Neuropsychopharmacology REVIEWS (2010) 35, 70–85

REVIEW

The Neural Circuitry of Executive Functions in Healthy Subjects and Parkinson's Disease

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In our constantly changing environment, we are frequently faced with altered circumstances requiring generation and monitoring of appropriate strategies, when novel plans of action must be formulated and conducted. The abilities that we call upon to respond accurately to novel situations are referred to as 'executive functions', and are frequently engaged to deal with conditions in which routine activation of behavior would not be sufficient for optimal performance. Here, we summarize important findings that may help us understand executive functions and their underlying neuronal correlates. We focus particularly on observations from imaging technology, such as functional magnetic resonance imaging, position emission tomography, diffusion tensor imaging, and transcranial magnetic stimulation, which in the past few years have provided the bulk of information on the neurobiological underpinnings of the executive functions. Further, emphasis will be placed on recent insights from Parkinson's disease (PD), in which the underlying dopaminergic abnormalities have provided new exciting information into basic molecular mechanisms of executive dysfunction, and which may help to disentangle the cortical/subcortical networks involved in executive processes.

Neuropsychopharmacology Reviews (2010) **35,** 70–85; doi:10.1038/npp.2009.88; published online 5 August 2009

Keywords: executive functions; Parkinson's disease; PET; fMRI; neuroimaging; dopamine

INTRODUCTION

On a daily basis, we are constantly faced with changing circumstances that require planning and generation of novel actions. The abilities that we call upon to respond accurately to new situations are often referred to as 'executive functions', and are frequently used for managing conditions in which routine activation of behavior would not be sufficient for optimal performance, and in which top-down control is required to modify behavior. Executive processes are those cognitive mechanisms by which performance is optimized in situations requiring the simultaneous operation of a number of different processes (Baddeley, 1986). They are regularly called upon when sequences of responses must be generated and scheduled, and when novel plans of action must be formulated and conducted (Owen, 2004).

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Received 2 May 2009; revised 1 July 2009; accepted 1 July 2009

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. Traditionally, the frontal cortex has been considered the major brain structure involved in executive functions (Luria, 1971; Shallice, 1982; Dubois *et al*, 1995). More recently, however, several studies in subjects with frontal lesions have shown a large variety of behavioral disturbances other than executive dysfunctions that include, for example, apathy, poor motivation, irritability, euphoric state, etc (Andrés, 2003; Godefroy, 2003), highlighting the importance of not using the term executive functions interchangeably with frontal functions.

As we have noted above, executive functions are widely associated with the frontal cortex, in particular, with the dorsolateral prefrontal cortex (DLPFC), which is involved in certain aspects of working memory (Petrides, 2000) and cognitive flexibility (Milner, 1963; Goldman-Rakic, 1987), and with the ventrolateral and orbital prefrontal cortex (PFC), which is involved in emotional processing, acquisition, and reversal of stimulus–reward associations (Nauta, 1971; Rolls, 2000) (Figure 1).

Patients with lateral frontal dysfunction may exhibit impaired mental flexibility, and difficulty in maintaining and re-directing their attention. On neuropsychological testing, impaired cognitive set shifting (flexibility) is often shown on the Wisconsin Card Sorting Test (WCST) (Milner, 1963) and various Go/No-go tests (Tekin and Cummings, 2002). In contrast, dysfunctions of the orbitofrontal circuit often lead to personality changes, behavioral disinhibition, emotional lability, and impaired reward processing (Eslinger and Damasio, 1985), and these patients very often perform normally on the WCST (Tekin and Cummings, 2002). More recently, it has been recognized that executive functions not only depend on frontal–cortical areas but also on several other brain areas that are closely linked with the frontal cortex and form larger executive neural networks (for example, see Andrés, 2003; Owen, 2004; Collette *et al*, 2006; Champod and Petrides, 2007). For instance, the frontal cortex is strongly linked with the limbic region of the medial temporal lobe, which includes the hippocampus, the amygdala, and the entorhinal/parahippocampal cortex, and these connections are critical for mnemonic interactions and the regulation of emotional responses (for example, see Petrides, 1996, 2007; Barbas, 2007; Bast, 2007). The PFC and the hippocampus both innervate the nucleus accumbens, which is essential for integrating cortical and limbic information into goal-directed behavior (Pennartz *et al*, 1994). Furthermore, it is connected with the globus pallidum, the substantia nigra, and the hypothalamus. A study in Parkinson's disease (PD) patients and age-matched controls using $H_2^{15}O$-PET (position emission tomography) and the Tower of London (TOL) (Dagher *et al*, 2001), a task that requires advance planning of action, documented that PD patients performed as well as the control group, but showed a different pattern of neuronal activation. PD patients did not show activity in the right caudate nucleus during the TOL task, but showed task-related rCBF increases in the right hippocampus. This recruitment of the hippocampus has been interpreted as a mechanism to overcome the striatal defect, possibly resulting from insufficient working memory capacity within the frontostriatal system. The frontostriatal system is involved in cognitive tasks, such as planning, skill learning, set shifting, and habit learning. All these tasks involve the gradual learning of responses through trial and error. The hippocampal system mediates a different, more rapid, and flexible type of learning. Experimental evidence suggests that the two systems may work independently, act together, or interfere with one another in different situations. In particular, when the short-term memory capacity of the frontostriatal system is exceeded, the hippocampal system may be recruited (Dagher *et al*, 2001).

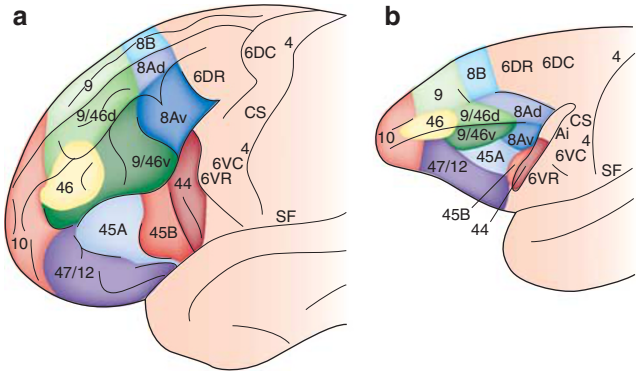

Figure 1. Cytoarchitectonic map of the lateral surface of the prefrontal cortex of (a) the human brain and (b) the macaque monkey brain by Petrides and Pandya (1994). Ai, inferior arcuate sulcus; CS, central sulcus; SF, Sylvian fissure. (Adapted and reproduced with permission from Petrides and Pandya, 1994).

There is also evidence of a frontoparietal network involved in executive functions, directing attention to space and memory (Baddeley, 1998; Diwadkar, Carpenter and Just, 2000; Petrides and Pandya, 2002; Sauseng *et al*, 2002). Both the mid-DLPFC region (area 9/46) and the posterior lateral frontal region (areas 8A and 8B), including the premotor rostral area 6, are connected with posterior parietal areas (Petrides and Pandya, 2002). The involvement of the parietal cortex in working memory processes is further supported by lesion (Carlesimo *et al*, 2001) and transcranial magnetic stimulation (TMS) studies (Oliveri *et al*, 2001), but its role has remained unclear. Recently, Champod and Petrides (2007) have provided evidence that cortex within the intraparietal sulcus has a role in the manipulation of information in working memory, whereas the monitoring of that information during working memory processes has been associated with the mid-DLPFC (Petrides, 1991, 1995, 2000). The linkage of a part of the posterior parietal cortex in the mental manipulation of information in memory (Champod and Petrides, 2007) extends into the field of working memory, the well-known critical interaction between parietal cortex and frontal cortex in reaching stimuli in space, in orienting attention to stimuli, and mentally manipulating them in space (for example, see Burnod *et al*, 1999; Petrides and Pandya, 2002).

