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EFFECT OF LEVODOPA ON CORTICO-STRIATAL AND C ORTICO-CEREBELLAR CIRCUITS IN PARKINSON'S DISEASE

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EFFECT OF LEVODOPA ON CORTICO-STRIATAL AND CORTICO-CEREBELLAR CIRCUITS IN PARKINSON'S DISEASE

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Résumé

La maladie de Parkinson (MP) est la deuxième maladie neurodégénérative la plus commune. Les symptômes principalement observés chez les patients atteints de la MP sont la rigidité, les tremblements, la bradykinésie et une instabilité posturale. Leur sévérité est souvent asymétrique. La cause principale de ces symptômes moteurs est la dégénérescence du circuit dopaminergique nigro-striatal qui mène à un débalancement d'activité du circuit cortico-striatal. Ce débalancement de circuits est le point essentiel de cette thèse. Dans les protocoles de recherche décrits ici, des patients atteints de la MP (avant et après une dose de levodopa) et des participants contrôles sains ont effectué des mouvements auto-initiés ou en réponse à des stimulis externes pendant que l'on mesurait leur activité cérébrale en imagerie par résonance magnétique fonctionnelle (IRMf). Dans cette thèse, nous abordons et mettons en évidence quatre (4) points principaux.

En première partie (chapitre 2), nous présentons un recensement de la littérature sur les cicruits cortico-striataux et cortico-cérébelleux dans la MP. En utilisant des méthodes de neuroimagerie, des changements d'activité cérébrale et cérébelleuse ont été observés chez les patients atteints de la MP comparés aux participants sains. Même si les augmentations d'activité du cervelet ont souvent été attribuées à des mécanismes compensatoires, nos résultats suggèrent qu'elles sont plus probablement liées aux changements pathophysiologiques de la MP et à la perturbation du circuit cortico-cérébelleux. En général, nous suggérons (1) que le circuit cortico-cérébelleux est perturbé chez les patients atteints de la MP, et que les changements d'activité du cervelet sont liés à la pathophysiologie de la MP plutôt qu'à des mécanismes compensatoires.

En deuxième partie (chapitre 3), nous discutons des effets de la levodopa sur les hausses et baisses d'activité observés chez les patients atteints de la MP, ainsi que sur l'activité du putamen pendant les mouvements d'origine interne et externe. De nombreuses études en neuroimagerie ont montré une baisse d'activité (hypo-activité) préfrontale liée à la déplétion de dopamine. En revanche, l'utilisation de tâches cognitives a montré des augmentations d'activité (hyper-activité) corticale chez les patients atteints de la MP comparés aux participants sains. Nous avons suggéré précédemment que ces hypo- et hyper-

activités des régions préfrontales dépendent de l'implication du striatum. Dans cette thèse nous suggérons de plus (2) que la levodopa ne rétablit pas ces hyper-activations, mais plutôt qu'elles sont liées à la perturbation du circuit méso-cortical, et aussi possiblement associées à l'administration de médication dopaminergique à long terme. Nous montrons aussi (3) que la levodopa a un effet non-spécifique à la tâche sur l'activité du circuit cortico-striatal moteur, et qu'elle n'a pas d'effet sur l'activité du circuit cortico-striatal cognitif.

Nous montrons enfin (chapitre 4) que la levodopa a un effet asymétrique sur les mouvements de la main droite et gauche. À peu près 50% des patients atteints de la MP démontrent une asymétrie des symptômes moteurs, et ceci persiste à travers la durée de la maladie. Nos résultats suggèrent (4) que la levodopa pourrait avoir un plus grand effet sur les patrons d'activations des mouvements de la main la plus affectée.

Mots clefs: Maladie de Parkinson, levodopa, circuit cortico-striatal, circuit cortico-cerebelleux, mouvements d'origine interne, mouvements d'origine externe, IRMf

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease, mainly manifested by tremor, rigidity, bradykinesia and postural instability, and often an asymmetry of symptom severity of the left and right sides of the body. The depletion of dopamine of the nigrostriatal pathway is the primary cause of the motor symptoms observed in patients with PD, leading to an imbalance in basal-ganglia prefrontal circuits. In the protocols described here, patients with PD before and after levodopa administration and healthy participants performed self-initiated (SI) and externally triggered (ET) movements with the left and right hand during functional magnetic resonance imaging (fMRI). In the chapters of this thesis, we argue and provide evidence for four main points.

The first portion (chapter 2) provides a literature review on cortico-striatal and cortico-cerebellar circuit disruption in PD. Using neuroimaging techniques, changes in cerebral and cerebellar activity have been observed in patients with PD compared with healthy participants. Although increases in activity in the cerebellum have often been interpreted as compensatory mechanisms, we provide evidence that they are more likely to be related to pathophysiological changes of the disease, and the disruption of the cortico-cerebellar circuit. In general, we argue (1) is that activity in the cerebellum is linked to the pathophysiology of PD.

In the second section (chapter 3) we discuss the effect of levodopa on the patterns of cortical hypo- and hyper-activity in PD, as well as the activity of the putamen in SI and ET movements. Many studies have shown cortical hypo-activity in relation to nigrostriatal dopamine depletion. In contrast, some cognitive studies have also identified increases in cortical activity in patients with PD as compared with healthy control participants. We have previously suggested that cortical hypo- and hyper-activations depend on striatal recruitment. In this thesis, we further show that hyper-activations in the prefrontal cortex are not reestablished with levodopa administration. We suggest (2) that they are rather associated with mesocortical dopamine circuit dysfunction, and perhaps linked with long-term dopaminergic medication administration. Furthermore, we show (3) that levodopa has

a non-task specific effect on the motor cortico-striatal loop, but does not affect the cognitive cortico-striatal circuit.

Finally (chapter 4), we show that the effect of levodopa on movements of the left and right hands is not symmetrical. Previous studies have shown that in about 50% of patients, one side of the body is more severely affected, and this asymmetry persists throughout the duration of the disease. Our results suggest (4) that levodopa may have stronger effects on the cerebral hemodynamic patterns related to the movements of the more affected hand than on those of the less affected hand.

Keywords: Parkinson's disease, levodopa, cortico-striatal, cortico-cerebellar, self-initiated, externally triggered, fMRI

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Abbreviations

aPFC: anterior prefrontal cortex
ASL: arterial spin labeling
BDI-II: Beck's depression inventory II
CBF: cerebral blood flow
COMT: Catechol-O-methyl transferase
CTL: control
DBS: deep brain stimulation
DLPFC: dorsolateral prefrontal cortex
DTI: diffusion tensor imaging
EC: externally cued
ECu: externally cued-urgent
ET: externally triggered
FDG: Fludeoxyglucose (^{18}F)
fMRI: functional magnetic resonance imaging
GP: globus pallidus
GPe: external segment of the GP
GPi: internal segment of the GP
HC: healthy controls
IFG: inferior frontal gyrus
LID: levodopa-induced dyskinesia
LTD: long-term depression
MAO-B: monoamine oxidase B
MCST: Montreal Card Sorting Task
MoCA: Montreal cognitive assessment
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR: magnetic resonance
MRI: magnetic resonance imaging
MSN: medium spiny neurons
PD: Parkinson's disease
PDRP: PD-related pattern
PDTP: PD tremor-related pattern
PET: positron emission tomography
PFC: prefrontal cortex
PMC: premotor cortex
PPC: posterior parietal cortex
pPFC: posterior prefrontal cortex
rCBF: regional cerebral blood flow
ROI: region of interest
rTMS: repetitive transcranial magnetic stimulation
SI: self-initiated
SMA: supplementary motor area
SNc: substantia nigra pars compacta
SNr: substantia nigra pars reticulata
STG: superior temporal gyrus
STN: subthalamic nucleus
TBS: theta-burst stimulation
TMS: transcranial magnetic stimulation
UPDRS: unified PD rating scale
VLPFC: ventrolateral prefrontal cortex
VTA: ventral tegmental area
WCST: Wisconsin Card Sorting Task

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This thesis has led to the following publications:

- Peer reviewed journals:

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Martinu, K., Degroot, C., Madjar, C., Strafella, A.P., Monchi, O. (2012) Levodopa influences striatal activity but does not affect cortical hyper-activity in Parkinson's disease. *Eur J Neurosci*

Monchi, O., Martinu, K., Strafella, A. (2010) The contribution of neuroimaging in the study of cognitive deficits in Parkinson's disease. Review. *Clin EEG Neurosci* 41(2): 76-81

Francois-Brosseau, F-E., Martinu, K., Strafella, A., Simard, F., Monchi, O. (2009) Basal ganglia and frontal involvement in self-generated and externally-triggered finger movements in the dominant and non-dominant hand. *Eur J Neurosci,* 29(6): 1277-86

C’est le temps que tu as perdu pour ta rose qui fait ta rose si importante.

– Antoine de Saint Exupéry, Le Petit Prince

Chapter 1: Introduction

1.1 Parkinson's disease

1.1.1 Shaking palsy

The first detailed description of what is known today as Parkinson's disease (PD) comes from 6 cases observed by James Parkinson, published in 1817. In his depiction of what he termed the 'shaking palsy', or *paralysis agitans*, the disease begins slowly, such that it is difficult for the patient to pinpoint its precise beginning. The patient first perceives a slight form of weakness, with a tendency to shake, most often in one of the hands and arms, followed by a change in posture. Fatigue and agitation slowly spreads to the lower limbs.

> *"At this period the patient experiences much inconvenience, which unhappily is found daily to increase. The submission of the limbs to the directions of the will can hardly ever be obtained in the performance of the most ordinary offices of life. The fingers cannot be disposed of in the proposed directions, and applied with certainty to any proposed point. As time and the disease proceed, difficulties increase: writing can now be hardly at all accomplished; and reading, from the tremulous motion, is accomplished with some difficulty. Whilst at meals the fork not being duly directed frequently fails to raise the morsel from the plate: which, when seized, is with much difficulty conveyed to the mouth. At this period the patient seldom experiences a suspension of the agitation of his limbs"* (Parkinson, 2002).

In the following stages of the disease, walking becomes increasingly difficult, sleep becomes troubled as tremor causes the patient to awaken, speech becomes unintelligible and feeding one's self becomes virtually impossible.

"As the debility increases and the influence of the will over the muscles fades away, the tremulous agitation becomes more vehement. It now seldom leaves him for a moment; but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room. The chin is now almost immoveably bent down upon the sternum. The slops with which he is attempted to be fed, with the saliva, are continually trickling from the mouth. The power of articulation is lost. The urine and faeces are passed involuntarily; and at the last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release" (Parkinson, 2002).

There were several accounts of what could be interpreted as PD from Egyptian papyrus, Leonardo da Vinci, Johannes Babtiste Sagar and Rembrandt (Lees, 2007). Shortly after James Parkinson's essay, Prussian diplomat Wilhelm von Humboldt (1767 – 1835) described the symptoms of his disease in a written correspondence with a friend:

"Trembling of the hands ... occurs only when both or one of them are inactive; now only the left one is trembling but not the right one that I am using to write – really odd to see ... every line is starting with best intentions in large letters only to end ... in barely legible small ones – in ageing one comes back to childhood's writing, because indeed childlike are these large [Latin] letters without connecting parts." (Horowski, 2000)

Despite this, Wilhelm von Humboldt associated his symptoms of tremor, rigidity and bradykinesia to common consequences of ageing (Horowski, 2000).

It is only in the 1860's that this 'shaking palsy' was further characterized by French neurologists Trousseau, Charcot and Vulpian at the Salpêtrières in Paris. Charcot in particular recognized bradykinesia, posture (Figure 1) and gait as important signs of the disease, but also noted that dementia, depression, affective disorders and hallucinations ensued, notes that were largely ignored until the late 20th century. He subsequently rejected

the term ‘shaking palsy’ and attributed Parkinson’s name to the disease (Playfer & Hindle, 2008). It took another hundred years for researchers to establish dopamine depletion as the source of Parkinson’s disease (PD) (Ehringer & Hornykiewicz, 1960), after which levodopa became the first neurotransmitter replacement treatment (Birkmayer & Hornykiewicz, 1961). Further knowledge of mechanisms behind PD stems from the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a by-product of meperidine synthesis. In 1976, 23-year old chemistry graduate Barry Kidston self-injected himself with a concoction of meperidine and MPTP developing parkinsonism within three days. He displayed dopaminergic neuron degeneration in the substantia nigra at his autopsy, 18 months later. The contamination of this illicit drug in northern California led to numerous additional cases of persistent parkinsonism in young drug abusers in 1982 (Langston *et al.,*1983), and spurred research with what became the animal model of PD.

Figure 1: Illustration of PD by William Richard Gowers (1886)

1.1.2 PD characteristics

The diagnosis of PD is not without downfalls. In a sample of 100 patients clinically diagnosed with PD, only 76 were found to have been correctly diagnosed post-mortem (Hughes *et al.*, 1992). Most common misdiagnoses were attributed to multiple system atrophy, progressive supranuclear palsy, Alzheimer's disease, and cerebrovascular pathology. The typical neuropathological signs of PD are a loss of at least 50% of the melanin-containing nerve cells of the substantia nigra and a depletion of tyrosine

hydroxylase (Figure 2), the rate-limiting step in catecholamine synthesis (dopamine, epinephrine and norepinephrine). It is this neuronal loss that results in the dopamine depletion in PD. Another characteristic of PD is the presence of Lewy bodies (Figure 3), primarily consisting of alpha-synuclein agglomerations (Spillantini *et al.*, 1997), in some of the remaining nerve cells (Perkin, 2008). According to Parkinson Society Canada, the prevalence of PD in Canada is estimated between 100 and 200 / 100,000, with an incidence rate of 10 to 20 / 100,000 each year; 85% of patients are over the age of 65.

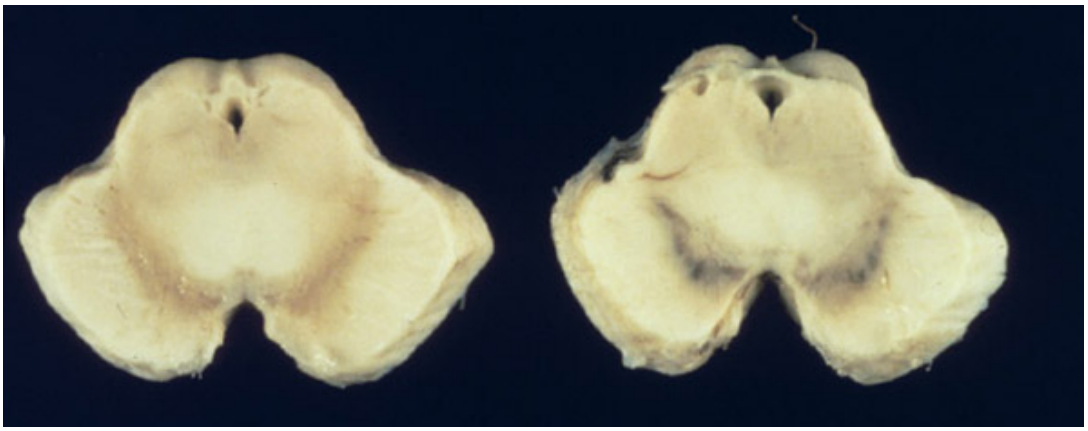


Figure 2: Midbrain showing loss of melanin-containing nerve cells of the substantia nigra in PD (left) compared to healthy controls (right) (pathology.mc.duke.edu)

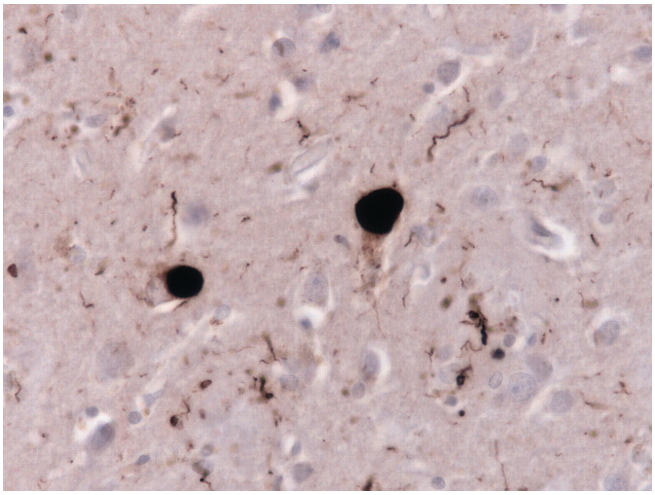
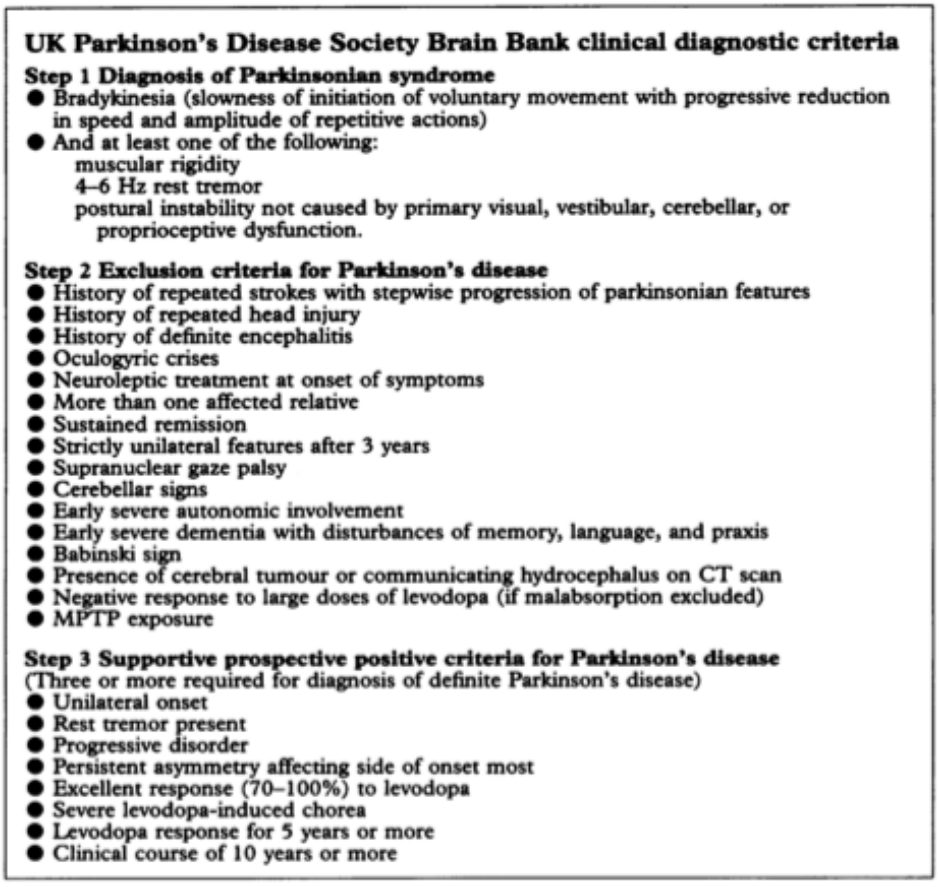


Figure 3: Lewy bodies the cerebral cortex (Love, 2005)

Symptoms of PD typically include tremor, rigidity, bradykinesia and postural disturbances. Bradykinesia mainly presents itself by the difficulty in performing tasks such

as lifting a fork or dressing, reduction in size of handwriting, reduced stride length and a stooped posture. In addition, patients have great difficulty maintaining their posture when pushed forwards or backwards. According to the United Kingdom PD society brain bank, the clinical criteria for a diagnosis of PD include bradykinesia, and either rigidity, tremor or postural instability (Hughes *et al.*, 1992). Exclusion criteria consist of neurological conditions or drug-induced symptoms (Figure 4). Further criteria, such as unilateral onset and response to levodopa, can support the diagnosis of PD. The unilateral onset is maintained throughout the disease as symptom asymmetry; the side of the body first affected remains more severely affected throughout the duration of PD. This intriguing aspect will be the main focus of chapter 4, where we discuss the possibility that the effect of levodopa may be linked to disease asymmetry.



UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Step 1 Diagnosis of Parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least one of the following:
  - muscular rigidity
  - 4–6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

Figure 4: UK clinical diagnostic criteria for PD (Hughes *et al.*, 1992)

Patients also often show changes in brain imaging scans. In particular, 6-[^{18}F]-fluorodopa (a radioactively labeled dopamine precursor) positron emission tomography (PET) scans can show reduced isotope uptake in the putamen (Figure 5), particularly in the hemisphere that is more affected. As we will see in chapter 3, the blood oxygenation level dependent (BOLD) activity of the putamen and the cortical regions it communicates with are substantially affected in PD.

