 2004). The rostral portions of the ACC, on the other hand, are engaged in emotional behaviours (Devinsky et al., 1995; Koski and Paus, 2000) and error-signal processing (Lie et al., 2006; Taylor et al., 2006). This distinction is in accord with recent fMRI studies, where error-likelihood and conflict levels were manipulated. Results showed an increased dorsal ACC BOLD signal as the conflict load increased while the error-likelihood decreased (van Eimeren et al., 2006). This is

also in agreement with MacDonald et al., (2000) who reported that only the dorsal ACC was activated during the response to incongruent stimuli of the Stroop task.

The hemispheric laterality issue concerning the ACC is more complicated due to the relatively low spatial resolution of the neuroimaging techniques. Lutcke and Frahm (2008) proposed the use of high-resolution fMRI (voxel size: 1.5 x 1.5 x 1.5 mm^3) for hemispheric distinction within the ACC. The authors reported a process-specific laterality, such that the right ACC was activated during correct inhibitions of the go/no-go task implicating conflict monitoring, while error-related processes activated the ACC bilaterally. A domain specific processing of the left and right dorso-caudal ACC has been also suggested, i.e. that the left ACC mediates the attentional top-down cognitive control during the decision making task in the verbal domain, while the right ACC mediates the counterpart of the visuo-spatial domain (Stephan et al., 2003). Further studies are required to delineate the above hypotheses, but the poor resolution of brain mapping techniques such as rTMS and fMRI prevent us from examining hemispheric differences of the ACC.

2.1.3. Striatum and executive function

Although the functional role of the basal ganglia has been traditionally associated with motor processes, it has been suggested that the basal ganglia are also highly involved with cognition (Middleton and Strick, 2000). For example, the medial striatum in rodents, which is analogous to the caudate nucleus in humans, has been shown to be responsible for cognitive flexibility (Ragozzino, 2003; Reading et al., 1991; White and Viaud, 1991) and goal-directed behaviour (Yin and Knowlton, 2006). In primates, Alexander et al. (1986) proposed a very elegant model for understanding the functional role of the basal ganglia and its organization, and showed that the cognitive loop originating from the DLPFC projects to the head of caudate, globus pallidus, substantia nigra and thalamus (Figure 2.1).

Based on the well-established hypothesis that the basal ganglia are involved with movement selection (Mink, 1996), it has been further suggested that the basal ganglia act as a core selection system for cognitive function as well (Middleton and Strick, 2000; Redgrave et al., 1999). This is consistent with the anatomical afferents that the caudate nucleus receives from high-level cognitive areas such as the DLPFC, VLPFC, frontal eye field and temporal cortex (Alexander et al., 1986; Parent and Hazrati, 1995; Selemon and Goldman-Rakic, 1985). The existence of this anatomical prefronto-striatal loop in humans has

been recently corroborated by diffusion tensor imaging (Leh et al., 2007) and rTMS-PET (Strafella et al., 2001) studies.

In humans, studies on Parkinson's disease (PD) have been the most influential source of knowledge regarding the functional role of the striatum. Although PD is traditionally known as a movement disorder, cognitive impairment is not unusual even at early stages of the disease (Downes et al., 1989). Due to the resemblance of executive deficits in PD to prefrontal lesions, the DLPFC-caudate network in PD has been the object of several recent studies (Grahn et al., 2008; Hazy et al., 2007; Owen, 2004; Zgaljardic et al., 2003). Cognitive deficits of patients suffering from PD have been correlated with dopaminergic dysfunction affecting the striatum (Bruck et al., 2001; Marie et al., 1999). In particular, it has been reported that the rostro-dorsal portion of the head of the caudate nucleus is subject to greater dopamine depletion than the ventro-caudal portion, which remains relatively intact (Kish et al., 1988). This observation explains the selective impairment of executive functions in PD, such that while set-shifting (linked to the dorsal caudate) is impaired, reversal learning (associated with ventral striatum) is minimally affected (Cools et al., 2001; Dias et al., 1996).

Studies with Huntington's disease (HD) also provide evidence on the involvement of cortical-subcortical circuits in executive function (Montoya et al.,

2006). For example, it has been reported that patients with HD are impaired in the WCST (Paulsen et al., 1995) and the Tower of London (Lange et al., 1995), while structural (Bamford et al., 1995; Harris et al., 1992; 1996; Kassubek et al., 2004) and functional (Bachoud-Levi et al., 2000; Backman et al., 1997; Hasselbalch et al., 1992; Pavese et al., 2003; Sanchez-Pernaute et al., 1999) abnormalities of the striatum are shown to be correlated with their impaired performance of various executive tasks such as the trail making test, digit span, the Cambridge neuropsychological test automated battery, face and word recognition tests and others.

Previous fMRI studies have shown that the caudate nucleus is activated when the planning of a set-shift is required, and, in healthy adults, its activation is coupled with the DLPFC (Monchi et al., 2001; 2006b). This co-activation of the PFC and the striatum was strongly diminished in patients with PD, confirming the strong engagement of this prefronto-striatal circuitry in executive functions (Monchi et al., 2004; 2007).

2.1.4. Dopamine and executive function

It has been shown that striatal dopamine is strongly involved in executive functions. In fact, while dopaminergic agents may influence executive functions in healthy adults (Harrison et al., 2004; Mehta et al., 1999; Roesch-Ely et al., 2005),

L-dopa withdrawal impairs various executive processes in PD patients (Lange et al., 1992). Striatal dopaminergic abnormality has been involved with significant cognitive dysfunction in PD (Bruck et al., 2001; Marie et al., 1999; Rinne et al., 1989). Furthermore, while some studies have reported that L-dopa intake in patients with PD may improve performance on the n-back task (Mattay et al., 2002), the simultaneous processing task (Duchesne et al., 2002; Fournet et al., 2000), the task-set switching (Cools et al., 2001), the sentence comprehension (Grossman et al., 2002) and the Tower of London (Cools et al., 2002) tests, it may impair other functions such as choice reaction time (Schubert et al., 2002) and probabilistic reversal learning task performance (Cools et al., 2001). The most plausible explanation for this discrepancy is the inverted-U-shape hypothesis (Arnsten, 1997; Cools et al., 2001). In PD patients, for instance, dopaminergic medication restores dopamine-depleted regions such as the putamen. However, due to its lack of specificity, the same medication overflows relatively dopamine-intact regions such as the ventral striatum and cortical areas.

Although the striatum receives the most abundant dopaminergic innervation, studies on non-human primates have suggested that prefrontal dopamine also plays a critical role in working memory tasks (Arnsten et al., 1994; Arnsten and Goldman-Rakic, 1998; Brozoski et al., 1979; Sawaguchi and Goldman-Rakic, 1991, 1994). In humans, it has been hypothesized that

dysfunction of the prefrontal dopaminergic system may be responsible for impaired working memory in patients with schizophrenia (Davis et al., 1991; Goldman-Rakic, 1994; Goldman-Rakic et al., 2000; Weinberger, 1987). Receptor imaging studies support this hypothesis by showing that patients with schizophrenia may have abnormal dopamine D_1- (Abi-Dargham et al., 2002; Okubo et al., 1997) and D_2-receptor (Suhara et al., 2002) availability in prefrontal regions. Another line of evidence for the involvement of the cortical dopamine in executive functions can be observed from neuroimaging studies in PD patients; increased [^{18}F]DOPA uptake in the DLPFC and ACC of PD is related to sustained attention in the Stroop interference effect (Bruck et al., 2005).

It is well known that dopamine can be released through two main mechanisms: tonic and phasic release (Grace, 1991). According to this model, tonic release of dopamine is mostly involved with D_1-receptors that are relatively abundant in PFC, and modulates the excitability of neighbouring neurons. Tonic dopamine release is low in amplitude, but has a relatively long lasting effect. Behaviourally, this type of dopamine release mediates the active maintenance of working memory (for review`, see Goto et al., 2007; Onn et al., 2000). On the other hand, the phasic release of dopamine is mostly involved with D_2-receptors that are relatively scarce in the PFC. Dopamine released in this manner is high in amplitude, but rapidly cleared by the dopamine transporter. Hence, its effect is

limited to synaptic transmission. Behaviourally, this type of dopamine release regulates adaptive behaviour and cognitive flexibility (for review, see Goto et al., 2007; Onn et al., 2000). It should be also noted that, while dopamine via D_1-receptors potentiates the NMDA-mediated responses in the striatum (Cepeda et al., 1992; 1998; 1999; Flores-Hernandez et al., 2002; Levine et al., 1996a; 1996b) and cortex (Seamans et al., 2001; Wang and O'Donnell, 2001; Zheng et al., 1999), D_2-agonists inhibit the NMDA-mediated responses (Huang and Kandel, 1995). These dopaminergic effects are found to be dose- (Stewart and Plenz, 2006) and time-dependent (Gribkoff and Ashe, 1984; Huang and Kandel, 1995; Seamans and Yang, 2004).

2.2. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a technique that has been widely used for non-invasive brain stimulation to examine motor, perceptual, and cognitive processes (Hallett, 2007; Pascual-Leone et al., 1998; Walsh and Cowey, 2000). TMS involves the induction of a brief electrical current through a stimulating coil, which produces a rapid rise of a magnetic field and induces eddy current in the underlying brain tissue for 250 μsec after pulse onset. This magnetically-induced electrical stimulation transiently synchronizes the neuronal activity underneath the coil (Pascual-Leone et al., 2000). The procedure is

relatively painless since the magnetic field passes through the scalp and skull virtually unattenuated (Hallett, 2007). The most widely used TMS coils are the round coil and the figure-of-eight coil. The round coil is used for stimulating a relatively a large brain area, while the figure-of-eight coil is used for stimulating focal brain area.

2.2.1. Single-pulse TMS

In the case of the figure-of-eight coil, the single-pulse TMS-induced current flows parallel to the plane of the coil and stimulates the cortical surface horizontally if the coil is held tangentially to the scalp. This TMS-induced current can stimulate different populations of neurons, depending on the orientation of the coil. For example, it has been demonstrated that TMS, at least at low stimulation intensity, preferentially stimulates superficial interneurons (for review, see Pascual-Leone et al., 1998).

When applied to the motor strip, single-pulse TMS elicits a motor-evoked-potential (MEP) in the muscle corresponding to the stimulated regions. The MEP size varies depending on stimulation intensity and resting motor threshold (RMT), i.e. the minimum stimulation intensity that induces an MEP > 50μV is strongly influenced by coil orientation (Cohen et al., 1990; Wagner et al., 2004). Another factor that influences MEP size and RMT is the functional state of the targeted

area. For example, voluntary contraction (Hess et al., 1986; Thompson et al., 1991) and mental imagery (Kasai et al., 1997; Kiers et al., 1997) influence both MEP responses and RMT.

After the MEP response, electromyogram (EMG) activity is suppressed in the actively contracted muscle (Fuhr et al., 1991). The length and depth of this silent period depends on the state of the targeted neurons (Classen et al., 1998; Mathis et al., 1998) as well as on the stimulation intensity and paradigm (Fuhr et al., 1991; Kujirai et al., 1993; Triggs et al., 1993). It has been proposed that the length and depth of the inhibition is coordinated by a balance of GABAergic (Ziemann et al., 1995; 1996b; 1996c), glutamatergic (Faig and Busse, 1996; Prout and Eisen, 1994; Yokota et al., 1996) and dopaminergic (Priori et al., 1994; Ziemann et al., 1996a) influences.

Day et al. (1989) demonstrated that single-pulse TMS may interfere with the “transmission of information” in the targeted area. This report provided the fundamental idea of creating a “virtual patient” using TMS to delineate the chronometry of the targeted area's involvement to the specific working memory processes (Mottaghy, 2006; Pascual-Leone et al., 2000). For example, it has been reported that single-pulse TMS over the DLPFC delivered at specific time-intervals interfered with the performance of memory-guided saccades (Muri et al., 1996; Muri et al., 2000; Nyffeler et al., 2004), the sequential-letter working

memory task (Mull and Seyal, 2001) as well as the verbal (Mottaghy et al., 2003) and the visual n-back tasks (Oliveri et al., 2001).

2.2.2. Repetitive TMS

Repetitive TMS (rTMS) has been shown to produce profound and long-lasting effects on neuronal excitability. Pascual-Leone et al. (1994) demonstrated that, while high-frequency rTMS (≥ 5Hz) temporally increases neuronal excitability, this was reversed by low-frequency rTMS (≤ 1Hz) (Chen et al., 1997). It has been demonstrated that a short train (4 pulses) of 20Hz rTMS inhibits the neuronal excitability, while a longer train (20 pulses) facilitates it (Modugno et al., 2001). These effects have been proposed to be the consequence of inhibitory neuronal network activation (for review, see Siebner and Rothwell, 2003).

Combining functional imaging techniques with TMS provides a valuable probe to study functional connectivity of the human brain. Fast and slow rTMS have been shown to modulate brain metabolism by increasing and decreasing [^{14}C]2DG uptake in the targeted area, repectively (Valero-Cabre et al., 2007). It has also been reported that rTMS modulates regional cerebral blood flow (rCBF) in dose- (Paus et al., 1998) and frequency-dependent manners (Siebner et al., 2001). Interestingly, both slow and fast rTMS result in an increase in rCBF in the targeted area (Eisenegger et al., 2008; Knoch et al., 2006b; Rounis et al., 2005).

The unexpected increase in rCBF after the inhibitory rTMS may be explained by the active inhibition process induced by low-frequency rTMS (Sohn et al., 2002; Waldvogel et al., 2000). In addition to the changes in rCBF in the targeted area, rTMS is able to affect excitability in remote cortical and subcortical areas (Eisenegger et al., 2008; Knoch et al., 2006b; Speer et al., 2003a, b). Interestingly, the remote effect of fast rTMS over the motor cortex and DLPFC was found to increase synaptic dopamine transmission in the ipsilateral putamen (Strafella et al., 2003) and caudate nucleus (Strafella et al., 2001), respectively. This was in line with the topographical projections from the neocortex to the striatum (Alexander et al., 1986). The combination of rTMS and PET has opened new possibilities for the investigation of neurochemical networks.

2.2.3. rTMS in cognitive neuroscience

Although TMS has been most widely used to assess motor responses, it can also be used as a tool to create a “virtual lesion” and to assess its effects on cognitive behavior (Pascual-Leone et al., 2000; Paus, 1999).

The application of rTMS over a cortical area that, at a particular point in time, is actively involved in processing task-relevant information should result in a decline in performance (Enomoto et al., 2001; Huang et al., 2005; Pascual-Leone et al., 1994). Several studies with short-train high-frequency rTMS showed that

stimulation transiently disrupts the cognitive processes of the targeted area. For example, 10 pulses of 20Hz-rTMS on the DLPFC during the delay phase of memory-guided saccades impaired task performance (Brandt et al., 1998). Similarly, 4 pulses of 10Hz-rTMS over the DLPFC modulated the habitual counting during random number generation (Jahanshahi et al., 1998), as well as the performance on the response-selection task when this area was actively involved in the performance of the task (Hadland et al., 2001). Furthermore, five pulses of 10Hz-rTMS over the pre-supplementary motor area (SMA) increased the reaction times of the sequential movement when the pre-SMA was actively engaged, i.e. at the chunking point of the sequence (Kennerley et al., 2004). It has also been demonstrated that 8 pulses of 25Hz-rTMS over the DLPFC during the decision phase of a spatial working memory task selectively interfered with task performance, while no effect was seen when stimulation was delivered over the posterior parietal cortex or the premotor cortex (Koch et al., 2005).

rTMS has also been applied offline to pre-treat a given cortical area to create a “virtual lesion” that outlasts the duration of the stimulation (Walsh and Cowey, 2000), providing considerable advantages as compared with online stimulation (Robertson et al., 2003). Since the stimulation is delivered before task performance, secondary effects of rTMS such as tactile and noise discomfort are minimized. It has been demonstrated that offline low-frequency 1Hz-rTMS over

the DLPFC disrupts motor learning (Robertson et al., 2001), spatial and non-spatial delay-matching tasks (Mottaghy et al., 2002), reciprocal fairness (Knoch et al., 2006a) and bimodal divided attention (Johnson et al., 2007). On the other hand, offline high-frequency rTMS (≥ 5Hz) has been shown to disrupt performance on the Stroop task (Vanderhasselt et al., 2006a), task-set switching (Vanderhasselt et al., 2006b) and divided attention tasks (Wagner et al., 2006). It should also be noted that high-frequency rTMS has often been used to disrupt cognitive processes by generating neural noise on the targeted area (Walsh and Cowey, 2000).

It is not uncommon that rTMS can enhance task performance as well. For example, Knoch et al. (2005) elegantly demonstrated the frequency-dependent rTMS effect over the DLPFC. More specifically, the authors showed that a 1Hz-rTMS over the left DLPFC suppressed habitual counting during random number generation, while a 10Hz-rTMS stimulation exaggerated it. These non-intuitive results are often described as the "paradoxical enhancement," i.e., the disinhibition of an inhibitory system (Fecteau et al., 2006; Kirschen et al., 2006; Knoch et al., 2005; Luber et al., 2007; Walsh and Pascual-Leone, 2003a). Although methodically hypothesized, the underlying mechanism behind this paradoxical facilitation is still a matter of debate.

2.2.4. Theta burst stimulation

It has been demonstrated that theta burst stimulation (TBS), a recently developed rTMS approach, has longer lasting after-effects with a shorter duration and a lower intensity of stimulation than conventional rTMS (Huang et al., 2005). In particular, continuous TBS (cTBS) has been shown to have a similar effect to that of slow rTMS (i.e. inhibitory) when applied to the motor cortex - 20 seconds of stimulation may result in a lasting effect of up to 20 minutes, and 40 seconds of stimulation up to 60 minutes. This long-lasting inhibitory effect of cTBS has been replicated by several groups over the primary motor area (Huang et al., 2007; Stagg et al., 2008; Stefan et al., 2008), the premotor area (Koch et al., 2007; Mochizuki et al., 2005), the primary sensory area (Schabrun et al., 2008), the primary visual areas (Franca et al., 2006), the frontal eye field (Hubl et al., 2008; Nyffeler et al., 2006) and the DLPFC (Vallesi et al., 2007). It has been reported that the cTBS effect is NMDA-dependent (Huang et al., 2007) and may increases GABA levels in the targeted area (Stagg et al., 2008). Furthermore, cTBS inhibits the BOLD fMRI signal for over 30 minutes when applied to the frontal eye field (Hubl et al., 2008). These studies suggest the potential benefits of using cTBS to study cognitive behaviour thanks to its potent inhibitory effect and relatively apparent underlying mechanisms.

2.2.5. Targeting non-motor areas (frameless stereotaxy)

Targeting areas such as the motor or visual cortex is relatively easy, as these areas induce detectable MEPs and phosphenes, respectively. However, the targeting of the DLPFC requires a more complicated approach. While one of the simpler ways to determine the location of the DLPFC is to use the international EEG electrode position (Pascual-Leone et al., 1991), a more sophisticated and precise technique has been proposed: the frameless stereotaxy system (Paus et al., 1997) (Figure 3.1). With this method, we can identify a target area given in the standardized stereotaxic space (Talairach and Tournoux, 1988) in each individual based on his/her high-resolution structural MRI (Collins et al., 1994).

2.3. Positron emission tomography

PET is a non-invasive nuclear medicine imaging technique which produces three-dimensional functional images. When applied to the brain, this technique estimates the changes in rCBF, metabolism or receptor binding by measuring the level of radioactivity emitted by the injected radioactive tracer (Hernandez-Garcia et al., 2002). The characteristics of the tracer used can allow us to selectively observe the synthesis, uptake or synaptic concentration of specific neuro-chemicals.

2.3.1. Physics of PET

The injected radiotracer emits positrons as it undergoes positron emission decay. The positron travels up to a few millimetres and annihilates with an electron, producing a pair of annihilation photons that move in opposite directions. These photons create a burst of light when they reach the scintillators that surround the subject and are detected by photomultiplier tubes. The detected photons are considered only when they form a pair within a few-nanosecond window, and are 180 degrees from each other. This allows us to determine the line along which the radioactive decay occurred. With the help of computed tomography, we can reconstruct the 3D or 4D images of radiotracer distribution (Sossi, 2007).

2.3.2. Investigation of the dopaminergic system

With the help of PET imaging, it is possible to investigate the pre-synaptic and post-synaptic dopaminergic system in the living human brain. The [^{18}F]DOPA is one of the most useful tracers to quantify pre-synaptic dopaminergic function by measuring aromatic acid decarboxylase activity. For example, patients with PD have significantly decreased striatal [^{18}F]DOPA uptake, which represents a loss of nigrostriatal dopaminergic projection neurons (Kuwabara et al., 1995; Morrish et al., 1995; Nurmi et al., 2001). It has been reported that the reduced [^{18}F]DOPA

uptake constant in the caudate nucleus is correlated with impaired cognitive processes in patients with PD (Bruck et al., 2001; Holthoff-Detto et al., 1997; Holthoff et al., 1994; Rinne et al., 2000; Weder et al., 1999). On the other hand, [^{18}F]DOPA uptake is upregulated in extrastriatal regions of PD patients (Kaasinen et al., 2001; Rakshi et al., 1999; Whone et al., 2003), and may be associated with other cognitive deficits (Bruck et al., 2005; Rinne et al., 2000).