Studies in rodents and non-human primates have shown regulation by the PFC of emotional/motivational processes linked to the amygdala (Rosenkranz and Grace, 1999; Maskati and Zbrozyna, 1989; Dias *et al*, 1996). In humans, functional magnetic resonance imaging (fMRI) studies and ^{18}fluorodeoxyglucose (FDG)-PET studies have provided evidence of a link between the amygdala and PFC (for example, see Pezawas *et al*, 2005; Hariri *et al*, 2000, 2003). The amygdala has particularly strong connections with the caudal and medial orbitofrontal areas, and these connections seem to be involved in modifying endocrine, autonomic, and involuntary behavioral responses, as well as emotional processing such as screening and assessing emotional aspects of the environment for further decisions and actions (Tekin and Cummings, 2002; Petrides, 2007; Barbas, 2007).

NEUROANATOMY AND NEUROIMAGING STUDIES OF EXECUTIVE FUNCTIONS

There is cumulative evidence that subcortical lesions affecting cortical input to the striatum may compromise executive functions (Godefroy, 2003). The striatum is the main entry point of cortical information to the basal ganglia, and receives afferents from anatomically and functionally different areas of the cerebral cortex. According to the current model of basal ganglia function, cortical information is processed in the basal ganglia nuclei and information is sent back to the cortex through the thalamus ('cortico-basal ganglia loop') (Alexander and Crutcher, 1990; Alexander *et al*, 1986). Experimental anatomical tracing studies in monkeys have identified three parallel loops of corticostriatal connections: (1) The limbic loop, which is involved in emotional/motivational and stereotyped behavior, and has been implicated in attention deficit disorder, hyperactivity disorder, compulsive disorders, and Tourette's syndrome (Grabli *et al*, 2004), includes the ventromedial striatum, nucleus accumbens, rostral/ventral caudate nucleus, and putamen, which receive input from orbital and medial PFC (Haber *et al*, 1995); (2) the associative loop, implicated in cognitive functions, such as attention, controlled retrieval, and monitoring of information within working memory (Kostopoulos and Petrides, 2003; Levy and Goldman-Rakic, 2000; Petrides, 2002, 2005; Petrides and Pandya, 2002; Grabli *et al*, 2004; Rizzuto *et al*, 2005), involving the head of the caudate and areas of the rostral putamen, which receive input from the lateral PFC, pre-supplementary motor area (SMA), and posterior parietal cortex (Haber *et al*, 2006; Calzavara *et al*, 2007; Parent, 1990; Parent and Hazrati, 1995); and (3) the sensorimotor loop, implicated in motor functions (Grabli *et al*, 2004), involving caudal and lateral aspects of the putamen, which receive input from the somatosensory, primary, and SMAs (Alexander and Crutcher, 1990). The PFC has significant connections with the head of the caudate nucleus, which are topographically organized (see Figure 2). The medial and dorsal prefrontal areas project predominantly to the dorsal and central area within the head of the caudate nucleus, whereas orbital and inferior prefrontal areas project mainly to the ventromedial and central caudate nucleus (Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991). A small number of axonal fibers has also been described to project to the putamen and the tail of the caudate nucleus.

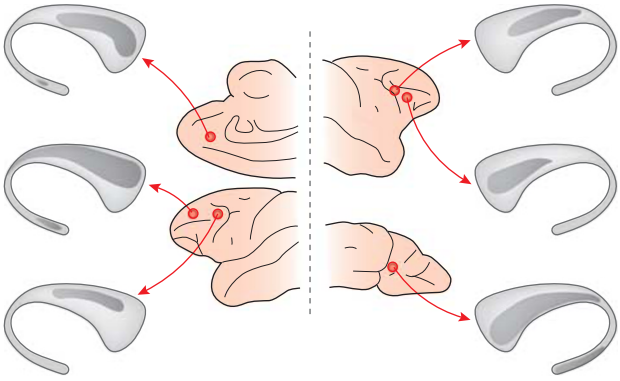

Figure 2. Summary diagrams showing the connectional relationships between the dorsal and the ventral architectonic trends of the prefrontal cortex and the caudate nucleus in the sagittal plane (adapted and reproduced with permission from Yeterian and Pandya, 1991).

Diffusion Tensor Imaging (DTI) Studies

At present, knowledge of the functional organization of corticostriatal networks originates largely from animal experiments (Nakano *et al*, 2000; Nambu *et al*, 2002; Selemon and Goldman-Rakic, 1985; Takada *et al*, 1998). However, recent advances in neuroimaging methods, such as DTI, are providing us with new approaches for investigating cortical connectivity in humans *in vivo*. Using this technique, a recent study provided evidence in the human brain for several corticostriatal pathways between the frontal cortex and the caudate nucleus and putamen (Leh *et al*, 2007). This study showed that, although the human caudate nucleus is interconnected with the PFC, inferior and middle temporal gyrus, frontal eye fields, cerebellum, and thalamus, the putamen was interconnected with the PFC, primary motor area, primary somatosensory cortex, SMA, premotor cortex, cerebellum, and thalamus (Figure 3). In addition, a connectivity-based seed classification analysis identified connections between the DLPFC and the dorsal-posterior caudate nucleus, and between the ventro-lateral prefrontal cortex (VLPFC) and the ventral-anterior caudate nucleus. For the putamen, connections existed between the SMA and dorsal-posterior putamen, while the premotor area projected to medial putamen, and the primary motor area to the lateral putamen.

The above DTI study (Leh *et al*, 2007) showed several striatal pathways in humans, and provided evidence of an anatomical organization between frontal cortex and the caudate nucleus and putamen. More specifically, while the DLPFC was strongly linked to the dorsal-posterior caudate ('associative loop'), the VLPFC was mainly interconnected with the ventral caudate ('limbic loop'). These results are in keeping with earlier anatomical reports by Yeterian and Pandya (1991), suggesting that prefrontal connections are organized topographically. The confirmation of dorsolateral prefrontal connections to the dorsal-posterior caudate is also consistent with previous functional imaging studies proposing the existence of a 'dorsolateral prefrontal loop' (Jueptner and Weiller, 1998). With regard to the connection between VLPFC and ventral caudate nucleus, corroboration can be found from functional MRI studies during set-shifting tasks (Monchi *et al*, 2006b; Nakano *et al*, 2000), as well as from anatomical studies in monkeys (Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991). This organization along a dorsal-ventral axis may be explained by the different functional contributions of these two loops. Several studies have shown that, whereas the DLPFC seems to have a part in divided attention and monitoring of