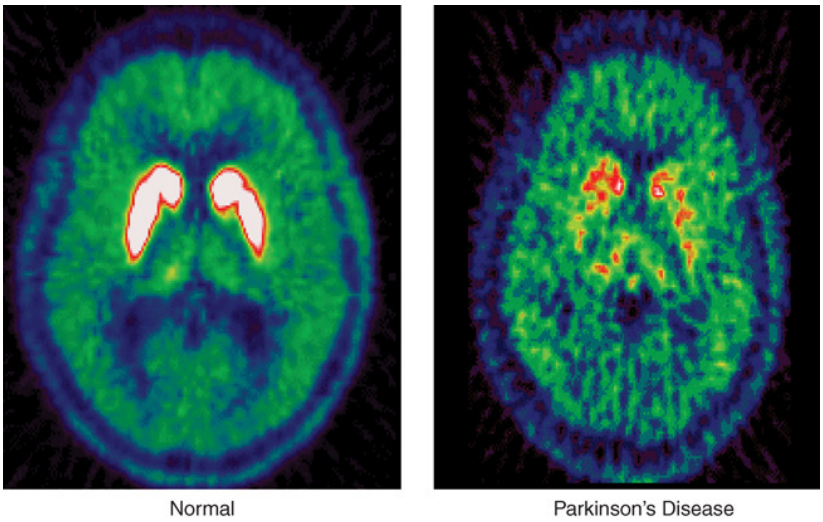


Figure 5: Fluorodopa PET in a healthy control and a PD patient (Longo *et al.*, 2011)

1.2 Levodopa

Several options exist for the treatment of PD, through the alteration of the different metabolic steps of dopamine synthesis, release and reuptake (Figure 6). Levodopa (a.k.a. L-dopa), the cornerstone of PD treatment, enhances dopaminergic activity by providing more dopamine precursor. The effect of dopamine can also be enhanced by dopamine agonists acting on receptors (dopamine agonists), or by inhibiting dopamine reuptake (COMT inhibitors).

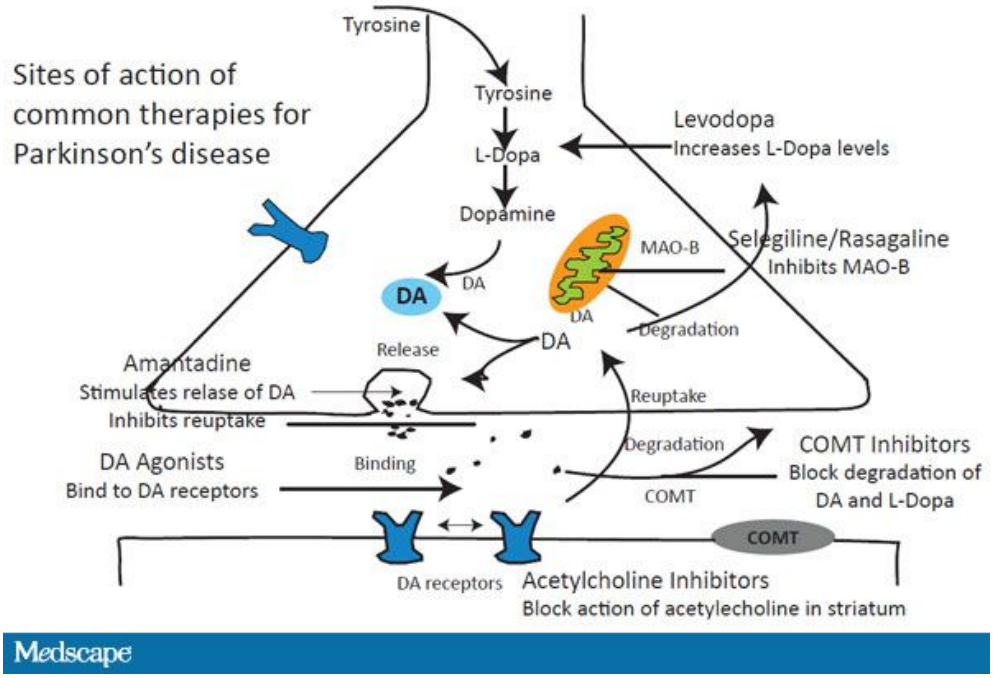


Figure 6: Dopamine, metabolism and drug treatment

COMT = Catechol-O-transferase; DA = dopamine; MAO = monoamine oxidase. Figure adapted from www.medscape.org

Levodopa, or L-3,4-dihydroxyphenylalanine, is one of the most common treatments for PD. Unlike dopamine, it crosses the blood brain barrier, increasing the concentration of dopamine. Because dopamine receptors also exist in the periphery, however, the administration of levodopa has many adverse effects such as nausea, hypotension, gastrointestinal complications, hair loss and sleep disturbance. It may also be the source of additional cell death and, as discussed in chapter 2, lead to levodopa-induced dyskinesias (LIDs).

1.3 Basal ganglia and cerebellum in PD

1.3.1 Anatomy

Given the importance of nigrostriatal degeneration in the pathophysiology of PD, describing basal ganglia anatomy and the dopaminergic pathways is crucial. Also, understanding the organization of the cortico-striatal circuits is fundamental for the remaining chapters. Finally, as will be discussed in chapter 2, the cerebellum plays an important role in the

pathophysiology of PD. We will therefore also introduce the cerebellum and cortico-cerebellar connections.

1.3.1.1 Basal ganglia

The basal ganglia are composed of the caudate nucleus, putamen, nucleus accumbens, subthalamic nucleus (STN), globus pallidus (GP) and substantia nigra, tightly interconnected regions that process information from all cortical regions. The caudate nucleus and putamen, forming the striatum, are deep grey matter nuclei embedded within the c-shaped lateral ventricles (Figure 7). The putamen and the adjacent GP (a.k.a. the lentiform complex) with its internal and external segments (GPi and GPe, respectively) are anterior to the thalamus, separated by the posterior arm of the internal capsule. The lentiform nucleus is covered laterally by the external capsule, claustrum, extreme capsule and insula. Anterior to the putamen, and joined to it at its most inferior point forming the nucleus accumbens, the caudate nucleus runs superiorly around the putamen, separated by the anterior arm of the internal capsule and forming the floor of the lateral ventricle. Inferior to the thalamus, as its name implies, lies the STN, just superior to the substantia nigra located in the midbrain.

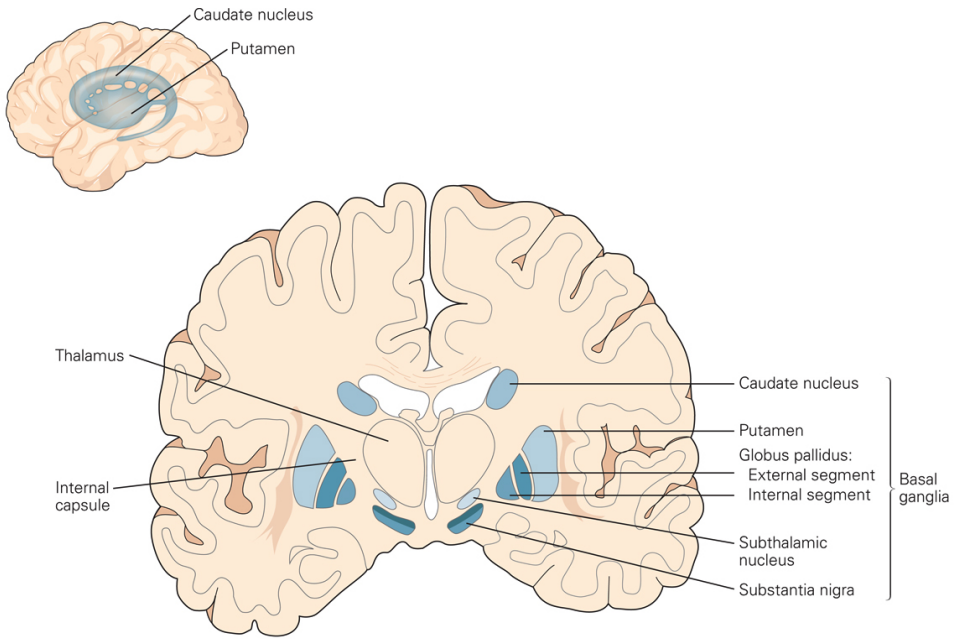


Figure 7: Anatomy of the basal ganglia (Kandel *et al.*, 2013)

1.3.1.2 Dopamine, dopamine receptors and dopaminergic pathways

Dopamine is a catecholamine neurotransmitter, synthesized from the amino acid tyrosine. Tyrosine hydroxylase first converts tyrosine to l-3,4-dihydroxyphenylalanine (L-dopa); this is the rate-limiting step of dopamine synthesis. The second step is the decarboxylation of L-dopa to dopamine by the enzyme aromatic L-amino acid decarboxylase (Vallone *et al.*, 2000). Dopamine is produced in the cell bodies of the ventral tegmental area (VTA) and the substantia nigra, whose axons project to different regions of the brain, forming several dopaminergic pathways. The three major projections are the nigrostriatal, meso-cortical and meso-limbic pathways (Figure 8).

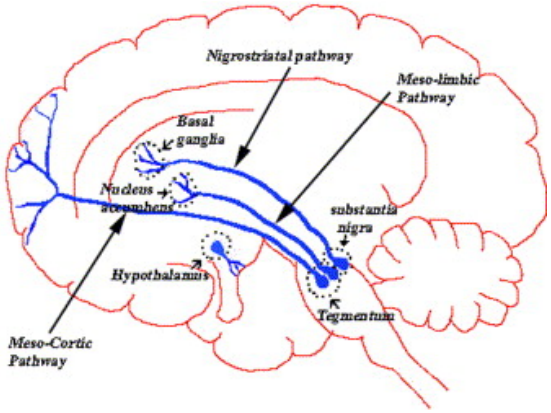


Figure 8: Dopaminergic projections showing the nigro-striatal, meso-limbic and meso-cortical pathways (Chinta & Andersen, 2005)

The nigro-striatal pathway runs from the substantia nigra pars compacta (SNc) to the dorsal striatum (putamen and caudate nucleus). It is strongly involved in movement, and its degeneration is the primary source of PD symptoms. The meso-limbic pathway runs from the VTA to the ventral striatum (nucleus accumbens), the olfactory tubercle and other parts of the limbic system, and is mainly involved in motivated behavior. The meso-cortical pathway projects from the VTA to the frontal cortex, and is involved in memory and learning (Le Moal & Simon, 1991).

There are five dopamine G-coupled protein receptors, generally classified as either D1-like or D2-like. This classification stems from their effect on the production of cyclic adenosine monophosphate (cAMP) through the stimulation or inhibition of the adenylyl

cyclase protein (Stoof & Kebabian, 1981). The D1-like subfamily (D1 and D5), found exclusively post-synaptically, stimulate cAMP production, whereas the D2-like subfamily (D2, D3 and D4), expressed both post- and pre-synaptically, lead to an inhibition of adenlylyl cyclase and a decrease in cAMP production (for a review, see Beaulieu & Gainetdinov, 2011). D1 receptors are primarily found in the nigrostriatal, mesolimbic and mesocortical regions (striatum, nucleus accumbens, substantia nigra, olfactory bulb, amygdala and frontal cortex), as well as in the hippocampus, cerebellum, thalamic and hypothalamic areas. D2 receptor density is highest in the striatum, nucleus accumbens, olfactory tubercle, and also in the substantia nigra, VTA, hypothalamus, cortical areas, septum, amygdala and hippocampus. Segregation of D1 and D2 receptors has been found within the basal ganglia, such that the medium spiny neurons (MSNs) that project to different regions will selectively express one or the other. In particular, MSNs that project to the GPi and substantia nigra pars reticulata (SNr) express the D1 receptor, whereas a different group of MSNs that project to the GPe selectively express the D2 dopamine receptor. There is, however, a small portion (5-15%) of MSNs that express both D1 and D2 receptors in the dorsal striatum. D1 and D2 receptors are estimated to compose the majority of dopamine receptors within the striatum (Levey *et al.*, 1993); D3, D4 and D5 receptors are expressed at much lower levels in several cortical and subcortical regions. All receptors are also expressed in the periphery, such as in the kidneys, adrenal glands, gastrointestinal tract, blood vessels and heart (Beaulieu & Gainetdinov, 2011).

1.3.1.3 Ganglia-thalamocortical circuits

The basal ganglia and cortex are linked through a series of ganglia-thalamocortical circuits, referred to in this thesis as cortico-striatal loops. Five parallel circuits have been described by Alexander et al., namely the “motor”, “oculomotor”, “dorsolateral prefrontal”, “lateral orbitofrontal” and “anterior cingulate” loops. Each one of these loops consists of non-overlapping regions of the striatum, GP, substantia nigra, thalamus and cortex (Figure 9). These circuits provide a topographical projection of information from functionally related cortical areas through the intermediate structures before being projected back to the cortex (Alexander et al., 1986). While the topography in these circuits is predominant, links

exist between these circuits at the cortical, striatal as well as thalamic levels. Furthermore, as discussed in the next chapter, there are important connections between the core of these circuits, in the thalamus, and the cerebellum. It must be noted, however, that the series of connections and funneling of information through these regions is part of the classical Albin-DeLong model (Albin *et al.*, 1989; DeLong *et al.*, 1990), and more complex models of basal ganglia function have been suggested (Bar-Gad & Bergman, 2001; Lanciego *et al.,* 2012).

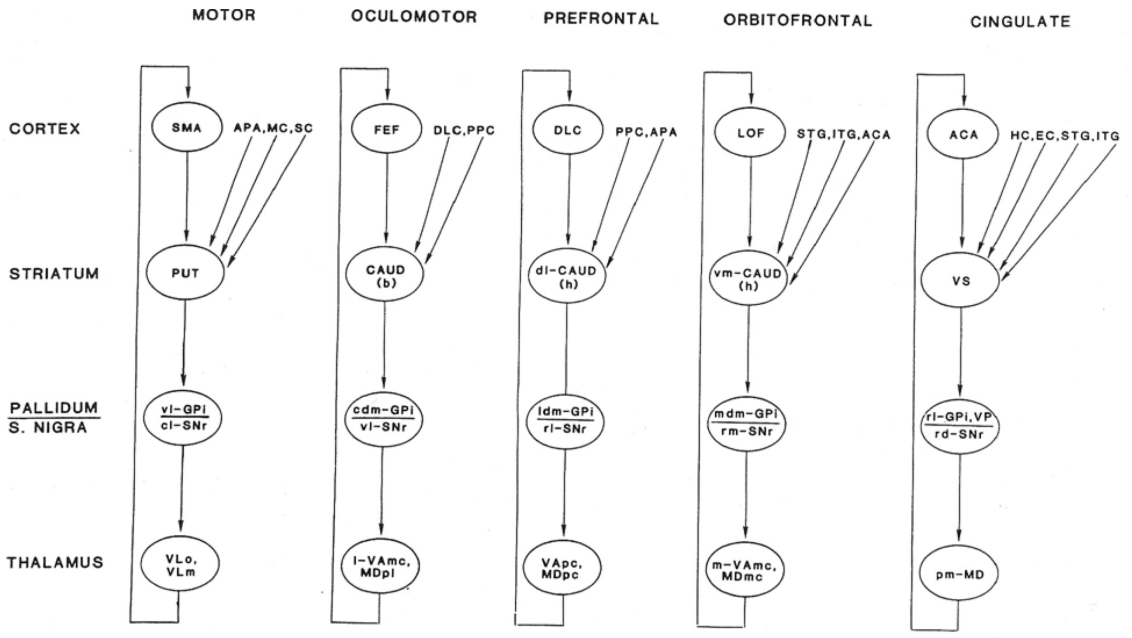


Figure 9: The five ganglia-thalamocortical circuits as described by Alexander *et al.*, 1986

The two circuits of particular interest for this thesis are the motor and "dorsolateral prefrontal", or cognitive, cortico-striatal circuits. The cognitive cortico-striatal loop consists of projections from the dorsolateral prefrontal cortex (DLPFC) and portions of the parietal cortex to the head of the caudate nucleus. From the latter, projections are sent to the dorsomedial one-third of the GP and rostral SNr, and finally to the thalamus before projecting back to the DLPFC. The disruption of the cognitive cortico-striatal circuit leads to specific cognitive disabilities, and is thought to play a key role in the cognitive deficits sometimes observed in PD.

The motor cortico-striatal circuit is a closed loop of topographically organized projections between the motor cortex, premotor cortex (PMC) and supplementary motor area (SMA), putamen, GP, SNr, STN and thalamus. The motor loop further consists of direct, indirect and hyperdirect pathways. The direct pathway relays projections from the putamen to the GPi and then the thalamus. The indirect pathway consists of projections from the putamen first to the GPe, then the STN, and finally back to the GPi before relaying to the thalamus. Through excitatory and inhibitory connections of these two pathways, driven by the differential effects of D1 and D2 receptors, the direct pathway disinhibits thalamic activity, whereas the indirect pathway increases the inhibition of the thalamus. The balance between these two systems, described in detail in chapter 2, plays an important role in the symptomatology of PD.

1.3.1.4 The cerebellum and the cortico-cerebellar circuit

While cortico-striatal dysfunction is important in PD, cortico-cerebellar changes have also been reported. The nature and origins of these cortico-cerebellar alterations are still under debate and will be the focus of a large proportion of this thesis (chapter 2).

The cerebellum consists of tightly packed sulci and gyri of a very regular cell composition, and several deep nuclei. The grey matter of the cerebellum is formed of three cell layers (Figure 10); the granular cell layer holds all the granule cells, interneurons and Golgi cells, the thin Purkinje cell layer contains the Purkinje cell bodies, and, finally, the molecular layer comprises of the thick Purkinje cell dendritic trees, parallel fibers, interneurons, stellate cells and basket cells.

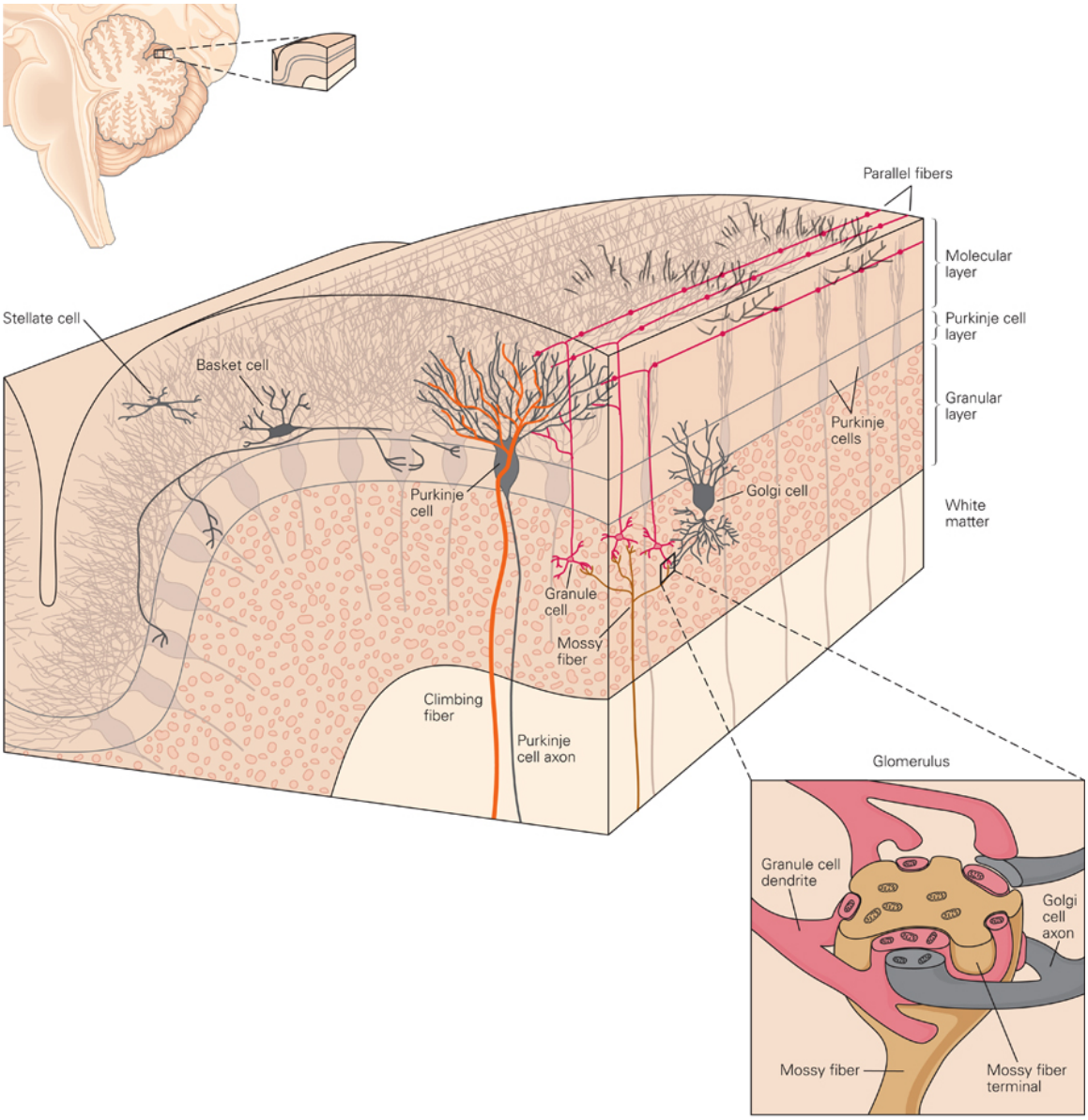


Figure 10: Cellular layers of the cerebellum (Kandel *et al.*, 2013)

The cortico-cerebellar circuit consists of connections from the cerebral cortex to the cerebellar cortex through a series of brainstem nuclei, and feedback connections from the cerebellar cortex to the cerebral cortex through thalamic nuclei. Input to the cerebellum is carried out by two types of cells, the mossy fibers that bring cortical information from the pons (corticopontine and pontocerebellar projections), and climbing fibers that bring cortical information from the red nucleus and inferior olive. Purkinje cells from the cerebellar cortex then send their output to the deep nuclei of the cerebellum, which then

project through the red nucleus to thalamic nuclei, and finally back to the cortical region where information originated from, forming a closed loop. The cortico-cerebellar circuit and its connections with the cortico-striatal circuit are described in detail in chapter 2.