Another widely used pre-synaptic target for PET studies is the dopamine transporter (DAT), which can be imaged with [^{11}C]methylphenidate, [^{11}C]cocaine, [^{11}C]nomifensine and [^{11}C]WIN 35428. It has been suggested that lower DAT binding may also be associated with cognitive impairment in PD patients (Duchesne et al., 2002; Marie et al., 1999; Muller et al., 2000).

At the post-synaptic level, D_1- and D_2-receptors can be imaged using different radio-labeled dopamine receptor agonists or antagonists. [^{11}C]NNC-112 and [^{11}C]SCH23390 are the most widely used radioligands to estimate D_1-receptor availabilities. It has been proposed that D_1-receptor abnormalities are associated with impaired performance of executive function in schizophrenia (Abi-Dargham et al., 2002; Okubo et al., 1997) but not in PD (Cropley et al., 2008a; Ouchi et al., 1999; Shinotoh et al., 1993). However, the high affinity of these radioligands to 5-HT(2A) receptors limits the interpretation of these D_1-receptor ligand results (Ekelund et al., 2007; Slifstein et al., 2007).

D_2-receptor tracers have a relatively higher selective affinity than D_1-receptor tracers. [^{11}C]raclopride is probably the most widely used radioligand to measure D_2-receptor availability in the striatum (Endres et al., 1997; Laruelle, 2000). It has been demonstrated that various interventions including drugs (Dewey et al., 1993; Laruelle et al., 1997b), behavioral tasks (Koepp et al., 1998; Monchi et al., 2006a) and rTMS (Strafella et al., 2001; 2003; 2005) are able to induce significant and reproducible changes in [^{11}C]raclopride binding potential (BP), which is inversely proportional to synaptic dopamine transmission (Laruelle, 2000).

While the high density of D_2-receptors in the striatum makes [^{11}C]raclopride a very useful tracer for post-synaptic dopamine system imaging, the scarceness of D_2-receptors in the cortex (20-fold less than D_1-receptors) (Goldman-Rakic et al., 2000) makes this tracer less appropriate for cortical dopamine transmission measurements (Farde et al., 1988). Despite this lower dopamine receptor density relative to the striatum, studies in non-human primates have shown that cortical dopamine plays a critical role in executive functions (Murphy et al., 1996; Watanabe et al., 1997). Recently, high affinity radioligands such as [^{18}F]Fallypride and [^{11}C]FLB 457 have been developed to image extrastriatal D_2-receptors. These tracers have provided evidence for extrastriatal dopamine effects in response to drugs (Aalto et al., 2005b; Cropley

et al., 2008b; Riccardi et al., 2006; Tsukada et al., 2005) and behavioral tasks (Aalto et al., 2005a; Christian et al., 2006). In previous reports, Olsson et al. (2004) have shown that [^{11}C]FLB 457 BP, calculated by a simplified reference tissue model (Gunn et al., 1997; Lammertsma and Hume, 1996; Sudo et al., 2001), may provide a reasonable estimate of receptor densities in different extrastriatal areas (e.g. cingulate cortex, frontal cortex, thalamus, temporal cortex), consistent with a postmortem study with [125I]epidepride (Kessler et al., 1993). Similarly, [^{11}C]FLB 457 has been demonstrated to be sensitive in detecting changes in extrastriatal endogenous dopamine concentration in non-human primates (Chou et al., 2000) and humans (Aalto et al., 2005a; 2005b; Hagelberg et al., 2004; Montgomery et al., 2007). Thus, it appears that [^{11}C]FLB 457 is well-suited to capture binding differences in prefrontal areas.

2.3.3. Image Analysis

PET image analysis using a radioligand such as [^{11}C]raclopride and [^{11}C]FLB 457 can be divided into three steps: preprocessing, BP-map generation and statistical analysis. Preprocessing includes motion correction, co-registration, normalization and smoothing. There are several methods that can generate the BP-map of [^{11}C]raclopride and [^{11}C]FLB 457, but the simplified reference tissue model (Gunn et al., 1997) is the most recommended. For the statistical analysis, the most

widely used functional neuroimaging toolbox is SPM (Wellcome Department of Cognitive Neuroscience, Institute of Neurology). SPM offers various statistical tests such as the standard t-test, paired t-test, factorial analysis and correlation analyses. For receptor imaging studies, however, the residual t-test proposed by Aston et al. (2000) provides some advantages by increasing sensitivity while reducing false positive results.

2.3.3.1. Preprocessing

The subject's head movements during PET scans (> 1 hour) is an inevitable confound of every PET study. There are two different approaches for correcting the subject's motion, which is 1) to track and compensate for the subject's head movement using an optical device (Bloomfield et al., 2003; Fulton et al., 2002; Lopresti et al., 1999), or 2) to realign the reconstructed PET images using co-registration algorithms (Montgomery et al., 2006; Perruchot et al., 2004; Zamburlini et al., 2004). Although the first approach is very promising for the future, the latter has some advantages in practice. The importance of motion correction in PET studies is broadly accepted, but there is not yet a consensus as to which is the most optimal method for receptor imaging studies.

The standard stereotactic coordinate system (Talairach and Tournoux, 1988) is the most commonly used cartesian system to report findings of brain

imaging studies. In order to normalize (i.e. transform) each individual's PET images into standard space, the individual's PET image must first be co-registered to the corresponding structural MRI (Friston et al., 1995a; Woods et al., 1993), after which the transformation matrix of the individual's structural MRI to standard space is used (Collins et al., 1994; Friston et al., 1995a). The nonlinear transformation from the native MRI to the standard space can be used to minimize the noise induced by individual anatomical variability (Ashburner and Friston, 1999; Robbins et al., 2004).

Although not universally accepted (Reimold et al., 2006; Wang et al., 2005), smoothing is also used to filter noise. There is no standard full-width-at-half-maximum (FWHM) for smoothing, but it is recommended that the FWHM should be smaller than the size of the anatomical structure under investigation, and three times larger than the resolution of the PET image.

2.3.3.2. BP-map generation using the simplified reference tissue model

In this thesis, BP is defined as a unit-less quantity that represents how likely the radiotracers such as [^{11}C]raclopride and [^{11}C]FLB 457 bind to the dopamine receptors (Laruelle, 2000). Since these tracers bind to the receptors in a competitive manner with dopamine, their BPs are inversely proportional to the

synaptic dopamine concentration (Laruelle, 2000, Figure 2.2). The BP is defined as:

$$BP = \frac{B_{max}}{K_D}$$

where B_{max} is the maximal number of D_2-receptors, K_D is the equilibrium dissociation rate constant of the radioligand.

There are several methods to generate the BP-map of [^{11}C]raclopride and [^{11}C]FLB 457; the kinetic three-compartment modeling using arterial metabolite-corrected tracer concentration as input function (Carson et al., 1997; Koeppe et al., 1991), the graphical method for reversible tracers developed by Logan et al. (1990), the Scatchard analysis (Farde et al., 1986; Ginovart et al., 1997), the displacement model in equilibrium using constant infusion (Laruelle et al., 1997a), and the simplified reference tissue model with basis functions (Gunn et al., 1997; Lammertsma and Hume, 1996).

This thesis limits its discussion to the simplified reference tissue model (Gunn et al., 1997; Lammertsma and Hume, 1996, Figure 2.3 & 2.4) due to its simplicity in experiments and the applicability to the residual t-test (Aston et al., 2000) which will be discussed in the next section. The cerebellum is chosen as a reference region and described by the two-compartmental model based on its negligible dopamine receptor densities (Martres et al., 1985). This method

generates the basis functions (Figure 2.4.b) to compute the physiologically possible time-activity-curve (TAC) of each voxel based on the TAC of the reference regions (Figure 2.3.a). The shape of the modeled TAC varies depending on θ_3, which is determined by the least squares fit (Figure 2.4.d). The range of θ_3 should be chosen beforehand to encompass all the plausible values of k_2 (the effective efflux rate constant from the tissue), BP and λ (radiation decay constant). By performing the least squares fit between the modeled TAC and the real TAC from the receptor-rich region such as the striatum, one can estimate the BP of each voxel of the PET image. One of the advantages of using this method is that it does not assume that the cerebral blood flow is the same for each region, since it also calculates R_I (the ratio of the influx rate constants of the receptor-rich region vs the reference region, k_1/k_1^r) (Gunn et al., 1997; Lammertsma and Hume, 1996). The use of the simplified reference tissue model in [^{11}C]raclopride PET study is widely validated (for review, see Laruelle, 2000). For the [^{11}C]FLB 457 PET, it has been reported that this method also best describes the results of the conventional nonlinear least-squares fitting analysis (Ito et al., 2001).

2.3.3.3. Statistical analysis of BP images

SPM tests the hypothesis of how well the modeled brain response fits with the observed data. The paired-t test and factorial analysis can be used for

intervention studies. With the proper design matrix, the T- or F-value of each voxel can be generated. Since multiple voxels are tested for the same hypothesis, the T- or F-value should be corrected for multiple comparisons, i.e. family-wise-errors (FWE). The Bonferonni correction is one way to do so. For example, if the significant T- or F-value is corrected for $p < 0.05$ of FWE, it means that the probability of a false positive anywhere in the image is less than 5%. Considering that each voxel is anatomically connected and correlated with adjacent voxels, the random field theory has been introduced to FWE, and has become a standard to detect significant effects (Friston et al., 1991; Worsley et al., 1992). Another widely accepted correction for multiple comparisons is the false-discovery-rate (FDR). The FDR controls the expected proportion of false positives among suprathreshold voxels. A FDR threshold is determined from the observed p-value distribution, and hence is adapted to the amount of generated signal in the data (Nichols and Hayasaka, 2003). However, the most often used correction for multiple comparisons in receptor imaging studies is the correction of cluster-level, since FWE and FDR are extremely conservative. The cluster-level analysis evaluates whether the size of the given cluster of the thresholded voxels (e.g. $p < 0.001$, uncorrected) is significant using the random field theory and the permutation method (Hayasaka and Nichols, 2003).

It should be noted that a BP image of [^{11}C]raclopride or [^{11}C]FLB 457 is a static 3D image. Performing a paired t-test using SPM, therefore, requires at least 10 to 20 percent changes between the two conditions to detect a significant t-value depending on the search volume (Aston et al., 2000).

The residual t-test has been proposed to increase the statistical power of dual scan PET studies (Aston et al., 2000). This method uses the residuals of the least-squares fit of the compartmental model (Figure 2.4) to estimate the standard deviation of the BP. In this way, the degrees of freedom are increased by a factor proportional to the number of time frames in the dynamic data, such that the t-value follows the Gaussian counterpart (Worsley et al., 1996) without generating false-positives. For example, it has been demonstrated that only 5% difference between two conditions with 6 subjects is required to detect significant changes. This method has been extensively used in drug-intervention- (Leyton et al., 2002), behavioural- (Monchi et al., 2006a; Zald et al., 2004) and rTMS- (Strafella et al., 2001; 2003) PET studies. It should be reminded here that according to previous microdialysis studies, a small fraction of changes in BP reflect a much greater synaptic dopamine release. For example, a 1% decrement of the [^{11}C]raclopride BP corresponds to 44% to 64% increase of extracellular dopamine release (Breier et al., 1997). It is often not sensitive enough, then, to detect a significant corrected t-value with SPM.

2.4. Summary

There is a considerable amount of human brain mapping studies aiming to elucidate neural mechanisms underlying executive function. However, although the involvement of the PFC and basal ganglia in executive functions are well documented, their functional roles remain unclear.

Using TMS and PET methodology, the next three chapters will examine the functional role of the right and left DLPFC as well as dopaminergic involvement in executive functions.

2.5. Figures

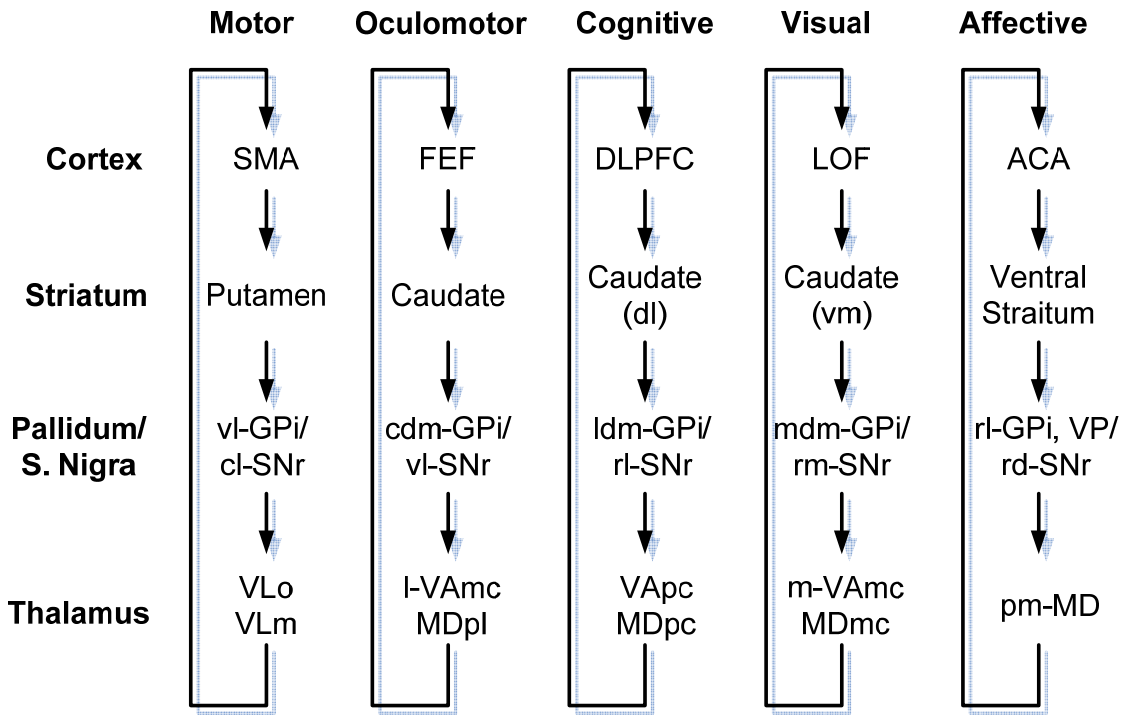

Figure 2.1. The cortico-striato-pallido-thalamo-cortical loop. Each loop engages specific regions of the cerebral cortex, striatum, pallidum/substantia nigra and thalamus depending on the given function. Abbreviations are as follows: ACA = anterior cingulate area, DLPFC = dorsolateral prefrontal cortex, FEF = frontal eye field, GPi = internal segment of globus pallidus, LOF = lateral orbitofrontal cortex, MD = mediodorsal nucleus of the thalamus, SMA = supplementary motor area, SNr = substantia nigra pars reticulata, VA = ventral anterior nucleus of the thalamus, VL = ventral lateral nucleus of the thalamus, VP = ventral pallidum, cd- = caudolateral, cdm- = caudodorsomedial, dl- = dorsolateral, l- = lateral, ldm- = laterodorsomedial, m- = medial, pm- = posteromedial, rd- = rostrodorsal, rl- =

rostrolateral, vm- = ventromedial, vl- = ventrolateral, -o = pars oralis, -m = pars medialis, -mc = pars magnocellularis, -pc = pars parvocellularis, -pl = parvocellular subnucleus. Adapted from Alexander et al. (1986).

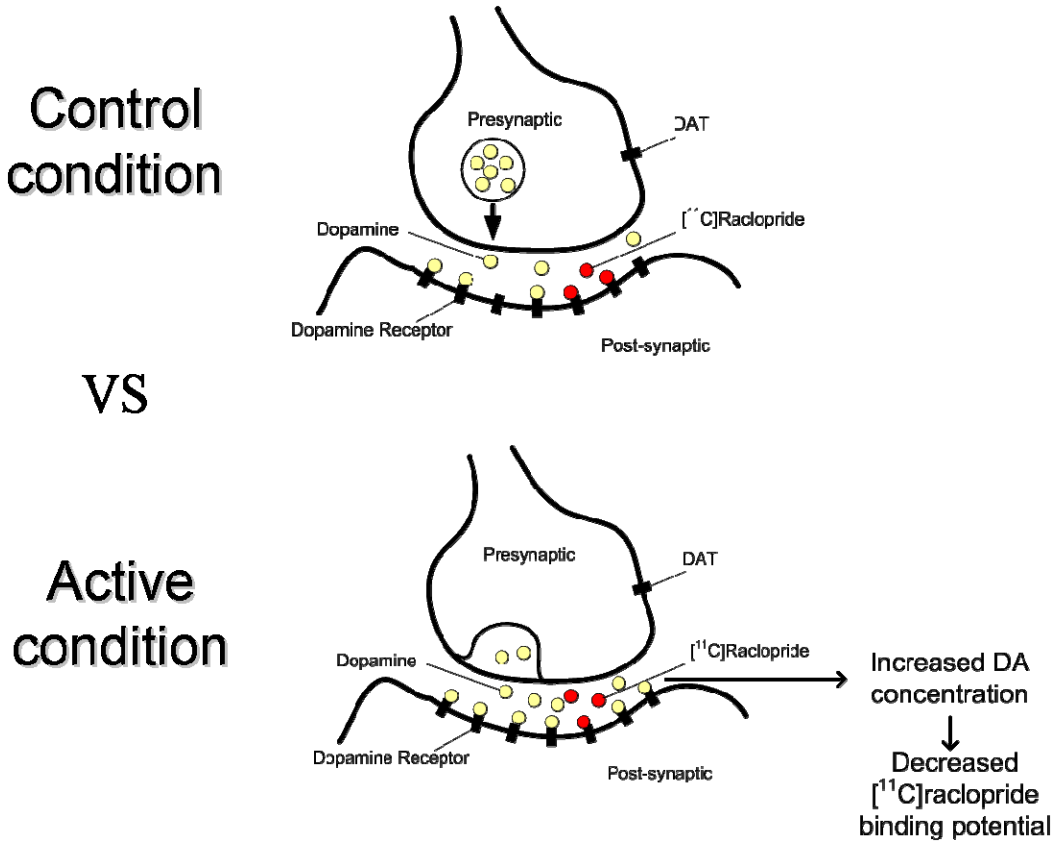

Figure 2.2. Synaptic dopamine competition hypothesis in receptor imaging. In the control condition (top), there is a baseline level of dopamine (yellow dots) in the synapse. [^{11}C]Raclopride (red dots) compete with synaptic dopamine to bind to dopamine D2-receptors (black rectangles). In the active condition (bottom), more dopamine is released in the synapse. Consequently, there is more competition for [^{11}C]raclopride binding, and BP of [^{11}C]raclopride is decreased. This demonstrates why [^{11}C]raclopride BP is inversely proportional to synaptic dopamine transmission. DAT = dopamine transporter.

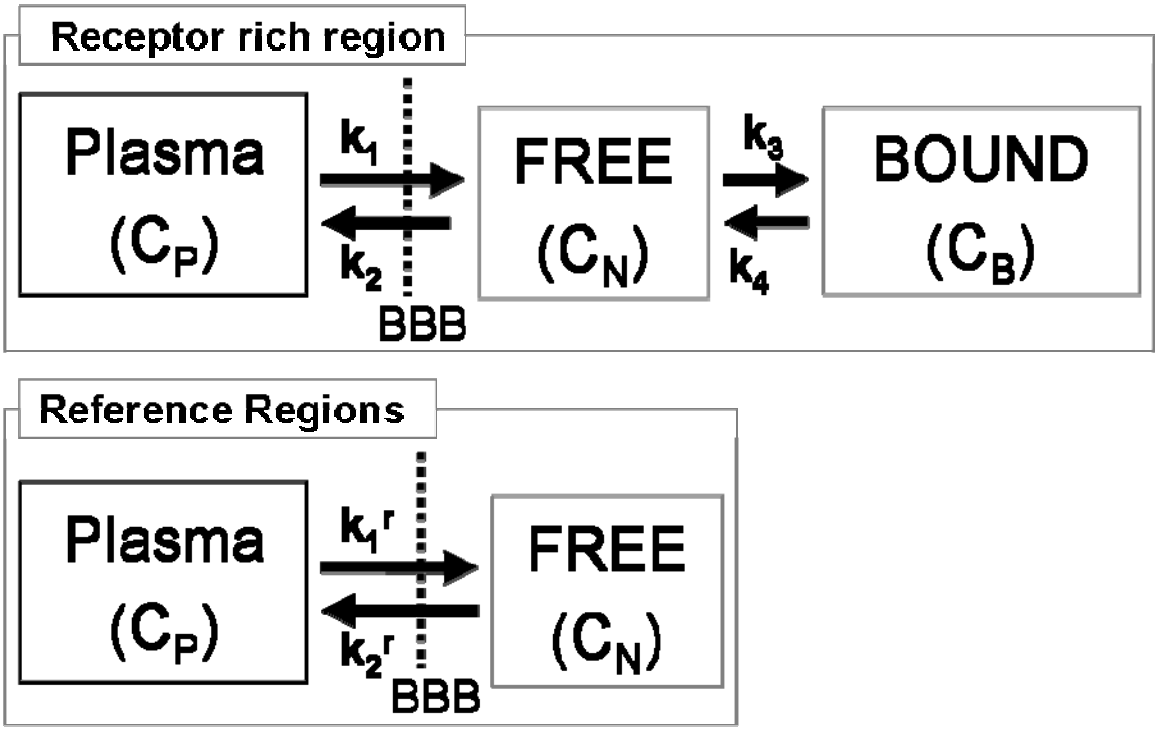

Figure 2.3. Simplified reference tissue model. C_P represents free radio-tracers in the plasma, C_N represents free and nonspecific binding in the tissue, and C_B represents specific binding. k_1, k_2, k_3 and k_4 are rate constants between the compartments of the receptor-rich region. k_1^r and k_2^r are rate constants between the compartments of the reference region. BBB represents blood-brain-barrier.