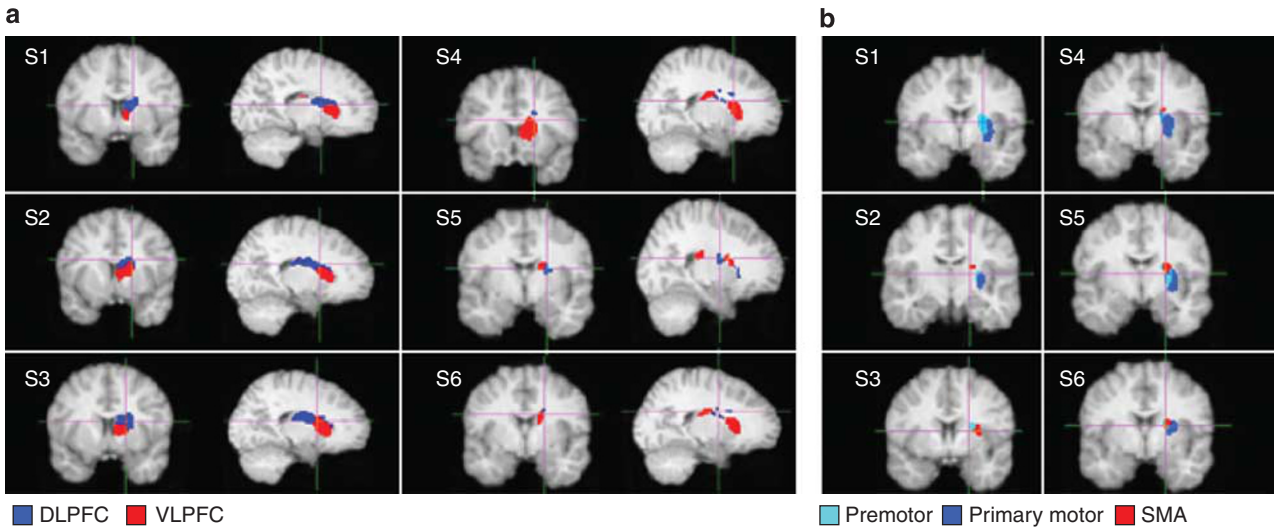

Figure 3. Connectivity-based seed qualification of the caudate (a) and putamen (b) in six subjects (S1–S6). (a) Connections between DLPFC and dorsal-posterior caudate, and VLPFC and ventral-anterior caudate. (b) Connections between SMA and dorsal-posterior putamen, premotor area and medial putamen, and primary motor area and lateral putamen. (Adapted and reproduced with permission from Leh *et al*, 2007).

information within working memory (Kostopoulos and Petrides, 2003; Petrides, 2005; Rizzuto *et al*, 2005), the VLPFC seems to have a specific role in memory retrieval (Kostopoulos and Petrides, 2003; Petrides, 2005).

Lehericy *et al* (2004) showed similar connections from the head of the caudate to the frontal pole, the pre-SMA, the medial, ventral, and dorsolateral PFC. Similar connections were found from the rostral putamen. The posterior putamen showed connections to the primary sensory/motor area and the posterior SMA, whereas the ventral striatum revealed connections to the orbitomedial frontal cortex, amygdala, hippocampus, and temporal lobe. These prefrontal–striatal connections may constitute the anatomical substrate underlying executive dysfunctions as well as the visuospatial disorientation associated with neurological (for example, PD) and psychiatric (for example, schizophrenia) conditions (Monchi *et al*, 2004; Park and Holzman, 1993; Parnetti and Calabresi, 2006; Prasad *et al*, 2005; Rodriguez-Sanchez *et al*, 2005). For instance, Matsui *et al* (2007) showed a significant reduction of the fractional anisotropy in the left parietal white matter in non-demented PD patients who performed poorly on the WCST.

fMRI Studies

Executive functions rely on interactions between many brain areas. Neuroimaging studies have shown increased activity in brain areas other than the PFC that have traditionally been linked to executive functions. Some of these studies using the WCST, for example, have shown activation in lateral prefrontal, parietal, temporal, and hippocampal cortex, as well as in the basal ganglia (Rezai *et al*, 1993; Berman *et al*, 1995; Nagahama *et al*, 1995; Barceló *et al*, 1997; Barceló and Rubia, 1998; Konishi *et al*, 1998; Mentzel *et al*, 1998; Ragland *et al*, 1998). In other neuroimaging studies using the Stroop test, orbitofrontal, parietal, temporal, left inferior frontal, as well as anterior cingulate gyrus seemed to be involved (Bench *et al*, 1993; Larrue *et al*, 1994; Pardo *et al*, 1990).

Furthermore, Konishi and colleagues (1998) were able to document how human cerebral hemispheres, during executive tasks, are asymmetrically specialized. In their event-related functional MRI study, set-shifting paradigms derived from the WCST were used, in which the subjects update behavior on the basis of environmental feedback. The cognitive requirements constituting the paradigms were decomposed into two components according to temporal stages of task events. Double dissociation of the component brain activity was found, bilaterally, in three regions in the lateral frontal cortex; the right regions being activated during exposure to negative feedback and the corresponding left regions being activated during updating of behavior, suggesting that both hemispheres contribute to cognitive set shifting, but in different ways. The asymmetrical hemispheric specialization within the same paradigms further implied an interhemispheric interaction of these task components that achieve a common goal.

Hemispheric lateralization within the PFC is an important aspect of executive function (Aron *et al*, 2004a, b; Johnson *et al*, 2003; Tulving *et al*, 1994), and there is some evidence that the left frontal lobe may be involved in task-setting, while the right frontal lobe may be more involved with monitoring (Stuss and Alexander, 2007). Several neuroimaging studies support this task-specific lateralization of the PFC in humans. During the performance of the WCST, left DLPFC activation has been reported when a set shift is required (Monchi *et al*, 2001; Nagahama *et al*, 2001), whereas right DLPFC activation was 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 consistent activation during color naming in the Stroop task (MacDonald *et al*, 2000) and when difficult planning is required during the TOL task (Owen *et al*, 1996).

Functional magnetic resonance imaging studies support the notion that the caudate nucleus also has a key role in executive functions, in particular, in set shifting (Rogers *et al*, 2000; Monchi *et al*, 2001; Cools *et al*, 2004). Most recent studies have shown that the caudate is involved in active planning of a novel action (Monchi *et al*, 2006a, b) and in cognitive manipulation (Lewis *et al*, 2004). In particular, Monchi *et al* (2001) (Figure 4) showed specific involvement of different prefrontal–striatal networks during different stages of WCST performance. The mid-DLPFC (area 9/46) increased activity while subjects received either positive or negative feedback, that is, at the point when the current information must be related to earlier events stored in working memory and, thus, increase the requirements for monitoring, which is known to be the major function of this part of the frontal cortex (see Petrides, 2005). In monkeys, lesions confined to the mid-dorsolateral prefrontal cortical region that covers areas 46, 9, and 9/46, impair severely the monitoring of stimuli or events within working memory, but not the maintenance of information *per se* (Petrides, 1991, 1995, 2000). The involvement of the mid-DLPFC in the monitoring (tracking) of information in humans has been supported by numerous functional neuroimaging studies across many sensory modalities including language (see Petrides, 2005 for a review). By contrast, a frontal-basal ganglia loop involving the mid-VLPFC (area 47/12), caudate nucleus, and mediodorsal thalamus increased activity, specifically when receiving negative feedback, which signals the need for a mental shift to a new response set. The posterior PFC response, in contrast, was less specific: its increase in activity occurred both during receiving feedback and the response period, indicating a role in the association of specific actions to stimuli. The putamen exhibited greater activity while making a matching response after negative feedback, but not while matching after positive feedback, implying greater involvement during novel than routine actions. Although these event-related fMRI studies with the WCST in young healthy adults (Monchi *et al*, 2001) confirmed a significant activation of the caudate nucleus, specifically when subjects received negative feedback (that is, when a set-shift was required), there was still no evidence of whether the caudate nucleus was most important for the execution of the shift *per se* or rather for its planning (that is, the cognitive decision to shift). In a study, using a new card-sorting task called the Montreal Card Sorting Task (MCST), Monchi *et al* (2006b) were able to dissociate these two aspects of set shifting. Using fMRI, in young healthy adults, they tested the hypothesis that the caudate nucleus was primarily involved in the preparation of a novel action and not in the execution of set shifting *per se*. In this mixed-design protocol, they were able to document increased activity in the caudate nucleus and putamen only in conditions in which cognitive planning was required to perform a set shift, whereas significant activation was seen in the subthalamic nucleus in all shifting conditions whether or not planning was required. These observations suggested that the caudate nucleus and putamen were particularly important, respectively, in the planning and motor initiation of a self-generated novel action, whereas the subthalamic nucleus may be required when a new motor