1.3.2 Functional roles of the striatum and cerebellum

1.3.2.1 The dorsal striatum and cortical activity

The dorsal striatum is an essential component of the cortico-striatal pathways (Alexander *et al.*, 1986). Using the Wisconsin Card Sorting Task (WCST) and the Montreal Card Sorting Task (MCST), Monchi *et al.* (2001, 2004, 2006, 2007) have been able to dissociate the roles of the components of the dorsal striatum, in particular those of the caudate nucleus and the putamen. The caudate nucleus has been shown to be involved different aspects of cognition such as the planning of a novel action (Monchi *et al.*, 2006; Owen *et al.*, 1996). In contrast, the putamen has been shown to be involved in the execution of novel actions. As discussed in the next two chapters, the recruitment of the caudate nucleus and the putamen lead to differences in cortical activity observed in patients with PD. More specifically, patients with PD don't simply have a hypoactive cortex, as the original model by Albin, Young & Penney suggests (1989); they display increased cortical activity as compared with healthy control participants in different cognitive and motor tasks. We define hypo-activations in patients with PD as a decrease in cortical activity compared with the activity of the same region in healthy participants during the same task or contrast, and hyper-activations as increases in activity in cortical regions as compared with those same regions in healthy participants. Based on results using the WCST, MCST, and self-initiated (SI) and externally triggered (ET) movements (Monchi *et al.*, 2004, 2007; Martinu *et al.*, 2012), we have suggested that the hypo-and hyper-activity patterns observed in PD are related to striatal requirement in the task at hand (Monchi *et al.*, 2010). Moreover, in a task where healthy controls specifically recruit the striatum, patients with PD will show hypo-activity of prefrontal regions. However, in tasks where healthy controls do not specifically require basal ganglia activity, patients with PD will show hyper-activity of prefrontal and parietal regions (Figure 11).

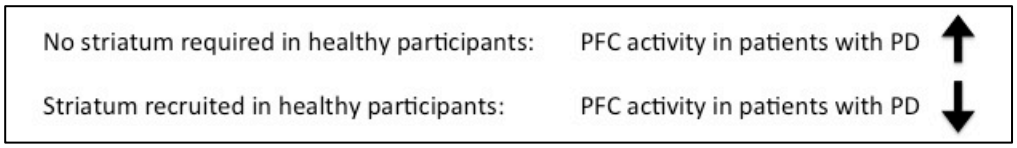


Figure 11: Schematic of cortical hypo- and hyper-activity in PD

Our laboratory had previously shown that while levodopa had a significant effect on the structures involved in the motor cortico-striatal loop, it did not seem to affect activity of the cognitive cortico-striatal loop during the WCST (Jubault *et al.*, 2009). We wanted to extend this concept to a motor task as well (chapter 3). But more specifically, we wanted to compare patients with PD to control participants to determine the effect of levodopa on the hypo- and hyper-activation patterns in PD. Does levodopa restore these hyper-activations to normal, or are they linked to the pathophysiology of PD and/or the prolonged use of dopaminergic medications?

1.3.2.2 Hand dominance

According to lesion studies of right-handed subjects performed between the 1920's and 1980's, it seemed that the left hemisphere (considered to be dominant) played an important role in ipsilateral hand control (Mattay *et al.*, 1998). A PET study with hand movements interpreted that the increase in left-hemispheric activity may be either due to a differential organization between the two hemispheres, or to the fact that more effort for right-handed subjects was necessary for movements of the left hand (Halsey *et al.*, 1979). Kawashima *et al.* (1993) concluded that the left non-dominant hand recruited ipsilateral motor areas, a sign of functional asymmetry. However, Mattay *et al.* (1998) argued that the dominant hand movements used in these studies were over-learned sequences, or automatized, and so required less 'conscious effort' to perform. The non-dominant hand, therefore, may require more resources to perform the same movements, and thus lead to the recruitment of ipsilateral regions. In their study, Mattay *et al.* (1998) compared a simple task performed by the left (non-dominant) hand to a more complex task performed by the right (dominant) hand, and found that subjects exhibited similar ipsilateral cortical activations in both tasks. The authors speculated, therefore, that ipsilateral activations in motor tasks represent the degree to which motor movements are automatic, rather than

differential organization for dominant and non-dominant hand control between the two hemispheres.

We have recently performed a functional magnetic resonance imaging (fMRI) study with healthy young adults while carrying out three conditions of a finger-moving task: a self-initiated (SI) button-press sequence, a computer-generated sequence, and a button-press repetition condition (François-Brosseau *et al.*, 2009; this study is directly relevant to this thesis as we have applied the same protocol to the studies we describe, and is therefore included as an appendix for easy reference). We showed that the three tasks increasingly recruit the putamen, the repetition condition requiring the putamen the least, followed by the externally triggered (ET) condition, and the SI sequence generation requiring the putamen the most. In this particular protocol, the putamen was more involved in the generation of SI movements than in ET ones, and there is increasing recruitment of cortical motor regions with the three tasks in the same order. The main finding of this study was that when comparing the dominant and non-dominant hands, task demand for striatal activity was higher when participants used the non-dominant hand. We wanted to use this same protocol with patients with PD to determine, first of all, whether they showed the same patterns of activity and whether levodopa reestablished this discrepancy, but mainly whether disease asymmetry could invert this effect. This would mean that if patients were more severely affected on the right side of their body, would they display opposite results? As discussed in chapter 4, however, this hypothesis turned out to be difficult to test considering the recruitment restraints we faced.

1.3.2.3 The cerebellum

For many decades, the cerebellum was considered to be involved in motor functions. Although Charcot had been adamant about its role in cognitive functions, this aspect has greatly been ignored. In the 1930's, Abbie (1934) observed that there were degenerated regions of the pons after major lesions to the so-called association cortices. These association areas are now known to be linked with the lateral hemispheres of the posterior lobe of the cerebellum through the pons and the thalamus (Schmahmann & Caplan, 2006). Additionally, Bard (1928) and Zanchetti & Zoccolini (1954) described animals that

developed sham rage after lesions and stimulations of the cerebellum. Even though early work hinted at its involvement in aspects such as emotional control and cognitive processes like executive functions and linguistic processing (Schmahmann & Caplan, 2006), it is only quite recently that experiments specifically designed to understand this involvement were developed. It is important to consider the cerebellum's implication in a combination of motor and cognitive tasks, such as the cognitive manipulation of motor sequences; a recent study showed that participants who perform worse at motor imagery compensated with the cortico-cerebellar network (Guillot *et al.*, 2008). Taniwaki *et al.* (2006) showed that in contrast to the involvement of the cortico-striatal loop in SI movements, the cortico-cerebellar loop is more involved in ET movements. Blouin *et al.* (2004), however, observed with PET that the cerebellum is involved in synchronized SI movements. As discussed in further detail in the following chapter, the involvement of the cerebellum in SI and ET movements is strongly dependent on the task used, partly relating to the type of planning involved in the individual movements. Not only do our results suggest that the cerebellum is preferentially involved in SI movements, we also find that levodopa has a significant effect on cerebellar activity. These results, discussed in chapter 2, support our hypothesis that levodopa increases activity in the cerebellum through connections between the cortico-striatal and cortico-cerebellar pathways, and suggest that it is this increase that eventually leads to the pathophysiological involvement of the cerebellum in symptoms such as LIDs.

1.4 Aims of this thesis

This general aim of this thesis is to understand the effect of levodopa on the neural processes as measured by BOLD fMRI underlying SI and ET movements of the left and right hands in patients with PD. The next section (chapter 2), recently accepted in *Journal of Behavioral Neuroscience*, reviews the current literature concerning cortico-striatal and cortico-cerebellar circuits in PD. In this section we will discuss the compensatory and pathophysiological involvement of these two circuits in PD, and the role that levodopa has to play in LIDs, a common side-effect. The following section (chapter 3) is a research article published in *European Journal of Neuroscience* on the effect of levodopa on cortico-striatal circuits in PD. There we demonstrate that striatal activity related to SI and ET

movements in PD is reduced compared with healthy controls, and that patients show hyper-activations linked to mesocortical dopamine pathway dysfunction. Finally, in the research article (chapter 4) that will be submitted to *Movement Disorders* shortly we describe the differential effect of levodopa on left and right hand movements in PD. More specifically, we suggest that levodopa leads to significant differences in cortico-striatal regions when patients use their left hand and not their right hand, implying that levodopa selectively acts on more affected / non-dominant hand movements.

1.5 Magnetic resonance imaging

1.5.1 What is MRI?

Magnetic resonance imaging (MRI) is an imaging technique that allows the visualization of internal structures. Using a powerful magnet, often in the order of 1.5 to 7 Tesla (the earth's magnetic strength is 0.00005 Tesla), and the magnetic properties of atomic nuclei in organ tissue and blood, MRI permits the imaging of the anatomical structures of body parts and brain function. The smallest unit of an MR image is called the voxel, i.e. the volumetric pixel, usually $1mm^3$ for an anatomical image. This is an extremely detailed spatial resolution when compared to other neuroimaging techniques such as electroencephalography (EEG) or PET (Figure 12). The temporal resolution of MRI is <1s (fMRI) to minutes (MRI). Although it is far from the temporal precision of EEG, MRI provides an adequate balance of spatial and temporal resolutions for a wide range of physiological and pathological studies.

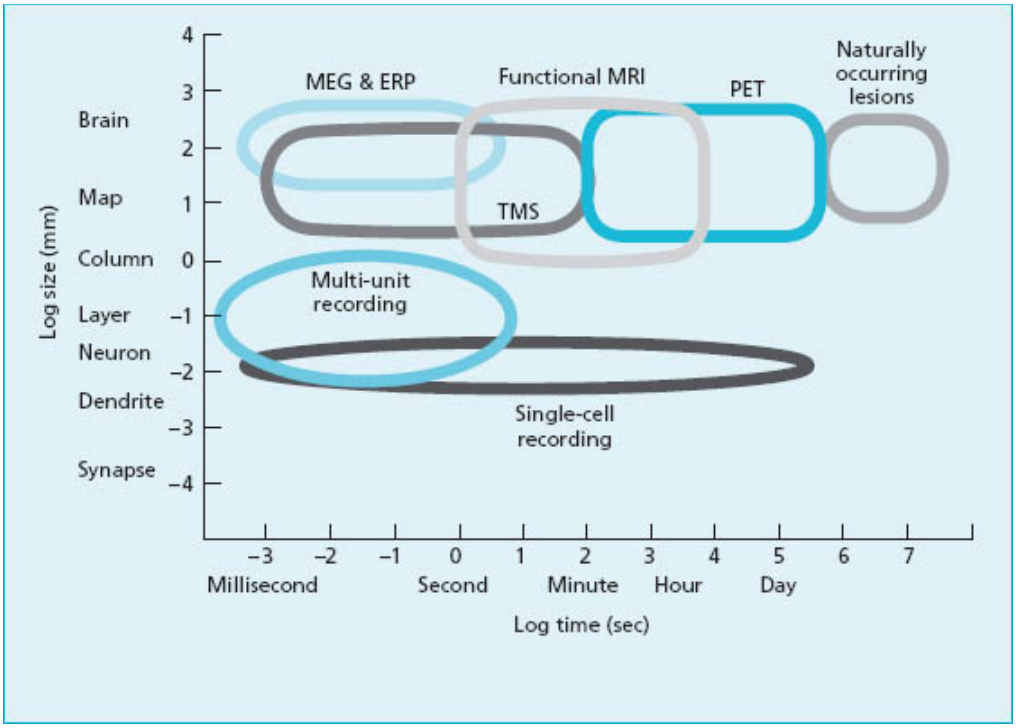


Figure 12: Spatial and temporal resolution of neuroscience techniques (Ward, 2006)

1.5.2 History

The development of the MRI technique was made possible by Wolfgang Pauli's observation, in 1924, that atomic nuclei (e.g. hydrogen) spin at specific frequencies and have a magnetic moment. When placed into a surrounding magnetic field, atomic nuclei align themselves with the field, a phenomenon referred to as relaxation time. As Isidor Rabi demonstrated in 1937, if a surrounding magnetic field oscillates at the same frequency as the atomic nucleus, the latter would absorb energy from the field, just like pushing a pendulum at the correct moment. This phenomenon was named magnetic resonance, and the frequency that has the most effect on the atomic nuclei in question is referred to as the resonant frequency. Just as the swing of a pendulum is highly dependent on gravity, the resonant frequency is highly dependent on the static magnetic field. In 1946, Edward Purcell and Felix Bloch independently developed experiments that tested the resonant frequency of solid matter (wax paper) and water. Bloch's experiment in *Physical Review* involved a transmitter coil and a detector coil that recorded the energy, or nuclear resonance, absorbed by the sample of water. Nuclear magnetic resonance (NMR) is still the basis of all

MRI acquisitions today. The term 'nuclear' was eventually dropped due to its negative connotations with health, and magnetic resonance imaging was adopted in its stead.

After the observation that water atomic nuclei had different relaxation times depending on their surrounding tissue, the medical application of NMR was clear. If the measure of resonant frequencies of atomic nuclei could be transformed into images, one could potentially distinguish between different types of tissue. The simple detection of emitted energy from atomic nuclei from an oscillating magnetic field, however, lacked spatial information. In 1972, Paul Lauterbur suggested that if the strength of the static magnetic field varied across space, the resonant frequency detected could give information about its location. In 1976, using an electromagnetic pulse and rapidly changing field gradients, Peter Mansfield developed the echo-planar imaging used today to record images in a fraction of a second, making the acquisition of images of humans possible.

1.5.3 Magnets and coils

The MR scanner consists of several main components. The first is a wire wrapped in tight loops (a solenoid), forming the principal magnet (Huettel, 2004). The electrical current runs through this solenoid generating the static magnetic field, B_0. The second important component is the radiofrequency antenna, placed directly around the item being scanned, is composed of two electromagnetic coils: a transmitter and a receiver. This antenna generates the electromagnetic field at the atomic nuclei's resonant frequency, and records the energy released (in the radiofrequency portion of the electromagnetic spectrum). Contrary to the static magnetic field, these coils are turned on and off during image acquisition. When placed in a static magnetic field, atomic nuclei align themselves with the field in what is referred to as relaxation time. The radiofrequency coils send pulses that disturb this equilibrium, exciting the atomic nuclei. Following the pulse, it is the release of the absorbed energy and the return to baseline, or relaxation, that defines the magnetic resonance (MR) signal.

The third important components of the MR scanner are the gradient coils. These are three sets of coils that will cause a transient gradient in the magnetic field in the x, y, and z

directions, one after the other. The controlled changes in magnetic field give the MR signal spatial information, in that different locations have a different contribution to the MR signal. An MR signal that codes spatial information about the resonating atomic nuclei permits the reconstruction of spatial frequency data into image-space data. Through mathematical manipulations (an inverse Fourier transformation), one can generate 2D images from the recorded MR signal. A slice-by-slice acquisition of 2D images can finally be reconstructed into a 3D volume encompassing the entire structure being scanned, e.g. a participant's head.

1.5.4 Hemodynamics

As different brain regions become involved in specific tasks, the energy consumed and therefore the demand for oxygen increases. The imaging of brain function is based on blood flow and the magnetic properties of hemoglobin. More specifically, water molecules in oxygenated hemoglobin have no magnetic moment, but deoxygenated hemoglobin has unpaired electrons and a significant magnetic moment; it is paramagnetic. In MR sequences sensitive to the changes in spin caused by deoxygenated blood, there will be a drop in MR signal. When measuring the BOLD response, however, what we observe is an initial dip followed by a strong increase in MR signal (Figure 13). One interpretation of this phenomenon is that when a region becomes more active and begins consuming oxygen, an excess of oxygenated blood flushes the region and displaces the deoxygenated hemoglobin, causing the rise in MR signal.

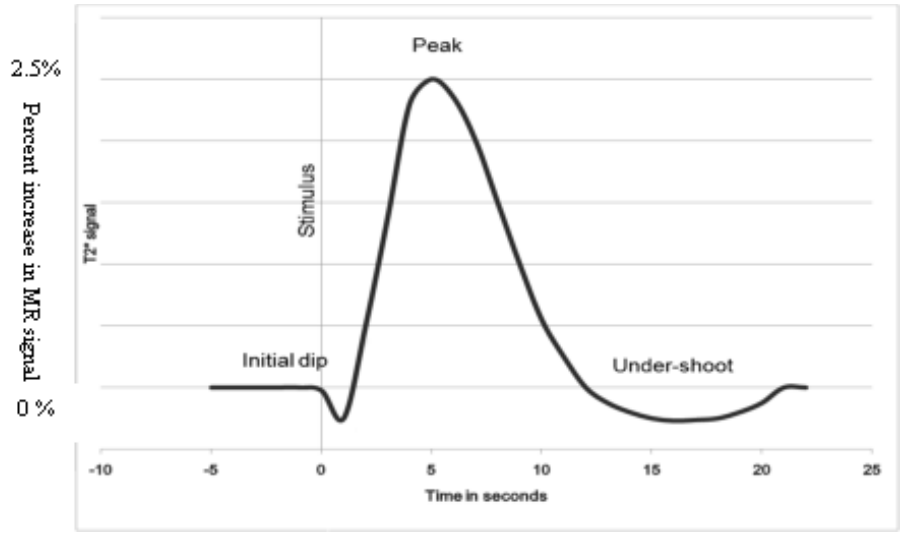


Figure 13: Model of the hemodynamic response

Figure adapted from BOLD imaging, Radiopaedia, BOLD imaging, www.radiopaedia.org

It is important to realize, when performing MRI experiments, that the changes in signal observed on a functional acquisition are a physiological phenomenon that correlates with changes in blood flow, which correlates with energy consumption of the underlying neurons, and which itself correlates with neuronal activity. It is not a direct measure of cellular activity; therefore interpretations of underlying cognitive processes have to be made with this in mind. The hemodynamic response is also very slow. The peak of the response occurs 4 to 6 seconds after the stimulus and the consequent neural response, and only returns to baseline after 12 to 14 seconds. This has important implications for the design of fMRI experiments.

1.5.5 Experimental design

In order to answer a scientific question, a proper experimental design needs to be put in place. Specific hypotheses require specific dependent and independent variables. Additionally, in order to be able to make interpretations on neural processes involved in specific tasks, the experimental condition has to be compared to an adequate control, so that the comparison between the two can most accurately test the hypothesis in question. An fMRI protocol consisting of a motor or cognitive task will therefore usually consist of a timeframe with at least two alternating conditions. Subsequent analyses are performed to

correlate the hemodynamic activity (i.e. the dependent variable) involved in each condition, and the difference in the dependent variable between the experimental condition and the control condition provide an answer to the question as precisely as possible. Because the hemodynamic response is slow, researchers first developed the blocked design, which separates the different conditions in the distinct sections of an extended period of time (Figure 14), ranging easily from 15 to 30 seconds:

Figure 14: Schematic of a blocked design, with alternating conditions A and B

The blocked design paradigm is a powerful method that involves a sustained hemodynamic response, giving maximal amplitude of the BOLD response. Some questions cannot be answered by using the blocked design. For example, comparing correct and incorrect responses, or measuring the response associated with an "oddball" task involves events of a very short duration. Event-related paradigms are more appropriate for such experiments. They involve brief stimulus presentations presented randomly throughout the duration of the scan, with an inter-stimulus interval between each. Although this method does not allow the hemodynamic response to reach its maximum amplitude, it is based on the assumption that short stimuli will evoke a transient change in neural activity. In a situation where participants need to make responses to the events, this method allows the researcher to remove events with incorrect responses, or to make a comparison between them. The choice of experimental design is crucial to the questions that stem from the research hypothesis. One must ascertain that there are no confounding variables that would correlate with the variables of interest.

Chapter 2: Pathophysiology versus compensation

The first article presented in this thesis is a review that has recently been accepted for publication in a special issue on controversies in PD in *Behavioral Neuroscience*. Our preliminary data indicated that in patients with PD, activity in the cerebellum was increased after levodopa administration. Some studies have argued for the potential compensatory role of the cerebellum in PD pathology (Glickstein & Stein, 1991; Palmer et al., 2009a). If levodopa re-established cerebral activity to patterns observed in healthy controls, it should cause a reduction in activity instead. We wanted to examine more closely the role of the cerebellum in PD. In reviewing the literature we realized that there were two possible explanations for cerebellar changes in activity in PD, which are not necessarily mutually exclusive. We have found more convincing evidence, however, that changes in activity in the cerebellum are more closely linked with pathophysiology than compensatory mechanisms, and that many studies suggesting that the cerebellum is involved in compensation are inconclusive. In the following chapter we introduce in greater detail the cortico-striatal and cortico-cerebellar circuits, and provide evidence that the cerebellum may also be strongly affected by PD pathology and/or treatment. We also discuss the effect of levodopa on cerebellar activity, supported by our own results.