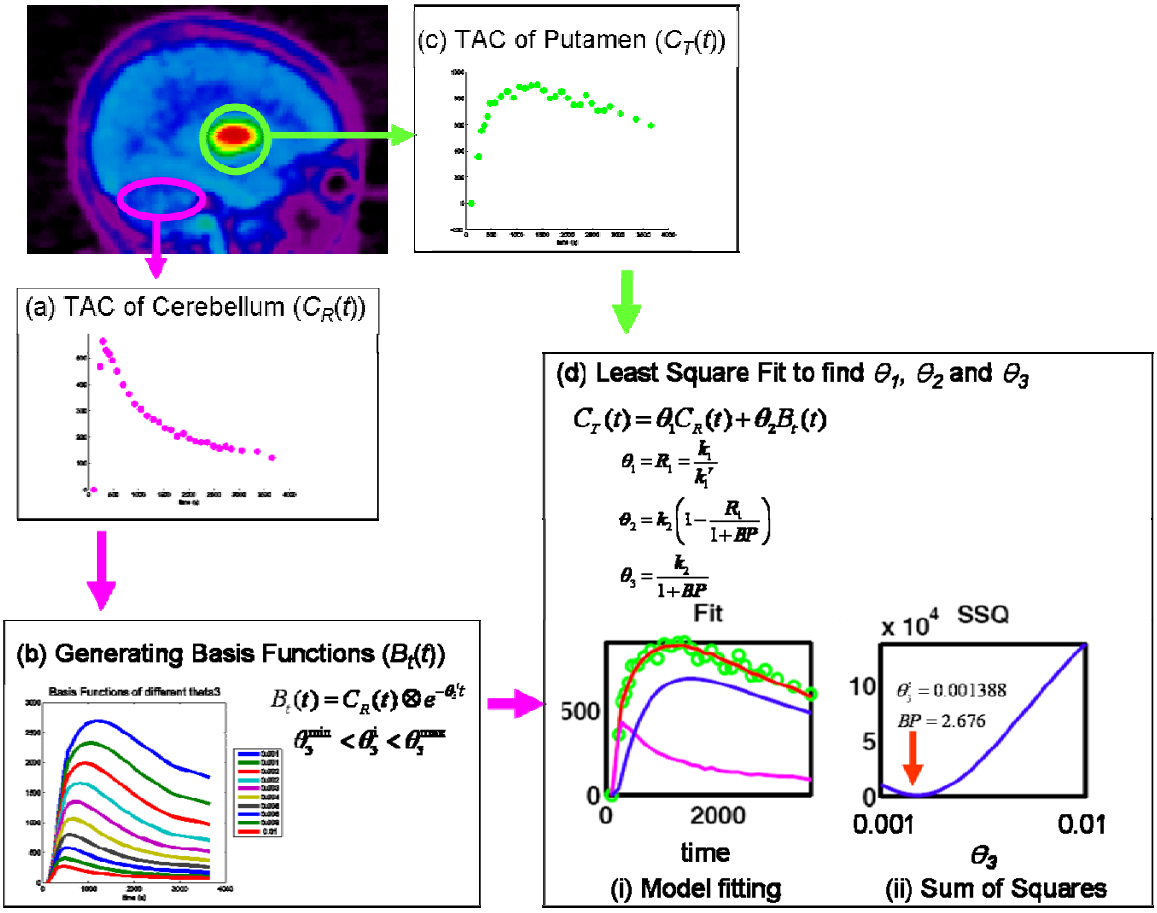

Figure 2.4. Basis function method with simplified reference tissue model. The top left panel shows a sample [^{11}C]raclopride PET image summed over time. (a) TAC of the cerebellum is extracted from the 4D [^{11}C]raclopride PET image. (b) The basis functions ($B_t(t)$) are computed by convolution product of the cerebellar TAC ($C_R(t)$) and the exponential of $-\theta_3^i t$. A sufficient number of θ_3^i is predefined within a physiologically plausible range ($\theta_3^{min} < \theta_3^i < \theta_3^{max}$). Only ten basis functions are shown for presentation purposes. For a voxel-wise [^{11}C]raclopride PET study, 100 basis functions are commonly used within θ_3^{min} = 0.001 and θ_3^{max} = 0.01. (c) Each voxel's TAC of any receptor-rich region can be extracted. For presentation

purposes, the TAC is extracted from the ROI drawn on the left putamen. (d) Using the least squares fit between the model ($C_T(t)$) and the real TAC of receptor-rich regions, one can find the optimal θ_3^j ($\theta_3^{min} < \theta_3^j < \theta_3^{max}$) that results in the minimal sum of squares. In this way, one can estimate the θ_1 and θ_2 which determines the BP. (d-i) The green circles represent the TAC of the real data (the left putamen). The red line represents $C_T(t)$, the model of the TAC of the receptor-rich region. The blue line represents $\theta_2 B_t(t)$, the specific binding of [^{11}C]raclopride. The pink line represents $\theta_1 C_R(t)$, the delivery of the [^{11}C]raclopride to the receptor-rich region (or cerebral blood flow), and its non-specific binding. θ_1 and θ_2 represents how much the delivery (or cerebral blood flow) and the specific binding is reflected in the $C_T(t)$, respectively. (d-ii) The residuals of the fitting are later used for the estimation of the standard deviation of the BP when the residual t-test is performed. The presented sample data is taken from one of the subjects that participated in the second study.

Chapter 3

The functional role of the right DLPFC in monitoring

3.1. Preface

Previously, Monchi et al., (2001) reported that the functional role of the right DLPFC lies in monitoring information held in working memory during the feedback periods of the WCST. However, functional imaging studies alone cannot make out whether the engagement of the activated area is essential or just epiphenominal (Walsh and Cowey, 2000).

In order to test this causality and to examine the role of the right DLPFC during the feedback period of WCST performance, the following event-related rTMS study, published in the International Journal of Biomedical Imaging in 2008, has been carried out. The study design was 3x2x2; brief rTMS (5 pulses in 20Hz) was delivered at three different timing periods of the task (feedback, matching and desynchronized) on two different targets (right DLPFC and vertex) while the subjects performed two different tasks (WCST and control task).

Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex affects performance of the Wisconsin Card Sorting Task during provision of feedback.

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3.2. Abstract

Early functional neuroimaging studies of tasks evaluating executive processes, such as the Wisconsin card sorting task (WCST), only assessed trials in blocks that may contain a large amount of different cognitive processes. More recently, we showed using event-related fMRI that the dorsolateral prefrontal cortex (DLPFC) significantly increased activity during feedback but not matching periods of the WCST, consistent with its proposed role in the monitoring of information in working memory. Repetitive transcranial magnetic stimulation (rTMS) is a method that allows to disrupt processing within a given cortical region and to affect task performance for which this region is significantly solicited. Here we applied rTMS to test the hypothesis that the DLPFC stimulation influences monitoring of working memory without interfering with other executive functions. We applied rTMS to the right DLPFC and the vertex (control site) in different time points of the WCST. When rTMS was applied to the DLPFC specifically during the period when subjects were receiving feedback regarding their previous response, WCST performance deteriorated, while rTMS did not affect performance during matching either when maintaining set or during set-shifting. This selective impairment of the DL-PFC is consistent with its proposed role in monitoring of events in working memory.

3.3. Introduction

There is considerable evidence that damage to the prefrontal cortex impairs performance on cognitive set-shifting tasks (Milner, 1963; Nelson, 1976; Stuss et al., 2000). In one such task, the Wisconsin card sorting task (WCST), the subject has to match, over successive trials, a test card to one of four reference cards based on a matching rule that the subject acquires on the basis of feedback provided after each matching response. Patients with prefrontal lesions are often impaired in shifting the principle of matching when the feedback provided indicates that a cognitive shift in mental set is required. Functional neuroimaging studies support these observations (Monchi et al., 2001; 2006b; Owen, 2004). In a recent study, conducted with functional magnetic resonance imaging (fMRI), we demonstrated differential activation of different parts of the prefrontal cortex during the performance of the WCST. In particular, we were able to show that the dorsolateral prefrontal cortex (DLPFC) was engaged when feedback was provided (Monchi et al., 2001). This selective engagement of the mid-DLPFC during the provision of feedback after each matching response by the subject is consistent with the proposed role of this part of the prefrontal cortex in the monitoring of events in working memory (Petrides, 1991, 1994, 2000). Neuroimaging studies, however, suffer from the limitation that they provide neuronal correlates of cognitive performance and cannot determine a causal

relation between observed brain activity and cognitive performance (Johnson et al., 2007; Rushworth et al., 2002). Thus the specific functional relevance of the DLPFC in monitoring the feedback provided during the performance of set-shifting tasks remains to be established.

Here we have used repetitive transcranial magnetic stimulation (rTMS) to examine this issue. The application of rTMS to an area of cortex that, at a particular point in time, is actively involved in the processing of task-relevant information should cause performance to decline (Enomoto et al., 2001; Huang et al., 2005; Pascual-Leone et al., 1994). In other words, rTMS acts as a "virtual lesion" producing a temporary interruption of processing (Walsh and Cowey, 2000). In the present study, we tested the hypothesis that rTMS of the human DLPFC influences monitoring of the information held in the working memory without interfering with other executive functions. To test this specific hypothesis, we used a computerized version of the WCST (Monchi et al., 2001) in which different stages of task performance can be isolated. We applied rTMS to the right DLPFC and over a control site (the vertex) in three different ways: at the beginning of the feedback period, at the beginning of the matching response period, and independently of task timing. Our previous functional neuroimaging study had indicated the involvement of the DLPFC during the provision of feedback, but not during the matching response. To further strengthen our

findings, we also added a control task (Figure 3.3.b) that only required matching to a twin card.

3.4. Materials and Methods

Ten healthy subjects (19–33 years) participated in the study after having given written informed consent. All subjects were right-handed according to the Edinburgh handedness inventory (Oldfield, 1971), they had no previous personal or family history of neurological or psychiatric disorders and were not taking any medication at the time of experiments. The experiments were approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital. Figure 3.2 displays an overview and timing of the experimental setup.

3.4.1. Cognitive task

Subjects were trained for 30 minutes on the WCST before the rTMS sessions. Prior to the training sessions, the subjects were instructed to perform as well as they could. During the WCST, four reference cards and one matching card were presented on a computer screen (Figure 3.3.a). On each trial, the subjects had to match a test card to one of the four reference cards according to one of three rules: shape, number, or color. The currently appropriate rule for classification is found by trial and error based on the 3-second positive or negative feedback that

is provided immediately after each matching decision. The rule for classification changed randomly after the subject answers correctly on six consecutive trials. In the control task, the matching card was identical to one of the reference cards so that the subject simply selected the identical card and did not have to find an appropriate rule for classification as in the WCST (Figure 3.3.b). Subjects performed the card-sorting tasks in six different rTMS sessions (2 × 3 design). Five-minute breaks were given in between sessions. Each session lasted six minutes.

3.4.2. Frameless stereotaxy system

In order to target the DLPFC and vertex (control site) in all our subjects (Figure 3.1), we used a procedure that takes advantage of the standardized stereotaxic space of Talairach and Tournoux (1988) and frameless stereotaxy (Paus, 1999; Strafella et al., 2001). A high resolution MRI of the subjects' brain was acquired and transformed into standardized stereotaxic space using the algorithm of Collins et al. (1994). The coordinates selected for the right DLPFC (X = 45, Y = 33, Z = 25) were based on a previous functional activation study that yielded increased activity during the feedback period (Monchi et al., 2001). Of note, in this study, we stimulated the DLPFC located in the right hemisphere because this side appeared to be more consistently and robustly activated (Monchi et al.,

2001). The control stimulation site (i.e., vertex region, X = 0, Y = −35, Z = 80) was also chosen based on its lack of activation during performance of the WCST in these previous studies.

The Talairach coordinates were converted into each subject's native MRI space using the reverse native-to-talairach transformation (Paus, 1999). The positioning of the TMS coil over these locations, marked on the native MRI (Figure 3.1), was performed with the aid of a frameless stereotaxic system (Rogue Research, Montreal, Canada).

3.4.3. TMS protocol

Repetitive TMS was carried out with the Magstim high-speed magnetic stimulator (Magstim, UK) using a figure-eight coil. The coil was held in a fixed position over the stimulation sites by a mechanical arm. It was positioned so that magnetically induced current under the coil flowed in a posterior-anterior direction. Stimulus intensities, expressed as a percentage of the maximum stimulator output, were set at 110% of the resting motor threshold (RMT). RMT was defined as the lowest stimulus intensity able to elicit, in the contralateral first dorsal interosseous (FDI) muscle, 5 motor evoked potentials (MEPs) of at least 50 uV amplitude in a series of 10 stimuli delivered over the right primary motor cortex at intervals longer than 5 seconds. MEPs were recorded from the FDI muscle with Ag\Cl

surface electrodes fixed on the skin with a belly-tendon montage. The EMG signal was filtered (10 Hz–1 kHz bandpass), digitized at 2 kHz, and displayed on a computer screen (Strafella et al., 2001).

Three rTMS blocks (6 minutes each) were applied to the right DLPFC and the vertex during the WCST and control task (Figure 3.2). Each block was separated by a 5-minute interval. In each block, 5 pulse trains of 250-millisecond duration were delivered at a stimulation frequency of 20Hz with between-train interval dependent on the subject's performance time (PT) (i.e., 4 to 6 second). For each block, rTMS was delivered either (block-1) at the beginning of each feedback period (number of trials: 72.05 ± 0.75) (Figure 3.4), (block-2) at the beginning of each matching period (number of trials: 74.15±1.19) (Figure 3.5), or (block-3) every 6 second regardless of the moment in the task (i.e., desynchronized condition) (number trials: 75.53 ± 2.14) (Figure 3.6). This last paradigm was applied in order to investigate whether the rTMS effect was timing dependent (i.e., block-1 and -2) or not (block-3). Block order was counterbalanced across subjects and performed on the same day (Figure 3.2). The stimulation parameters followed safety guidelines for rTMS (Wassermann, 1998).

3.4.4. Data Analysis

PT and error rate were calculated. Each subject's PT and error rate were averaged within each condition (stimulation site, timing, and task). PT was measured from the presentation of the test card to the subject's response, that is, the selection of a reference card (Figures 3.4, 3.5 and 3.6).

Repeated-measures ANOVA was used to compare the effect of the two different stimulation sites, the three timings of stimulation, and the two different tasks on PT.

The paired samples t-test (two-tailed) was used to compare the mean PT and error rate in the WCST between the DLPFC and vertex stimulations during the three different rTMS timing conditions (rTMS during feedback, during matching, and desynchronized). The mean PT for the control task was also compared in the same manner. Data are presented as mean ± SE. All statistical analysis was performed using SPSS 13.0 for Windows (SPSS Inc., USA).

3.5. Results

TMS intensity was 58.4±2.8%. There was no significant difference between numbers of trials among different blocks. Repeated-measures ANOVA on PT revealed a significant main effect of different tasks (WCST versus control; $F(1,9) = 71.3$; $P < .001$) confirming that the WCST was more demanding than the control task. There was also a significant main effect of stimulation timing on PT

(beginning of feedback versus beginning of matching versus desynchronized; $F(2,18) = 23.845$; $P < .001$) indicating that the timing of stimulation, overall, was an important factor influencing task performance more than stimulation site (DLPFC versus vertex; $F(1,9) = 2.516$; $P = .147$). A significant interaction effect was observed between tasks and stimulation site ($F(1,9) = 7.642$; $P = .022$) indicating that stimulation site affected PT differently depending on which task was used.

To test the effect of different stimulation sites within each task and stimulation timing condition, a paired *t*-test (two tailed) was performed. When comparing DLPFC versus vertex during the WCST, PT increased significantly when rTMS was delivered at the beginning of the feedback period (DLPFC = 1840.04 ± 87.18 ms, Vertex = 1682.46 ± 61.23 ms; $t(9) = 2.727$; $P = .023$) (Figure 3.4). Further analysis revealed that the magnitude of impairment did not correlate with intensity of TMS ($r = -0.063$; $P = .863$). No changes in PT were observed when rTMS was given at the beginning of the matching period (DLPFC = 1419.19 ± 107.48 ms, Vertex = 1309.87 ± 88.07 ms; $t(9) = 1.382$; $P = .200$) (Figure 3.5) nor when it was desynchronized with task performance (DLPFC = 1739.13 ± 148.26 ms, Vertex = 1659.70 ± 98.24 ms; $t(9) = 0.944$; $P = .370$) (Figure 3.6). When comparing DLPFC versus vertex during the control task, rTMS did not induce significant changes in PT either during the feedback

(DLPFC = 1491.66 ± 65.47 ms, Vertex = 1459.48 ± 59.60 ms; $t(9) = 0.669$; $P = .521$) (Figure 4), matching (DLPFC = 1084.92 ± 62.15 ms, Vertex = 1080.26 ± 77.11 ms; $t(9) = 0.074$; $P = .943$) (Figure 3.5), or desynchronized (DLPFC = 1517.38 ± 147.72 ms, Vertex = 1490.91 ± 90.36 ms; $t(9) = 0.314$; $P = .760$) conditions (Figure 3.6).

The repeated-measures ANOVA on error rate did not show any significant main effect of task conditions, stimulation timing, or the sites of stimulation, nor significant interaction effects except when comparing DLPFC and vertex at the beginning of feedback which came close to significance. More specifically, the results obtained when performing a paired *t*-test on the error rates between DLPFC and vertex stimulation during the WCST were at the beginning of the feedback (DLPFC = 6.10 ± 1.71, Vertex = 3.28 ± 1.16; $t(9) = 2.120$; $P = .063$); at the beginning of matching (DLPFC = 4.79 ± 1.04, Vertex = 4.86 ± 1.27; $t(9) = -0.057$; $P = .956$); during the desynchronized condition (DLPFC = 5.21±0.83, Vertex = 3.56 ± 0.51; $t(9) = 1.941$; $P = .084$).

3.6. Discussion

The present study demonstrated that when rTMS was applied to the DLPFC specifically during the period when the subject was receiving feedback regarding his/her matching response, performance of the WCST deteriorated. It appeared

that the effect of rTMS was significantly timing dependent. In fact, rTMS-induced interference of DLPFC affected performance specifically during the receiving of feedback (Figure 3.4), but not during the matching response (Figure 3.5) nor when the interference was desynchronized with specific stages of the WCST (Figure 3.6).

This observation of a selective rTMS-induced impairment in task performance during specific timing of a task has already been reported in the literature in relation to several of the tasks and cortical areas stimulated. For instance, rTMS of the medial frontal cortex affected task switching and at the time of response set switching when delivered before or at time of response selection (Kennerley et al., 2004; Rushworth et al., 2002). Similarly, rTMS affected DLPFC depending on whether this area, at a particular point in time, is actively involved in processing task relevant information (Hadland et al., 2001; Johnson et al., 2007).

The selective rTMS-induced impairment in WCST performance of DLPFC during the receiving of feedback is in accordance with imaging, lesion, and neurophysiological investigations. In a previous fMRI study, Monchi et al. (2001) have shown that DLPFC is engaged when the subject is receiving feedback during the WCST. That is, the period when monitoring of information held in working memory, as demonstrated by lesion studies in monkeys, is critical

(Petrides, 1994, 2005). This specific involvement has also been confirmed with neuronal recordings from DLPFC in monkeys during a WCST analog which have shown the activation of DLPFC cells during monitoring and use of feedback information. A large population of DLPFC cells were strongly engaged in assessing behavioral outcome/feedback (Mansouri et al., 2006).

Interestingly, while rTMS induced selective impairment in WCST performance, it did not affect error rate very significantly. This observation is consistent with previous work by Wagner et al. (2006) who, stimulating the DLPFC, observed no significant effect on error making during the WCST. There are two potential alternatives that could explain these findings.

The first explanation is that error making may be influenced by a different prefrontal area. In fact, lesions of DLPFC in monkeys have shown impairment in monitoring of information but did not compromise maintenance of information and set shifting per se (Petrides, 1994, 2000, 2005), which presumably may influence errors during set-shifting tasks. Set shifting from a previously relevant to a new response mode engages a more ventral area of the PFC (i.e., ventrolateral PFC) (Monchi et al., 2001) and is impaired by lesioning of this area (Iversen and Mishkin, 1970; Petrides, 2005). Another cortical area that may also have a relevant role is the medial PFC which can influence error trials during performance monitoring processes (Mansouri et al., 2006).

A second explanation, considering the fact that rTMS induced error trials have been reported less frequently in relation to different tasks and cortical area stimulated (Hadland et al., 2001; Kennerley et al., 2004; Rushworth et al., 2002; Walsh and Pascual-Leone, 2003b), it may also be that rTMS parameters (e.g., intensity, frequency, and unilateral stimulation) used so far in different studies have not been strong enough to induce a complete "virtual lesion." Against the latter hypothesis, however, stands the fact that the magnitude of selective impairment in WCST performance observed in this study did not correlate with intensity of TMS which at least excludes a possible relationship between intensity and effect on performance.

While our study provides some insights over the debate regarding the role of DLPFC during set-shifting tasks, overall it emphasizes the importance of rTMS in delineating the functional relevance of neuronal correlates of performance observed during neuroimaging studies (Johnson et al., 2007; Rushworth et al., 2002). In other words, our results suggest that just because a cortical area (i.e., DLPFC) is functionally activated during the course of an executive task (Monchi et al., 2001), it may not necessarily play the same critical and essential role during the whole task, and that rTMS may be a useful tool to complement fMRI in order to infer functionality of a cortical region of the human brain.