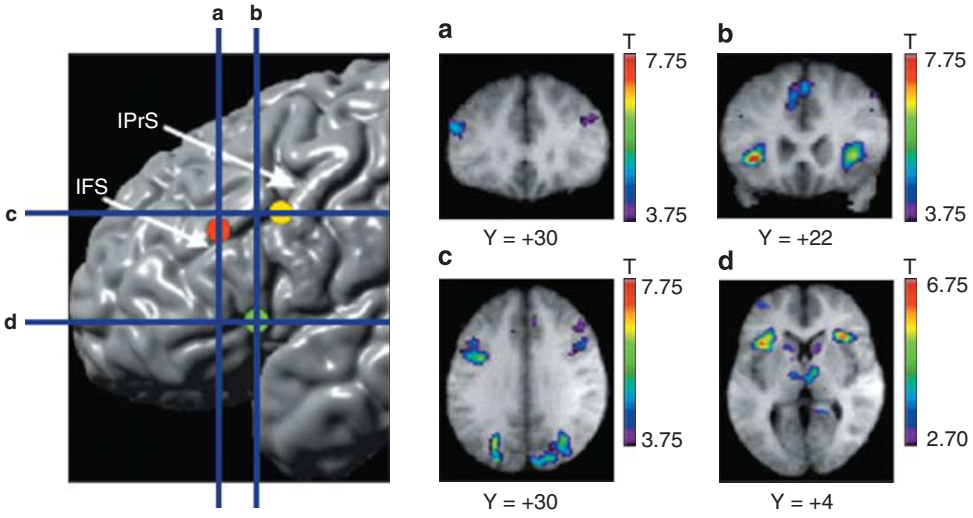

Figure 4. The top left panel displays the sites of the main prefrontal areas identified in the fMRI experiment during Wisconsin Card Sorting Task on a cortical surface rendering an MRI in standard stereotaxic space. The vertical blue lines indicate the anteroposterior level of the coronal sections in (a) and (b). The horizontal blue lines indicate the dorsoventral level of the sections displayed in (c) and (d). The focus in the mid-DLPFC is indicated by the red circle, in mid-VLPFC by the green circle, and in posterior PFC by the yellow circle. (a) Coronal section through the mid-DLPFC peak at $Y = +30$ mm. (b) Coronal section through the mid-VPFC peak at $Y = +22$ mm. (c) Horizontal section through the posterior PFC peak at $z = +30$ mm. (d) Horizontal section through the mid-VLPFC peak at $z = +4$ mm. Note also caudate and thalamus activation. All activation peaks shown here occurred during receiving negative feedback minus control feedback. IFS, inferior frontal sulcus; IPrS, inferior precentral sulcus. (Adapted and reproduced with permission from Monchi *et al*, 2001).

program was solicited independently of the choice of strategy.

PET Studies

Position emission tomography has also been used to investigate the neural basis of executive functions. Dagher *et al* (1999), for example, investigating complex planning with the TOL have described increases in activity in several cortical areas, including the lateral PFC, the lateral premotor areas, anterior cingulate, and caudate nucleus. Although activation studies have a task-specific temporal and spatial resolution, they do not allow determining the underlying neurochemical processes of a given task. To tackle this aspect, the use of PET with specific receptor-binding radioligands has been very promising. Particular attention has been placed on dopaminergic modulation, as it can alleviate or worsen 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).

Changes in [^{11}C]raclopride-binding potential (BP) provide a reasonable estimate of synaptic dopamine (DA) release in the striatum (Farde *et al*, 1986). This method has been widely used for investigation of the striatal dopaminergic transmission during various cognitive tasks (Goerendt *et al*, 2003; Ko *et al*, 2008a; Monchi *et al*, 2006a; Ouchi *et al*, 2002; Zald *et al*, 2004). To investigate the contribution of striatal DA during set shifting, Monchi *et al* (2006a) tested young healthy subjects using PET during retrieval with and without shift on a variant of the WCST, the MCST. In this card sorting task, the subject had to match a test card to one of four reference cards by comparing the test card to a previously shown cue card held in memory to find the classification rule. Using D2-DA receptor ligand [^{11}C]raclopride, which has a BP known to be inversely proportional to the concentration of extracellular DA (Endres *et al*, 1997; Laruelle *et al*, 2000), Monchi *et al*

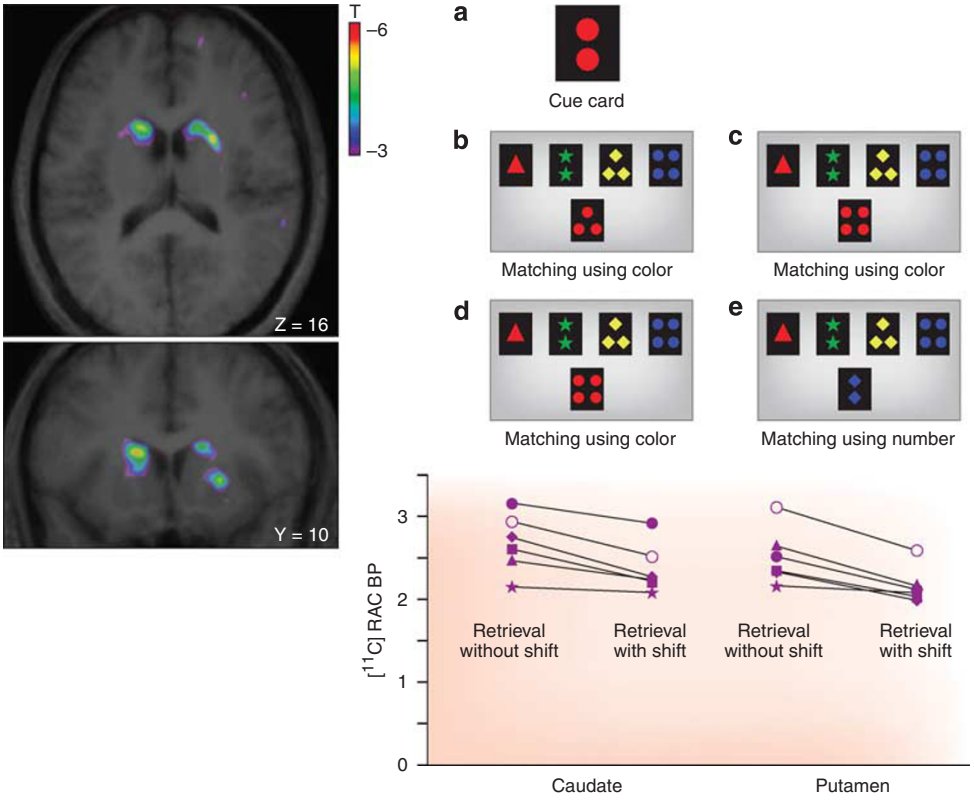

Figure 5. Axial ($Z = 16$) and coronal ($Y = 10$) sections of the statistical parametric map of the change in [^{11}C]raclopride BP overlaid on the average MRI of all subjects in stereotaxic space. The figure displays the significant areas of striatal dopamine release (that is, reduction in [^{11}C]raclopride BP) during the retrieval with shift condition compared with retrieval without shift condition (control) of Montreal Card Sorting Task: (a) left caudate: $t = 4.1$; cluster size: 83 voxels, 670 mm^3, (b) right caudate: $t = 4.1$; cluster size: 42 voxels, 336 mm^3, (c) right putamen: $t = 4.3$; cluster size: 94 voxels, 752 mm^3. (Adapted and reproduced with permission from Monchi *et al*, 2006a). On the bottom right, individual [^{11}C]raclopride binding potentials for each subject during retrieval with shift condition and retrieval without shift condition (control), from the left caudate ($p = 0.03$) and right putamen ($p = 0.01$), 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. On the top right, the Montreal Card Sorting Task. (a) An example of the cue card that appears for 3.5 s at the beginning of a block of retrieval trials. In this example, the cue card contains two red circles. The cue card changes for each block. (b, c) An example of two consecutive trials in the retrieval without shift condition. In (b), as the color red is the only attribute shared by the test card and the cue, matching must be based on color. In the following trial (c) the test card is red and the matching is performed according to the same rule. (d, e) An example of two consecutive retrieval trials with shift condition. (d) The test card contains four red stars and hence shares the color attribute with the cue card (containing two red circles, shown in (a). (e) On the subsequent trial, the test card shares a different attribute with the cue card (in this example 'number').