Cortico-striatal and cortico-cerebellar circuits in Parkinson's disease: pathophysiology or compensation?

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Abstract

The basal ganglia and the cerebellum are anatomically and functionally linked to the cerebral cortex through a series of well-established circuits. The disruption of dopaminergic projections in PD leads to an imbalance within these circuits, leading to motor and cognitive symptoms. The cortico-cerebellar network has often been viewed as a compensatory

network, helping the dysfunction of the cortico-striatal circuits in PD. However, evidence for this compensatory role is scarce; most changes in cerebellar activity could equally be attributed to pathophysiological changes underlying PD. This paper will review the anatomy, interaction and function of the cortico-striatal and cortico-cerebellar circuits, the pathophysiological, metabolic and functional changes observed in PD, as well as the effect of levodopa and deep brain stimulation (DBS) on these changes. We will use this framework to discuss the pathophysiological and compensatory mechanisms behind cortico-striatal and cortico-cerebellar circuit activity in PD.

Keywords: Parkinson's disease, Cerebellum, Striatum, Compensation, Levodopa

Introduction

PD is a debilitating neurodegenerative illness associated with the loss of dopaminergic neurons of the substantia nigra. Patients classically suffer from motor symptoms such as tremor, rigidity and bradykinesia, although cognitive deficits in executive functioning, memory, language, and visuo-spatial processing are also pervasive (Taylor & Saint-Cyr, 1995). The cortex, thalamus, basal ganglia and cerebellum form a series of anatomically and functionally segregated circuits sub-serving a multitude of cognitive and motor functions. The disruption of these circuits through the degeneration of dopaminergic neurons in the substantia nigra leads to widespread changes in brain activity and connectivity. It is not yet known whether these extensive neural changes are strictly the result of PD pathophysiology or, alternatively, are manifestations of compensatory mechanisms in response to the disease. It has been suggested that the recruitment of cortico-cerebellar networks is one possible compensatory mechanism for the generation of movement in PD (Rascol *et al.*, 1997, Palmer *et al*., 2009a), such as SI and ET movements. However, many of the changes in the cortico-cerebellar circuits may be the result of disruptions caused by PD or by the prolonged used of dopaminergic medication. In this review we will suggest that the pathophysiology behind changes in cerebral and cerebellar activity cannot be ignored, and that future research will be necessary to disentangle these

two alternative hypotheses. To this end, we will first describe the anatomy and function of the cortico-basal ganglia and cortico-cerebellar circuits, as well as the pathophysiological, metabolic and functional changes in these circuits as a result of the disease. We will then discuss the effect of levodopa and its side effects in the treatment of PD, DBS, and provide suggestions for future research that may help distinguish between compensatory and pathophysiological mechanisms.

Cortico-basal ganglia circuits

Anatomical connections

It is well established that motor, sensory and association areas of the cortex are extensively connected with specific subdivisions of the basal ganglia to form a series of 'basal ganglia-thalamocortical' circuits. Several distinct circuits have been described, including the motor, oculomotor, limbic and associative circuits (Alexander *et al.*, 1986). These functionally and anatomically segregated pathways mainly relay information from functionally related cortical regions, the striatum, pallidum and substantia nigra and the thalamus. Understanding the connections within and between these circuits is crucial for procedures such as DBS, as an intervention in one area will have specific effects across a wide range of areas (Wichmann & DeLong, 2011). In the motor basal ganglia-thalamocortical circuit, somatotopically organized information from the somatosensory, motor, premotor and supplementary motor cortices is projected through the putamen, STN, GPi, GPe and SNr to the ventrolateral nucleus of the thalamus. The thalamus finally projects back to the cortex, forming a closed loop of tightly interconnected regions

The motor cortico-striatal loop can further be divided into 'direct' and 'indirect' pathways, by which competing processes between the putamen, GP, STN and SNr determine overall thalamic activity (Alexander *et al.*, 1990). Specifically, the direct pathway connects the striatum to the GPi/SNr by a single inhibitory projection. By contrast, the indirect pathway connects the striatum to the GPi via inhibitory projections to the GPe and the STN and ultimately excitatory connections to the GPi/SNr. An overall output is finally sent from the GPi/SNr to the thalamus; the direct pathway causes the striatum to disinhibit

the thalamus, whereas the indirect pathway causes the striatum to inhibit thalamic activity (Figure 15). The signals from the direct and indirect pathways create a balance of opposing contributions, allowing movement to be regulated via thalamocortical connections. However, these pathways are not entirely independent as evidence suggests that there are synaptic connections between the direct and indirect motor cortico-striatal pathways (Yung *et al.*, 1996).

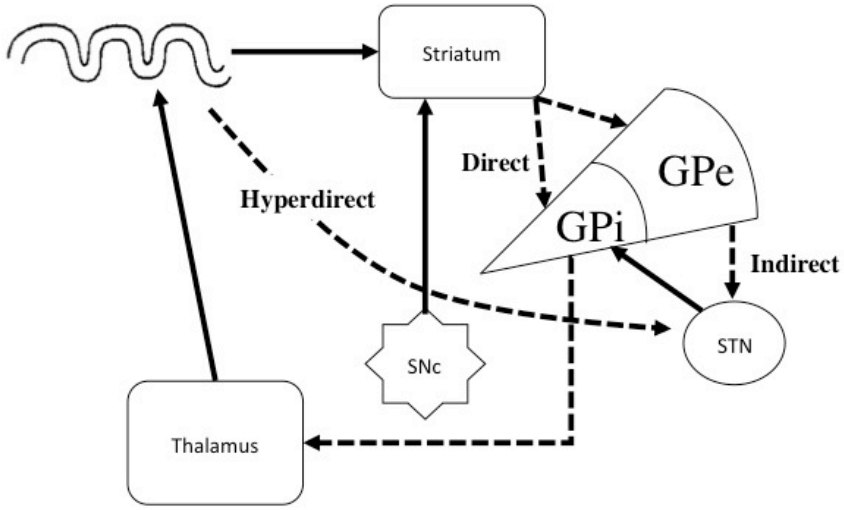

Figure 15: Schematic of cortico-basal ganglia circuits in healthy individuals

Solid lines represent excitatory connections, dashed lines represent inhibitory connections.

There is also evidence for additional connections directly from the cortex to the STN (Monakow *et al.*, 1978), referred to as the 'hyperdirect' pathway. One possibility would be that signals to the thalamus are first modulated by the inhibitory hyperdirect pathway, followed by the excitatory direct pathway, and finally by the inhibitory indirect pathway (Nambu *et al.*, 2002). The STN, reflecting the organization of the basal ganglia into motor and associative and limbic portions, functions as a major relay station and modulator in the processing of cortico-striatal information (Hamani *et al.*, 2004).

Neuromodulators

Dopamine is a prominent neurotransmitter in the basal ganglia, and, among other functions, plays a major role in movement through the cortico-striatal pathway. Although

many different neurotransmitters are implicated in brain circuitry and PD, this review will focus on dopamine in particular. Dopaminergic projections are sent from the substantia nigra to the striatum, forming the nigrostriatal pathway. Additional dopaminergic projections run from the VTA to the nucleus accumbens (mesolimbic pathway) or frontal cortex (mesocortical pathway). In the context of the motor cortico-striatal circuit, dopamine has a contrasting effect on the direct and indirect pathways through a differential effect on D1 and D2 receptors (Gerfen *et al.*, 1990; DeLong & Wichmann, 2007). Specifically, dopamine has a net inhibitory effect on the indirect pathway and a net excitatory effect on the direct pathway. The end result is that dopamine effectively favours the direct pathway, and its depletion or excess creates an imbalance in the two circuits, affecting activity in most cortical regions through the different cortico-striatal loops. This ultimately leads to the movement-related difficulties observed in different patient populations.

Cortico-cerebellar circuit

Anatomical connections

The cortico-cerebellar circuit is similarly organized into functionally segregated pathways that connect regions of the cerebellar cortex with the cerebral cortex. Lateral portions of the cerebellar cortex send projections, via the dentate nucleus, to the thalamus, which in turn projects to specific cortical areas (Figure 16). Retrograde transneuronal transport methods using neurotropic viruses have shown that these cortical areas include the motor, premotor, oculomotor, prefrontal cortex (PFC) and posterior parietal cortex (PPC) with minimal overlap between different termination sites (Clower *et al.*, 2001; Middleton & Strick, 2001; Strick *et al.*, 2009). Projections from the cortex back to the lateral cerebellum pass either through the pons or the red nucleus and inferior olive (Leiner *et al.*, 1989). Furthermore, the segregation of connections to the cerebral cortex is maintained in the cerebellar cortex (Kelly & Strick, 2003), such that the separate compartments of the cerebellum form closed anatomical loops with the specific cortical region they send projections to and receive input from (Strick *et al.*, 2009).

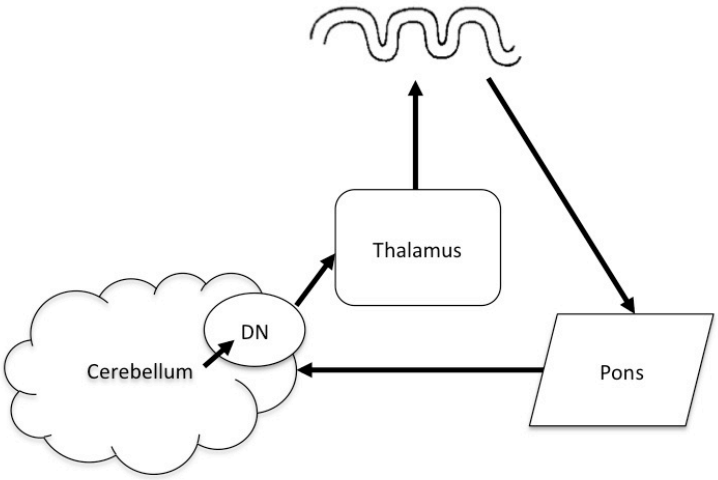

Figure 16: Schematic of the cortico-cerebellar circuit

Wave: cortex; DN: dentate nucleus.

The cerebellar cortex is organized into very regular molecular, Purkinje and granular cell layers, suggesting that the type of information processing in the cerebellar cortex is mainly related to its associations with different cortical regions, rather than local circuitry (Ramnani, 2006). The dentate nucleus seems to consist of distinct sections that process motor and non-motor information (Dum & Strick, 2003), with the non-motor portion of the dentate nucleus substantially larger than the motor section (Matano, 2001). In fact, two main circuits have been described, notably the 'motor' loop that projects from the motor and PMC to the dorsal part of the dentate nucleus, and the 'prefrontal' loop that connects Brodmann area 9/46 and the ventral dentate nucleus (Glickstein *et al.*, 1985; Orioli & Strick, 1989; Schmahmann & Pandya, 1995; Kelly & Strick, 2003). This segregation of motor and non-motor connections from the dentate nucleus is maintained in the cerebellar cortex, with separate locations being connected to areas such as the primary motor cortex and area 46 (Strick *et al.*, 2009). Diffusion tensor imaging (DTI) examining the distribution of fibers in the cerebellar peduncle in humans and macaque monkeys in vivo has revealed that the majority of fibers in the macaque consist of motor fibers, whereas humans have a much

larger prefrontal component (Ramnani et al., 2006). Thus, the cerebellum, similar to the basal ganglia, has underlying connections linked to both motor and cognitive functions (Strick *et al.*, 2009).

Neuromodulators

Although the cerebellum receives mainly noradrenergic and serotonergic projections, there is also evidence for dopamine, acetylcholine and histamine (Schweighofer *et al.*, 2004). In particular, dopaminergic neurons from the rat's VTA send projections to the cerebellar cortex (Ikai *et al.*, 1992). In fact, animal studies have shown that DARPP-32, a dopamine and cAMP regulated phosphoprotein of M(r) 32 kDa, is expressed in the cerebellar's Purkinje cells and may be involved in the regulation of long term depression (LTD; Alder & Barbas, 1995). The cerebellum was long thought to contain almost no dopamine D2/D3 receptors compared with the striatum (Hall *et al.*, 1994). Consequently, D2/D3-receptor binding [^{11}C]raclopride PET studies have sometimes used the cerebellum as a reference tissue for raclopride binding (e.g. Hilker *et al.*, 2003; Ko *et al.*, 2008; Steeves *et al.*, 2009). Other evidence suggests, however, that the cerebellar cortex contains a high density of dopamine D3 receptors that may help regulate locomotor activity and provide a form of cellular modulation by dopamine (Sokoloff *et al.*, 1990; Bouthenet *et al.*, 1991; Barik & de Beaurepaire, 1996; Schweighofer *et al.*, 2004). The presence and the modulation by dopamine imply that cerebellar activity may be affected by dopamine depletion in PD, and consequently by dopamine replacement therapy.

Dopamine, norepinephrine (a.k.a. noradrenaline) and epinephrine are catecholamines synthesized from tyrosine through a series of metabolic events (Nagatsu *et al.* 1964). It is important to note that there are substantial noradrenergic projections to the cerebellum from the locus coeruleus and VTA, regions significantly affected in PD (Hornykiewicz, 1975; Szot *et al.*, 2012). Decreases in cerebellar norepinephrine levels have been shown in PD patients (Kish *et al.*, 1984) as well as the MPTP monkey model of PD (Pifl *et al.*, 1991).

Synaptic connections between cortico-striatal and cortico-cerebellar loops

Initially, the cortico-striatal and cortico-cerebellar circuits have been considered to be anatomically distinct. In particular, the cerebellum and basal ganglia relay information to separate regions of the thalamus (Asanuma *et al.*, 1983) and retrograde labeling using the herpes simplex virus has shown that the segregation of cortico-striatal and cortico-cerebellar circuits remains at the level of the cortex, cerebellum and dentate nucleus as well as in the thalamus and the substantia nigra [for a review, see (Middleton & Strick, 2000)]. However, more recent evidence suggests there are direct connections between the cortico-striatal and cortico-cerebellar circuits (Bostan & Strick, 2010). Studies using the rabies virus and retrograde labeling in non-human primates report bi-synaptic projections from the STN to the cerebellar cortex via pontine nuclei (Bostan *et al.*, 2010) and tri-synaptic connections between the GPe and the dentate nucleus (Hoshi *et al.*, 2005). A synaptic link between the cortico-striatal and cortico-cerebellar pathways implies that changes in one circuit may affect the other circuit. This has implications for diseases such as PD as connections between the cortico-striatal and cortico-cerebellar circuits mean that dynamic fluctuations in the cortico-striatal pathway related to disease pathophysiology can affect the activity observed in the cortico-cerebellar pathway.

Cortico-striatal and cortico-cerebellar loop function

Functional MRI studies have provided evidence of cortico-striatal involvement in movement planning, initiation, motor learning, timing control and their modulation by task complexity (Alexander *et al.*, 1990; Rao *et al.*, 1997; Boecker *et al.*, 1998; Mattay *et al.*, 1998; Jenkins *et al.*, 2000; Cunnington *et al.*, 2002; Taniwaki *et al.*, 2003; Elsinger *et al.*, 2006; Purzner *et al.*, 2007; Boecker *et al.*, 2008; Doyon *et al.*, 2009; Francois-Brosseau *et al.*, 2009). Furthermore, single-cell recording studies in monkeys demonstrated the involvement of the putamen and caudate nucleus in SI and ET movements, where some neurons would respond to SI movements only, and others for both SI and ET movements (Romo *et al.*, 1992; Romo & Schultz, 1992). Activity in the substantia nigra has been observed for both internally and externally guided actions and movements (Monchi *et al.*,

2006; Boecker *et al.*, 2008). Taken together, these findings suggest that the striatum is especially involved in the planning and the execution of novel and SI movements (Elsinger *et al.*, 2006; Boecker *et al.*, 2008).

Consistent with the motor and non-motor anatomical connections of the cortico-cerebellar pathway, the cerebellum consists of specific topographically organized compartments used for the integration of motor and non-motor functions (e.g. emotion, working memory and language) (Stoodley & Schmahmann, 2009). There are also task-dependent and task-independent neurons in the dentate nucleus that respond to the planning phase of internally and externally cued movements (Middleton & Strick, 2000). Functional MRI studies have additionally demonstrated that slightly different regions of the dentate nucleus are activated during movement planning and execution (Kim *et al.*, 1994), and that the lateral cerebellum is involved in the planning phase (Boecker *et al.*, 2008). When looking at the temporal involvement of motor regions in the planning and execution of simple self-paced movements, both cortical and cerebellar regions show gradual spatial and temporal changes (Hulsmann *et al.*, 2003); activity within the cerebellum shifted spatially in the same time-frame as the activity shift from the anterior cingulate cortex to the SMA and the PMC.

The acquisition of complex motor skills can be divided into motor sequence learning and motor adaptation. Motor sequence learning consists of the gradual performance of a specific sequence of movements, whereas motor adaptation denotes the ability to compensate for changing environments (Doyon & Ungerleider, 2002; Doyon *et al.*, 2003; Doyon & Benali, 2005). Doyon and his colleagues have proposed that both types of learning initially recruit regions within the cortico-striatal and cortico-cerebellar pathways. When learning is more advanced and the subject has reached asymptotic performance, however, there is a shift of representation between the regions within the cortico-striatal or the cortico-cerebellar loop, depending on the type of learning. At that stage, sequence learning relies mostly on the cortico-striatal loop, while motor adaptation depends predominantly on the cortico-cerebellar loop (Doyon *et al.*, 2003; Doyon *et al.*, 2009). It has been shown that motor learning is affected even in early PD (Shin *et al.*, 2003), with considerable changes in brain activity (Mentis *et al.*, 2003). Since this framework allows a

clear distinction between the cortico-striatal and cortico-cerebellar pathways functionally, it holds great promise for future research that aims to address whether or not the cortico-cerebellar circuit is recruited in PD to compensate for cortico-striatal deficiency.

Parkinson's disease

Motor and cognitive symptoms can arise in parallel with the disruption of normal function of the putamen and caudate nucleus, with almost complete dopamine depletion seen in the putamen (Kish *et al.*, 1988). In PD patients, nigrostriatal dopamine depletion leads to a net increase in STN and GPi discharge, but a decrease in GPe discharge, creating an imbalance in the direct and indirect pathways (DeLong & Wichmann, 2007) (Figure 17). Specifically, the indirect pathway becomes hyperactive and the direct pathway becomes hypoactive, resulting in an excess of inhibitory output from the GP, leading to bradykinesia and rigidity (Bergman *et al.*, 1994). In addition, according to the functional deafferentation hypothesis, the increase in GPi tonic activity leads to cortical inhibition (Albin *et al.*, 1989). The depletion of dopamine in the motor system is associated with important changes in the entire brain that gradually spread from the brainstem to the cortex (Braak *et al.*, 2003). These changes effectively result in autonomic dysfunction, olfactory and sleep disorders, emotional impairment and cognitive deficits.

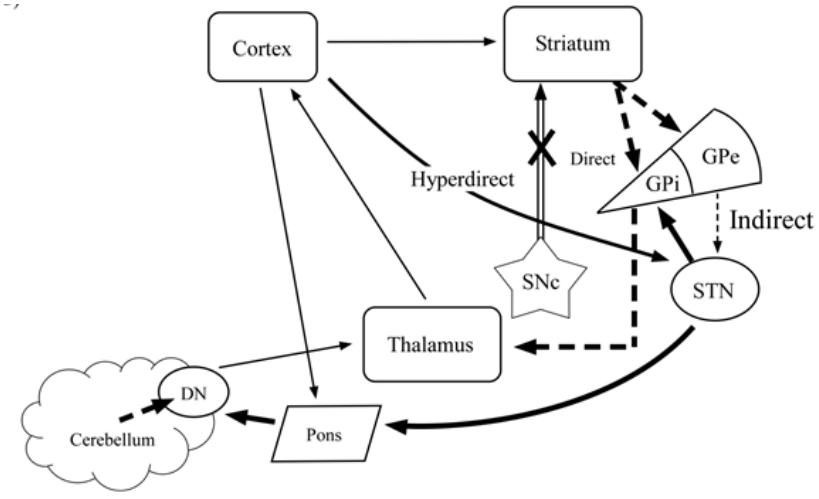

Figure 17: Schematic of the interaction between cortico-striatal and cortico-striatal circuits in PD (Martinu & Monchi, 2012)

Arrow weight represents increases and decreases of synaptic output in PD as compared with healthy individuals. Solid lines represent excitatory connections, dashed lines represent inhibitory connections, double lines represent a mixture of inhibitory and excitatory projections. The change in synaptic output in the cortico-cerebellar circuit is the hypothesized effect in tasks that involve the cortico-striatal pathway. Note that the nature of connections to and from the cerebellum are still under debate.