To date, the neural mechanisms underlying executive processes are still poorly understood, even less are the mechanisms by which rTMS interferes with cortical information processing and induces such a “temporary lesion.” It is believed that the rTMS-induced “noise” into neural processes may, perhaps, be the consequence of a stimulation-induced synchronization of neuronal firing disrupting active processing in the underlying cortex (Pascual-Leone et al., 2000; Walsh and Cowey, 2000). A valid alternative, however, may also be represented by a suppression in cortical excitability (lasting up to 1 second) observed following short trains of rTMS at 20 Hz (Modugno et al., 2001) or induced abnormality in the release of prefronto-striatal dopamine (Strafella et al., 2001).

The latter is suggested by the contribution of the striatum and role played by dopamine during the performance of tasks requiring executive processes. Indeed, studies of dopamine depletion in non-human primates suggest a possible involvement of striatal dopamine in set-shifting tasks (Collins et al., 2000; Roberts et al., 1994) while other neuroimaging studies have proposed that changes in striatal dopamine levels can modulate certain set-shifting processes (Monchi et al., 2006a) and that level of cognitive impairment may be dependent on the level of dopamine depletion (Cropley et al., 2006).

Whatever the rTMS mechanisms may be, the ultimate outcome appears to be a transient interruption of the specific normal cortical processing (i.e. provision of feedback) in a restricted area of the prefrontal cortex (i.e. DLPFC).

3.7. Acknowledgments

This work was funded by the Canadian Institutes of Health Research and Canadian Foundation Innovation (CFI) to APS, Fonds de la Recherche en Santé du Québec to APS and OM, and Regroupement Provincial en Imagerie Cérébrale to APS and OM.

3.8. Figures

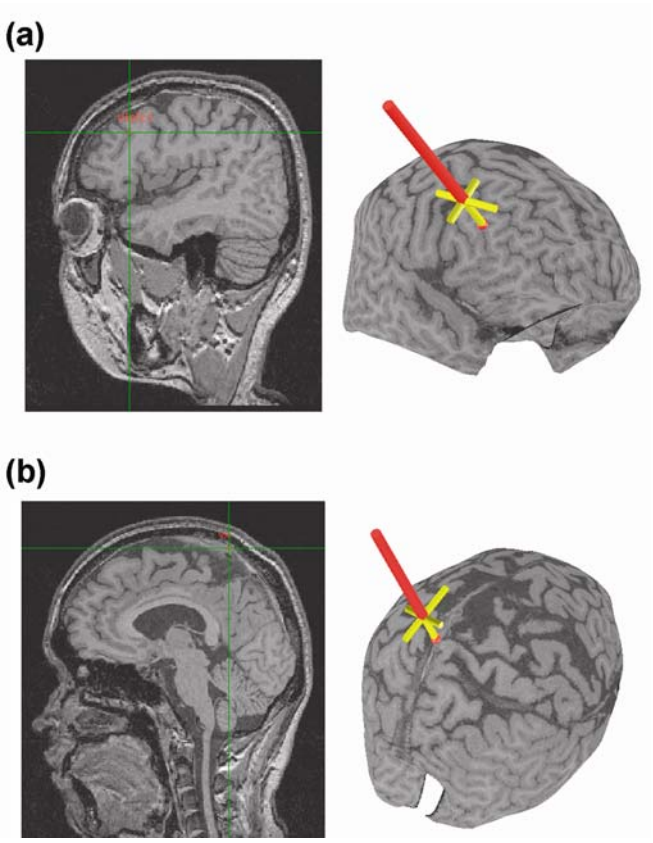

Figure 3.1. TMS targeting with frameless stereotaxy. The TMS coil was located over (a) the right DL-PFC (X=45 Y=33 Z=25) or (b) the vertex (control) (X= 0 Y= -35 Z= 80). Positioning of the TMS coil over these locations, marked on the native MRI, was performed with the aid of a frameless stereotaxic system.

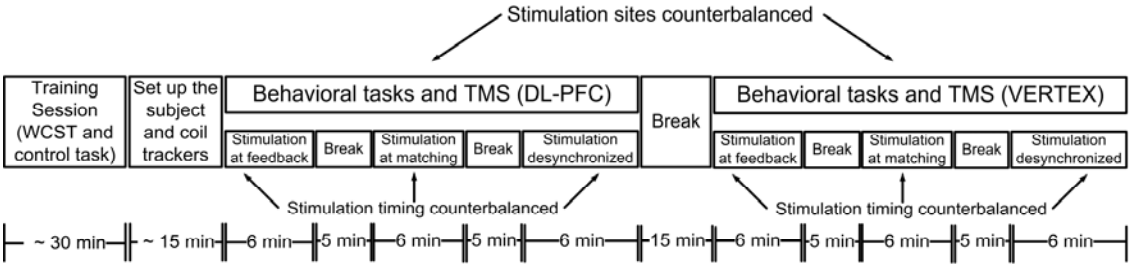

Figure 3.2. Timeline of the experimental setup. All subjects were trained for approximately 30 minutes at the beginning of the experiment. After registering the subjects' anatomical land marks to their structural MRIs, the subjects performed six minutes of the behavioral tasks while rTMS was administered at DL-PFC or vertex (control) in three different timing conditions. The order of stimulation sites and timings were counterbalanced. The behavioral tasks consisted of the WCST and the control task.

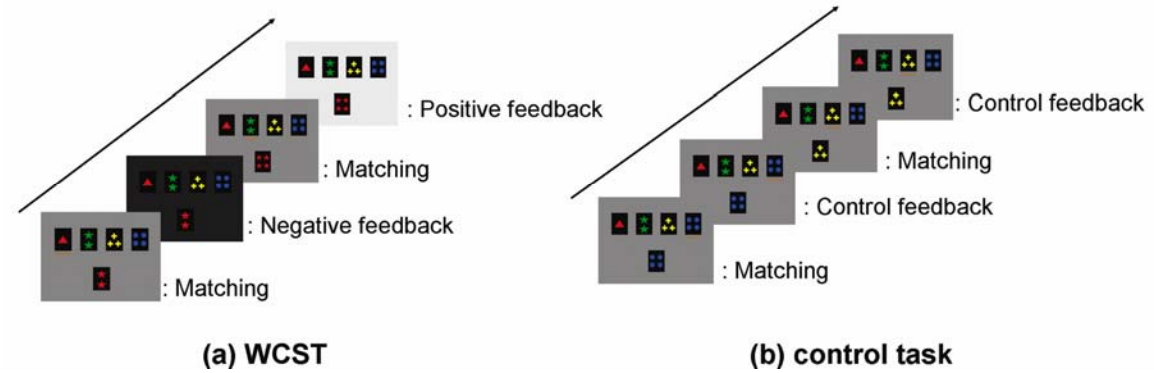

Figure 3.3. Behavioral tasks. (a) WCST: for each stimulus, the four symbols on top are reference symbols, and the symbol on the bottom is the test symbol. The subjects could move a yellow bar which was displayed under the reference symbols by pressing the left button of a mouse with his/her index finger. Pressing the right button with the middle finger confirmed the selection of the symbol followed by negative or positive feedback. The subjects had to find out the rule of classification (color, shape, number) by trial and error. (b) Control task: the test symbol was identical to one of the reference symbols. The rest was the same as WCST.

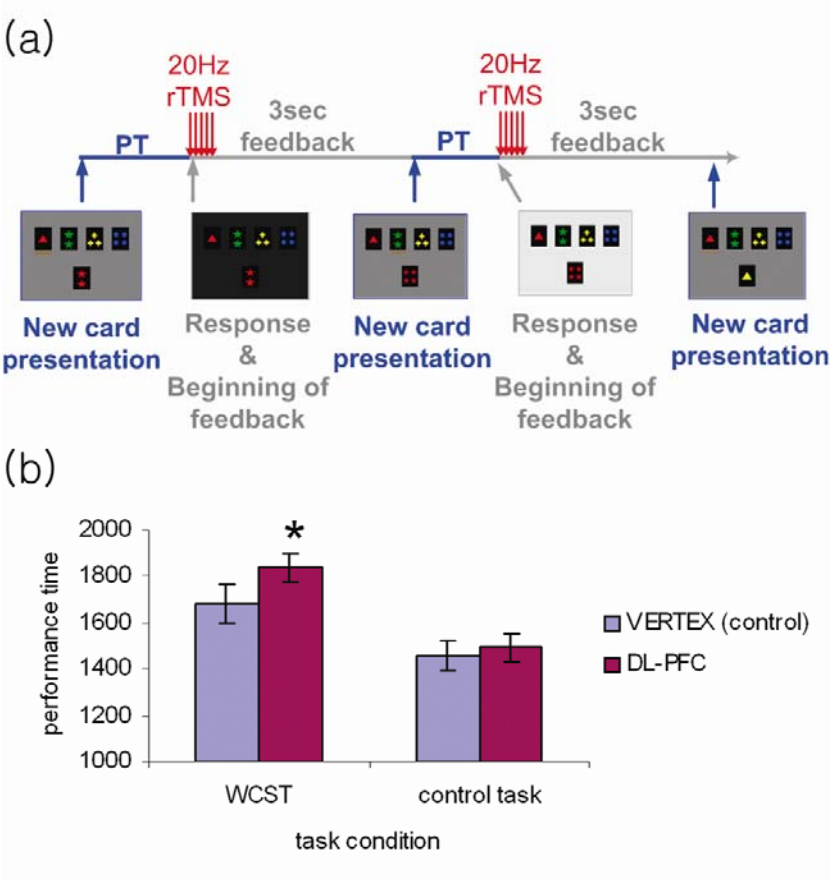

Figure 3.4. rTMS at the beginning of feedback (a) while the subject performed the WCST or control task, rTMS was applied over the right DL-PFC or vertex at the beginning of receiving feedback. (b) DL-PFC stimulation during the feedback phase of the WCST increased performance time (PT) compared to the vertex stimulation (* p = 0.023; two-tailed). No stimulation effect was observed in the control task.

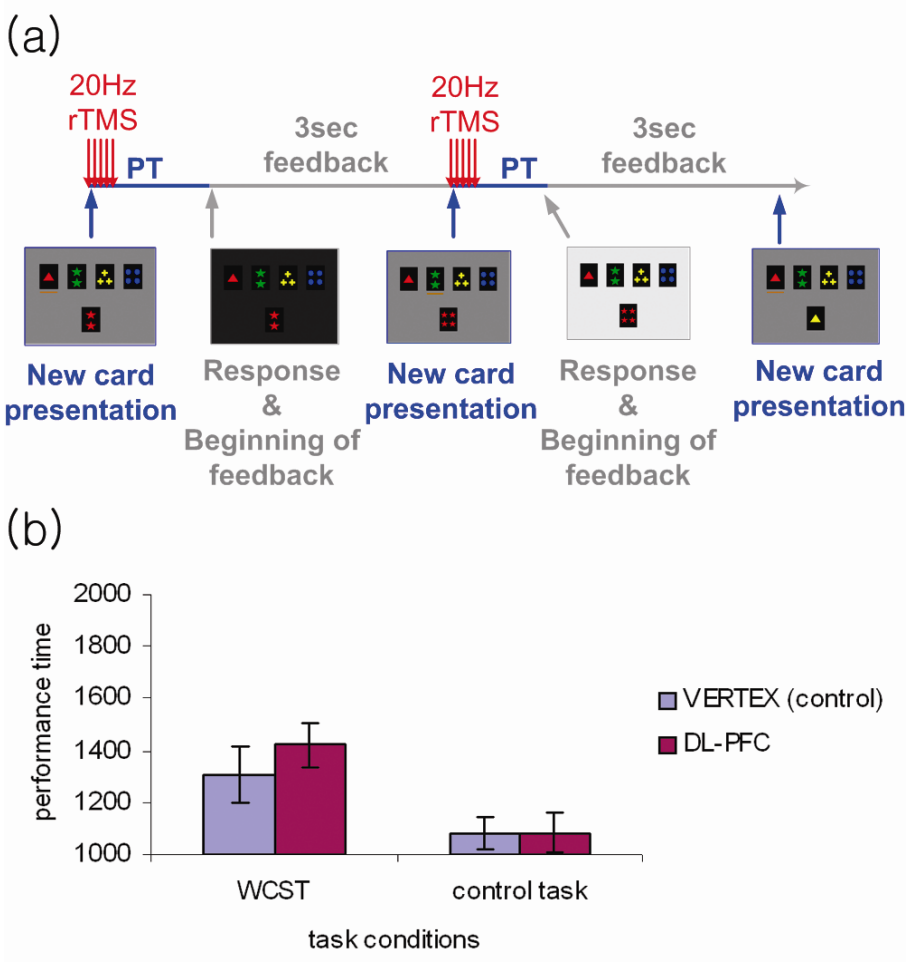

Figure 3.5. rTMS at the beginning of matching (a) while the subject performed the WCST or control task, rTMS was applied over the right DL-PFC or vertex at the beginning of matching. (b) DL-PFC stimulation during the matching phase of WCST or control task had no effect on PT compared to the vertex stimulation.

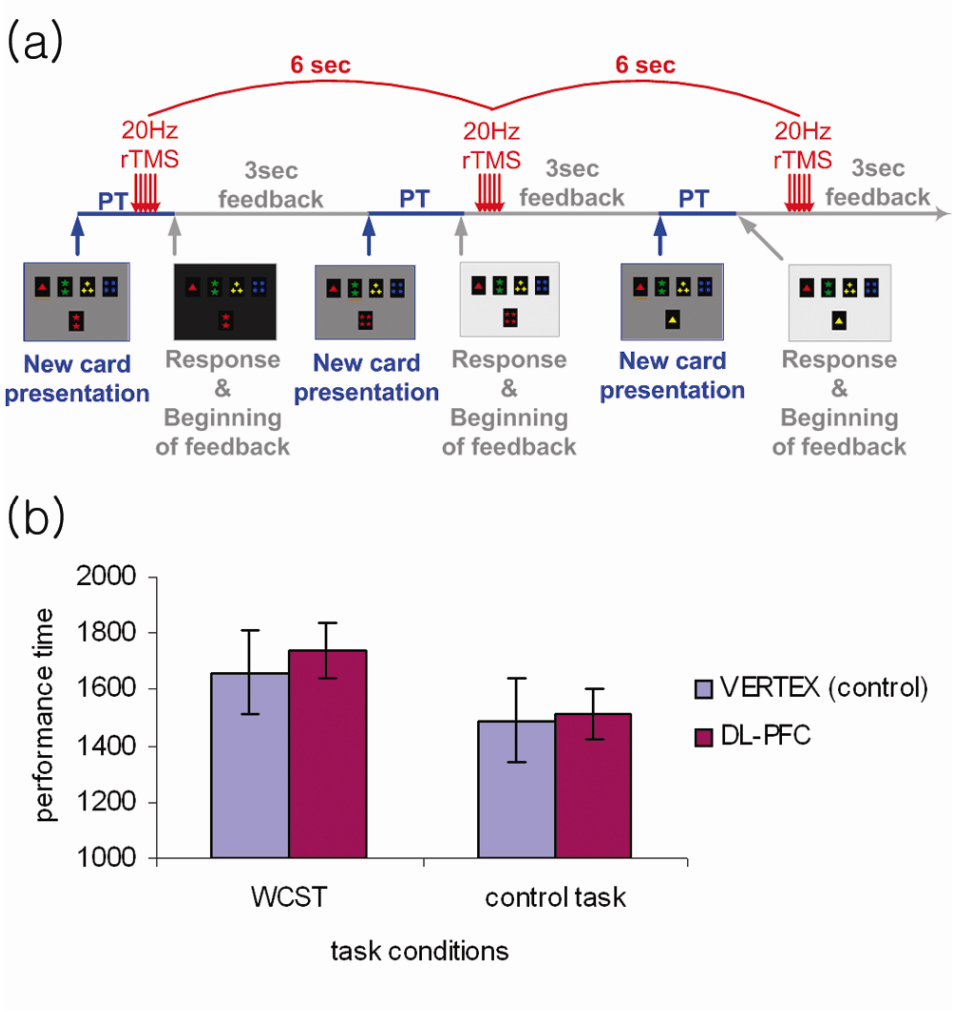

Figure 3.6. Desynchronized rTMS (a) while the subject performed the WCST or control task, rTMS was applied over the right DL-PFC or vertex at every 6 seconds which was desynchronized with the tasks. (b) Desynchronized DL-PFC stimulation had no effect on PT compared to the vertex stimulation.

Chapter 4

The functional role of the left DLPFC in set-shifting and its connection to striatal dopamine

4.1. Preface

Having demonstrated the crucial role of the right DLPFC in monitoring of working memory in the previous chapter, we proceeded to test the functional role of the left DLPFC. As indicated in previous chapters, it has been hypothesized that the left DLPFC is engaged in set-shifting processes (Monchi et al., 2006a; 2006b; 2007), and that its activation is associated with the caudate nucleus.

In order to test this causality and to examine the functional role of the left DLPFC and its influences on task-induced striatal dopamine transmission (Monchi et al., 2006a), the following TMS-[^{11}C]raclopride PET study, published in European Journal of Neuroscience in 2008, has been carried out. This manuscript has received the EJN Best Publication Award in 2009 (see appendix)

Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during set-shifting task: a TMS/ [^{11}C]raclopride PET study

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* Reprinted with permission from European Journal of Neuroscience, 2008, Ko JH, Monchi O, Ptito A, Bloomfield P, Houle S, Strafella AP: "Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during set-shifting task: a TMS/ [11C]raclopride PET study", vol. 28 (10), pp. 2147–2155, 2008.

4.2. Abstract

The prefronto-striatal network is considered to play a key role in executive functions. Previous neuroimaging studies have shown that executive processes tested with card-sorting tasks requiring planning and set-shifting [e.g. Montreal-card-sorting-task (MCST)] may engage the dorsolateral prefrontal cortex (DLPFC) while inducing dopamine release in the striatum. However, functional imaging studies can only provide neuronal correlates of cognitive performance and cannot establish a causal relation between observed brain activity and task performance. In order to investigate the contribution of the DLPFC during set-shifting and its effect on the striatal dopaminergic system, we applied continuous theta burst stimulation (cTBS) to left and right DLPFC. Our aim was to transiently disrupt its function and to measure MCST performance and striatal dopamine release during [^{11}C]raclopride PET.

A significant hemispheric asymmetry was observed. cTBS of the left DLPFC impaired MCST performance and dopamine release in the ipsilateral caudate / anterior putamen and contralateral caudate nucleus, as compared to cTBS of the vertex (control). These effects appeared to be limited only to left DLPFC stimulation while right DLPFC stimulation did not influence task performance and [^{11}C]raclopride binding potential in the striatum.

This is the first study showing that cTBS, by disrupting left prefrontal function, may indirectly affect striatal dopamine neurotransmission during performance of executive tasks. This cTBS-induced regional prefrontal effect and modulation of the fronto-striatal network may be important for understanding the contribution of hemisphere laterality and its neural bases with regard to executive functions as well as for revealing the neurochemical substrate underlying cognitive deficits.

4.3. Introduction

There is clear evidence that damage to the prefrontal cortex impairs performance on cognitive set-shifting tasks (Milner, 1963; Nelson, 1976; Stuss *et al.*, 2000). Functional neuroimaging investigations support these observations (Monchi *et al.*, 2001; 2006b; Owen, 2004). In a previous study, conducted with functional magnetic resonance imaging (fMRI), our group demonstrated differential activation of parts of the prefrontal cortex during performance of a sorting task. In particular, we were able to show that the engagement of the dorsolateral prefrontal cortex (DLPFC) during the provision of feedback after each matching response was consistent with the proposed role of this region in the monitoring of events in working memory (Monchi *et al.*, 2001; Petrides, 2000). From this and other studies, it emerged however, that not only the DLPFC but also the striatum plays a significant role during executive processes requiring planning and set-

shifting (Lewis et al., 2004; Monchi et al., 2001; 2004; 2006a; 2006b; 2007; Owen, 2004; Rogers et al., 2000). This co-activation of the DLPFC and the striatum during set-shifting tasks is in line with the well-described cognitive anatomical loop proposed by Alexander et al. (1986). In addition, recent positron emission tomography (PET) studies conducted with D_2-dopamine receptor ligand [^{11}C]raclopride in healthy subjects while performing the Montreal Card Sorting Task (MCST) (Monchi *et al.*, 2006a) have shown that planning of a set-shift may also be associated with bilateral striatal (i.e. caudate nucleus) reduction in [^{11}C]raclopride binding potential (BP), suggesting that striatal dopamine neurotransmission may increase significantly during the performance of specific executive processes.