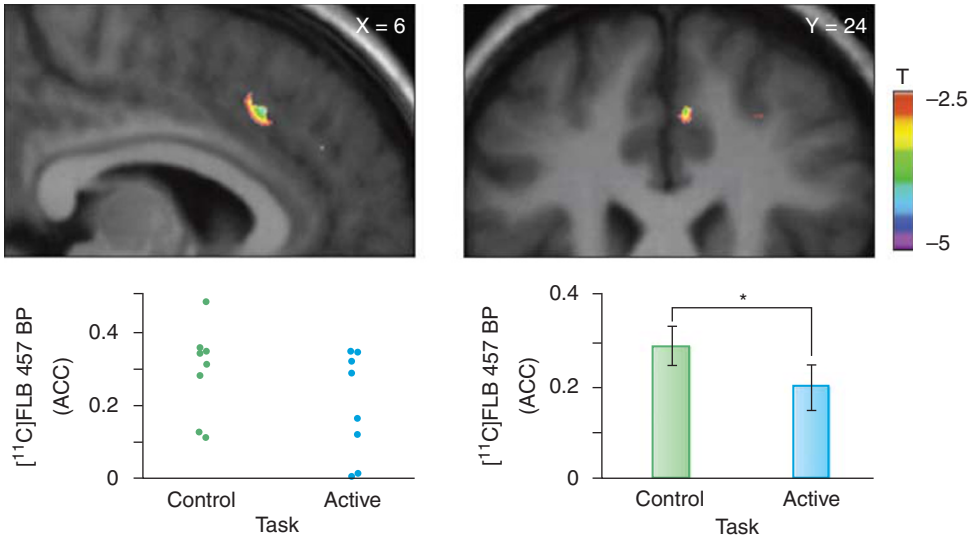

Figure 6. Sagittal ($X = 6$) and coronal ($Y = 24$) section of the statistical parametric map of the change in [^{11}C]FLB 457 BP overlaid on the average MRI of all subjects in standardized stereotaxic space. The figure displays the significant area of dopamine changes (that is, reduction in [^{11}C]FLB 457 BP) during active task performance of the Montreal Card Sorting Task compared with the control task at the level of dorsal ACC. (Adapted and reproduced with permission from Ko *et al* (2009)). On the bottom, individual ACC-[^{11}C]FLB 457 BP and mean ± SE of ACC-[^{11}C]FLB 457 BP during control and active task extracted from a spherical region of interest ($r = 3$ mm) 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, $t(7) = 3.85$, $^*p = 0.006$).

(2006a) revealed striatal reduction in [^{11}C]raclopride BP during planning of a set shift (Figure 5). These findings suggest that striatal DA neurotransmission increases significantly during the performance of specific executive processes. Although [^{11}C]raclopride may offer important insights in striatal DA neurotransmission during executive functions (Ko *et al*, 2008a; Monchi *et al*, 2006a), its low affinity limits its application to extrastriatal regions such as the PFC (Goldman-Rakic *et al*, 2000).

In fact, it has been shown that cortical DA has a critical role in executive functions and high-level cognition (Murphy *et al*, 1996; Watanabe *et al*, 1997). For instance, during the performance of working memory tasks, DA release increases in the PFC (Aalto *et al*, 2005a; Sawamoto *et al*, 2008), and anterior cingulate cortex (ACC) DA receptor density has been shown to be significantly correlated with performance level on the WCST in normal control subjects (Lumme *et al*, 2007). Recently, Ko *et al* (2009) (Figure 6) addressed the role of prefrontal DA during set-shifting tasks in healthy subjects by using [^{11}C]FLB 457, a chemical compound with a greater affinity (Kd = 20 nM) for D2 receptors, which allows evaluation of extrastriatal DA release (Aalto *et al*, 2005a; Olsson *et al*, 1999; Sudo *et al*, 2001). Olsson *et al* (2004) had previously 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 (for example, in cingulate cortex, frontal cortex, thalamus, and temporal cortex), consistent with postmortem studies using [^{125}I]epidepride (Kessler *et al*, 1993). Similarly, [^{11}C]FLB 457 has been shown to be sensitive in detecting changes in extrastriatal endogenous DA concentration in non-human primates (Chou *et al*, 2000) and in humans (Aalto *et al*, 2005a, b; Hagelberg *et al*, 2004; Montgomery *et al*, 2007). Recently, a study has compared the ability of [^{11}C]FLB 457 with another high-affinity DA D2 radioligand, [^{11}C]Fallypride, to measure amphetamine-induced changes in DA transmission in the human cortex. Under controlled conditions, [^{11}C]FLB 457 BP was 30–70% higher compared with [^{11}C]Fallypride BP in cortical regions. Amphetamine-induced DA release led to a significant decrease of [^{11}C]FLB 457 BP in five out of eight cortical regions evaluated. In contrast, no significant decrease in [^{11}C]Fallypride BP was detected in cortex after amphetamine administration. It was concluded that the difference between these two ligands in detecting changes in the cortical D2 receptor availability after amphetamine administration is related to the higher signal to noise ratio provided by [^{11}C]FLB 457. These findings suggest that [^{11}C]FLB 457 is superior to [^{11}C]Fallypride for measurement of changes in cortical synaptic DA (Narendran *et al*, 2009). A similar observation has been made with the use of [^{18}F]Fallypride, which may be useful for measuring amphetamine-induced DA release, but may be unreliable for estimating tonic DA levels in striatum and extrastriatal regions (Cropley *et al*, 2008).

On the basis of these premises, and previous anatomical and functional imaging studies on card sorting tasks (Buchsbaum *et al*, 2005; Konishi *et al*, 2002; Koski and Paus, 2000; Lie *et al*, 2006; Monchi *et al*, 2001, 2007), in their study, Ko *et al* (2009) hypothesized that performance of the MCST may be associated with increases in DA release (decrease BP of [^{11}C]FLB 457) in different prefrontal areas, such as the DLPFC (areas 46 and 9/46) and ACC (areas

32/24). Ko *et al* (2009) found that extrastriatal DA can influence the performance on a working memory task in healthy subjects with a reduction in [^{11}C]FLB 457 BP in the right dorsal ACC during the active component of the task (Figure 6). They concluded that neurotransmission may increase in the right dorsal ACC during certain executive processes.