Lesions of the cerebellum also cause a range of deficits, from motor to non-motor symptoms, depending on the location of the lesion (Strick *et al.*, 2009). It has been shown that changes in the cortico-cerebellar pathway are involved in resting tremor, as well as the suppression of tremor during voluntary movements (Deuschl *et al.*, 2000). Lesions of the superior cerebellar peduncle seemed to alleviate parkinsonian tremor (Cooper, 1956), although the removal of cerebellar lobes does not seem to treat tremor consistently. Recent work with macaque monkeys has shown a correlation between persistent Purkinje cell activity in the cerebellum and dopaminergic degeneration (Heman *et al.*, 2012). Deep brain electrode recordings in PD and essential tremor patients (Pedrosa *et al.*, 2012) as well as in the MPTP model of PD (Guehl *et al.*, 2003) also indicate that there are tremor-related cells in the thalamus. It has been suggested that it is the disruption of competitive balance between cerebellar and basal ganglia output that leads to certain types of tremor in PD (Stein & Aziz, 1999; Deuschl *et al.*, 2000). More specifically, Helmich et al. hypothesize that the disruption of the cortico-striatal pathway sends transient fluctuating signals to the cortico-cerebellar circuit leading to tremor (Helmich *et al.*, 2011). In accordance, a recent voxel-based morphometry study has shown a decrease in cerebellar gray matter in patients with PD that present with tremor (Benninger *et al.*, 2009).

Metabolic alterations in PD

Some of the first functional neuroimaging studies in PD were aimed at understanding the change in metabolism and activity fluctuations. Fluorodeoxyglucose (^{18}F) (FDG) PET results suggested a decreased global metabolism, with additional decreased

inferior parietal an increased basal ganglia metabolism (Kuhl *et al.*, 1984; Martin *et al.*, 1984; Schapiro *et al.*, 1993). Using a scaled subprofile model (SSM) to study spatially distributed networks (Moeller & Strother, 1991), Eidelberg et al. (1994) were able to detect a pattern of metabolic increases and decreases related to PD pathology, the PD-related pattern (PDRP), reproducible across parkinsonian patients and tomographs (Moeller *et al.*, 1999). Although there was no difference between healthy control and PD patient global brain metabolism levels, authors found a major topographic profile consisting of metabolic decreases in the lateral frontal, paracentral and parietal association cortices, and increases in the lentiform nucleus, thalamus, pons and cerebellum (Eidelberg *et al.*, 1994). Furthermore, the individual topographic profile score correlated with the patients' Hoehn & Yahr stage and motor unified Parkinson's Disease rating scale (UPDRS) symptom severity score. The PDRP is also strongly associated with STN activity, and lesioning the STN in return affects the PDRP activity (Su *et al.*, 2001). The PDRP can be detected at an individual level before the onset of symptoms, giving it great potential for early diagnosis. The metabolic increases and decreases of this topographic profile accentuate with disease progression; longitudinal data show an increase in metabolism in the pedunculopontine nucleus, STN, GPi and motor cortex and a decrease in metabolism in prefrontal and parietal association cortices over disease progression (Huang *et al.*, 2007). Furthermore, Mure et al. (2011) recently used FDG PET to describe a PD tremor-related pattern (PDTP) that plays an important role in parkinsonian tremor, and which consists mainly of structures involved in the cortico-cerebellar pathway.

The altered patterns of brain metabolism could reflect a form of network adaptation to disease pathology (Eidelberg, 2009). However, results from these methods do not allow the distinction between compensatory mechanisms and pathological consequences of circuit imbalance. Because the structures implicated in the PDRP and PDTP are linked through the cortico-striatal and cortico-cerebellar circuits, fluctuations in one will cause fluctuations in the other, resulting in widespread changes in metabolism that increase as the disease progresses.

Hypo- and hyper-activations in PD

Many neuroimaging studies have reported hypo- and hyper-activations in patients with PD compared with healthy controls during motor and cognitive tasks. In this section we will focus on the basis of these patterns, and whether hyper-activations in the cerebellum in particular can be attributed to compensatory mechanisms.

The classic model of motor deficits in PD (Albin *et al.*, 1989) depicts that the increased inhibitory drive to the thalamus leads to a decreased excitatory drive to the cerebral cortex. Consistent with this model, observations of original functional neuroimaging studies in PD indeed found decreases in motor, premotor, and PFC activity (Playford *et al.*, 1992). A series of studies, however, later showed overactivity in certain cortical regions (Sabatini *et al.*, 2000; Haslinger *et al.*, 2001), indicating that patients with PD do not simply have a hypoactive cortex. Models have been suggested to account for these changes in activity; one proposition was that hypo- and hyper-activity patterns in PD were related to a distinction between motor and cognitive tasks, respectively (Mattay *et al.*, 2002). Based on our previous work with set-shifting tasks (the MCST and WCST), we have observed that the increases and decreases in cortical activity seen in patients with PD are related to whether the striatum is necessary for the task at hand or not (Monchi *et al.*, 2004; Monchi *et al.*, 2007; Monchi *et al.*, 2010), rather than whether the basis of the task is motor or cognitive. More specifically, we have observed a decrease in activity in the prefrontal regions of patients with PD off medication compared with control participants for tasks that require the striatum in healthy controls (e.g. planning a set-shift; hypo-activation). In contrast, when performing tasks that do not require the striatum (e.g. task execution without changes in rules) in healthy controls, patients with PD showed significant prefrontal and parietal increases in activity (hyper-activation) (Monchi *et al.*, 2007). Moreover, in a given task where healthy participants recruit the striatum, patients with PD will show a reduction in cortical activity as the model by Albin, Young and Penney suggests. On the other hand, in tasks where healthy participants do not recruit the striatum, patients with PD present increases in cortical regions usually unrelated to the task. These hyper-activations may be related to compensatory mechanisms, but it has been proposed that they are due to an exacerbation of dopaminergic tones in the cortex originating from the VTA; because

dopamine neurons in the VTA and the substantia nigra degenerate at different rates and at different times, activity during motor and cognitive tasks of the cortical regions they project to will be related to their integrity and the long-term effects of dopamine replacement therapy (Monchi *et al.*, 2010; Macdonald & Monchi, 2011).

Patients with PD have difficulty with movement initiation (akinesia), which is distinguishable from slowness of movement (bradykinesia) (Hallett, 1990). In an $H_2{}^{15}O$ PET study, Turner *et al.* (2003) also observed regions normally involved in a task to be hypoactive, and different regions normally not involved in the task to be hyperactive. The authors used a 'visuomanual tracking task' with three increasing velocities to investigate bradykinesia in patients with PD. Participants did not perform more temporal errors compared with healthy controls, but their movement amplitudes decreased to remain synchronized with the moving target. Interestingly, when comparing velocity-related activity between PD patients and controls, only the cerebellum showed a decrease in activity in PD, suggesting its involvement in bradykinesia. The authors also consider the debate that overactivations in PD are related to compensatory mechanisms, and propose that instead they may be a correlate of PD pathology (Turner *et al.*, 2003).

Using SPECT, Rascol *et al.* (1997) argued for a compensatory role of the cerebellum by showing that compared with healthy controls and PD patients on medication, patients off medication had an increase in ipsilateral cerebellum and a decrease in the SMA activity during a sequential finger-to-thumb opposition task. One could have just as well argued, however, that due to the neuronal connections, the pathophysiology of PD generates an imbalance that leads to an increase in cerebellar activity [for a review on compensatory mechanisms in PD, see (Appel-Cresswell *et al.*, 2010)]. Similarly, Sen et al. (2010) described an increase in cortico-cerebellar loop involvement in internally generated movements with disease progression that can again be attributed to either compensation or pathophysiology. Yu *et al.* (2007) have also argued for a compensatory role of the cortico-cerebellar pathway by correlating cortico-striatal and cortico-cerebellar region activity. The authors have shown a negative correlation between the contralateral putamen and ipsilateral cerebellum in PD patients during a motor timing task, indicating that as the cortico-striatal pathway is affected and shows decreases in activity, the cortico-cerebellar pathway

compensates by increasing its activity. A shift in this balance, however, could still simply be due the pathophysiological imbalance. Palmer et al. (2009a) were driven to similar conclusions using a sinusoidal force task of varying frequencies to demonstrate that as movement frequency (and therefore difficulty) increases, PD patients first increasingly recruit the cortico-striatal and cortico-cerebellar circuits, and then recruit additional areas in the bilateral cerebellum and primary motor cortex. In this study, the authors worked with the assumption that disease-related activation changes are constant, whereas compensatory changes are not. The communication between the two circuits can lead to altered dynamics relating to disease pathology, and these dynamics vary through direct synaptic input with the level of activity necessary for the task at hand. It is possible, then, that not only compensatory regional involvement varies with task difficulty, but the level at which the same regions are affected by the disease vary as well.

Another interpretation of the compensatory role of cerebellar and cortical regions comes from a study on movement automaticity. Wu & Hallett (2005) showed that when performing automatic movements, patients with PD have increased activity in the cerebellum, premotor area, parietal cortex, precuneus and PFC compared with healthy aged participants. Although there were no behavioral differences between PD patients and healthy controls, patients needed more time to reach automaticity, suggesting that the increases in activity are part of compensatory mechanisms. There is however no evidence of any correlation of activity in these regions with performance. One could also argue that since patients have more difficulty performing the movement sequences automatically, the differences in cerebral activity may be due to the pathophysiological changes in PD. In a subsequent study, Wu *et al.* (2011) report a decrease in cortico-striatal and striato-cerebellar effective connectivity in PD during SI finger tapping movements, but an increased cortico-cerebellar connectivity. Once again, as there were no differences in performance between PD patients and healthy controls, and no correlation with performance was described, these changes in effective connectivity can be due to compensatory mechanisms or pathophysiological changes. In contrast, Mattay et al. (2002) showed a significant correlation with cortical activity and the number of errors made during a working memory task. More specifically, the increases in cortical activity correlated with the number of errors

during an n-back working memory task when patients were off medication. In contrast, increased activity in the motor regions when patients were on medication correlated with an improvement on a motor task (the 0-back version of the working memory task). These results are consistent with the motor involvement of the more dopamine depleted nigro-striatal projections and the cognitive involvement of the less affected mesocortical projections.

One reason why the cerebellum is thought to be involved in compensatory mechanisms stems from the observation that patients with PD present difficulty in performing SI voluntary movements (Benecke *et al.*, 1987), but perform better when visual cues are available (Georgiou *et al.*, 1994). The cerebellum is strongly modulated by visual feedback (Debaere *et al.*, 2003), which is thought to be the basis of paradoxical movements observed in PD (Glickstein & Stein, 1991). Signals through connections between the visual cortex and cerebellum may bypass the cortico-striatal pathway and allow an otherwise immobile PD patient to catch a ball being thrown to them or get up and run in the case of a fire. In agreement with this theory, a study where patients performed externally cued movements in urgent situations showed significant cerebellar involvement in PD patients (Ballanger *et al.*, 2008). More specifically, patients were asked to perform SI, externally cued (EC) and externally cued-urgent (ECu) arm movements to a contact plate. In the ECu condition, participants had to reach to the contact plate fast enough to stop a ball, rolling on a ramp, from falling. Ballanger *et al.* showed that patients performed movements faster in the context of a 'temporally pressing situation'. Furthermore, when comparing the ECu to the EC condition, PD patients had greater activity in the cerebellum that correlated with movement speed. Based on cerebellar, basal ganglia and thalamic surgeries, there appears to be a competitive balance between the cortico-striatal and cortico-cerebellar pathway inputs within the thalamus (Stein & Aziz, 1999), the disruption of which would lead to the rigidity and tremor observed in PD. Moreover, a recent study has shown that patients presenting primarily with tremor have a different brain activity profile than those presenting with akinesia and rigidity (Lewis *et al.*, 2011). During internally guided hand movements, patients with tremor displayed increases in activity in the cerebellum and thalamus, whereas patients with akinesia/rigidity showed increases in the putamen and GP.

An imbalance between the affected cortico-striatal pathway and an intact cerebellum could mean that the cerebellum becomes recruited in order to compensate for the cortico-striatal pathway, and therefore display increases in activity. Evidence suggests, however, that the cerebellum is not intact in PD (Stevenson *et al.*, 2010). Furthermore, an increase of activity does not necessarily mean it is beneficial, and the lack of association between increases in activity and improvement in performance in most of the studies mentioned above does not support a compensatory role. Although both may be involved, the association of the cerebellum with tremor and bradykinesia would rather suggest that such activity is related to the pathophysiological changes in PD.

Levodopa treatment

Levodopa is a common choice of treatment for PD, and is used in the hopes of restoring activity in the networks through dopamine replacement. Levodopa has been shown to decrease the PDRP by suppressing metabolic activity in the putamen, motor cortex and cerebellum. In fact, using FDG PET, Feigin et al. (2001) reported that the degree of PDRP decline correlated significantly with symptom improvement. The authors also observed a significant correlation between UPDRS motor symptom ratings and metabolic decreases in the area of the GP and ventral thalamus.

Although levodopa has no effect on global cerebral blood flow (CBF), it has been shown to reestablish activity in the SMA (Buhmann *et al.*, 2003; Jenkins *et al.*, 1992). The increases and decreases in activity seen after levodopa administration could be attributed to its focusing effects (Ng *et al.*, 2010) of otherwise spatially spread-out activity (Monchi *et al.*, 2004). It has been suggested that this focusing effect may be due to a dopamine-induced increase in signal-to-noise ratio of cellular activity (Winterer, 2006). Moreover, Ng et al. (2010) showed that spatial changes in activity patterns could be observed in the contralateral motor cortex and ipsilateral cerebellum at low movement frequencies, whereas a change in amplitude can only be detected at higher frequency movements.

Levodopa has been shown to sometimes normalize task-related activity and improve performance on motor and cognitive tasks (Mattay *et al.*, 1998; Cools *et al.*, 2002). When

patients in the early stages of PD performed volitional movements, levodopa was shown to restore the activity of the lateral PMC and SMA, but with no improvement on execution times (Haslinger *et al.*, 2001). Although cerebellar changes would also be expected, acquisition parameters did not include the cerebellum in the field of view. Others have demonstrated a worsening of performance on a motor sequence-learning task as well, which correlated with the regional CBF (rCBF) of occipital association areas (Feigin *et al.*, 2003). Interestingly, an H_2O^{15} PET study showed an increase in spatial errors of movement that correlated with changes in the cerebellum (Feigin *et al.*, 2002), arguing against a compensatory role. Using the WCST with patients on and off levodopa in fMRI, we have previously shown that levodopa does not restore PFC activity during the WCST (Jubault *et al.*, 2009). In accordance with these results, we have recently indicated that even within a motor task that solicits both motor and cognitive cortico-striatal regions, levodopa has an effect on the motor cortico-striatal circuit, but not the cognitive one (Martinu *et al.*, 2012). Although the effect of levodopa on motor symptoms is beneficial, improvement can be seen in some tasks whereas performance on others worsens (Gotham *et al.*, 1988; Cooper *et al.*, 1992).

Taken together, the effect of levodopa seems to strongly depend on the regions implicated in the task at hand, and too much dopamine can be detrimental to processes linked to mesocortical pathway and the ventral striatum. For example, tasks that require the activity of the dorsal striatum may show improvement after levodopa administration, whereas tasks that depend on ventral striatal activity will show a worsening (Monchi *et al.*, 2010; MacDonald *et al.*, 2011; Macdonald & Monchi, 2011).

We have recently used an SI and ET task to describe the effect of levodopa on the cortico-striatal circuit in patients with PD using fMRI (Martinu *et al.*, 2012). Healthy controls and patients at stage I and II of PD were asked to use their right or left hand to either press a sequence of buttons following visual cues, button by button (ET task), or create a 'random' sequence on their own (SI task), with no working memory component. Task-related activations were contrasted with a simple single-button repeat control. PD patients participated in two scanning sessions, both following overnight withdrawal of dopaminergic medication. For one session, patients were asked to take their levodopa one

hour before scanning. We observed that healthy controls recruit the putamen at different levels for our SI and ET tasks, with the SI task requiring higher activity levels. This effect was greatly reduced in patients off medication, and levodopa partially restored the putamen's activity. Results also indicated that cerebellar activity in SI and ET movements follows that of the putamen (Figure 18). Activity in the cerebellum of patients with PD was also greatly reduced for both SI and ET movements. Most importantly, however, levodopa significantly increased the activity in the cerebellum for both types of movements, restoring activity at least partially to that observed in healthy controls. We suggest that the activity pattern observed is due to the direct connections between the cortico-striatal and cortico-cerebellar loops, and that levodopa therefore leads to a boost in activity in the striatum as well as the cerebellum. Our results with this paradigm further support the notion that the pathophysiology of PD affects cerebellum function, and give further support to the implication of the cerebellum in the development of LIDs.

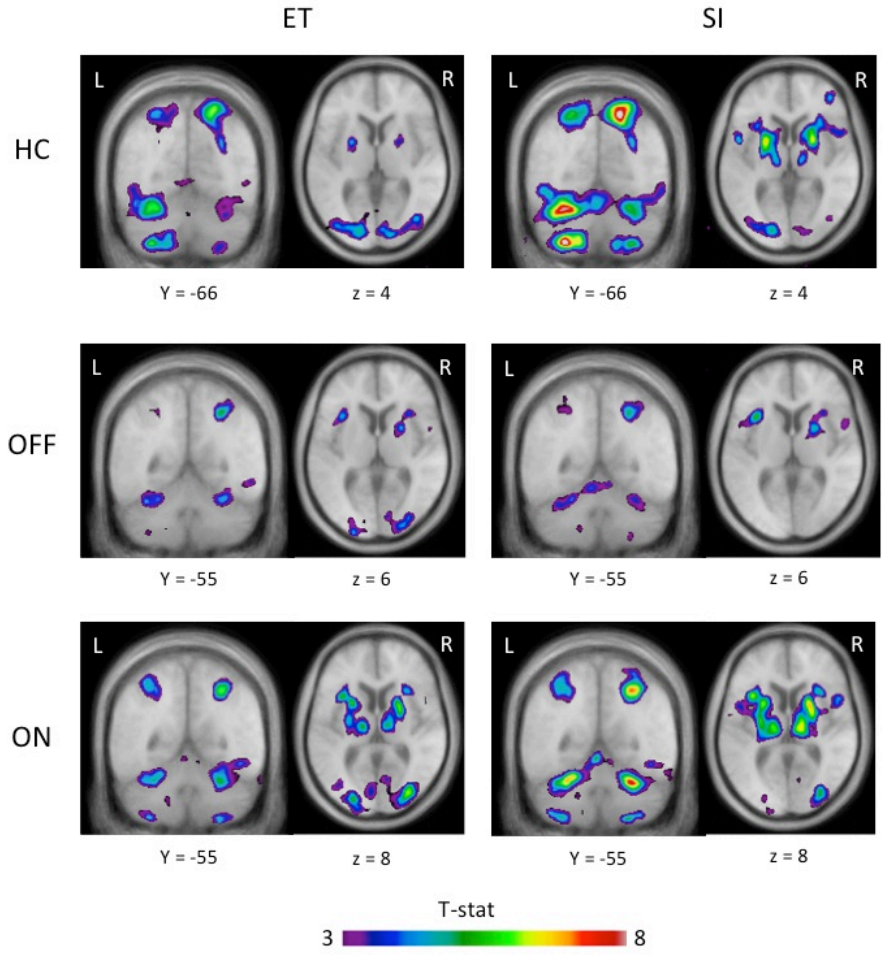

Figure 18: Activation peaks during ET and SI movements in healthy controls and PD patients before and after levodopa

Location of peaks in the ET versus control (left) and SI versus control (right) for the three groups of healthy controls (top), PD patients off medication (middle) and on medication (bottom). Anatomical images shown are the average of the T1 acquisitions of all participants transformed into stereotaxic space. The functional peaks are shown for t-stat values between 3 and 8. Healthy controls have significant activity in cortico-striatal and cortico-cerebellar circuits during ET and SI movements. Patients show a decrease in cortico-striatal and cortico-cerebellar loop activity before levodopa administration, and an increase in cortico-striatal and cortico-cerebellar circuit activity after levodopa administration.