Even though functional neuroimaging studies have provided great insights in the role of DLPFC and striatum during set-shifting tasks, neuroimaging alone suffers from the limitation that it provides only neuronal correlates of cognitive performance and often cannot determine a causal relation between observed brain activity and cognitive performance (Johnson *et al.*, 2007; Rushworth *et al.*, 2002). Thus, in the human brain, the specific functional relevance of the DLPFC and striatal dopamine release during set-shifting tasks remains to be established. Here, we used continuous theta burst stimulation (cTBS), a type of repetitive transcranial magnetic stimulation (rTMS) technique (Huang et al., 2005), to

address this issue. We predicted that such application of rTMS to an area of cortex that at a given time point is actively involved in processing of task-relevant information would cause performance to decline (Enomoto *et al.*, 2001; Huang *et al.*, 2005; Pascual-Leone *et al.*, 1994) by acting as a "virtual lesion" (Walsh and Cowey, 2000). In the present study, we tested whether cTBS-induced "lesioning" of the DLPFC during a set-shifting task would interfere with striatal dopamine release measured with [^{11}C]raclopride PET. D_2-dopamine receptor ligand [^{11}C]raclopride binding has been shown to be inversely proportional to the concentration of extra-cellular dopamine (Endres *et al.*, 1997; Laruelle, 2000). In humans, this method has been used to measure striatal dopamine release in response to drugs (Dewey et al., 1993; Laruelle et al., 1997a), behavioral tasks (Koepp *et al.*, 1998) and rTMS (Strafella et al., 2001; 2003; 2005). To test our hypothesis, we used a computerized sorting task, the MCST, which in our previous fMRI studies showed an engagement of the DLPFC and displayed bilateral release of dopamine in the striatum (i.e. caudate) during [^{11}C]raclopride PET (Monchi et al., 2006a; 2006b; 2007). We hypothesized that if DLPFC-cTBS affects task performance and indirectly interferes with task-induced striatal release of dopamine, an increase in [^{11}C]raclopride BP as compared to the control site would result.

Although it has been previously proposed that the role of the DLPFC resides in monitoring of working memory during wisconsin card sorting task, our group reported some differences between left and right hemisphere. In fact while the right DLPFC was more consistently activated during both positive and negative feedback (monitoring working memory), the left DLPFC was more engaged with processing of negative feedback (set-shifting) (Monchi *et al.*, 2001). Greater activation in left DLPFC was also observed in older control subjects during set-shifting with the MCST (Monchi *et al.*, 2007). Other fMRI studies have also pointed out evidences of hemispheric asymmetry in the human lateral prefrontal cortex during cognitive set-shifting (Konishi *et al.*, 2002; Lie *et al.*, 2006). Thus, since hemispheric specialization constitutes an important aspect of executive behavior, we aimed to test such asymmetry. Given the fact that the MCST is designed to have an emphasis on set-shifting compared to other cognitive task (i.e. wisconsin card sorting task) and based on our previous imaging observations (Monchi et al., 2007) we hypothesized that only the left DLPFC stimulation may interfere with task performance, but not the right DLPFC stimulation.

4.4. Method

4.4.1. Subjects and Experimental design

Ten healthy young right-handed adults (20 – 28 years, 4 males and 6 females) participated in the present study after having given written informed consent. They were investigated with [^{11}C]raclopride PET while performing the MCST to measure changes in striatal dopamine release. Each subject underwent three [^{11}C]raclopride PET scans: one after cTBS of the left DLPFC, one following cTBS of the right DLPFC, and one after cTBS of the vertex (control site). The scan order was randomized across subjects and scans were performed at the same time on different days. The experiments were approved by the Research Ethics Committee of the Centre for Addiction and Mental Health.

4.4.2. TMS protocol

cTBS was carried out with the Magstim Rapid^2 (Magstim, UK) using a figure-of-eight coil. The coil was held in the scanner in a fixed position by a mechanical arm over the stimulation sites. It was oriented so that the induced electric current flowed under the coil in a posterior-anterior direction. Stimulus intensities, expressed as a percentage of the maximum stimulator output, were set at 80% of the active motor threshold (AMT). AMT was defined as the lowest stimulus intensity able to elicit five motor evoked potential (MEP) of at least 200 μV averaged over 10 consecutive trials delivered at intervals longer than 5 s. During the determination of AMT, subjects were instructed to maintain a steady muscle

contraction of 20% of maximum voluntary contraction. Audio-visual feedback was given to assist them in maintaining a steady muscle activation (Strafella and Paus, 2000). MEPs were recorded from the contralateral FDI muscle with Ag\Cl surface electrodes fixed on the skin with a belly-tendon montage. Electromyogram (EMG) signal was filtered (50–50 KHz bandpass) and displayed on the EMGrapher screen (Keypoint, Medtronic, Canada) (Strafella *et al.*, 2001). Motor thresholds were measured during the recruitment session and just before PET scans.

Three cTBS blocks (20 seconds each) were applied to the left and right DLPFC and to the vertex (control site) prior to the MCST (Figure 4.1). Each block was separated by a 1 minute interval. Each 20-sec block consisted of bursts containing 3 pulses at 50 Hz repeated at 200 ms intervals (i.e., 5 Hz) (Huang *et al.*, 2005). In total, sixty seconds of cTBS (900 pulses) were administered before each PET acquisition scan. This off-line TMS paradigm has two main advantages: it produces a long-lasting (up to 60 min) inhibitory effect limited to the underlying cortex (Di Lazzaro *et al.*, 2005; Huang *et al.*, 2005; Hubl *et al.*, 2008) and it prevents any exogenous influence of the sound and proprioceptive sensation (given by the TMS) during the task performance (Vallesi *et al.*, 2007).

4.4.3. Location of the target site

In order to target the left and right DLPFCs and vertex (control site), we used a procedure that takes advantage of the standardized stereotaxic space of Talairach and Tournoux (1988) and frameless stereotaxy (Paus, 1999; Strafella *et al.*, 2001) (Figure 4.2). A high-resolution MRI (GE Signa 1.5 T, T1-weighted images, 1 mm slice thickness) of every subject's brain was acquired and transformed into standardized stereotaxic space using the algorithm of Collins et al. (1994). The coordinates selected for the left DLPFC (x=-30, y=40, z=26) and right DLPFC (x=30, y=40, z=26) were based on previous functional activation studies (Monchi *et al.*, 2006b). The chosen control stimulation site (i.e. vertex region, x=0, y=-35, z=80) was based on the lack of activation during performance of the MCST observed in previous studies (Monchi *et al.*, 2001; 2006b) and preliminary TMS-behavioral studies.

The Talairach coordinates were converted into each subject's native MRI space using the reverse native-to-Talairach transformation (Paus, 1999). The positioning of the TMS coil over these locations, marked on the native MRI, was performed with the aid of a frameless stereotaxic system (Rogue Research, Montreal, Canada).

4.4.4. Cognitive Task

During the three PET sessions, we used the same set-shifting condition as that of the MCST, i.e. retrieval with shift task, (Figure 4.3) which, in our previous PET studies, was associated with release of dopamine in the striatum (Monchi *et al.*, 2006a). The task was displayed via a video eyewear (DV920; Icuiti Corporation, New York, USA) placed on the plastic thermal mask. In the retrieval with shift task of the MCST (Figure 4.3), four reference cards were displayed in a row at the top of the screen in all trials. Blocks of twenty classification trials (block duration: 4 minutes) (Figure 4.1) were preceded by the brief presentation of a single cue card. The cue card did not reappear and had to be remembered throughout the block. On each classification trial, a new test card was presented below the reference cards and the subject had to match the test card to one of the four reference cards using one of four buttons with the right dominant hand. Matching each test card to one of the reference cards was based on a classification rule (color, shape or number) determined by making a comparison between the previously viewed cue card and the current test card (Figure 4.3).

The test cards on consecutive trials never shared the same attribute with the cue card. Therefore, matching had to be performed according to a different attribute in each trial. A different cue card was presented before each block. Thirteen blocks separated by one-minute interval were repeated on a given scanning session (Figure 4.1). Subjects underwent a training session of the set-

shifting task before the first PET session in order to reduce a possible learning effect.

4.4.5. Positron Emission Tomography

PET scans were obtained with a high resolution PET CT, Siemens-Biograph HiRez XVI (Siemens Molecular Imaging, Knoxville, TN, U.S.A.) operating in 3D mode with an in-plane resolution of approximately 4.6 mm full width at half-maximum. To minimize subject's head movements in the PET scanner, we used a custom-made thermoplastic facemask together with a head-fixation system (Tru-Scan Imaging, Annapolis). Before each emission scan, following the acquisition of a scout view for accurate positioning of the subject, a low dose (0.2 mSv) CT scan was acquired and used for attenuation correction.

Within five minutes of the ending of the cTBS session (Figure 4.1), 10 mCi of [^{11}C]raclopride was injected into the left antecubital vein over 60 seconds and emission data were then acquired over a period of 60 minutes in 28 frames of progressively increasing duration (5 one-minute frames, 20 two-minute frames, 3 five-minute frames).

High-resolution MRI (GE Signa 1.5 T, T1-weighted images, 1 mm slice thickness) of each subject's brain was acquired and transformed into

standardized stereotaxic space (Talairach and Tournoux, 1988) using automated feature-matching to the MNI template (Collins *et al.*, 1994).

PET frames were summed, registered to the corresponding MRI (Woods *et al.*, 1993) and transformed into standardized stereotaxic space using the transformation parameters previously determined for the MRI. Voxelwise [^{11}C]raclopride BP was calculated using a simplified reference tissue (cerebellum) method (Gunn et al., 1997; Lammertsma and Hume, 1996) to generate statistical parametric images of change in BP (Aston *et al.*, 2000). This method uses the residuals of the least-squares fit of the compartmental model to the data at each voxel to estimate the standard deviation of the BP estimate, thus greatly increasing degrees of freedom. Only peaks falling within the striatum were considered.

A threshold level of $t \geq 4.0$ was considered significant ($p < 0.05$, 2-tailed) corrected for multiple comparisons (Worsley *et al.*, 1996), assuming a search volume equal to the entire striatum and 276 degrees of freedom (Aston *et al.*, 2000). Binding potential values were extracted from a spherical region of interest (radius 5 mm) centered at the x, y, and z coordinates of the statistical peak revealed by the parametric map.

To confirm our results, two additional analyses (three-way ANOVA and direct contrast) using SPM2 (Wellcome Department of Cognitive Neuroscience,

Institute of Neurology) were carried out. For both analyses, averaging over subjects was performed using a random effects-analysis. First, we performed a three-way ANOVA with the factors 'left DLPFC-TMS', 'right DLPFC-TMS' and 'vertex-TMS' (multi-subject PET design with three conditions, F-contrast vector = $[1\ -1\ 0;\ 0\ 1\ -1;\ -1\ 0\ 1]^T$). Then, separately, we performed a paired T-test between the conditions 'left DLPFC-TMS' and 'right DLPFC-TMS' (multi-subject PET design, contrast vector = $[1\ -1]^T$). Parametric images of [^{11}C]raclopride BP transformed into standardized brain space were smoothed with an isotropic Gaussian of 12 mm full-width at half-maximum to accommodate inter-subject differences in anatomy and enable the application of Gaussian fields to the derived statistical images (Friston et al., 1995b). Uncorrected threshold $P < 0.005$ (with extent voxels > 10) was considered significant based on the facts that this analysis was driven by a specific*, a priori,* hypothesis within a small search region (striatum) not involving the whole brain (Friston *et al.*, 1996) and that this was also a confirmatory analysis.

Coordinates listed below are expressed in Talairach space. During the MCST, behavioral responses (i.e. performance time and error trials) were measured. Performance time was calculated from the presentation of the test card to the subject's response, i.e., the selection of a reference card. Error trials were counted as number of incorrect responses. Error trials and performance

time of the left and right DLPFC were normalized and expressed as a percentage of the vertex-cTBS induced behavioral responses (control site). All values are presented as mean ± SE.

4.5. Results

cTBS of the left DLPFC affected MCST-induced striatal dopamine release resulting in a bilateral increase in [^{11}C]raclopride BP in the striatum as compared to control condition (vertex-cTBS) (Figure 4.4). More specifically, [^{11}C]raclopride BP increased by 14.67 % (vertex condition: 2.22 ± 0.12, DLPFC condition: 2.56 ± 0.20) in the ipsilateral caudate nucleus (x=-12, y=5, z=15; t=4.6, cluster size: 48 mm^3) and by 12.59 % (vertex condition: 2.50 ± 0.08, DLPFC condition: 2.80 ± 0.10) in the contralateral caudate (x=18, y=8 z=14; t= 4.8, cluster size: 40 mm^3) (Figure 4.4, 4.5). A significant area of change in [^{11}C]raclopride binding was also observed in the ipsilateral putamen, 12.98 % (vertex condition: 3.29 ± 0.13, DLPFC condition: 3.69 ± 0.18) with its peak (t=4.6) at coordinates x=-21, y=6, z=3. No changes in BP were detected in the contralateral putamen or anywhere in the ventral part of the striatum.

While cTBS of the left DLPFC interfered with the MCST-induced striatal dopamine release, cTBS of the right DLPFC did not affect MCST-induced

dopamine release and did not induce any changes in striatal [^{11}C]raclopride BP as compared to control condition (vertex-cTBS).

Additional analysis using SPM2 confirmed our results. Three-way ANOVA (left DLPFC, right DLPFC and vertex stimulation) showed a significant effect on BP in the left and right caudate nucleus and left putamen ($F(2,18)>3.5$, $p<0.005$ uncorrected, extent threshold >10 voxels). A direct contrast of the left vs right DLPFC stimulation revealed a greater [^{11}C]raclopride BP (i.e. reduced task-related dopamine release) in the bilateral caudate nucleus and left putamen ($T(9)>2.5$, $p<0.001$ uncorrected, extent threshold > 10 voxels) (Figure 4.6).

Behaviorally, cTBS of the left DLPFC induced an increase of 75.38 ± 44.18 % in error trials during the MCST as compared to the right DLPFC-cTBS (error trials: -3.95 ± 18.03 %) (paired t-test $t(9)=2.264$; $p<0.05$) (Figure 4.7). A direct comparison between left and right DLPFC-cTBS induced error trials confirmed the significant difference (paired t-test $t(9)= 2.383$; $p<0.05$). Performance time, however, was not affected by either left (0.75 ± 4.78 %) or right DLPFC (-4.37 ± 5.03 %) stimulation (paired t-test $t(9)=1.665$; $p>0.05$).

4.6. Discussion

In the present study, cTBS of the left DLPFC affected MCST performance and resulted in interference upon dopamine release in the ipsilateral caudate /

anterior putamen and contralateral caudate nucleus, as compared to cTBS of the control site (i.e. vertex). These effects appeared to be limited to the left DLPFC stimulation while cTBS of the right DLPFC did not impair task performance and did not influence [^{11}C]raclopride BP anywhere in the ipsilateral and/or contralateral striatum (as compared to control site) (Figure 4.4, 4.5, 4.7).

Subthreshold cTBS of the frontal cortex is believed to produce a long-lasting inhibition (up to 60 minutes) of the underlying cortex (Huang et al., 2005; Nyffeler et al., 2006; Vallesi et al., 2007) and seem to involve plasticity like-changes at the synaptic connections possibly mediated by NMDA receptors (Huang *et al.*, 2007). These observations has been confirmed both with neurophysiological studies (Di Lazzaro *et al.*, 2005) and more recently with fMRI investigations (Hubl *et al.*, 2008). The latter has demonstrated that cTBS of the frontal eye field is responsible for a long-lasting decrease of the task-related BOLD response recovering to a pre-stimulation level about 60 min after stimulation. Based on these reports and according to our predictions, cTBS affected DLPFC activity and indirectly interfered with the task-induced striatal release of dopamine (Monchi *et al.*, 2006a) resulting in an increase in [^{11}C]raclopride BP (as compared to the control site stimulation).

These findings confirm and further extend our previous observations that set-shifting tasks, such as the MCST, while engaging DLPFC may also influence dopamine release in the striatum (Monchi et al., 2006a; 2006b; 2007).

These observations are in keeping with several reports. In fact, while it is well known that damage to the prefrontal cortex impairs performance on set-shifting tasks (Milner, 1963; Nelson, 1976; Stuss *et al.*, 2000), other studies of dopamine depletion in non-human primates have proposed a possible involvement of striatal dopamine in set-shifting tasks (Collins *et al.*, 2000; Roberts *et al.*, 1994). Similarly, neuroimaging studies have demonstrated that changes in striatal dopamine levels can modulate certain cognitive processes and that the level of cognitive impairment may depend on the level of dopamine depletion (Cropley *et al.*, 2006). Consistent with this hypothesis, PET studies performed in patients with Parkinson's disease (PD) and healthy subjects following tyrosine and phenylalanine-induced depletion (Lozza *et al.*, 2004; Marie *et al.*, 1999; Owen, 2004) have shown a significant correlation between executive task performances and striatal dopamine denervation.

In support of our working hypothesis, particularly intriguing was the observation that only left and not right DLPFC stimulation-induced interference was responsible for the observed results in these right-handed young healthy subjects (Figure 4.4, 4.5, 4.6, 4.7). This is consistent with previous lesion studies.

The impaired top-down control of task-set reconfiguration has been reported to be involved with left frontal lesion while right frontal lesion has been associated with inhibition of inappropriate responses (Aron et al., 2004a; Rogers et al., 1998). Stuss and Alexander (2007) argued in their extensive review of frontal lesions and executive function that task-setting processes are consistently impaired after damage to the left prefrontal cortex. This task setting-left frontal relationship has also been observed during the Wisconsin card sorting task in relation to set-loss errors. Other lesion studies have attempted to identify regional frontal effects using the Stroop task and have defined underlying impaired neural mechanisms supporting, in general, the assumption that left prefrontal cortex lesions affect setting of stimulus-response contingencies (Richer *et al.*, 1993). More recently, fMRI studies using variations of the standard Stroop paradigm and Wisconsin card sorting task have also supported these observations and confirmed hemispheric asymmetry in DLPFC during cognitive tasks (Derrfuss *et al.*, 2005). Specific regional prefrontal effects as consequence of cTBS have also been observed in other recent studies (Vallesi *et al.*, 2007), where these authors while testing different cognitive processes such as implicit temporal processing (e.g., foreperiod [FP] effect) have provided evidence of a specific contribution, this time, of the right (but not left) DLPFC.

cTBS-induced changes in BP were observed both in the caudate and anterior putamen (Figure 4.4, 4.6), in accordance with anatomical (Alexander *et al.*, 1986) and functional imaging studies (Monchi et al., 2001; 2006a; 2006b). In rhesus monkeys, these striatal areas receive axonal afferents mainly from the prefrontal cortex and form part of the 'cognitive' corticostriatal loop proposed by (Alexander *et al.*, 1986). Similarly, in our previous fMRI studies, we reported co-activation of the prefrontal cortex with the caudate nucleus and putamen, respectively, during planning and execution of a set-shift (Monchi *et al.*, 2001; 2006b). Other imaging studies conducted in PD patients have also revealed a significant correlations between executive processes and dopamine transporter densities in the caudate and putamen (Muller *et al.*, 2000). A similar relationship between executive functioning and [^{18}F]DOPA uptake in the putamen has been observed in more recent PET studies (van Beilen and Leenders, 2006). Traditionally, the putamen, unlike the caudate nucleus, has always been associated with motor-related activities rather than with cognitive functions. However, there is clear evidence that the role of the putamen may not be directly linked to the movement itself, but rather to the condition under which it is made (Tolkunov *et al.*, 1998).

Left cTBS of the DLPFC affected release of dopamine in bilateral caudate nucleus (Figure 4.4, 4.6). This TMS-induced prefrontal-striatal network

modulation is consistent with the bilateral involvement of striatal dopaminergic function in relation to working memory task recently been documented by Landau et al. (2008). These results confirmed our previous PET study (Monchi et al., 2006a) which showed changes in [^{11}C]raclopride BP during the same set-shifting condition in the left and right caudate nucleus. Thus, assuming that this behavioral task engages both caudate nuclei, it follows that cTBS-induced interference of the task affects both caudate nuclei similarly. In the context of a prefrontal-striatal network modulation induced by TMS, however, it is important to keep in mind that TMS may influence neural activity both locally in the tissue under the coil and remotely to stimulation site, presumably through trans-synaptic connections (Pascual-Leone et al., 2000; Strafella et al., 2001; Walsh and Cowey, 2000).

Our study provides indirect evidence of fronto-striatal modulation of striatal dopamine during the performance of set-shifting processes. To our knowledge, this is the first study showing that rTMS may indirectly affect task-induced striatal dopamine neurotransmission by disrupting left prefrontal function while involved in processing task-relevant information. This rTMS-induced regional prefrontal inhibition and its modulation of the fronto-striatal network may be important for understanding the contribution of hemisphere laterality and the neural bases of executive functions such as planning and set-shifting. It may also help identify

the neurochemical substrate underlying deficits in cognitive functions observed in neurological disorders associated with dopamine dysfunction, such as PD.

4.7. Acknowledgments

We wish to thank all the staff of the CAMH-PET imaging centre for their assistance in carrying out the studies. This work was funded by the Canadian Institutes of Health Research to APS (MOP-64423).