Transcranial Magnetic Stimulation

Even though functional neuroimaging studies have provided insights into the role of PFC 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 the observed brain activity and cognitive performance (Johnson *et al*, 2007; Rushworth *et al*, 2002). In other words, the functional imaging studies alone cannot determine whether the engagement of the activated area is essential or just epiphenomenal (Walsh and Cowey, 2000). TMS 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). Repetitive TMS (rTMS) has been shown to produce profound and long-lasting effects on neuronal excitability. Combining functional imaging techniques with rTMS provides a valuable probe to study functional connectivity of the human brain (Strafella and Paus, 2000; Strafella *et al*, 2001, 2003), and can, under certain conditions, be used as a tool to create a 'virtual lesion' and to assess its effects on cognitive behavior (Pascual-Leone *et al*, 2000; Ko *et al*, 2008a, b). 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 and Hallett, 1994). Several studies with short-train high-frequency rTMS showed that the stimulation may transiently disrupt the cognitive processes of the targeted area. For example, it has also been shown that 25 Hz rTMS over the DLPFC during the decision phase of a spatial working memory task selectively interfered with task performance, whereas no effect was seen when the 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). Offline high-frequency rTMS over the left DLPFC has been shown to disrupt performance on the Stroop task (Vanderhasselt *et al*, 2006b), task-set switching (Vanderhasselt *et al*, 2006a), and divided attention tasks (Wagner *et al*, 2006).

Recently, Ko *et al* (2008b) applied rTMS (stimulation train consisted of five pulses of 20 Hz rTMS; the stimulation intensity was set to 110% of resting motor threshold of FDI and the total stimulation time was 36 min) to the mid-DLPFC region to test the hypothesis that such stimulation affects monitoring of information in working memory without interfering with other executive functions. They applied rTMS to the right DLPFC and the vertex (control site) at different time points of the WCST. When rTMS was applied to the DLPFC during the period when subjects were receiving feedback regarding their previous response, WCST performance deteriorated, whereas rTMS did not affect performance during matching, either when maintaining set or during set shifting. This selective impairment of the DLPFC is consistent with its proposed role in monitoring of events in working memory.

A recently developed rTMS approach, theta burst stimulation (TBS), has been shown to have longer lasting after effects with a shorter duration and a lower intensity of stimulation than the conventional rTMS (Huang *et al*, 2005). In particular, continuous TBS (cTBS) has been shown to have a similar but longer effect to that of slow rTMS (that is, inhibitory) when applied to the motor cortex—20 s of stimulation may result in a lasting effect of up to 20 min, and 40 s of stimulation up to 60 min. This long-lasting inhibitory effect of cTBS has been replicated by several groups over the primary motor area (Huang *et al*, 2007a), 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), and the DLPFC (Vallesi *et al*, 2007). Furthermore, cTBS inhibits the BOLD fMRI signal for over 30 min when applied to the frontal eye field (Hubl *et al*, 2008). It has been reported that the cTBS effect is NMDA-dependent (Huang *et al*, 2007a) and may increase the GABA levels in the targeted area (Stagg *et al*, 2009). Owing to its potent inhibitory effects, cTBS is suitable to study TMS-induced effects on cognitive behavior. To investigate the contribution of the DLPFC during set shifting in the MCST and its effect on the striatal dopaminergic system, Ko *et al* (2008a) applied cTBS to left and right DLPFC (Figure 7). Three cTBS blocks (20 s each) were applied to the left and right DLPFC, and to the vertex before the MCST. Each block was separated by a 1-min interval. Each cTBS block consisted of 5 Hz of theta burst administered continuously. Each burst consisted of three pulses in 50 Hz (Huang *et al*, 2005). Therefore, 60 s of cTBS (900 pulses) were administered in total on each session.

The aim of the study by Ko *et al* (2008a) was to transiently disrupt the function of DLPFC and to measure MCST performance and striatal DA release during [^{11}C]raclopride PET. A significant hemispheric asymmetry was observed. cTBS of the left DLPFC impaired MCST performance and DA release in the ipsilateral caudate, anterior putamen, and contralateral caudate nucleus as compared with cTBS of the vertex (control). These effects seemed to be limited only to left DLPFC stimulation, whereas right DLPFC stimulation did not influence task performance and [^{11}C]raclopride BP in the striatum (Figure 7). This was the first study showing

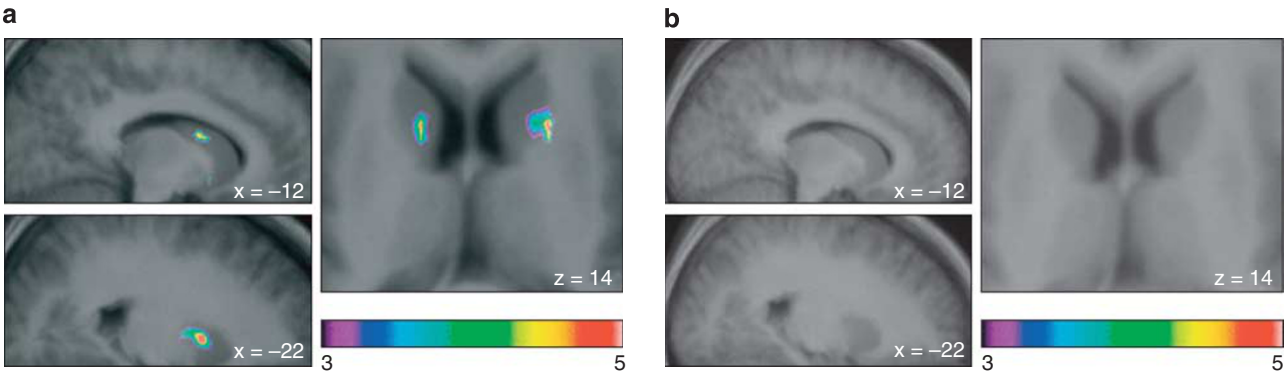

Figure 7. Comparison between left DLPFC and vertex stimulation: (a) Comparison between left DLPFC and vertex stimulation (control condition). Sagittal ($x = -12$ and $x = -22$) and axial ($z = 14$) sections of the statistical parametric map of the change in [^{11}C]raclopride BP overlaid on the average MRI of all subjects in stereotaxic space. The figure displays the significant areas of striatal dopamine changes during Montreal Card Sorting Task performance after left DLPFC stimulation compared with vertex stimulation (control). (b) Comparison between right DLPFC and vertex stimulation showing the lack of changes in [^{11}C]raclopride BP. (Adapted and reproduced with permission from Ko *et al*, 2008a).

that cTBS, by disrupting left prefrontal function, may indirectly affect striatal DA neurotransmission during performance of executive tasks. This cTBS-induced regional prefrontal effect and modulation of the frontostriatal 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.