Dyskinesia

Levodopa has few short-term side effects (Hauser & Zesiewicz, 2007), but its long-term administration leads to the development of LIDs in about 50% of patients (Rinne, 1989; Montastruc *et al.*, 1994). These are mainly manifested by chorea and dystonia at the peak of drug dose (Bezard *et al.*, 2001), and are difficult to treat once they appear (Fahn, 2000). The course of treatment methods and the order of administration for the highest benefit and lowest number of side effects were long under debate; keeping a constant dopamine intake throughout the length of the disease is difficult (Quinn, 1995; Durif, 1999; Khan, 2012). One study reports that over 5 years, 45% of patients in their levodopa group developed dyskinesias compared to 20% in the dopamine agonist group (Rascol *et al.*, 2000). The development of LIDs is associated with a series of changes in genes and proteins involved with dopamine receptors as well as non-dopamine transmitters (Bezard *et al.*, 2001). More specifically, dyskinesias are linked with an imbalance between the direct and indirect motor pathways, and in particular with a decrease in GPi activity (Lozano *et al.*, 2000), although the latter does not account for the symptoms in their entirety. PET studies have shown an overactivation of motor regions in dyskinetic patients (Brooks *et al.*, 2000). Using ^{11}C-diprenorphine PET, the authors suggest that dyskinesias are mediated by changes in opioid receptor binding in the basal ganglia, resulting in the overactivity of fronto-striatal projections (Piccini *et al.*, 1997; Brooks *et al.*, 2000). More recently, Nimura et al (2004) have shown the implication of sigma-receptors in LIDs. These receptors are localized in the substantia nigra, red nucleus and cerebellum (Jansen *et al.*, 1991). Sigma-active neuroleptics have been shown to cause dystonic responses in rats after an injection to the red nucleus, and their effect on behavior correlated with their affinity with sigma-receptors (Matsumoto *et al.*, 1990). Using ^{11}C-nemonapride PET with PD patients presenting with LIDs, Nimura et al. (2004) detect sigma-receptor binding potential in the cerebellum; the authors showed a correlation of $r = 0.893$ between receptor binding potential in the cerebellum and LID severity score. Moreover, an almost complete disappearance of LID symptoms after pallidal surgery coincided with a decrease in receptor binding potential. Although the function of

these receptors in LIDs and the reason for their up-regulation after levodopa administration is still unclear, these results imply that important changes associated with levodopa administration may take place in the cerebellum.

Repetitive transcranial magnetic stimulation (rTMS) has been suggested as a potential treatment for LIDs. Stimulation over the SMA or the primary motor cortex has been shown to reduce LIDs transiently (Koch *et al.*, 2005; Brusa *et al.*, 2006). More specifically, Koch et al. (2005) showed that 1Hz (inhibitory) rTMS stimulation over the SMA reduced dyskinesias, whereas 5Hz (excitatory) rTMS increased them. More recently, however, Koch et al. (2009) have attempted theta-burst stimulation (TBS), a sequence that can produce changes for over 30 minutes, over the cerebellum of patients with LIDs. A single session of inhibitory continuous TBS (cTBS) over the cerebellum was able to reduce LIDs (Koch *et al.*, 2009), and one week of cTBS treatment showed considerable symptom improvement along with a decrease in cerebellar metabolism as shown by FDG PET (Brusa *et al.*, 2012). Taken together, these results suggest that the metabolic and receptor changes in PD lead to an imbalance between the cortico-striatal and cortico-cerebellar pathway, and underline the importance of the cerebellum's role in dyskinesias.

Deep brain stimulation

DBS is a very effective form of treatment, mostly used in advanced stages of PD when symptoms and medication side effects (e.g. dyskinesia and motor fluctuations) become too severe. One main advantage of DBS is that unlike ablation, stimulation is reversible and adjustable. The most common targets of DBS in PD are the STN and GPi (Volkmann, 2004; Ostergaard & Sunde, 2006; Deuschl *et al.*, 2006; Wider *et al.*, 2008), although DBS of the ventral intermediate nucleus of the thalamus seems to be the most effective to treat tremor (Lyons & Pahwa, 2008). Stimulations often consist of bilateral stimulations of 60-185Hz pulses (Wichmann & DeLong, 2011). STN-DBS in particular seems to be effective, helping patients reduce their medication doses and, consequently, dyskinesias (Rodriguez-Oroz *et al.*, 2004). The exact mechanisms behind DBS treatment, however, are unclear. It appears that the effect of STN stimulation has different effects on

cell bodies, afferent and efferent axons, modulated by stimulation parameters, leading to both complex excitatory and inhibitory effects on the GPi (Wichmann & DeLong, 2011).

As the treatment effect and regional metabolism changes of STN-DBS are generally similar to ablation (Su *et al.*, 2001), one would expect stimulation to have an inhibitory effect on the STN, decreasing cortical inhibition. However, according to neuroimaging (Hershey *et al.*, 2003; Payoux *et al.*, 2004; Asanuma *et al.*, 2006; Grafton *et al.*, 2006) and electrophysiological recordings (Hashimoto *et al.*, 2003), it appears that STN and GPi output is in fact increased. The stimulation of the STN was shown to increase rCBF to the midbrain, GP and thalamus, but to reduce blood flow to the SMA and PMC (Hershey *et al.*, 2003). These changes correlated with motor improvement in PD (Karimi *et al.*, 2008). Using $H_2{}^{15}O$ PET, Payoux *et al.* (2004) showed that PD patients at rest had significant reductions in rCBF in the sensorimotor cortex, PMC, anterior cingulate, SMA and cerebellum during high-frequency STN-DBS. When patients performed fist-clenching movements in the stimulator-on condition, patients displayed a significant increase in activity of the sensorimotor cortex, cingulate cortex and ipsilateral cerebellum. The authors report that these activations were in fact due to the reduction of activity at rest, rather than an increase in activity during movements. Interestingly, rCBF of the cerebellum off-stimulator in this study correlated positively with patients' akinesia (Payoux *et al.*, 2004). Additional PET studies also found rCBF increases in the STN and lentiform nucleus, and rCBF decreases in the thalamus and cerebellum at rest during STN stimulation (Hilker *et al.*, 2004; Geday *et al.*, 2009). Furthermore, DBS appears to cause task-specific adaptation changes in brain activity, possibly via decreases in pathologic network activity (Grafton *et al.*, 2006). Indeed, STN-DBS, just like levodopa, has been shown to reduce PDRP, inherently reducing cerebellar overactivity (Trost *et al.*, 2006; Asanuma *et al.*, 2006), suggesting that STN-DBS leads to symptom improvement through the alteration of network communication within and between the cortico-cerebellar and cortico-striatal pathways.

Concluding remarks

In this review, we have shown the important implication of both the cortico-striatal and cortico-cerebellar pathways in PD, and the changes related to levodopa administration and DBS. Direct evidence that the patterns of activity of the cerebellum and the cortico-cerebellar loop are truly compensatory is still lacking, and traditional neuroimaging studies showing increases or decreases in activity always depend on interpretation. It has been suggested that externally cued movements are mainly processed by the cortico-cerebellar loop and remain intact for the most part, whereas internally cued movements are processed through the dysfunctional cortico-striatal loop (Lewis et al., 2007).

Based on the results reviewed, we propose that the cortico-cerebellar pathway activity in PD does not remain intact, as is often suggested, but that it is also affected by the disease, and related to some of the observed symptoms. In other words, the cortico-striatal and cortico-cerebellar circuits are very closely related through direct interactions as well as cortical associations, and the changes in PD affecting the cortico-striatal circuits will therefore also affect the cortico-cerebellar pathway. Changes in cerebellar activity should consistently correlate with improvements in performance in order to show clear compensatory involvements. The opposite seems to have been shown so far (Feigin *et al.*, 2002). Although both compensatory and pathophysiological changes are most likely present in PD, the interpretation of neuroimaging studies as supporting one or the other must be done with care.

An increase in cerebellar activity after levodopa administration can be due to different reasons, such as by a direct effect of dopamine on cerebellar receptors, or indirectly though the connections between the cortico-cerebellar and cortico-striatal pathways, as previously suggested by Stevenson et al. (2011). Additional research will be necessary to establish the effect of levodopa on the cerebellum.

It has been suggested that oxidative stress and mitochondrial dysfunction plays an important role in the cell degeneration in PD (Jenner, 2003). A recent PET study has demonstrated an enhancement of oxidative stress in PD patients that increased with disease progression, suggesting that neurodegeneration in PD is associated with oxidative stress (Ikawa *et al.*, 2011). Paradoxically, levodopa has pro-oxidant properties that promote free radical formation, and lead to cell death in cellular models of PD (Martignoni *et al.*, 1999;

Sabens *et al.*, 2010), explaining the growing number of side effects with long-term administration. The increase in activity after levodopa administration seems to be detrimental in the long run, leading to symptoms such as dyskinesia. Indeed, one major confound in most PD studies (including our own) is that one cannot completely distinguish between the pathophysiology of the disease and the accumulated effect of dopaminergic medication. It may be useful in the future to study cerebellum function via neuroimaging in non-medicated *de novo* PD patients.

It is interesting to note that the cortico-cerebellar pathway has been shown to be strongly involved in dystonia, also originally considered a disorder of the basal ganglia (Niethammer *et al.*, 2011), and the cerebellum may not necessarily be involved in compensatory mechanisms (Sadnicka *et al.*, 2012). Inversely, several types of spinocerebellar ataxias, primarily disorders of the cerebellum, have also been shown to lead to considerable basal ganglia degeneration (Seidel *et al.*, 2012).

The limitations of neuroimaging make the distinction between compensatory mechanisms and disease pathophysiology difficult. TMS may prove to be a useful tool in the study of living PD patients. We propose a few ways in which the compensatory mechanisms may be separated from the pathophysiological changes in PD. By using tasks of sequence learning and motor adaptation, one can separate, for the most part, activity between the cortico-striatal and cortico-cerebellar loops. As mentioned above, when participants reach the final stages of learning, sequence learning tasks are mainly operated by the cortico-striatal loop, whereas motor adaptation tasks by the cortico-cerebellar loop. Following inhibitory TBS over the cerebellum, both PD patients and healthy controls should show a decrease in performance on the adaptation task. On the other hand, if cerebellar activity in PD compensates for cortico-striatal loop dysfunction, patients with PD should show a decrease in performance on sequence learning tasks, and there should be no effect on performance of healthy controls. In contrast, if cerebellar activity is related to pathophysiology, performance of PD patients on sequence learning tasks should be improved. A similar protocol in a task that recruits the cerebellum or basal ganglia selectively, such as the SI and ET model suggested by Lewis et al. (2007) should lead to similar conclusions. More specifically, their task consists of SI movements associated with

cortico-striatal loop activity, whereas the ET movements are associated with cortico-cerebellar loop activity. Inhibitory cerebellar TBS in PD patients should decrease performance of SI movements if cerebellar activity is compensatory.

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Chapter 3: Striatal activity and cortical hyper-activity in PD

The next chapter of this thesis is an article published in *European Journal of Neuroscience* in 2012. Although it follows the preceding article, these were the first analyses performed, and the conclusions drawn from them have been described and used in support of the pathophysiology hypothesis we suggested in the previous section.

Prior to the acquisitions of data for this protocol, our laboratory's results had suggested that levodopa increased motor cortico-striatal loop activity during the WCST, but not cognitive cortico-striatal loop activity (Jubaut *et al.*, 2009). The primary focus of this chapter was to extend these findings to a motor task, namely the SI and ET finger movement task used in our previous protocol (Francois-Brosseau *et al.*, 2009; see appendix). In contrast to the WCST project, we wanted to compare the cerebral patterns of patients with PD with a group of healthy participants. Our major findings here are that the hyper-activations observed in patients with PD that are unrelated to the task, as described in chapters 1 and 2, are not normalized by levodopa. More specifically, healthy participants showed increases in activity at the junction of the ventrolateral prefrontal cortex (VLPFC) and the insula when comparing SI to ET movements, but not when comparing ET movements to the control condition. On the other hand, patients with PD had the opposite pattern (i.e. increased activity in this region in ET vs. control, but not SI vs. ET). Instead of restoring this discrepancy, levodopa has no effect; in this chapter we suggest that these hyper-activations are associated with the pathophysiology of PD, and that they may even be related to the prolonged use of dopaminergic medication.

The second goal of this study was to examine the response of the putamen and other regions involved in the motor cortico-striatal circuit to SI and ET movements. In healthy young adults, we had demonstrated that the putamen is increasingly recruited for control, ET, then SI movements. In this study, we show that in patients with PD the differences in activity between these three types of movements are greatly reduced, and levodopa partially restores these differences to those observed in healthy participants. We suggest that levodopa has an equivalent effect on regions of the motor cortico-striatal circuit for both SI and ET movements (i.e. a non-task specific effect).

Levodopa influences striatal activity but does not affect cortical hyper-activity in Parkinson's disease

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Abstract:

Motor studies of PD have shown cortical hypo-activity in relation to nigrostriatal dopamine depletion. Cognitive studies also identified increased cortical activity in PD. We have previously suggested that hypo-/hyper-activity patterns observed in PD are related to striatal contribution. Tasks that recruit the striatum in control participants are associated with cortical hypo-activity in PD patients, whereas tasks that do not result in cortical hyper-activity. The putamen, a structure affected by neuro-degeneration observed in PD, shows increased activation for ET and SI movements. The first goal of this study was to evaluate the effect of levodopa on the putamen's response to ET and SI movements. Our second goal was to assess the effect of levodopa on hypo/hyperactivity patterns in cortical areas. Both PD patients on and off levodopa and healthy volunteers performed SI, ET and control finger movements during fMRI. Healthy participants displayed significant differences in putamen activity in ET and SI movements. These differences were reduced in patients off medication, with non-task specific increases in activity after levodopa administration. Furthermore, the VLPFC showed significant increases in activity during SI movements in healthy controls, while it was hypo-active in PD. This region showed significantly increased activity during ET movements in patients off medication. Levodopa had no effect on this discrepancy. Our results suggest that dopamine replacement therapy has a non-task specific effect on motor

cortico-striatal regions, and support the hypothesis that cortical activity increases and decreases in PD are related to mesocortical dopamine pathway imbalance.

Introduction:

The substantia nigra, thalamus, basal ganglia and cortex are a part of motor and cognitive ganglia-thalamocortical loops originally described by Alexander *et al.*, (1986). Using the WCST, we previously reported that the caudate nucleus and VLPFC (cognitive loop) were involved in set-shifting, and the putamen and PMC (motor loop) in shift execution (Monchi *et al.*, 2001; Monchi *et al.*, 2006).

Early motor neuroimaging studies in patients with PD showed a decrease in premotor and motor cortical activity (Playford *et al.*, 1992). Decreases in cortical activity were thought to stem from nigrostriatal dopamine depletion (Albin *et al.*, 1989). More recent cognitive neuroimaging studies, however, identified cases of increased cortical activity (Cools *et al.*, 2002). Our previous work suggested that cortical activity modulation observed in PD patients depends on striatal involvement (Monchi *et al.*, 2004; Monchi *et al.*, 2007). More specifically, we suggest that for tasks that require the striatum (e.g., shifting attention), PD patients exhibit decreased activity in prefrontal regions compared to control participants (hypo-activation). In contrast, when performing tasks that do not require the striatum (e.g., task execution without shifting attention) in healthy controls, PD patients show significant prefrontal and parietal increases in activity (hyper-activation) (Monchi *et al.*, 2007). Mesocortical dopamine disruption may prevent cortical functioning and lead to these abnormal increases in activity (Monchi *et al.*, 2010).

Levodopa has considerably beneficial effects on PD motor symptoms, and therefore remains one of the most commonly used medications. We have recently looked at the effect of levodopa on patterns of cerebral activity in PD patients while performing the WCST (Jubault *et al.*, 2009). After drug administration, patients showed an increase in regions that are a part of the motor loop, while regions that are a part of the cognitive loop remained unaffected. These results are consistent with the observation that dopaminergic medication has a much stronger effect on motor rather than cognitive symptoms.

Greater involvement of the putamen in SI compared to ET movements has been observed in healthy controls (Cunnington *et al.*, 2002). In a previous study, we reported increased activity in the putamen when comparing control (CTL), ET and SI finger movements (Francois-Brosseau *et al.*, 2009). In healthy individuals, activity in the putamen increased depending on movement type. ET movements recruited higher levels of activity than control movements, and SI movements were associated with even higher levels of activity in the putamen. Furthermore, ET movements recruited the putamen and the PMC, while SI movements additionally involved the caudate nucleus and DLPFC.

Our first goal was to investigate the response of the putamen to different types of movements in PD, and the effects of dopaminergic medication. We hypothesized that differences in putamen activity between tasks would be reduced in PD patients off medication, but that medication would help re-establish the putamen's involvement. The second aim was to assess effects of levodopa on the hypo/hyperactivity pattern of cortical regions previously observed in PD patients. Striatum-related cortical hypo-activity observed in PD could be a result of nigrostriatal degeneration. Cortical hyper-activity, however, could either be a form of compensation and/or mesocortical imbalance. We propose that cortical hyperactivity in PD patients is primarily due to mesocortical dopamine pathway disruption (Monchi *et al.*, 2007; Monchi *et al.*, 2010; Macdonald & Monchi, 2011). We consequently do not expect cortical activity to correlate with performance on the task, and medication intended to optimize dopamine levels in the dorsal striatum to have no significant effect on this pattern of activity.

Methods

Participants

All participants gave informed consent. This project was approved by the Joint Ethics Committee of the Regroupement Neuroimagerie Quebec (RNQ), which follows the guidelines of the Tri-Council Policy Statement of Canada, the civil code of Quebec, the Declaration of Helsinki and the code of Nuremberg.

Patients. 12 right-handed patients diagnosed with PD [mean age 62.89±6.70 (SD), 6 women and 6 men] participated in the study. All PD participants met the core assessment program for surgical interventional therapy criteria for the diagnosis of idiopathic PD (Langston *et al.*, 1992; Defer *et al.*, 1999). All patients also met the UK brain bank criteria for the diagnosis of PD (Hughes *et al.*, 1992). Motor disability of individuals within the PD group was in the mild to moderate severity range according to the Hoehn and Yahr staging criteria (Hoehn & Yahr, 1967). Handedness was assessed with the Edinburgh Handedness Inventory (mean average 91.57±14.47), all individuals were screened for early signs of dementia prior to the experiment using the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005) (mean average ON 26.92±1.88, OFF 27.55±1.51), the presence and severity of depression in all PD participants was estimated using the Beck Depression Inventory II (BDI-II) (mean average 12.58±11.74), and at each session, the motor symptoms of all PD patients were measured with the UPDRS-III (OFF 31.17±4.87 and ON 23.42±6.95). In addition to levodopa, most patients were also taking other antiparkinsonian drugs such as COMT inhibitors (n=5), MAO-B inhibitors (n=6), dopamine agonists (n=3) and others (n=3). Detailed patients' demographic and clinical scores are given in Table Ia.

Healthy controls. 14 right-handed healthy controls [mean age 61.74±6.62, 6 males and 8 females] were also recruited. All controls completed the MoCA (mean average 27.79±1.89), the BDI-II (mean average 4.21±4.34) and the Edinburgh Handedness Inventory (mean average 84.85±13.15). Detailed demographic and scores are given in Table Ib.

Procedure

Each PD patient came for two scanning sessions, at least one week apart. For each session they were asked to withdraw from all their antiparkinsonian medications for at least 12 hours prior to the appointment. All patients stayed off all medications for their OFF session, and took only their usual levodopa 1 hour before the scanning hour for the ON session. ON and OFF sessions were counterbalanced across patients. Healthy controls (HC) came for

one scanning session only, and performed the same tests as patients except for the UPDRS. All participants practiced three blocks (for a total of 9 times per condition) of the task to ensure they could perform adequately in the scanner.

Behavioral tasks

Using the right hand, participants performed a SI random movement condition, an ET follow condition, and a single-button repeat condition (control). Five blue squares were displayed, each square corresponding to a button on the response box; all fingers were used except for the pinky, as it was considered difficult for patients. The blue square representing the pinky was present nonetheless as a reference for finger positioning. The task included a total of twenty button presses per condition. Instructions were given for 2.5 seconds before the five blue squares appeared to indicate which task should be performed.

Control task. During the control task, one colored square switched from blue to green, indicating that the corresponding button must be pressed. For the duration of every button-press, the square would turn yellow to show the subject's response, and then turn green again to illustrate that it was ready to be pressed again. This continued until the subject successfully completed all button-presses. The button to be pressed during the control task was randomly selected by the computer, and remained the same for the duration of the condition.

ET task. During the ET follow task, the button to be pressed varied at random each time. The subject had to follow the sequence as the blue squares alternately turned green. Every button-press resulted in the corresponding square turning yellow if it was correctly pressed, or red if an error was made (i.e., an incorrect selection). The computer program was designed to avoid repetitive sequences and patterns or selecting the same button twice in a row.

SI task. For the SI random condition, all four squares would turn green, and the subject had to choose his/her own sequence. Once again, the buttons pressed made the green squares turn yellow, after which the next button was ready to be selected. For this particular task we asked the participants to switch buttons continuously. The same button being pressed twice in a row was considered an error, and the equivalent square would turn red. We also asked that participants refrain from automatic and repeated sequences such as 1-2-3-4 or 4-3-2-1.

fMRI

Data acquisition. Participants were scanned using the 3T Siemens TIM MRI at the Functional Neuroimaging Unit (UNF) of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM). Each scanning session comprised a T1-weighted three-dimensional volume acquisition (voxel size $1mm^3$) for anatomical localization, followed by four T2*-weighted functional echoplanar acquisitions with BOLD contrast. Each run consisted of 146 frames of 43 slices (matrix size 128x128, voxel size 2.34 x 2.34 x 3mm) acquired at a repetition time of 3.5 seconds.