4.8. Figures

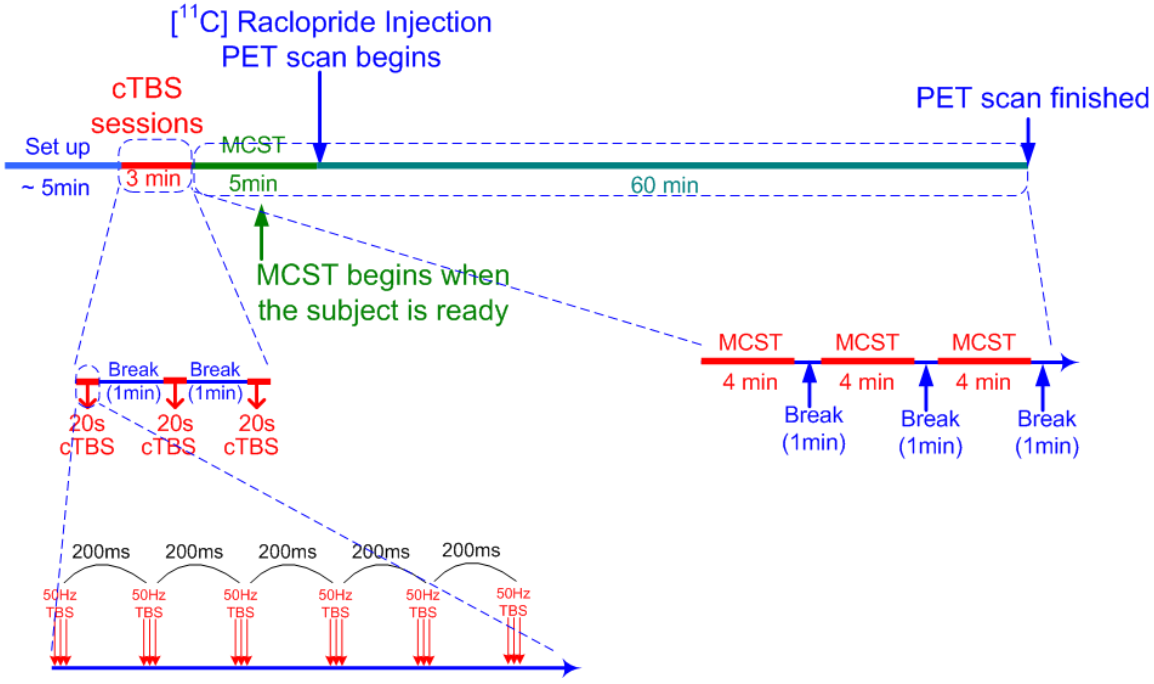


Figure 4.1. Timeline of the experimental setup. All subjects went through three [11C]raclopride PET scans on different day at the same time. On each day, the TMS coil was positioned on either the left DLPFC, the right DLPFC or the vertex (control site). Three cTBS blocks (20 seconds each) were applied prior to the MCST. Each block was separated by a 1 minute interval. Each 20-sec block consisted of bursts containing 3 pulses at 50 Hz repeated at 200 ms intervals (i.e., at 5 Hz). In total, sixty seconds of cTBS (900 pulses) were administered for each PET session. Participants started the MCST after the cTBS sessions until the end of PET scan. The [11C]raclopride was injected within five minutes following cTBS. Thirteen 4-minute blocks separated by 1-minute interval were repeated on a given scanning session.

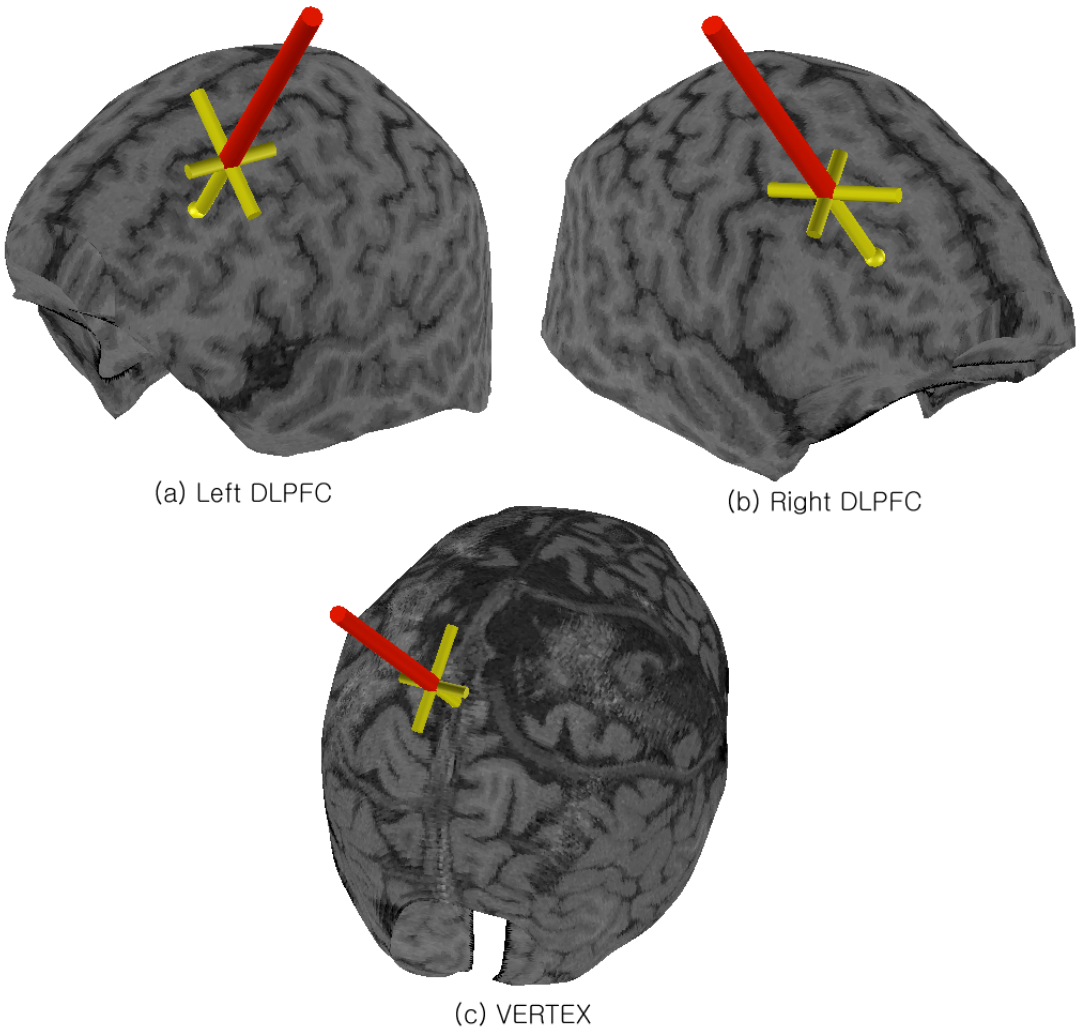


Figure 4.2. TMS targeting with the frameless stereotaxy. TMS coil was located over (a) the left DLPFC (X=-30, Y=40, Z=26), (b) the right DLPFC (X=30, Y=40, Z=26) or (c) the vertex (control site) (X= 0 Y= -35 Z= 80). The positioning of the TMS coil over these locations, marked on the native MRI was performed with the aid of a frameless stereotaxic system.

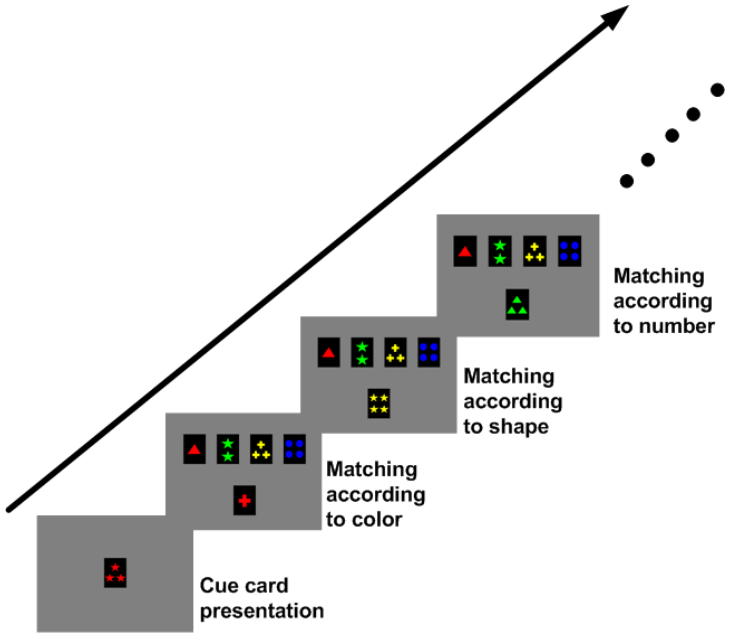


Figure 4.3. Montreal Card Sorting Task. A cue card appears for 3.5 sec at the beginning of a block of twenty classification trials. A different cue card was presented before each block. In this example, the cue card contains three red stars. After the cue card disappears, four reference cards were displayed in a row at the top of the screen in all trials. On each classification trial, a new test card was presented below the reference cards and the subject had to match the test card to one of the four reference cards using one of four buttons with the right hand. The match of each test card to one of the reference cards was based on a classification rule (color, shape or number) that is determined by making a comparison between the previously viewed cue card and the current test card. The test cards on consecutive trials never shared the same attribute with the cue card. Therefore, matching had to be performed according to a different attribute in each trial.

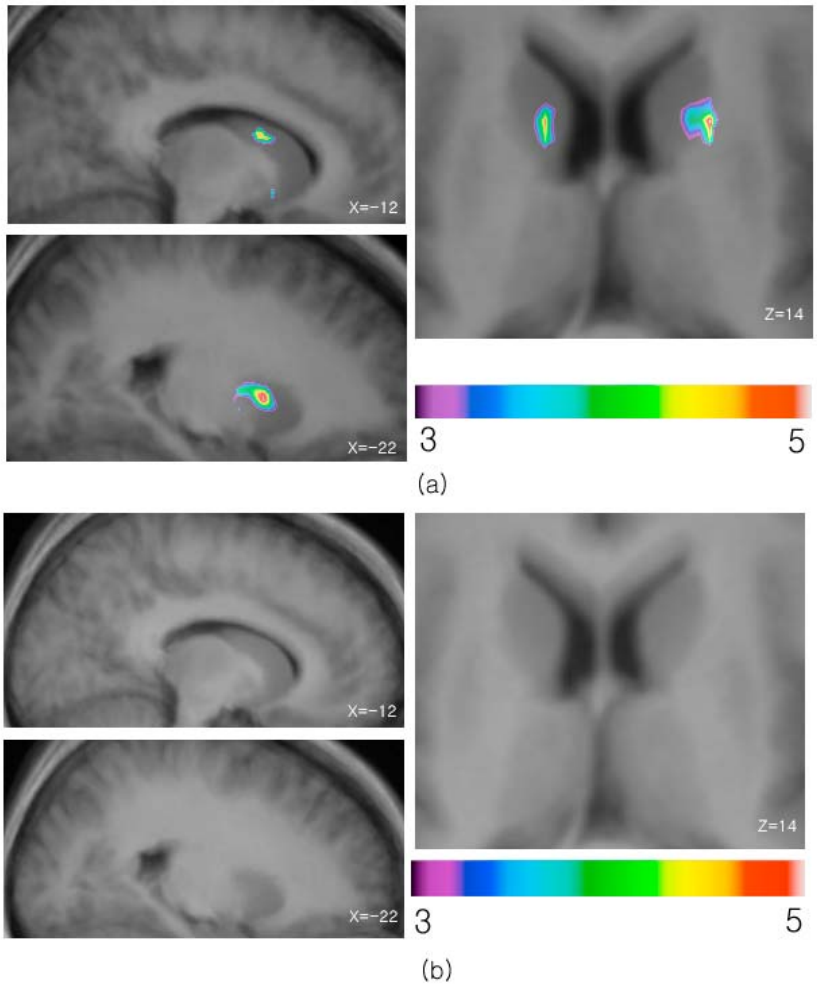
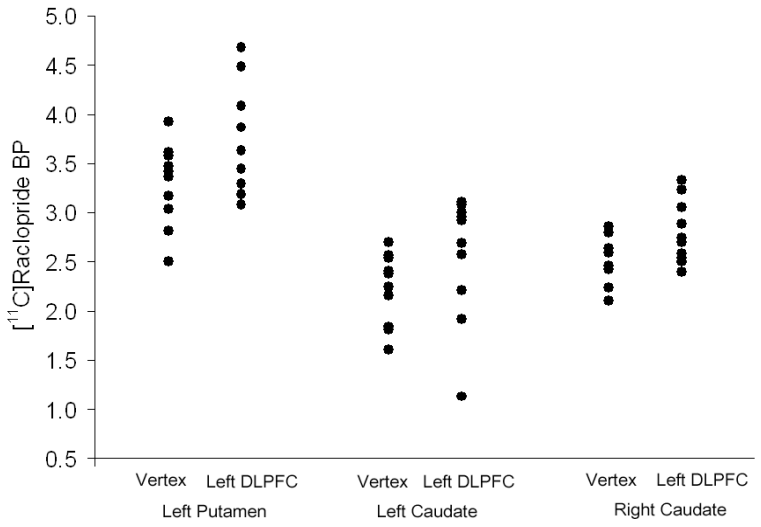
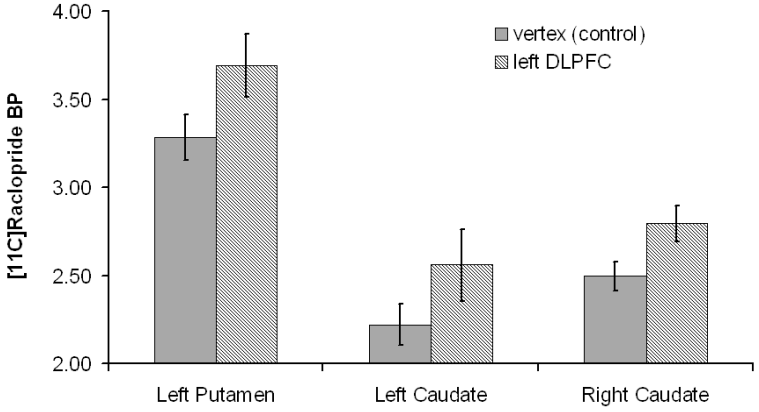


Figure 4.4. Voxel-wise image analysis. (a) Comparison between left DLPFC and vertex stimulation (control condition). Sagittal (x = -12 and x = -22) and axial (z = 14) sections of the statistical parametric map of the change in [^{11}C]raclopride BP overlaid upon the average MRI of all subjects in stereotaxic space. The figure displays the significant areas of striatal dopamine changes during MCST performance after left DLPFC stimulation compared to vertex stimulation (control). (b) Comparison between right DLPFC and vertex stimulation showing the lack of changes in [^{11}C]raclopride BP.



(a) Individual [^{11}C]raclopride BP



(b) Average [^{11}C]raclopride BP

Figure 4.5. ROI image analysis. In the lower figure, [^{11}C]raclopride binding potential (mean ± SE) during MCST performance after left DLPFC stimulation and vertex stimulation (control), from left caudate ($p < 0.05$), right caudate ($p < 0.05$) and left putamen ($p < 0.05$), extracted from a spherical region of interest centered at the x, y and z coordinates of the statistical peak revealed by the parametric map. In the upper figure, the solid dots represent individual BP.

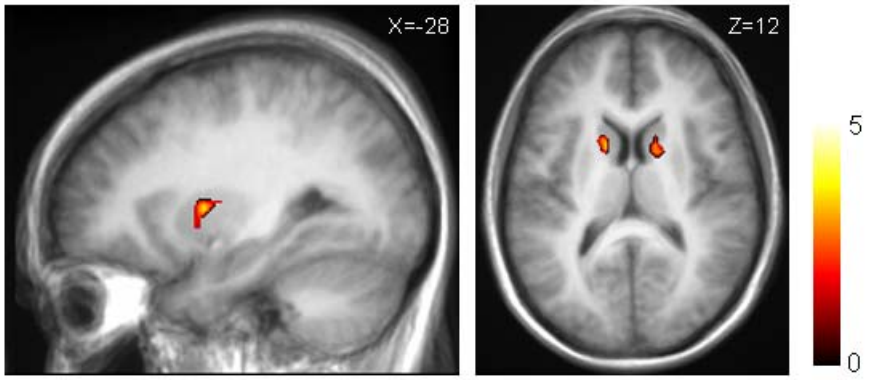


Figure 4.6. Direct contrast of the left vs right DLPFC stimulation showed higher BP (i.e. reduced task-related dopamine release) in the bilateral caudate nucleus (Z= 12) and left putamen (X = -28) ($T(9)>2.5$, $p<0.001$ uncorrected, extent threshold >10 voxels).

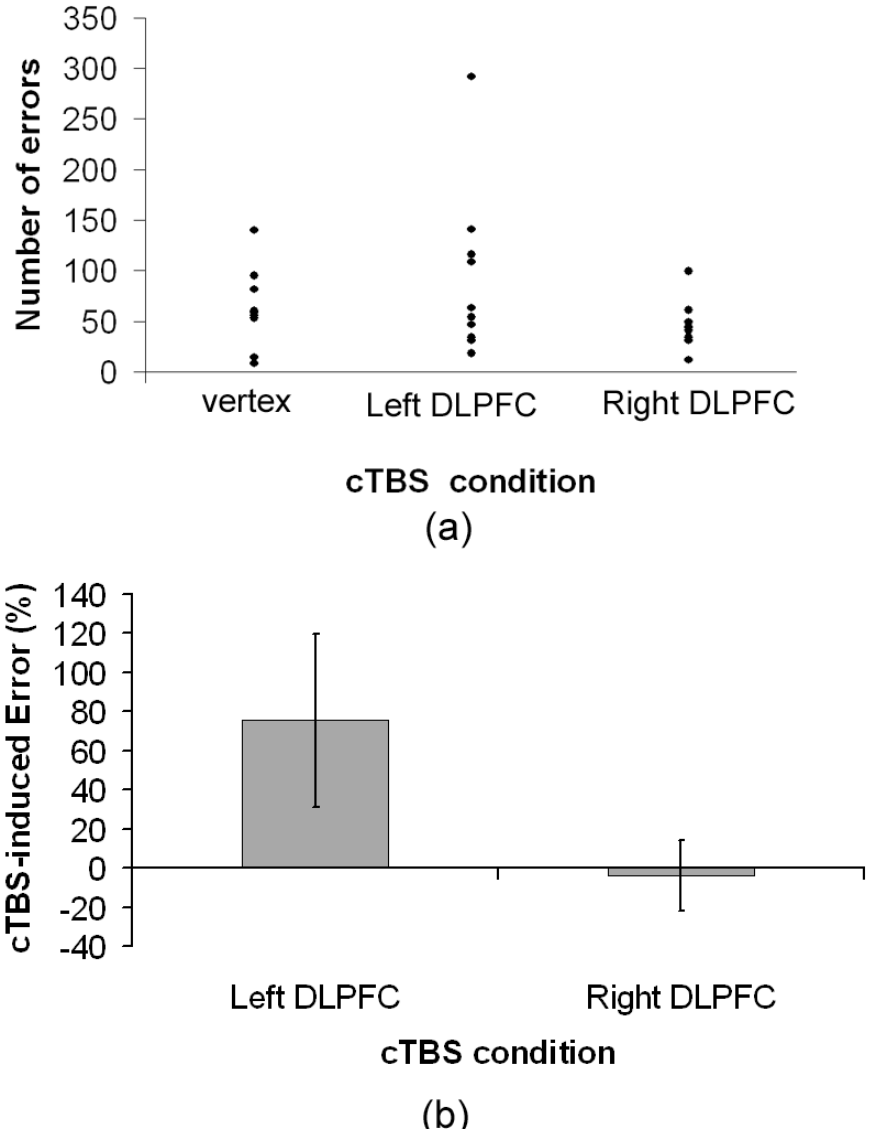


Figure 4.7. Behavioural results. In the lower figure, DLPFC-cTBS induced error trials during MCST expressed as a percentage of the error trials of the vertex-cTBS (control site). Left DLPFC increased error trials of 75.38 ± 44.18 % as compared to right DLPFC-cTBS which did not affect task performance (error trials: -3.95 ± 18.03 %) (paired t-test $t(9)=2.264$; $p<0.05$). Error bars indicate SE. In the upper figure, individual number of errors during MCST after cTBS.

Chapter 5

Cortical dopamine transmission during a card sorting task

5.1. Preface

We have demonstrated the role of the left DLPFC-caudate dopamine circuitry in set-shifting tasks in the previous chapter. The involvement of extrastriatal (i.e. prefrontal) dopamine transmission, however, remained unclear. Based on previous neuroimaging studies (Monchi et al., 2001; 2004; 2007) and as discussed in previous chapters, it was hypothesized that performing the MCST would modulate cortical dopamine transmission in the DLPFC and the ACC.

In order to demonstrate dopamine transmission in the extrastriatal regions, a [^{11}C]FLB 457 PET study, in press in NeuroImage, has been carried out.

Increased dopamine release in the right anterior cingulate cortex during the performance of a sorting task: a [^{11}C]FLB 457 PET study

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5.2. Abstract

There is clear evidence that the prefrontal cortex is strongly involved in executive processes and that dopamine can influence performance on working memory tasks. Although, some studies have emphasized the role of striatal dopamine in executive functions, the role played by prefrontal dopamine during executive tasks is unknown. In order to investigate cortical dopamine transmission during executive function, we used D2-dopamine receptor ligand [^{11}C]FLB 457 PET in healthy subjects while performing the Montreal Card Sorting Task (MCST). During the retrieval with shift task of the MCST, the subjects had to match each test card to one of the reference cards based on a classification rule (color, shape or number) determined by comparing the previously viewed cue card and the current test card. A reduction in [^{11}C]FLB 457 binding potential in the right dorsal anterior cingulate cortex (ACC) was observed when subjects performed the active task compared to the control task. These findings may suggest that right dorsal ACC dopamine neurotransmission increases significantly during the performance of certain executive processes, e.g., conflict monitoring, in keeping with previous evidence from fMRI studies showing ACC activation during similar tasks. These results may provide some insights on the origin of cognitive deficits underlying certain neurological disorders associated with dopamine dysfunction, such as Parkinson's disease and schizophrenia.