EXECUTIVE DYSFUNCTION IN PD

Parkinson's disease is a progressive neurodegenerative disorder, traditionally associated with motor symptoms such as bradykinesia, rigidity, and resting tremor (Strafella *et al*, 2007, 2008). However, neuropsychological studies have also revealed deficits across a range of cognitive functions even at the early stages of the disease (Dubois and Pillon, 1997; Taylor *et al*, 1986; Taylor and Saint-Cyr, 1995). Indeed, approximately 15–20% of the patients tend to develop severe cognitive impairments, and the risk of developing dementia is two to three times higher in PD patients than in aged-matched controls (Aarsland *et al*, 1996). The non-motor cognitive and behavioral disabilities include deficits of executive function, language, visuospatial/visuoconstructive abilities, memory, attention, skill learning, as well as behavioral changes such as depression, apathy, and impulse control disorders (Taylor and Saint-Cyr, 1995; Zgaljardic *et al*, 2004; Monchi *et al*, 2004; Owen, 2004; Monchi, 2007; Steeves *et al*, 2009). Although Roberts *et al* (1994) have shown that prefrontal DA depletion may cause marked working memory deficits in monkeys, cognitive disabilities in PD have also been associated with DA depletion within the caudate nucleus (Lewis *et al*, 2003; Carbon *et al*, 2004; Grahn *et al*, 2008). Several studies have documented that in PD, DA depletion is restricted in the earlier stages to the putamen and the dorsal caudate nucleus, and only later progresses to the more ventral parts of the striatum and the mesocorticolimbic dopaminergic system (Kish *et al*, 1988; Rosvold, 1972;. Swainson *et al*, 2000; Cools *et al*, 2001). Thus, the evolving pattern of cognitive impairments observed in these patients may be best explained in terms of the spatiotemporal progression of DA depletion within the striatum and the terminal distribution of its cortical afferents. This is highlighted by postmortem neurochemical analysis, which showed uneven patterns of striatal DA loss in patients with PD (Kish *et al*, 1988). The study revealed that the putamen is more severely depleted than the caudate nucleus, and that the caudal putamen is more affected than its rostral area. Within the caudate nucleus, DA depletion was greatest in the rostrodorsal extent of the head of the nucleus, an area heavily connected with dorsolateral regions of the frontal lobe (Yeterian and Pandya, 1991). By contrast, ventral regions of the caudate, which are preferentially connected with more ventral regions of the frontal lobe (including the ventrolateral PFC) (Yeterian and Pandya, 1991), are relatively spared in early PD. This uneven dopaminergic loss explains why dopaminergic therapy, while improving motor symptoms, may not necessarily have the same effects on various cognitive functions (Swainson *et al*, 2000; Cools *et al*, 2001). In fact, there is evidence that cognitive disabilities improve differently to dopaminergic replacement therapy depending on the neural pathways underlying the cognitive function being tested (Gotham *et al*, 1988). Cognitive tasks, such as probabilistic reversal learning, that challenge the ventral frontostriatal circuit, which is relatively spared from DA depletion (at least in early stages) in PD, reveal decreased performance with dopaminergic treatment (Cools *et al*, 2001). In contrast, PD patients showed improved cognitive abilities after DA therapy on tests that engaged the dorsal frontostriatal circuit (that is, DLPFC, posterior parietal cortex, and dorsal caudate) associated with a severe DA depletion (Cools *et al*, 2001). According to the 'dopamine overdose model', in the parkinsonian brain, DA replacement therapy normalizes

DA levels in severely depleted areas, such as the dorsal striatum and its connections to the DLPFC, while detrimentally 'overdosing' the relatively intact ventral striatum and its connections to the VLPFC.

Several neuroimaging studies in PD patients have documented the involvement of the frontostriatal networks in executive dysfunctions, in particular, in engaging the nigrostriatal and mesocortical pathways (Owen *et al*, 1998; Dagher *et al*, 2001; Cools *et al*, 2002; Mattay *et al*, 2002). Monchi *et al* (2004), using fMRI, showed in PD patients (with no history of neuropsychiatric problems, including depression) during the performance of the WCST a decreased activation both in the VLPFC (when receiving negative feedback) and the posterior PFC (when matching after negative feedback). In the healthy controls, these prefrontal regions specifically co-activated with the striatum during those stages of task performance. In contrast, greater activation was found in the PD patients in prefrontal regions, such as the posterior and DLPFC, when receiving positive or negative feedback that were not co-activated with the striatum in controls. These findings suggested that both decreased and increased activation can occur in prefrontal areas during cognitive performance, and that the pattern of activity observed in a specific area of the PFC depended on its specific relationship with the striatum for the task at hand. Later, these observation where confirmed in another fMRI study in a similar group of PD patients using a different set-shifting task (that is, MCST) (Monchi *et al*, 2007) (Figure 8), in which a pattern of cortical activation was characterized by either reduced or increased activation depending on whether the caudate nucleus was involved or not in the task. This activation pattern included not only the prefrontal regions but also posterior cortical areas in the parietal and prestriate cortex. These findings did not agree with the traditional model, which proposes that the nigrostriatal DA depletion results in decreased cortical activity, and provided evidence in favor of the hypothesis that not only the nigrostriatal but also the mesocortical dopaminergic substrate may have a significant role in the cognitive deficits observed in PD. A $H_2^{15}O$-PET study in healthy and mildly affected PD patients with no history of neuropsychiatric problems (Dagher *et al*, 2001), showed no behavioral differences on the TOL test, but nevertheless showed different neuronal activation pattern. In the two groups, overlapping areas of the PFC were activated but, although the right caudate nucleus was activated in the control group, this was not evident in the

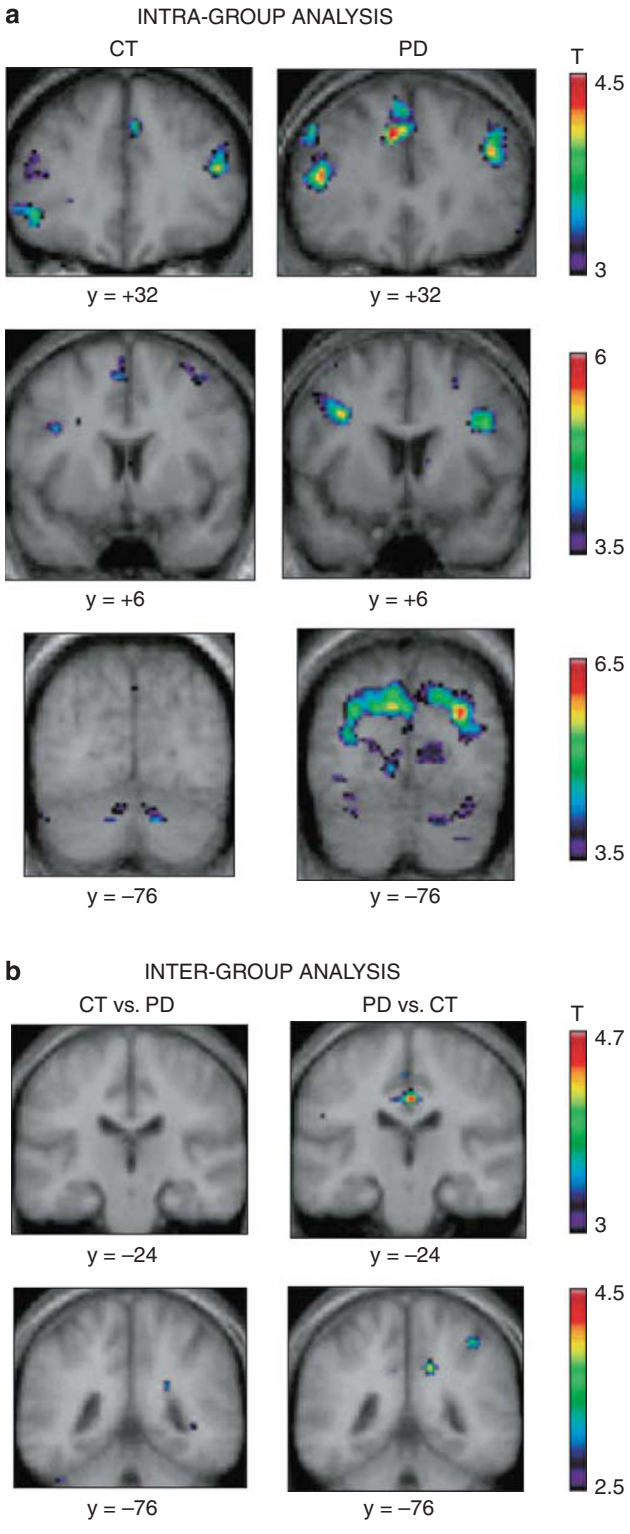

Figure 8. Location of peaks within the retrieval with shift *vs* the retrieval without shift condition of the Montreal Card Sorting Task in PD and healthy controls during fMRI. Coronal sections are shown. The anatomical MRI images shown are the average of T_1 acquisitions transformed into stereotaxic space for each group in the intra-group analysis and for both groups in the inter-group analysis. (a) Intra-group analysis. The images display significant activation in the left VLPFC and caudate nucleus in the control group, whereas none is observed in the Parkinson's disease group. They also show larger activations in the control group than in the patient group in the posterior cingulate cortex and the posterior parietal cortex bilaterally. (b) Inter-group analysis. Images display significantly greater activity in the control group *vs* the patient group in the left dorsolateral PFC and orbitofrontal cortex, as well as the right VLPFC, whereas no significantly increased activity is observed in the patient *vs* control group subtraction. (Adapted and reproduced with permission from Monchi *et al*, 2007).