Data analysis. Data analysis was performed using fmristat software (Worsley *et al.*, 2002). For a detailed depiction, see François-Brosseau et al., (2009). Briefly, each run was first realigned to the fourth frame for motion correction and smoothed using a 6 mm full width half-maximum (FWHM) isotropic Gaussian kernel. The statistical analysis of the fMRI data was based on a linear model with correlated errors. Effect and standard effect files were spatially normalized by linear transformation into the Montreal Neurological Institute (MNI) standard proportional stereotaxic space, based on that of Talairach and Tournoux (Talairach & Tournoux, 1988), using the algorithm of Collins et al. and the ICBM152 atlas as an approximation (Collins *et al.*, 1994). Anatomical images were also normalized to the same space. Runs, sessions and subjects were combined using a mixed effects linear model. For each group (HC, OFF and ON), the average BOLD signal obtained during the SI and ET movement conditions were compared with those of the control condition. Additionally, the SI condition was compared with the ET condition, for a total of three contrasts per

group. We also performed inter-group comparisons (HC vs. ON, HC vs. OFF and ON vs. OFF) for each one of these three contrasts (SI vs. CTL, ET vs. CTL and SI vs. ET).

Significant peaks are reported using the minimum p value of the single peak and cluster analysis. All peaks (minimum 10mm cortical inter-peak distance and excluding cerebellar regions) that reached $p<0.05$ corrected are reported. Predicted peaks (present in Francois-Brosseau *et al.*, 2009) that reached $p<0.0001$ uncorrected are also reported, and indicated by an asterisk in result tables.

Results

Clinical scores:

There were no significant differences between PD and HC in age or handedness. Patients ON had significantly lower UPDRS scores than OFF ($p=0.005$). PD patients had significantly higher BDI-II scores ($p=0.023$) and lower MoCA scores ($p=0.048$) than HC, but there were no significant correlations between MoCA or BDI-II scores and their behavioral performance during our finger-movement task. There was no significant effect of session order on MoCA scores.

Behavioral performance during scanning:

Reaction times. For our SI, ET and CTL, healthy controls' performance was as follows: SI mean average 748±203ms, ET mean average 1001±153ms, and CTL mean average 818±48ms. Parkinson's patients performance was as follows: SI mean average OFF 842±168ms and ON 870±150ms, ET mean average OFF 1106±303ms and ON 1149±171ms, and CTL mean average OFF 717±119ms and ON 746±169ms. PD patients had significantly slower reaction times than HC in the ET condition ($p=0.041$).

Errors. The percentage of errors was calculated by (number of errors) / (total button presses) for each condition. For our SI, ET and CTL tasks, healthy controls' error

percentages were: SI: 1.03%, ET: 2.85% and CTL: 0.27%. Parkinson's patients error percentages were: SI: OFF 2.87% and ON 2.55%, ET: OFF 8.92% and ON 10.96%, CTL: OFF 0.76% and ON 1.48%. PD patients in the ON condition made significantly more errors than HC in the ET condition ($p=0.005$).

fMRI results:

In the healthy control participants, significant differences in activity were observed in the caudate nucleus, the putamen and the PFC during the SI condition, and the PMC in ET and SI tasks. Significant differences in activity in the putamen were observed in all three contrasts (SI vs. CTL, SI vs. ET and ET vs. CTL), showing increasing involvement of the structure in CTL, ET and SI movements (Figure 19). PD patients off medication displayed significant putamen activity for the SI vs. CTL contrast only, with a trend in the ET vs. CTL contrast. After levodopa administration, significant putamen activation was observed in SI vs. CTL and ET vs. CTL. In PD patients, the administration of dopaminergic medication was associated with a significant difference in activity in the PMC but not in the caudate nucleus or the DLPFC. Interestingly, we also observed significant differences in activity in the VLPFC at the junction of the insula in patients off medication during ET movements. The VLPFC was not recruited for ET movements in healthy controls, and levodopa did not normalize this activity.

1. ET versus control (Table II):

Healthy controls. The comparison of the ET and CTL tasks in HC showed a significant increase in activity in the bilateral PMC (area 6), PPC (areas 7 and 40), and the occipital cortex (areas 17, 18, 19 and 37). Significant activation was also observed in the right SMA (area 6) and the left sensory cortex (area 3). Subcortical activations included the bilateral putamen.

OFF session. Patients off medication presented significantly increased bilateral activity in the PMC (area 6), SMA (area 6), PPC (areas 7 and 40), and occipital cortex (areas 17, 18 and 19). Significant activation was also observed in the left VLPFC at the junction of the insula (junction of areas 47/12 and 13) and the left somatosensory cortex (area 3). Subcortical activations included the bilateral putamen.

ON session. Patients on medication revealed significant activations bilaterally in the VLPFC / insula (area 47/12 - 13), the PMC (area 6), SMA (area 6), PPC (areas 7 and 40) and occipital cortex (areas 17, 18, 19 and 37), as well as in the right somatosensory cortex (area 3). Subcortical activations included the bilateral putamen and thalamus.

2. SI versus control (Table III):

Healthy controls. When comparing the SI and CTL conditions, HC displayed significant activations bilaterally in the VLPFC / insula (area 47/12 - 13), PMC (area 6), SMA (area 6), PPC (areas 7 and 40) and visual cortex (areas 17, 18, 19, 31 and 37). HC also displayed a significant increase in activation in the left anterior PFC (area 10), sensory cortex (areas 2 and 3) and the right DLPFC (area 8,9). Subcortical activations were observed bilaterally in the putamen and thalamus.

OFF session. In the SI minus CTL comparison, patients off medication had significant bilateral activations in the DLPFC (area 9 - 9,46), VLPFC / insula (area 47/12 - 13), PMC (area 6), SMA (area 6), PPC (areas 7 and 40). Significant activation was also observed in the left motor cortex (area 4), as well as the right visual cortex (area 19). Subcortical activations were observed in the putamen bilaterally and the left thalamus.

ON session. Patients ON medication displayed significant increases in activity in the bilateral DLPFC (area 9 - 9,46), VLPFC / insula (area 47/12 - 13), PMC (area 6), SMA (area 6), and PPC (areas 7 and 40). They also showed significant activations in the left

motor (area 4) and sensory (area 2) cortex, and the right visual cortex (area 19). Significant subcortical activations were observed bilaterally in putamen and thalamus.

3. SI versus ET (Table IV):

Healthy controls. In the contrast of SI versus ET, HC showed a significant increase in activity bilaterally in the anterior PFC (area 46/10), mid-DLPFC (area 9 - 9,46 and 46), VLPFC / insula (area 47/12 - 13), PMC (area 6), pre-SMA (area 6,8) and PPC (areas 7 and 40). Other significant activations were also observed in the left posterior PFC (pPFC) (area 6,44), the right sensory cortex (area 2), and left SMA (area 6). Subcortical significant activations included the caudate and putamen bilaterally, and the left thalamus.

OFF session. Patients OFF medication displayed significant increases in activity in the left DLPFC (area 9 - 9,46) and the left PPC (area 40). No subcortical activation was observed.

ON session. Patients ON medication showed significant increases in activity in the bilateral PMC (area 6), the right DLPFC (area 9 - 9,46) and PPC (area 7), as well as the left sensory cortex (area 3), SMA (area 6) and superior parietal lobule (area 5). No significant subcortical activity was observed.

4. Between-group comparisons:

All statistically significant inter-group differences between HC, ON and OFF for SI vs. CTL, ET vs. CTL and SI vs. ET are reported in Table V.

Discussion:

Our first major goal was to explore the patterns of brain activity in PD patients during the performance of control, ET and SI movements that increasingly solicit the putamen. As hypothesized, the putamen's response to these movements is reduced in PD

patients as compared with control participants. The second goal of this study was to understand the effect of levodopa on the striatum-dependent cortical hypo- and hyper-activity patterns often observed in PD patients in fMRI (Monchi *et al.*, 2007). Using a finger movement task, we hypothesized that patients would display prefrontal hyper-activations not normally activated in control participants in the same task, and that levodopa would have no significant effect. Consistent with our hypotheses, we observed a significant increase of activity in the depth of the horizontal ramus of the Sylvian fissure (at the intersection between the VLPFC and insula) in patients while they performed the ET task. In contrast, this region's activity was significantly increased in the SI task in healthy controls. Levodopa administration did not have a significant effect on this discrepancy.

Healthy participants

In accordance with our previous study on young adults (François-Brosseau *et al*., 2009), control participants displayed increased putamen activity for the two tasks compared with control movements (Figure 19). Furthermore, healthy controls significantly recruited regions involved in the cognitive and motor ganglio-thalamocortical loops described by Alexander et al. (1986). More specifically, there was an increase in activity in structures that make up the motor loop (putamen and PMC) in ET movements. Additionally, there was an increase in activity in regions associated with two cognitive loops (caudate / DLPFC and caudate / VLPFC) when comparing SI to ET movements. In agreement with previous studies, these results support the hypothesis that SI movements require larger basal ganglia and prefrontal input than ET movements (Gordon *et al.*, 1998; Jenkins *et al.*, 2000; Cunnington *et al.*, 2002; Elsinger *et al.*, 2006). Moreover, the parietal cortex is significantly more active during both SI and ET conditions, which is consistent with its purported role in visual cue-based representation of movements and spatial attention (Deiber *et al.*, 1996; Harrington *et al.*, 2000).

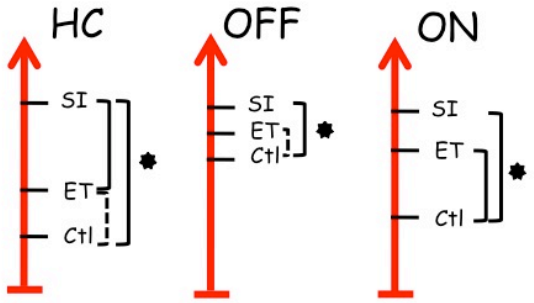

Figure 19: Diagram of putamen activity during control, ET and SI movements in HC, ON and OFF

Units are arbitrary and hold a symbolic relationship between groups. Solid lines indicate significant statistical difference in putamen activity between conditions, dotted lines indicate sub-threshold peaks. Healthy participants show sub-threshold putamen activity in ET movements but significant activity in SI and SI vs. ET movements. Patients off medication display sub-threshold putamen activity in ET movements and significant putamen activity in SI movements. Finally, after levodopa administration, patients show significant putamen activity in both ET and SI movements.

PD patients - Motor loop:

During SI movements, a significant increase in activity was observed in the motor loop (putamen and PMC) in both healthy controls and PD patients (Figure 20). There was a statistical trend in those regions for ET movements in controls or patients OFF, and a significant increase in patients ON. Levodopa does not seem to affect SI or ET movement-related activity differently, indicating that its effect on the putamen does not depend on the type of movement.

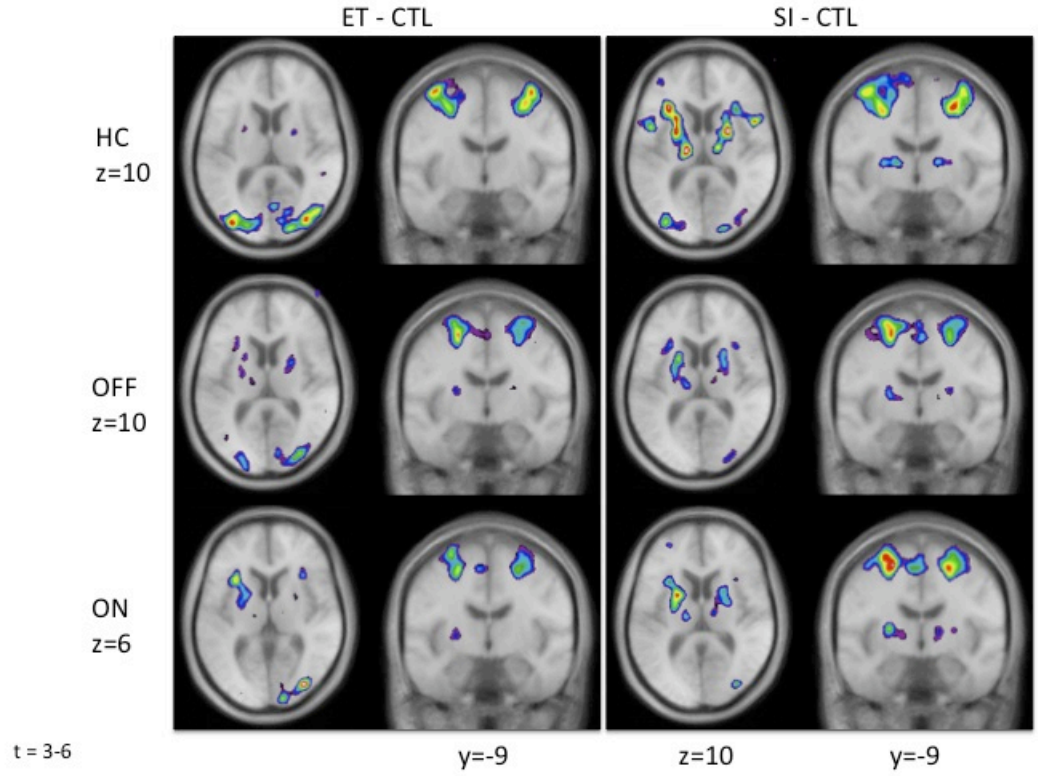

Figure 20: Location of peaks in the ET versus control (left) and SI versus control (right) for the three groups of participants

Anatomical images shown are the average of the T1 acquisitions of all participants transformed into stereotaxic space. The functional peaks are shown for t-stat values between 3 and 6. Healthy controls (top row) show sub-threshold putamen activity in ET movements (left), and significant bilateral putamen in SI movements (right). Patients off medication (middle row) display sub-threshold bilateral putamen activity in ET movements (left), and significant bilateral putamen in SI movements. Patients on medication (bottom row) have significant left putamen in ET movements (left), and significant bilateral putamen in SI movements (right). Healthy controls, patients on and off medication have significant PMC activity in SI and ET movements.

Lewis et al. investigated SI and ET movements in a pair of twins discordant for PD. Movement-related activity was significantly increased in the basal ganglia-cortical circuitry after levodopa administration for SI movements, and a trend for ET movements in the

affected twin (Lewis *et al.*, 2007). Further studies showed that while PD patients can reach movement automaticity, the level of cortical activity observed is greater. This may be necessary to compensate for basal ganglia dysfunction (Wu & Hallett, 2005). Furthermore, PD patients require higher brain activity levels to perform movements of different speeds, compared with healthy controls (Palmer *et al.*, 2009a). Boecker et al. (2008) studied the role of the basal ganglia in the planning of motor sequences. Their results showed that the putamen was involved in the planning of SI movements, whereas the substantia nigra was involved in both internally and externally generated movements (Boecker *et al.*, 2008). They did not however observe increased activation in the putamen. This may have been due to pre-training, leading to increased automaticity of the sequence. Increased activity in the putamen was observed in our protocol likely because finger movement sequences were randomly generated, and therefore unpredictable.

Similar to the healthy volunteers, the putamen was activated for ET and more so for SI movements compared to the control condition in patients before and after levodopa administration (Figure 19). The degree to which the putamen was recruited differed depending on the group of participants. In healthy controls, there was a statistical trend between the ET and CTL condition, and significant bilateral increases in activity between the SI and ET conditions. Consistent with previous studies, these results support the role of the putamen in the planning and self-generation of movements (Helmich et al., 2006; Boecker et al., 2008). PD patients off medication displayed sub-threshold putamen activity increases between the ET and CTL conditions, and significant bilateral increases between the SI and CTL tasks. There was no significant difference in the putamen between the SI and ET conditions.

Levodopa administration globally increased activity in the motor loop. The difference between SI and CTL tasks was significant in patients on medication. There was also a significant difference between ET and CTL tasks (Figure 20). While no significant differences in the motor loop were detected for comparisons between groups of patients on and off medication (Table V), the PMC and SMA were more active after levodopa administration based on within-group comparisons (Table IV). There were no statistical differences in task performance before or after drug administration, and BOLD activity did

not correlate significantly with performance in any of the tasks (results not shown). We can suggest, then, that levodopa increases motor loop activity in general rather than modulating it by movement type.

PD patients - Cognitive loop:

The cognitive loops formed by the caudate nucleus and the DLPFC and VLPFC were involved in SI movements in healthy controls compared with the ET condition (Figure 21). In PD patients, regions that make up the cognitive loop show no significant activity before or after levodopa administration. This is consistent with our previous study where levodopa did not change activity in cognitive loop structures (caudate nucleus, DLPFC, VLPFC) normally observed in the performance of the WCST (Jubault *et al.*, 2009). Because the latter study did not involve healthy controls, however, we couldn't distinguish healthy and parkinsonian activity patterns.

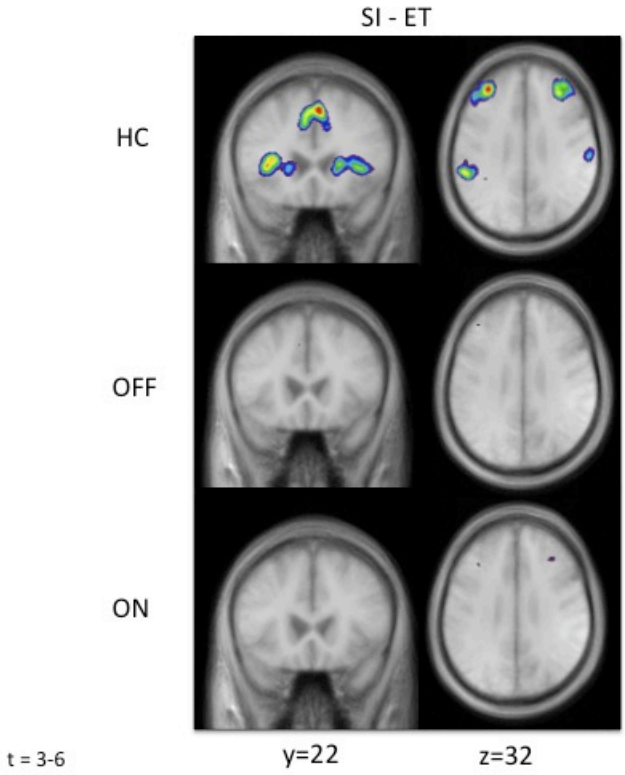

Figure 21: Location of peaks associated with the cognitive portion of SI movements

The functional peaks are shown for t-stat values between 3 and 6. Healthy controls (top) show significant activity in the VLPFC (left) and the DLPFC. No significant differences are observed in patients off medication (middle), and there is no effect of levodopa (bottom).

The results of our current study implicate the VLPFC / insula. This region is paired with the caudate nucleus when it is involved in SI movements in healthy controls. In PD patients, however, there was an over-activation of the VLPFC / insula in the ET condition (Figure 22), a condition that does not normally recruit the caudate nucleus. Consistent with previous research, we observed hyper-activation of the PFC in PD patients off medication for tasks that do not normally activate the striatum in healthy participants, and a hypo-activity of these regions in tasks that do (Monchi *et al.*, 2004; Monchi *et al.*, 2007; Monchi *et al.*, 2010). Importantly, in the present study, levodopa did not normalize this effect. This is in agreement with the hypothesis that medication leads to a dopamine overload in the mesocortical pathway at the early stage of the disease leading to over-activation of prefrontal regions that are not solicited with dorsal striatum in healthy individuals for the task (Macdonald & Monchi, 2011). This result also supports the idea that the hyper- and hypo-activity effect is linked to dopaminergic medication administration. However, it seems unlikely that it is performance-dependent, as there is no difference in task performance between the three groups of participants, and no areas correlated with task performance in any of our three conditions (results not shown).

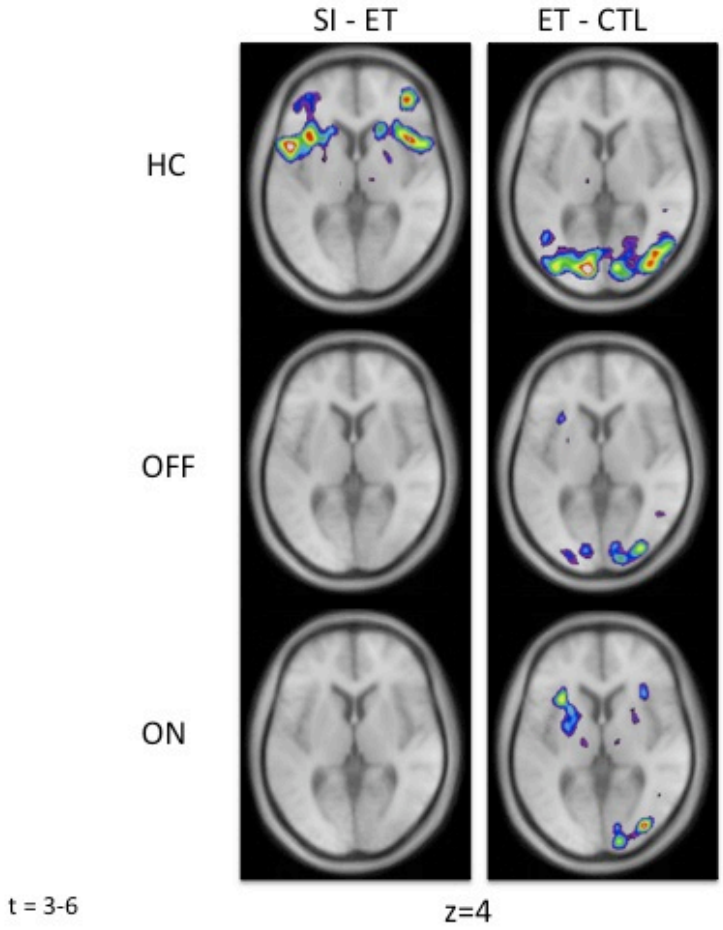

Figure 22: Peaks at the intersection of the VLPFC and the insula in healthy controls and patients

The functional peaks are shown for t-stat values between 3 and 6. Healthy controls (top) show VLPFC / insula activity in SI movements (left) but not in ET movements (right), whereas patients off medication show VLPFC / insula activity in ET (right) but not SI (left) movements. Medication has no significant effect on this discrepancy (bottom).