5.3. Introduction

There is clear evidence that damage to the prefrontal cortex impairs performance on executive function tasks (Milner, 1963; Nelson, 1976; Stuss et al., 2000) and functional neuroimaging investigations support these observations (Buchsbaum et al., 2005; Konishi et al., 2002; Lie et al., 2006; Monchi et al., 2001). In a previous fMRI study, we demonstrated that performing the Wisconsin card sorting task activates prefrontal areas including the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC), and the anterior cingulate cortex (ACC) (Monchi et al., 2001). More specifically, the DLPFC is most engaged during the provision of feedback after each matching response, a fact which is consistent with the proposed role of this region in the monitoring of events in working memory (Petrides, 2000). VLPFC and ACC are more engaged during negative feedback reception and we hypothesized that these activations are related to preparation to shift set and monitor conflicts of previous versus current rule of classification, respectively. The functional specificity of different prefrontal regions has been further investigated and supported by fMRI studies that used the Montreal card sorting task (MCST), a test specifically designed for the investigation of the different subcomponents of executive function, i.e., retrieval of information and set-shifting (Monchi et al., 2006b; 2007).

While fMRI studies can identify task-specific neuronal correlates with high temporal and spatial resolutions, they cannot provide information on the neurochemical bases of a given function. Identifying the type of neurotransmission involved in executive function is crucial for understanding its underlying mechanism. Since it is known that dopaminergic modulation can alleviate or worsen the performance on working memory tasks (Fournet et al., 2000; Kimberg et al., 1997; Kimberg and D'Esposito, 2003; Kulisevsky et al., 1996; Mehta et al., 1999; 2001), this neurotransmitter has received particular attention.

Changes in [^{11}C]raclopride binding potential (BP) provide a reasonable estimate of synaptic dopamine release in the striatum (Farde et al., 1986). This method has been widely used for investigating the striatal dopaminergic transmission during various cognitive tasks (Goerendt et al., 2003; Ko et al., 2008; Monchi et al., 2006a; Ouchi et al., 2002; Zald et al., 2004). However, although [^{11}C]Raclopride may offer important insight on striatal dopamine neurotransmission during executive functions (Ko et al., 2008; Monchi et al., 2006a), its low affinity limits its application to extrastriatal regions such as the prefrontal brain (Goldman-Rakic et al., 2000).

As revealed by studies in primates, despite a lower density of dopamine receptors relative to the striatum, cortical dopamine plays a critical role in

executive function (Murphy et al., 1996; Watanabe et al., 1997). In humans, converging evidence suggests that cortical dopamine is involved with high-level cognition. Performing working memory task has been shown to increase dopamine release in the frontal cortex (Aalto et al., 2005a; Sawamoto et al., 2008) and ACC dopamine receptor density has been shown to be significantly correlated with performance level on the Wisconsin card sorting task in normal healthy adults (Lumme et al., 2007). To address the role of the prefrontal dopamine during set-shifting tasks (e.g. MCST) in healthy human subjects, we used [^{11}C]FLB 457, a chemical compound with a greater affinity (Kd=20nM) for D2 receptors which allows evaluation of extrastriatal dopamine release (Aalto et al., 2005a; Olsson et al., 1999; Sudo et al., 2001). In previous reports, Olsson et al., (2004) have shown that [^{11}C]FLB 457 BP calculated by simplified reference tissue model (Gunn et al., 1997; Lammertsma and Hume, 1996; Sudo et al., 2001) may provide a reasonable estimate of receptor densities in different extrastriatal areas (e.g. cingulate cortex, frontal cortex, thalamus, temporal cortex) consistent with postmortem study with [125I]epidepride (Kessler et al., 1993). Similarly, [^{11}C]FLB 457 has been demonstrated to be sensitive in detecting changes in extrastriatal endogenous dopamine concentration in non-human primates (Chou et al., 2000) and humans (Aalto et al., 2005a; 2005b;

Hagelberg et al., 2004; Montgomery et al., 2007). Thus, it appears that [^{11}C]FLB 457 is well-suited to capture binding differences in prefrontal areas.

Based on previous anatomical and functional imaging studies with card sorting tasks (Buchsbaum et al., 2005; Konishi et al., 2002; Koski and Paus, 2000; Lie et al., 2006; Monchi et al., 2001; 2007), we hypothesized that performance of the MCST would be associated with increases in dopamine release (decrease BP of [^{11}C]FLB 457) in different prefrontal areas such as the DLPFC (BA 9/46) and ACC (BA 32/24).

5.4. Method

5.4.1. Subjects and experimental design

Eight healthy young right-handed adults (20-33 years, 4 males) participated in the present study after having given written informed consent. They were investigated with [^{11}C]FLB 457 PET while performing the MCST to measure changes in cortical dopamine release. Each subject underwent two [^{11}C]FLB 457 PET scans at the same time on two separate days while they performed either the MCST (retrieval with shift) or the control task (Figure. 5.1) (Ko et al., 2008). Scan order was counterbalanced across subjects. The experiments were approved by the Research Ethics Committee of the Centre for Addiction and Mental Health.

5.4.2. Cognitive task

The tasks were displayed via a video eyewear (VR920; Vuzix Corporation, New York, USA) placed on the plastic thermal mask. Details of the current task have also been described in our previous studies (Ko et al., 2008). In the retrieval with shift condition of the MCST (the active task, Figure 5.1.b), four reference cards were displayed in a row at the top of the screen in all trials. Each one of them encompasses three kinds of characteristics, i.e., number (one to four), shape (triangle, star, cross and circle) and color (red, green, yellow and blue). Their position changed pseudo-randomly on every trial. A block of twenty classification trials was preceded by the brief presentation of a single cue card. The cue card did not reappear and had to be remembered throughout the block. On each classification trial, a new test card was presented below the reference cards and the subject had to match the test card to one of the four reference cards using one of four buttons with the right dominant hand. Matching each test card to one of the reference cards was based on a classification rule (color, shape or number) determined by making a comparison between the previously viewed cue card and the current test card (Figure. 5.1.b). The test card and the cue card shared only one characteristic among number, shape and color. The test cards on consecutive trials never shared the same attribute with the cue card, resulting in a pseudo-random sequence which allowed for a set-shift on each trial. Each

selection of the reference card was followed by a one-second positive (white) or negative (dark) feedback. Five blocks of twenty classification trials (total: 100 trials) were followed by a two-minute break. A different cue card was presented before each block. At the end of each block, the subjects were asked if they remembered the cue card.

In the control task, the test card was identical to one of the reference cards so that the subject simply selected the identical card without having to find an appropriate rule for classification as was required in the active task (Figure. 5.1.c).

Subjects underwent a training session of the task before each PET session in order to reduce a possible learning effect. Error trials were counted as number of incorrect responses and they were averaged for each scan. The reaction time was measured from the presentation of new test card to the selection of the reference card. All values are presented as mean ± SE.

5.4.3. Positron emission tomography

PET scans were obtained with a high resolution PET CT, Siemens-Biograph HiRez XVI (Siemens Molecular Imaging, Knoxville, TN, U.S.A.) operating in 3D mode with an in-plane resolution of approximately 4.6 mm full width at half-maximum. To minimize subject's head movements in the PET scanner, we used a custom-made thermoplastic facemask together with a head-fixation system

(Tru-Scan Imaging, Annapolis). Before each emission scan, following the acquisition of a scout view for accurate positioning of the subject, a low dose (0.2 mSv) CT scan was acquired and used for attenuation correction.

[^{11}C]FLB 457 was injected into the left antecubital vein over 60 seconds and emission data were then acquired over a period of 90 minutes in 15 one-minute frames and 15 five-minute frames. The injected amount was 10.19 ± 0.16 mCi for the active condition and 10.42 ± 0.16 mCi for the control condition.

High-resolution MRI (GE Signa 1.5 T, T1-weighted images, 1 mm slice thickness) of each subject's brain was acquired and transformed into standardized stereotaxic space (Talairach and Tournoux, 1988) using nonlinear automated feature-matching to the MNI template (Collins et al., 1994; Robbins et al., 2004).

PET frames were summed, registered to the corresponding MRI (Woods et al., 1993) and transformed into standardized stereotaxic space (Talairach and Tournoux, 1988) using the transformation parameters of the individual structural MRIs (Collins et al., 1994; Robbins et al., 2004). Voxelwise [^{11}C]FLB 457 BP was calculated using a simplified reference tissue (cerebellum) method (Gunn et al., 1997; Lammertsma and Hume, 1996; Sudo et al., 2001) to generate statistical parametric images of change in BP (Aston et al., 2000). This method uses the residuals of the least-squares fit of the compartmental model to the data at each

voxel to estimate the standard deviation of the BP estimate. Parametric images of [^{11}C]FLB 457 BP were smoothed with an isotropic Gaussian of 6 mm full width at half-maximum to accommodate for intersubject anatomical variability. A threshold level of $t > 4.1$ was considered significant ($p < 0.05$, 2-tailed) corrected for multiple comparisons (Friston, 1997; Worsley et al., 1996) for the regions with a priori hypothesis, i.e., DLPFC and ACC and a more stringent threshold ($t > 4.9$) when the search was extended to the entire brain. Regions within our a priori hypothesis were extracted from bilateral brodmann areas (BA) 32/24 (ACC), 9/46 (DLPFC) using the WFU PickAtlas (SPM extension toolbox). The volume of interest included 6624 voxels and 52992 mm3. As stated above, the reason for choosing BA 32/24 and 9/46 was based on their consistent activations during sorting task in the previous fMRI studies conducted by our and other groups (Buchsbaum et al., 2005; Konishi et al., 2002; Lie et al., 2006; Monchi et al., 2001; 2007). The functional connectivity between these regions and their contribution has been well documented in previous anatomical and functional imaging studies (for review, see Koski and Paus, 2000).

5.5. Results

5.5.1. MCST performance

There was no significant difference in task performance; subjects performed with a mean accuracy of 96.68 ± 0.95 % in the active task and 98.49 ± 0.53 % in the control task (paired $t(7)=1.76$, $p > 0.1$). Depending on individual speed, subjects completed a mean of 1471 ± 45 classification trials for the active task and 1429 ± 36 trials for the control task ($p > 0.05$). The mean reaction time was 1199 ± 141 ms in the active task and 844 ± 97 ms in the control task ($p > 0.05$). Thus, we can safely assume that the observed dopamine release could not be the consequence of different motor performances.

5.5.2. PET results

Performing the active task of MCST decreased [^{11}C]FLB 457 BP in the right ACC (X=6 Y=26 Z=40) ($t=4.3$; $p < 0.05$, corrected for multiple comparison) compared to the control task (Figure. 5.2). The mean BP of [^{11}C]FLB 457 extracted from a spherical region of interest (r = 3mm) centered at the statistical peak revealed by the parametric map was 0.292 ± 0.042 during control task and 0.199 ± 0.049 during active task (paired-t test, $t(7)=3.85$, $p = 0.006$, Figure. 5.3).

While at more stringent threshold, voxel-based analysis did not reveal changes in other prefrontal areas defined in our a priori hypothesis, when using a less conservative threshold (uncorrected for multiple comparisons) a change in binding was observed in the left DLPFC (X=-22 Y=20 Z=44; $t=3.7$). The mean BP of [^{11}C]FLB 457 extracted from a spherical region of interest (r = 3mm) centered

at the statistical peak revealed by the parametric map was 0.229 ± 0.037 during the control task and 0.171 ± 0.046 during the active task (paired-t test, t(7)=3.16, p = 0.016).

When the search was extended to the entire brain, to areas not defined by our a priori hypothesis, a significant area of decrease in [^{11}C]FLB 457 binding was identified at the level of the left occipital cortex (OCC) (X=-10 Y=-98 Z=-10) (t=5.1; $p < 0.05$, corrected for multiple comparison). The mean BP of [^{11}C]FLB 457 in this region was 0.323 ± 0.049 during the control task and 0.255 ± 0.046 during the active task (paired-t test, t(7)=2.81, p = 0.026).

Correlation analyses did not reveal any relationship between extrastriatal [^{11}C]FLB 457 BP and performance measures such as error trials and reaction times.

5.6. Discussion

In the present study, performing the active task of the MCST decreased [^{11}C]FLB 457 BP in the right dorsal ACC compared to the control task. This finding confirms our previous observation that ACC is functionally involved during performance of the MCST (Monchi et al., 2007) and further extends our initial working hypothesis that ACC dopamine may play a relevant role during executive functioning.

A distinction exists in the literature between the functions of the supracallosal (i.e.dorsal), rostral and subcallosal regions of the ACC (Devinsky et al., 1995; Koski and Paus, 2000; Mayberg, 1997; Vogt et al., 1995). It has been proposed that dorsal regions of the ACC are involved in cognition while rostral and subcallosal portions of the ACC are engaged in emotional behaviour (Devinsky et al., 1995; Koski and Paus, 2000).

There is a consensus that dorsal ACC is one of the core components associated with executive function, but its precise role is still a matter of debate (Bush et al., 2000). In a meta-analysis of neuroimaging studies of executive function, dorsal ACC was activated during task-switching, response suppression, and the wisconsin card sorting task (Buchsbaum et al., 2005). Stuss and Alexander (2007) reported that lesions of frontal medial cortex that comprise ACC impairs several cognitive task performances including simple and choice reaction time, feature integration, verbal fluency and Stroop task (naming color patches and incongruent interference) as well as some tasks measuring sustained attention. Botvinick et al. (2004) also argued that dorsal ACC is involved in several cognitive tasks that engage response override, underdetermined responding and error commission. Other authors have emphasized the role of ACC in detecting and processing error signals (Debener et al., 2005; Luu et al., 2000). The common underlying feature of the

aforementioned tasks and our MCST is that the subject has to monitor conflicts because previous rule classification and current response-rule are different. Our findings suggest that dopamine neurotransmission in ACC may play an important role in this type of executive function often described as “conflict monitoring” (Botvinick et al., 1999; Carter et al., 1998; MacDonald et al., 2000).

However, while ACC may be involved in detecting and processing error signals (Debener et al., 2005; Luu et al., 2000), we did not find a significant correlation between observed changes of [^{11}C]FLB 457 BP in the right ACC and error trials on the MCST. This may be explained by the functionally distinct anatomy of the ACC. In fact, while the dorsal ACC (where our peak is located) is prevalently engaged during conflict monitoring (Kerns et al., 2004), the more rostral ACC is involved in error-signal processing (Lie et al., 2006; Taylor et al., 2006). Therefore, it is likely that the observed dopamine release in the right dorsal ACC was triggered when conflict monitoring was required and that it was unrelated to error-signal processing.

This interpretation is in keeping with other fMRI studies manipulating error-likelihood and conflict level (van Eimeren et al., 2006) which showed an increased right dorsal ACC BOLD signal as conflict load increases and error-likelihood decreases. Thus, it is likely that dopamine release may be involved during conflict monitoring rather than in error-signal processing or prediction of

error-likelihood. However, while these observations may find some evidence in previous literature, it is also true and important to keep in mind that we cannot exclude the possibility that other aspects of cognitive function of MCST may have played a role in the observed dopamine release. In fact, a number of other executive functions such as monitoring information held in working memory, rule extraction, subsequent rule application and inhibition of response conflict induced by the non-relevant stimulus features may have contributed to this dopaminergic changes.

An interesting finding of the present study is the unilateral release of dopamine in the right ACC. We and others have observed this in previous fMRI studies. We showed that only the right ACC was activated when comparing retrieval with shift (active task in the present study) versus continuous shift (Monchi et al., 2007) during the MCST. Similarly, Lutcke and Frahm (2008) reported that while the right ACC was activated for correct inhibitions of go-no go task implicating conflict monitoring, error-related processes activated ACC bilaterally. This is also in agreement with MacDonald et al., (2000) who reported that only the right ACC was activated during response to the incongruent stimuli of the Stroop task. These observations seem to suggest that right ACC may play an important role in this type of executive function described as “conflict monitoring”.

The lack of a strong significant effect in other prefrontal areas other than ACC should be interpreted carefully since MCST has been previously shown to be involved with other lateral prefrontal cortices (Monchi et al., 2007). In fact, while voxel-based analysis corrected for multiple comparisons did not reveal significant changes, with a less stringent threshold (uncorrected for multiple comparisons) changes in binding could be observed in one the areas defined by our a-priori hypothesis, i.e. the DLPFC. The causality of left DLPFC in set-shifting has been recently confirmed in a transcranial magnetic stimulation-intervention study (Ko et al., 2008). A possible explanation on why DLPFC did not survive correction for multiple corrections may have multiple explanations. In fact, in demonstrating relationships between prefrontal areas, Koski and Paus (2000) have described that increases in activity within a particular subdivision of the cingulate occur most often along with increases in activity in specific regions of the frontal cortex. In particular, the relationship between supracallosal (i.e. dorsal) cingulate and the middle frontal gyrus is significantly stronger when greater is the difficulty level of the task. Thus, more difficult tasks may demand the joint efforts of both supracallosal cingulate and middle frontal cortex areas. Although our subjects during the active task appeared to take more time to respond than in control task due to the higher cognitive demand (1199 ± 141 ms vs 844 ± 97 ms), the lack of significant difference between these two conditions

and the high accuracy of their performance during the MCST (active task: 96.68 %; control task: 98.49 %) suggest that the training session of the MCTS (before PET) may have significantly reduced the task challenge for them and possibly produced a ceiling effect preventing the detection of reasonable correlations between behavior and imaging. In alternative, another possible explanation could be methodological and linked to the different density of D2 and D1 receptors in the cortex where there are 20-fold more D1 receptors than D2 receptors (Goldman-Rakic et al., 2000). This agrees with the fact that in primates, performance on a working memory task has been shown to be impaired by D1 receptor antagonist administration to DLPFC, but not by D2 receptor antagonist (Brozoski et al., 1979; Sawaguchi and Goldman-Rakic, 1991, 1994; Seamans et al., 1998). Since [^{11}C]FLB 457 is mainly a D2-receptor antagonist, it is possible that this radio-tracer may have not been sensitive enough to pick-up significant dopaminergic changes over certain areas of the prefrontal cortex (i.e. DLPFC) that were not significantly engaged.

When we extended the search to the entire brain, outside PFC regions, the left OCC (BA 17/18) also showed a significant increase in dopamine release during the active task. Although this region has been consistently reported to present increased activation during imaging studies associated with sorting tasks (Buchsbaum et al., 2005) and it is known that visual stimulation can induce

detectable changes in dopamine activity in the OCC (Muller and Huston, 2007), the relationship between dopamine and sorting tasks at the level of this occipital region is unclear at the moment. One possible explanation could be a greater attentional effect due to the higher task demands.

In conclusion, the present study showed that performing the MCST increased dopamine release in selective cortical areas. We propose that the dopaminergic transmission in the right ACC may be related to conflict monitoring during set-shifting processes. These results may provide some insights on the origin of cognitive deficits underlying certain neurological and psychiatric disorders associated with dopamine dysfunction, such as Parkinson's disease and schizophrenia.

5.7. Acknowledgments

We wish to thank all the staff of the CAMH-PET imaging centre for their assistance in carrying out the studies. This work was funded by the Canadian Institutes of Health Research to APS (MOP-64423). APS is supported by the CIHR New Investigator Research Award.

5.8. Figures

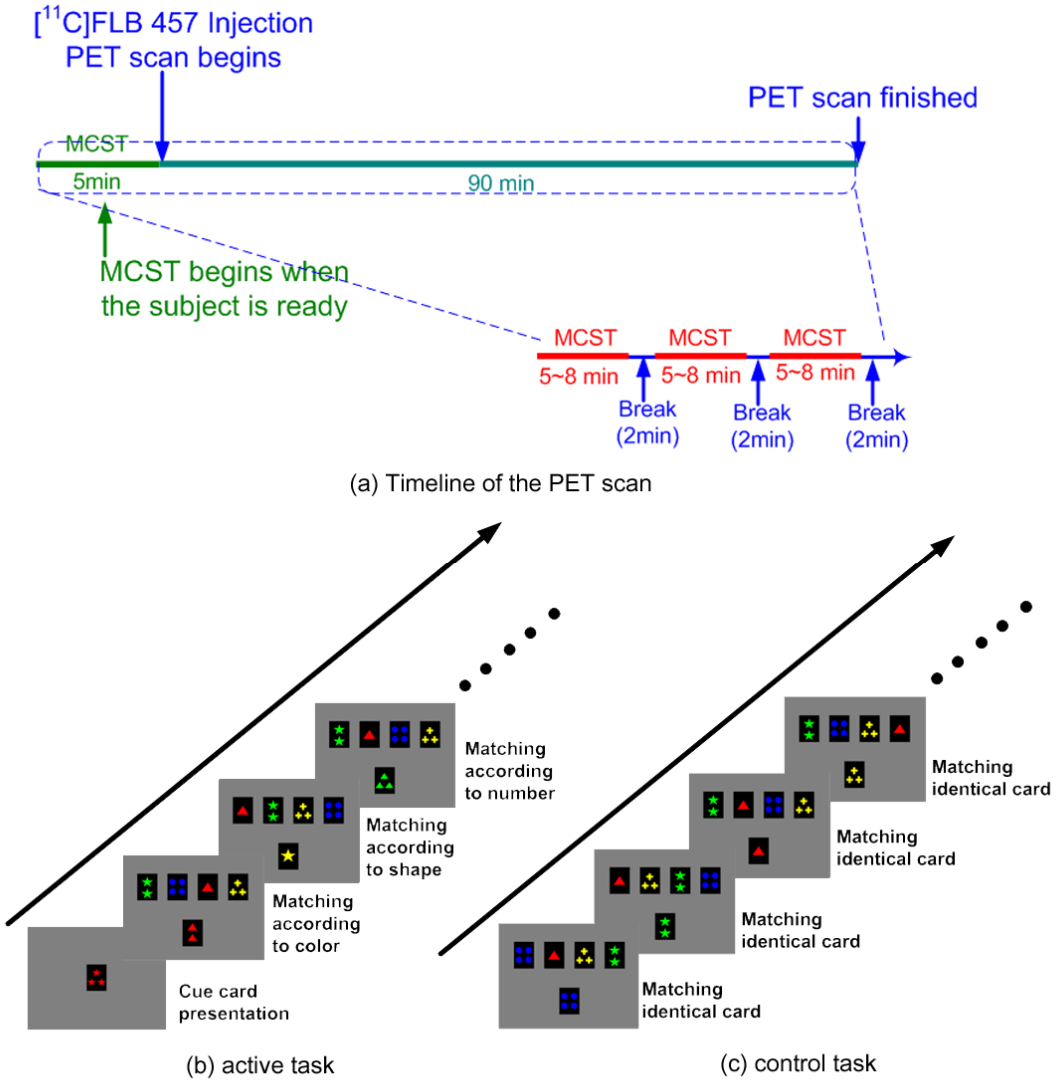

Figure 5.1. Study design. (a) Each subject underwent two [11C]FLB 457 PET scans at the same time on two separate days while performing either the MCST (retrieval with shift) or the control task. Scan order was counterbalanced across subjects. Participants started the MCST five minutes before the radio-ligand injection and continued until the end of PET scanning with two-minute breaks between blocks; (b) active task; (c) control task.