PD patients. This suggested that normal frontal lobe activation can occur in PD despite abnormal processing within the basal ganglia. Moreover, they found that right hippocampus activity was suppressed in the controls and enhanced in the PD patients. This could represent a shift in PD during performance of the TOL task, possibly resulting from insufficient working memory capacity within the frontostriatal system. In another study, Owen *et al* (1998) examined the effects of striatal DA depletion on cortical and subcortical blood flow changes using the same task (that is, TOL) in patients with moderate PD and age-matched controls. Relative to control conditions, the planning task was associated with an increase in cerebral blood flow in the internal segment of the right globus pallidus in the age-matched control subjects and a decrease in the same region in the patients with PD. They concluded that striatal DA depletion disrupts the normal pattern of basal ganglia outflow in PD and consequently, affects the expression of frontal-lobe functions by interrupting normal transmission of information through frontostriatal circuitry.

To date, there is some interesting imaging evidence that DA replacement therapy may not have the same effect on the identified motor and cognitive frontostriatal networks. In fact, previous FDG-PET studies have shown that, unlike the PD-related motor pattern (PDRP), the PD-related cognitive pattern (PDCP) expression is not significantly altered by antiparkinsonian treatment with either intravenous levodopa or deep brain stimulation (Huang *et al*, 2007b). In these studies, network analysis in non-demented PD patients with no history of depression identified a spatial covariance pattern associated with cognitive function, and significant correlations between this PDCP expression and performance on tests of memory and executive function. However, antiparkinsonian treatment failed to detect significant changes in PDCP expression, despite concurrent improvement in motor ratings and reductions in abnormal PDRP activity.

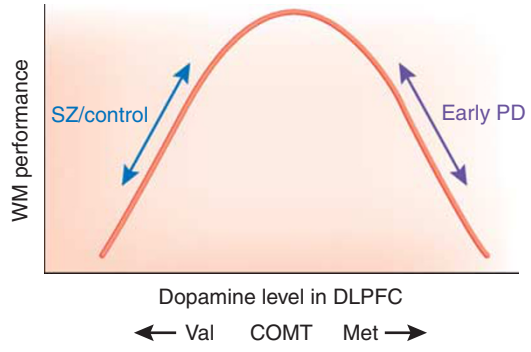

Figure 9. Inverted U-shaped relationship between working memory (WM) performance and dopamine level in the DLPFC. The COMT met/met genotype is expected to confer a higher baseline dopamine level than the val/val genotype. This has opposing behavioral consequences in schizophrenics (SZ)/controls and those with early PD, suggesting that their relative positions on the curve differ. (Adapted and reproduced with permission from Williams-Gray *et al*, 2007).

Recently, it has been proposed that, in PD, the dysfunction in dopaminergic frontostriatal networks may be influenced by a common functional polymorphism (val^{158}met) within the catechol *O*-methyltransferase (COMT) gene. COMT is an enzyme that regulates DA levels in cortical areas. A polymorphism in COMT, resulting in a substitution of valine for methionine at codon 158 (val^{158}met), may affect PD cognitive performance (Williams-Gray *et al*, 2008). A low activity COMT genotype (met/met), for example, causes higher DA levels in the PFC, decreases performance on the TOL test, and decreases frontoparietal activity (Williams-Gray *et al*, 2007) (Figure 9). Williams-Gray *et al* (2008) compared PD patients with high (val/val) to low (met/met) activity COMT genotypes using an attentional control task. The genotype had a critical impact on task strategy, whereas patients with high-activity COMT genotypes (val/val) adopted a typical approach of preferentially shifting attention, those with low activity genotypes (met/met) failed to adopt such a strategy, suggesting an inability to form an attentional 'set'. Moreover, this behavior was associated with significant underactivation across the frontoparietal attentional network. Furthermore, they showed an interactive effect of COMT genotype and dopaminergic medication on task performance and BOLD response.

Exogenous levodopa caused a larger decrease of prefrontal functions in val/val compared with met/met PD patients (Williams-Gray *et al*, 2008). A demonstration of this inverted U-shaped function between DA levels and prefrontal functions can be seen in Figure 9. A similar inverted U-shaped relationship was found by Rowe *et al* (2008a) between the severity of motor dysfunctions in PD patients and the activity in prefrontal areas and the caudate. They observed that the lateral PFC and caudate nucleus had a non-linear U-shaped relationship between motor disease severity and regional brain activation. Dopaminergic treatment led to a shift in this U-shaped function, supporting the hypothesis of differential neurodegeneration in separate motor and cognitive cortico–striato–thalamo–cortical circuits. In a separate study (Rowe *et al*, 2008b), they also investigated whether the val^{158}met functional polymorphism of COMT influenced age-related changes in gray matter density and volume, both in healthy individuals and PD patients. val/val homozygotes (low prefrontal cortical DA) had more gray matter in early adulthood, but this difference disappeared with increasing age. The insula and ventral PFC had higher gray matter volume in younger, but not older, val/val homozygotes. Conversely, the dominant premotor cortex revealed genotypic differences in gray matter density in later life. There were no global or local interactions between PD and COMT val^{158}met genotype on morphometry. As the val^{158}met polymorphism is associated with differences in cortical DA metabolism, these data suggest a role for DA in cortical development followed by differential vulnerability to cortical atrophy across the adult life span.

It is important to acknowledge that other neurotransmitters may have a role in the cognitive deficits observed in PD (Grahn *et al*, 2008). For example, noradrenergic, serotoninergic, and cholinergic deafferentations of the cortex also occur in PD (Agid *et al*, 1987a) and may have a significant role in some of the cognitive deficits observed. Similarly, cortical Lewy bodies, which may occur even in the early stages of PD, may have a contributory role (Byrne *et al*, 1989; Gibb *et al*, 1989). Finally, patients with PD have DA depletion within the frontal cortex itself (Scatton *et al*, 1983) through the degeneration of the mesocortical DA pathway. However, this system is known to be less severely affected than the nigrostriatal DA system in PD (Agid *et al*, 1987b) and possibly at a later stage of the disease process.

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

We are constantly faced with changing circumstances in which executive processes are regularly called upon when generation and monitoring of appropriate strategies are required, and novel plans of action must be formulated and conducted. As we have observed in the above review, executive functions are not exclusively linked to frontal–cortical areas, and involve a complex network of frontal–cortical and subcortical circuitries. In fact, lesion studies have shown that executive disabilities do exist in patients with damage to areas other than frontal area. The recent developments in imaging techniques, such as DTI, fMRI, and PET ligand studies, along with non-invasive brain stimulation techniques (that is, TMS) and genetic studies are offering valuable insights into the neuronal networks and molecular mechanisms of executive functions. In addition, the key role played by dopaminergic pathways and their underlying networks make PD an ideal and probably the best available human model of dopaminergic dysfunction. This neurodegenerative condition with the assistance of the rapidly developing cutting-edge imaging technology may be able to provide *in vivo* valuable insights into the basic molecular mechanisms of executive dysfunction and may aid to disentangle the cortical/subcortical networks and neurobiological underpinnings of executive processes.

ACKNOWLEDGEMENTS

SEL is supported by a postdoctoral scholarship from FRSQ, APS is supported by CIHR Investigator Award.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

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