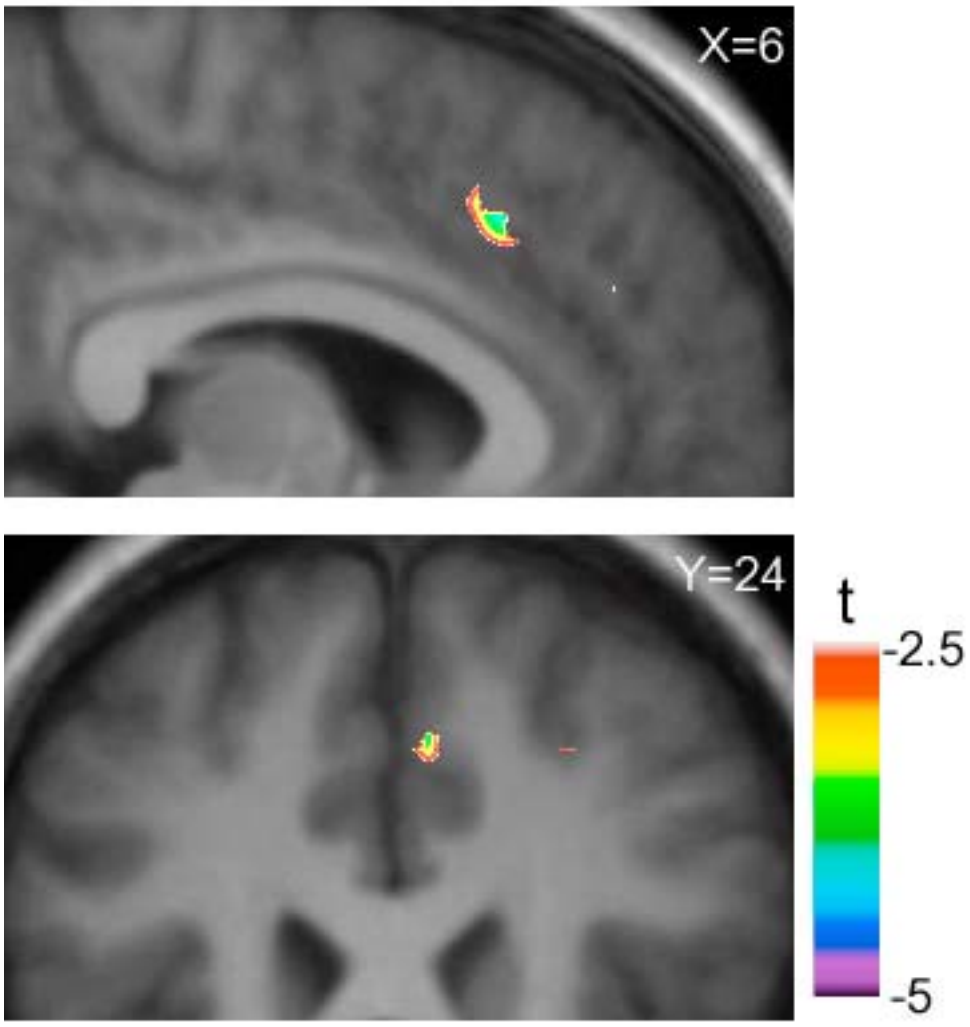

Figure 5.2. Active vs. control tasks condition. Sagittal (X = 6) and coronal (Y=24) section of the statistical parametric map of the change in [^{11}C]FLB 456 BP overlaid upon the average MRI of all subjects in standardized stereotaxic space. The figure displays the significant area of dopamine changes during active task performance compared to the control task at the level of dorsal ACC.

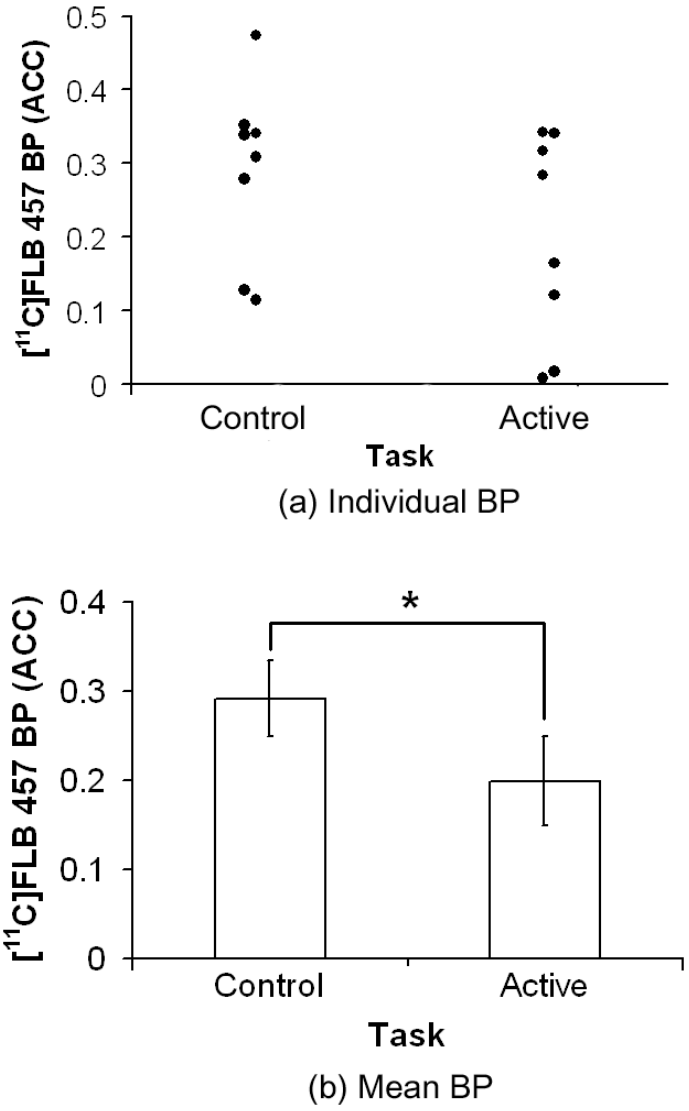

Figure 5.3. Active vs. control tasks condition. (a) Individual ACC-[^{11}C]FLB 457 BP and (b) mean ± SE of ACC-[^{11}C]FLB 457 BP during control and active task extracted from a spherical region of interest (r = 3mm) centered at the x, y and z coordinates of the statistical peak (X=6, Y=26, Z=40) revealed by the parametric map (paired-t test, $t(7) = 3.85$, *$p = 0.006$).

Chapter 6

Conclusion

6.1. Summary and implications

The primary objective of this doctoral dissertation was to investigate the prefronto-striatal network underlying executive functions in normal healthy subjects. Using rTMS, we induced a transient “virtual lesion” to study the functional role of different prefrontal regions during specific executive processes, and demonstrated how the prefrontal-striatal network modulates dopamine transmission during performance of executive tasks. Three studies were carried out with the following specific objectives: 1) to evaluate the functional role of the right DLPFC in monitoring information held in working memory during the feedback periods of the WCST, 2) to examine the functional role of the left DLPFC and its modulation of striatal dopamine during set-shifting in the MCST, and 3) to investigate extrastriatal (i.e. prefrontal) dopamine transmission during the performance of the MCST.

Study 1 was essential in demonstrating the importance of the right DLPFC in the monitoring of information held in working memory (Konishi et al., 2002; Lie et al., 2006; Monchi et al., 2001). This study showed that when rTMS was

applied to the right DLPFC specifically during the period when the subject was receiving feedback regarding his/her last response, performance on the WCST deteriorated (Figure 3.4). Furthermore, task performance was not affected when rTMS was delivered either during the execution of the response (matching) (Figure 3.5), or when the rTMS was desynchronized with specific stages of the WCST (Figure 3.6). Results on the control task were not influenced by rTMS under any conditions (Figure 3.4, 3.5, 3.6). We therefore demonstrated a time- and task-specific involvement of the right DLPFC in monitoring processing of information.

Overall, study 1 highlights the importance of rTMS as a useful tool to complement functional imaging studies in order to infer functionality of a given cortical region in human brains *in vivo*.

The observation that rTMS did not influence error rate significantly during the WCST is consistent with the previous report by Wagner et al. (2006) who observed no significant effect on error making during the WCST when stimulating the DLPFC. There are two potential explanations for these findings. The first is that the right DLPFC is not responsible for error making as proposed by studies with non-human primates (Petrides, 1994, 2000, 2005). The second is that, considering the fact that rTMS-induced error trials have been reported less frequently in relation to different tasks and cortical areas stimulated (Hadland et

al., 2001; Kennerley et al., 2004; Rushworth et al., 2002; Walsh and Pascual-Leone, 2003b), it may be that rTMS parameters (e.g. intensity, frequency, and unilateral stimulation) used so far in different studies have not been strong enough to induce a complete "virtual lesion."

The mechanisms underlying rTMS-induced cortical interference are still poorly understood. It is believed that the rTMS-induced "noise" into neural processes may, perhaps, be the consequence of a stimulation-induced synchronization of neuronal firing, disrupting active processing in the underlying cortex (Pascual-Leone et al., 2000; Walsh and Cowey, 2000). A valid alternative, however, may also be represented by rTMS-induced suppression in cortical excitability (Modugno et al., 2001) or rTMS-induced abnormality in the release of prefronto-striatal dopamine (Strafella et al., 2001). Whatever the rTMS mechanisms may be, the ultimate outcome appears to be a transient interruption of specific cortical processing (i.e. provision of feedback) in a restricted area of the prefrontal cortex (the DLPFC).

Study 2 confirmed the involvement of the left DLPFC-caudate network in the set-shifting process during the MCST (Konishi et al., 2002; Monchi et al., 2001; 2007). The most interesting finding of this study was the significant hemispheric asymmetry of DLPFC functions, such that only the left, but not the right, DLPFC stimulation disrupted the set-shifting process and reduced task-

induced dopamine release in the striatum. This observed functional hemispheric asymmetry is consistent with previous lesion studies (Aron et al., 2004a; Richer et al., 1993; Rogers et al., 1998; Stuss and Alexander, 2007).

The left DLPFC stimulation-induced changes in dopamine release were observed both in the caudate and anterior putamen (Figure 4.4, 4.6), in accordance with anatomical (Alexander *et al.*, 1986) and functional imaging studies (Monchi et al., 2001; 2006a; 2006b). This finding strengthens the hypothesis of the involvement of the prefrontal-caudate circuitry in executive function, and may provide a strong support in the pathogenesis of executive dysfunction in Parkinson's disease (Monchi et al., 2004; 2007; Owen, 2004; Zgaljardic et al., 2003).

These investigations also demonstrated the usefulness of cTBS in cognitive neuroscience studies. In fact, while most rTMS studies have shown the modulation of cognitive task performance only in terms of altered reaction times (for review, Walsh and Pascual-Leone, 2003b), here we demonstrated the potent effect of cTBS stimulation through increased error rates.

Study 3 demonstrated, for the first time, that performing a card sorting task increases synaptic dopamine transmission in prefrontal regions. It also further extended our initial working hypothesis that ACC dopamine may play a relevant role during executive functioning, and in particular, in conflict monitoring.

Although the prefrontal areas express far less dopamine D_2-receptors than the striatum, this finding strengthens the possibility that cortical dopamine is involved in dysexecutive symptoms in patients with schizophrenia (Abi-Dargham et al., 2002; Takahashi et al., 2006) and Parkinson's disease (Bruck et al., 2005; Ito et al., 2002; Rinne et al., 2000).

6.2. Suggestion for future research

While the functional role of the left DLPFC during the WCST is confirmed, the involvement of other important areas still needs to be established. For example, it is hypothesized that the ventrolateral and posterior PFCs are engaged in planning and execution of set-shifting, respectively (Monchi et al., 2001). Applying event-related rTMS over these areas during the WCST or the MCST may shed some light on the functional engagement of these prefrontal areas in the set-shifting processes. In addition, it would be of utmost interest to examine whether these areas are involved in a similar manner in a patient population such as PD. It has been hypothesized that PD patients show greater prefrontal activations in order to compensate for the reduced functioning of the striatum (Monchi et al., 2004; 2007). For example, if these increased activations are truly a compensatory mechanism, right DLPFC stimulation in PD patients may worsen WCST performance (Monchi et al., 2004).

Secondly, the application of a “virtual lesion” with cTBS may allow a clarification on functional hemispheric asymmetry of the DLPFC for different types of errors during the WCST, such as perseverative vs. non-perseverative errors. This technique can also be used to test whether hyper- or hypo-activity of the PFC in PD patients is a direct consequence of the neuro-degeneration of dopaminergic input, or a compensatory mechanism.

Using [^{11}C]FLB 457 in study 3, it has been demonstrated that performing the MCST increased cortical dopamine transmission in the right dorsal ACC and in the left DLPFC in healthy subjects. The coactivation of the DLPFC and the ACC has been consistently observed in previous activation studies with executive function tasks (Koski and Paus, 2000; MacDonald et al., 2000; Monchi et al., 2001; 2007). As discussed in study 2, if cTBS disrupts functional connectivity of a given network only when the given network is functionally demanded, it would be interesting to examine whether the inhibition of the left DLPFC would modulate the functional cortico-cortical connectivity and reduce task-induced dopamine transmission in the ACC.

Another potential study could test the inverted U-shape dopamine hypothesis in PD (Arnsten, 1997; Cools, 2006; Williams and Castner, 2006; Zahrt et al., 1997). The origin of L-dopa-induced executive dysfunction may involve the dopaminergic overflow of still relatively preserved cortical areas in early PD

(Sawamoto et al., 2008; Scatton et al., 1982). [^{11}C]FLB 457 PET could be used to investigate the cortical dopaminergic system, more specifically, to examine how L-dopa intake affects cortical dopamine transmission during the performance of the MCST in PD patients.

The above study design can be similarly applied to the patient population who received deep brain stimulation of the subthalamic nucleus (STN-DBS). STN-DBS is a standard procedure to alleviate drug-resistant symptoms of PD. However, our understanding of the effect of DBS on cognition and cortical dopaminergic transmission is in its infancy and underinvestigated.

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Appendix

Centre universitaire de santé McGill
McGill University Health Centre

August 30, 2005

Dr Antonio Strafella
Movement Disorders Clinic
Neuro-Oncology Clinic
MNH

Re: 6.a. **NEU-05-021**
Functional specificity of the prefrontal cortex: A TMS study
PI: Dr. Antonio Strafella

- Application for Initial Review
- English Consent Form dated version August 24, 2005;
- French Consent Forms dated August 24, 2005;
- French Consent form Validation Certificate dated August 27, 2005;

Dear Dr. Strafella,

Thank you for submitting your Application for Initial Review for the above-cited research protocol.

The above submission, reviewed by the full REB at the August 8, 2005 meeting # 6.a., was found to be acceptable for continuation at the McGill University Health Centre (MUHC). This was entered accordingly into the minutes of the REB meeting.

The approval of the study is valid until August 30, 2006.

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of "at least once per year," it is the responsibility of the investigator to submit an Application for Continuing Review to the REB prior to expiry. However, should the research conclude for any reason prior to approval expiry, you are required to submit a Termination Report to the board once the data analysis is complete to give an account of the study findings and publication status.

The Research Ethics Boards (REBs) of the McGill University Health Centre are registered REBs working under the published guidelines of the Tri-Council Policy Statement, in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998) and the Food and Drugs Act (2001.06.07), acting in conformity with standards set forth in the (US) Code of Federal Regulations governing human subjects research and functioning in a manner consistent with internationally accepted principles of good clinical practice.

Should any revision to the study or other development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval of the amendment.

We trust this will prove satisfactory to you. Thank you for your consideration in this matter.

Yours very truly,

Eugene Bereza, MD CM, CCFP,
Chair, MNH/I Research Ethics Board
EB/lz

August 8, 2005 meeting # 6.a

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PROTOCOL REFERENCE #252/2006

November 20, 2006

Antonio Strafella, MD, PhD, FRCP(C)
Pet Imaging Centre
Centre for Addiction and Mental Health
250 College Street
Toronto, ON M5T 1R8

Dear Dr. Strafella:

Re: Research protocol #252/2006 entitled, "Frontal-striatal functional interactions in the human brain" by Strafella A, Ko JH, Houle S

We are writing to advise you that the Centre for Addiction and Mental Health Research Ethics Board (CAMH REB) has granted approval to the above-named research study **for a period of one year from the date of this letter**[1]. If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval by submitting the CAMH REB "Annual Renewal of Ethics Approval" form on or before **October 1, 2007**. Should the study be completed prior to the annual renewal date, please submit a final report. **The level of continuing review for this study is Level 2.**

The Consent Forms and the advertisement, revised November 14, 2006, have been approved and are attached. **Subjects should receive a copy of their consent form.**

Please contact Leah Young, Manager, CAMH Research Communications, ext. 4932 prior to using any advertisement.

During the course of the research, any significant deviations from the approved protocol (**that is, any deviation which would lead to an increase in risk or a decrease in benefit to human subjects**) and/or any unanticipated developments within the research should be brought to the attention of the Research Ethics Office. Best wishes for the successful completion of your project.

Yours sincerely,

Susan Pilon, MHSc
Manager, Research Ethics Office, CAMH

SP/lw

Encl.

cc: P. Darby G. Czukar S. Kapur L.Young

[1] CAMH investigators are reminded that should they leave CAMH, they are required to inform the Research Ethics Board of the status of any on-going research. If a study is to be closed or transferred to another facility, the REB must be informed and any advertisements must be discontinued.

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November 1, 2007

Strafella, A.

Dear Dr. Strafella,

Re: Renewal Approved for Research Protocol #252/2006 - "Frontal-striatal functional interactions in the human brain"

Thank you for returning the Annual Renewal of Ethics Approval form for the above-named research protocol.

We are writing to advise you that the Centre for Addiction and Mental Health Research Ethics Board has granted approval to the above-named research protocol for a period of one year.[1] Please keep a copy of this letter in your files.

If the research is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval by submitting the CAMH "Annual Renewal of Ethics Approval" form by ***1 October 2008****.*

During the course of research, any significant deviations from the approved protocol (**that is, any deviation which would lead to an increase in risk or a decrease in benefit to human subjects**) and/or any unanticipated developments within the research should be brought to the attention of the Research Ethics Office. *Best wishes for the successful completion of your project.*

Sincerely,

Susan Pilon, MHSc
Manager, Research Ethics Office
Centre for Addiction and Mental Health

SP/dk

[1] CAMH Investigators are reminded that should they leave CAMH, they are required to inform the Research Ethics Board of the status of any on-going research. If a study is to be closed or transferred to another facility, the REB must be informed and any advertisements must be discontinued.

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From: Jean-Marc Fritschy [fritschy-ejn@pharma.uzh.ch] Sent: Thu 19/03/2009 4:57 PM

To: jihyun.ko@camhpet.ca

Cc: msarter@umich.edu; Sue Fromant; w.waleszczyk@nencki.gov.pl

Subject: EJN Best Publication Award

Dear Ji Hyun Ko,

We are delighted to inform you that you have won the 2009 EJN Best Publication Award with your manuscript entitled "Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during a set-shifting task – a TMS–[11C]raclopride PET study" published in EJN, volume 28/10. We warmly congratulate you for this distinction and would like to thank you for having choosen EJN for publishing your very interesting and highly relevant manuscript. The award will be presented at the FENS Featured Regional Meeting in Warsaw (September 9-12, 2009), where you will have the opportunity to briefly present your work. The local organizers will contact you shortly for arranging the details of your venue. In any case, you will be asked to register for the meeting before March 30, 2009, in time for your presentation to be announced in the final program.

We very much hope that you will accept this invitation and are looking forward to meeting you as this opportunity.

Best wishes,

Jean-Marc Fritschy and Martin Sarter
co-Editors in Chief, EJN