In a study comparing PD patients on and off levodopa performing the Tower of London, Cools et al. (2002) observed a task-specific decrease in the DLPFC and a task-specific increase in the occipital lobe after levodopa administration. Medication restored DLPFC activity to normal. Another study looking at the effect of levodopa on volitional movements observed decreased activity in premotor and parietal regions after levodopa

administration (Haslinger *et al.*, 2001). In the present study, we observed a global decrease in prefrontal activity in PD patients compared with healthy controls (Table V). The difference between the VLPFC / insula activity observed in our study and the prefrontal activity decreases observed in SI vs. ET in Cools et al. (2002) is that the VLPFC / insula activity is not task-related (i.e., it is not activated for the condition at hand in control participants). Dopamine has been shown to improve corticostriatal connectivity, thereby affecting performance efficiency (Nagano-Saito *et al.*, 2008). Moreover, levodopa may partially restore task-related activity, as we saw previously with the motor loop, but may not affect, or may be detrimental instead, to non-task-related processes. The recruitment of novel areas may either be interpreted as compensation (Palmer *et al.*, 2009a), or as an indicator of neurological dysfunction (Dagher & Nagano-Saito, 2007) of the mesocortical pathway. Our results support the idea that increases in prefrontal regions that are unrelated to the task are not due to a compensatory mechanism, but are rather related to an imbalance of dopamine in the mesocortical pathway.

Other studies have reported different effects of levodopa on performance (Gotham *et al.*, 1988). Some demonstrate changes in cortical activity after levodopa administration linked with improvement (Cools *et al.*, 2002; Fera *et al.*, 2007), others with deterioration of task accuracy (Swainson *et al.*, 2000; Mattay *et al.*, 2002) (for review, see Macdonald & Monchi, 2011). Perhaps due to practice sessions prior to scanning, task performance did not change before or after levodopa administration in our protocol. Other authors report differences in striatal and frontal region activity depending on cognitive impairment in patients (Lewis *et al.*, 2003). There was also no difference in cognitive performance between our PD patients and our healthy controls. It is unlikely that these changes in cortical activity were attributed to differences in depression (BDI-II) or cognitive performance (MoCA) between patients and controls since neither test correlated with performance.

Conclusion:

We have shown the modulation of the putamen by three types of movements. The putamen was increasingly implicated in control, ET and SI finger movements. These

differences in activity were reduced in patients affected by PD. Levodopa partially restored this pattern by a general increase in activity irrespective of the task being performed. While levodopa affected the putamen and pre-motor regions involved in SI and ET tasks, no effect was observed in the caudate nucleus and DLPFC involved in the cognitive components of the task. In line with an imbalance of mesocortical dopamine tone, levodopa appears to play no significant role in the striatum-related hyper-activity patterns of cortical regions in PD. In conclusion, our results suggest that dopamine replacement therapy has a beneficial effect on motor cortico-striatal regions, but no significant effect on task-related cognitive cortico-striatal regions, and no significant regulation of cortical hyper-activations in cognitive regions not usually required for the task. Further research comparing medicated and non-medicated patients will be necessary to fully understand the interaction between medication and cortical activity variations at different stages of the disease.

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Table I - Demographics of patients (A) and healthy controls (B)

(A)

Subject	Gender	Age (years)	Dur. (years)	Other meds	BDI-II	Hand.	MoCA On/Off	Med. admin. (h)	UPDRS On	Med. w/d	UPDRS Off
23	F	69	2	1, 2	0	100	27/27	2	33.5	13.5	39.5
25	F	51	5	1, 4	12	58	27/27	5	18.5	15	31
29	M	67	2	1, 3	6	68.5	24/27	–	26	–	29
33	M	69	9	1, 4, 5	27	89	28/25	2.25	23	17	34.5
35	M	58	2	1, 2, 3	16	100	26/30	2	16.5	48	21.5
37	M	54	5	1, 2, 3, 5	6	83.3	30/30	3	25.5	14	36
39	M	68	3	1	6	100	27/28	0.67	26.5	15	27.5
41	F	62	5	1, 3, 4	12	100	29/28	1	19.5	12	31.5
45	F	68	11	1, 3, 5	15	100	26/27	2.17	25	10	31.5
47	F	68	1	1, 2	42	100	24/–	1.83	21.5	13.5	27
49	F	65	1	1, 2	3	100	29/26	1.83	26	14	36
51	M	55	2	1, 3	6	100	26/28	2	12.5	15.5	29
Average		62.89	4.0		12.6	91.57	26.9/27.5	2.15	23.42	17	31.17

(B)

Subject	Gender	Age (years)	BDI-II	Hand.	MoCA
1	F	61.80	2	80	29
2	F	65.38	1	100	27
3	M	56.12	9	100	26
4	F	57.16	2	80	27
5	M	58.95	1	66.7	30
6	F	51.33	7	100	30
7	M	69.50	0	80	24
8	F	49.93	1	80	27
9	F	60.25	2	100	29
10	F	70.85	1	81.2	30
11	M	67.34	1	80	28
12	M	63.00	9	60	25
13	M	62.69	12	80	29
14	F	70.00	11	100	28
Average		61.74	4.21	84.85	27.79

Abbreviations: Sub: subject, G.: gender, Dur.: duration of illness in years from onset, Other Meds: patients' medications (1 = levodopa; 2 = Com-T inhibitor; 3 = MAO-B inhibitor; 4 = dopamine agonist; 5 = other), Hand.: Edinburgh Handedness Inventory score, Med. admin: time from administration of levodopa to the UPDRS evaluation, Med. w/d: hours of medication withdrawal for OFF session (time is with respect to the UPDRS score). Patients were counterbalanced in the order in which they performed the task on or off. The session recorded first is underlined in the MoCA column.

Table II - Activity peaks associated with ET movements, compared with the control condition

		HC					OFF					ON				
Anatomical area (BA)		*x*	*y*	*z*	*t*	Cluster	*x*	*y*	*z*	*t*	Cluster	*x*	*y*	*z*	*t*	Cluster
VLPFC/insula	(47/12–13) L	–	–	–	–	–	−32	18	2	3.87	536	−32	18	4	5.29	>3000
	R	–	–	–	–	–	–	–	–	–	–	34	24	4	3.96*	384
PMC	(6) L	−38	−12	66	6.11	>5000	−22	−10	58	5.61	>3000	−24	−12	56	5.32	>3000
		−20	0	64	5.12	sc	−54	2	40	5.79	2016	−54	0	40	6.46	>3000
		−56	4	38	4.91	1760	–	–	–	–	–	–	–	–	–	–
	R	32	−6	56	5.77	>5000	26	−4	58	5.12	>3000	26	−4	58	5.54	>3000
		–	–	–	–	–	50	6	30	4.26	1880	48	6	38	4.96	>3000
		–	–	–	–	–	48	8	20	3.91	sc	–	–	–	–	–
SMA	(6) L	–	–	–	–	–	−2	6	56	3.59	>3000	−8	−4	56	5.05	2184
	R	8	2	56	3.91*	232	4	−6	56	3.59*	432	4	2	60	3.8	sc
Sensory	(3) L	−42	−24	54	4.9	>5000	−58	−22	38	3.97	>5000	–	–	–	–	–
	R	–	–	–	–	–	–	–	–	–	–	54	−22	40	3.92	1584
PPC	(7) L	−24	−70	54	5.17	>5000	−26	−64	64	4.59	>5000	−14	−74	58	5.67	>5000
		–	–	–	–	–	–	–	–	–	–	−26	−64	64	4.75	sc
	R	20	−70	62	6.17	>10 000	30	−58	52	5.49	>5000	20	−72	62	5.14	>10 000
		34	−54	64	5.76	sc	–	–	–	–	–	–	–	–	–	–
	(40) L	−46	−36	56	4.5	>5000	−42	−34	44	6.09	>5000	−42	−36	38	5.86	>5000
		–	–	–	–	–	–	–	–	–	–	−36	−50	46	4.93	sc
	R	32	−48	44	5.05	>10 000	40	−46	52	5.23	>5000	36	−44	56	4.31	>5000
		–	–	–	–	–	48	−34	46	4.57	sc	–	–	–	–	–
Visual	(17) L	−14	−88	−6	8.56	>10 000	–	–	–	–	–	–	–	–	–	–
	R	12	−86	−8	6.89	sc	18	−96	2	4.48	>10 000	14	−96	4	4.96	2400
	(18) L	−4	−74	6	4.42	sc	−24	−90	14	4.36	2600	–	–	–	–	–
	R	20	−92	16	6.27	sc	34	−86	4	5.12	>10 000	–	–	–	–	–
	(19) L	−30	−78	−12	7.26	sc	–	–	–	–	–	−42	−84	−10	4.35	>3000
		−30	−88	18	6.77	sc	–	–	–	–	–	–	–	–	–	–
	R	34	−74	−12	6.08	sc	32	−72	28	5.49	>10 000	34	−84	8	6.57	>5000
		36	−82	6	5.91	sc	34	−84	14	4.89	sc	28	−72	34	5.73	sc
		32	−76	26	4.43	sc	42	−66	−12	4.79	sc	–	–	–	–	–
	(37) L	−46	−64	−2	5.09	sc	–	–	–	–	–	–	–	–	–	–
	R	50	−70	2	5.24	sc	–	–	–	–	–	42	−62	−14	4.96	>5000
Putamen	L	−24	2	10	3.29*	40	−24	−8	12	3.61*	344	−22	2	6	4.1	>3000
	R	24	0	10	3.5*	80	24	2	10	3.79*	720	28	4	2	3.55*	144
Thalamus	L	–	–	–	–	–	–	–	–	–	–	−14	−16	0	4.03	1760
	R	–	–	–	–	–	–	–	–	–	–	12	−18	−2	4.46	sc

*The coordinates (x,y,z) are in standard MNI stereotaxic space. Cluster sizes are reported in mm^3. sc indicates that the peak is part of the same cluster as the peak listed immediately above in the table and that its size is therefore included in the preceding reported volume. The same abbreviations are used for tables 2-5. ET = externally triggered movements; SI = self-initiated movements; CTL = control movements; HC = healthy controls; OFF = patients off medication; ON = patients on medication; BA = Brodman area; aPFC = anterior PFC; DLPFC = dorsolateral PFC; PMC = premotor cortex; PPC = posterior parietal cortex; pPFC = posterior PFC; SMA = supplementary motor area; SPL = superior parietal lobule; VLPFC = ventrolateral PFC. *P < 0.001 non-corrected for multiple comparisons.*

Table III - Activity peaks associated with SI movements, compared with the control condition

		HC					OFF					ON				
Anatomical area (BA)		*x*	*y*	*z*	*t*	Cluster	*x*	*y*	*z*	*t*	Cluster	*x*	*y*	*z*	*t*	Cluster
aPFC	(10) L	−38	50	14	4.6	1176	–	–	–	–	–	–	–	–	–	–
DLPFC	(8,9) R	36	42	36	3.49*	224	–	–	–	–	–	–	–	–	–	–
	(9,46) L	–	–	–	–	–	−42	36	34	3.93	560	−40	28	34	3.93	704
	R	–	–	–	–	–	36	36	28	3.71*	272	34	34	32	5.05	2344
VLPFC/insula	(47/12–13) L	−32	24	10	6.05	>5000	−30	20	8	3.79	856	−32	18	4	5.39	>5000
	R	32	20	12	4.83	>5000	36	20	8	3.87*	248	34	20	6	4.78	>3000
PMC	(6) L	−36	−14	64	6.35	>10 000	−22	−10	60	5.72	>5000	−24	−12	58	6.14	>10 000
		−20	0	64	5.74	sc	−54	2	40	4.76	744	−54	0	42	5.39	1776
		−56	6	34	5.82	>5000	–	–	–	–	–	–	–	–	–	–
		−56	12	2	5.03	sc	–	–	–	–	–	–	–	–	–	–
	R	28	−6	52	6.59	>5000	26	−6	56	5.44	>3000	24	−4	58	6.47	>10 000
		56	8	34	4.53	>5000	54	6	32	4.58	1248	58	10	20	4.54	1928
		50	10	10	5.64	sc	–	–	–	–	–	–	–	–	–	–
Motor	(4) L	–	–	–	–	–	−36	−16	58	5.05	>5000	−36	−20	60	5.89	>10 000
Sensory	(2) L	−58	−20	30	5.18	>10 000	–	–	–	–	–	−44	−32	64	5.56	sc
	(3) L	−40	−28	50	6.44	sc	–	–	–	–	–	–	–	–	–	–
		−54	−22	42	5.51	sc	–	–	–	–	–	–	–	–	–	–
SMA	(6) L	−4	0	52	4.64	sc	−4	10	50	4.14	>3000	−8	−4	56	5.26	>10 000
		−6	14	46	4.53	sc	–	–	–	–	–	−6	10	50	4.86	sc
	R	8	2	56	5.32	sc	4	−6	56	4.47	>3000	6	−2	54	4.57	sc
		6	18	48	6.25	sc	–	–	–	–	–	–	–	–	–	–
PPC	(7) L	−22	−70	58	6.64	sc	−14	−74	58	5.22	>5000	−14	−74	58	6.97	>10 000
		−34	−52	64	5.77	sc	–	–	–	–	–	−38	−50	56	4.57	sc
	R	18	−66	60	7.16	sc	18	−72	66	5.05	>5000	12	−72	54	6.2	>10 000
		34	−54	64	6.06	sc	32	−58	52	4.74	sc	40	−46	60	5.37	sc
	(40) L	−42	−32	50	6.29	sc	−44	−34	46	6.24	>5000	−46	−36	48	6.06	>10 000
	R	46	−32	38	7.75	sc	48	−36	44	6.18	>5000	34	−42	52	4.91	>10 000
		–	–	–	–	–	–	–	–	–	–	50	−34	44	4.89	sc
Visual	(17) L	−14	−90	−4	7.11	>10 000	–	–	–	–	–	–	–	–	–	–
	R	24	−84	−14	6.94	sc	–	–	–	–	–	–	–	–	–	–
	(18) R	40	−84	2	4.85	sc	–	–	–	–	–	–	–	–	–	–
		20	−92	12	4.74	sc	–	–	–	–	–	–	–	–	–	–
	(19) L	−30	−76	−10	5.88	sc	–	–	–	–	–	–	–	–	–	–
	R	32	−72	28	4.93	sc	32	−72	28	4.75	>5000	28	−70	36	5.33	>5000
		–	–	–	–	–	–	–	–	–	–	34	−84	8	4.78	960
	(31) L	−26	−74	26	5.78	>10 000	–	–	–	–	–	–	–	–	–	–
	(37) L	−48	−64	0	4.51	sc	–	–	–	–	–	–	–	–	–	–
	R	50	−68	2	4.49	sc	–	–	–	–	–	–	–	–	–	–
Putamen	L	−24	0	10	5.92	>5000	−20	8	10	4.79	>3000	−24	4	8	5.76	>5000
		−24	12	10	5.88	sc	–	–	–	–	–	–	–	–	–	–
	R	24	0	10	6.21	>5000	24	12	10	4.27	1672	22	8	8	4.54	>3000
		–	–	–	–	–	24	0	8	4.1	sc	–	–	–	–	–
Thalamus	L	−14	−18	8	6.5	>5000	−14	−14	6	3.9	>3000	−12	−18	4	4.53	>5000
	R	14	−16	8	5.38	>5000	–	–	–	–	–	12	−16	0	4.4	>3000

Abbreviations as in Table II.

Table IV - Activity peaks associated with SI movements, compared with ET movements

Anatomical area (BA)		HC					OFF					ON				
		x	*y*	*z*	*t*	Cluster	*x*	*y*	*z*	*t*	Cluster	*x*	*y*	*z*	*t*	Cluster
aPFC	(46/10) L	−42	46	16	5.6	>5000	–	–	–	–	–	–	–	–	–	–
	R	44	48	18	5.42	>5000	–	–	–	–	–	–	–	–	–	–
Mid-DLPFC	(9,46) L	−36	40	30	6.01	>5000	−40	34	36	3.38*	96	–	–	–	–	–
		−46	34	26	5.41	sc	–	–	–	–	–	–	–	–	–	–
	R	36	40	38	5.53	>5000	–	–	–	–	–	34	32	36	3.53*	160
		30	40	28	5.33	sc	–	–	–	–	–	–	–	–	–	–
	(46) R	40	46	6	5.81	sc	–	–	–	–	–	–	–	–	–	–
pPFC	(6,44) L	−58	4	22	5.37	>5000	–	–	–	–	–	–	–	–	–	–
VLPFC/insula	(47/12–13) L	−32	16	10	6.21	>5000	–	–	–	–	–	–	–	–	–	–
	R	42	14	2	6.24	>5000	–	–	–	–	–	–	–	–	–	–
PMC	(6) L	−22	6	52	4.14	1896	–	–	–	–	–	−24	−8	62	5.75	>5000
		−52	10	4	6.36	>5000	–	–	–	–	–	–	–	–	–	–
	R	18	−8	72	4.36	>5000	–	–	–	–	–	20	4	62	4.92	>3000
		30	10	50	5.5	2272	–	–	–	–	–	–	–	–	–	–
		50	10	12	5.94	>5000	–	–	–	–	–	–	–	–	–	–
Sensory	(3) L	–	–	–	–	–	–	–	–	–	–	−44	−18	60	5.01	>5000
	(2) R	62	−22	30	4.22	>5000	–	–	–	–	–	–	–	–	–	–
Pre-SMA	(6,8) L	−6	18	44	5.89	>3000	–	–	–	–	–	–	–	–	–	–
	R	6	20	48	6.21	sc	–	–	–	–	–	–	–	–	–	–
SMA	(6) L	−4	−4	64	5.5	>5000	–	–	–	–	–	−4	−2	66	4.23	>5000
		−2	0	52	4.57	sc	–	–	–	–	–	–	–	–	–	–
SPL	(5) L	–	–	–	–	–	–	–	–	–	–	−46	−32	60	5.07	>5000
PPC	(40) L	−54	−44	42	5.88	>5000	−18	−62	72	4.07	592	–	–	–	–	–
		−36	−44	36	4.59	sc	–	–	–	–	–	–	–	–	–	–
	R	54	−40	46	5.61	>5000	–	–	–	–	–	–	–	–	–	–
	(7) L	−16	−76	46	5.74	>5000	–	–	–	–	–	–	–	–	–	–
		−40	−48	62	4.91	sc	–	–	–	–	–	–	–	–	–	–
	R	8	−66	58	5.53	>3000	–	–	–	–	–	42	−60	52	4.16	2864
		40	−50	62	3.94	sc	–	–	–	–	–	10	−66	54	4.11	1560
Caudate	L	−20	22	4	4.01	>5000	–	–	–	–	–	–	–	–	–	–
		−18	10	14	3.87	sc	–	–	–	–	–	–	–	–	–	–
	R	22	22	8	4.73	>5000	–	–	–	–	–	–	–	–	–	–
		20	18	10	4.45	sc	–	–	–	–	–	–	–	–	–	–
Putamen	L	−24	−2	10	4.11	>5000	–	–	–	–	–	–	–	–	–	–
		−22	6	−4	4.11	sc	–	–	–	–	–	–	–	–	–	–
	R	24	2	12	4.36	>5000	–	–	–	–	–	–	–	–	–	–
Thalamus	L	−14	−20	8	4.11	>5000	–	–	–	–	–	–	–	–	–	–

Abbreviations as in Table II.

Table V - Inter-group comparisons for the ET versus control, SI versus control, and SI versus ET contrasts between healthy participants, patients on and patients off medication

		ET–CTL					SI–CTL					SI–ET				
Anatomical areas		*x*	*y*	*z*	*t*-Values	Cluster	*x*	*y*	*z*	*t*-Values	Cluster	*x*	*y*	*z*	*t*-Values	Cluster
HC>OFF																
aPFC	(46,10) R	–	–	–	–	–	40	48	4	3.59	120	40	46	4	3.97	1120
DLPFC	(46) R	–	–	–	–	–	–	–	–	–	–	44	48	18	4.06	328
	(46,9) L	–	–	–	–	–	–	–	–	–	–	−36	36	22	3.55*	104
	(44) L	–	–	–	–	–	–	–	–	–	–	−50	10	4	4.33	904
VLPFC	(45) L	–	–	–	–	–	–	–	–	–	–	−36	22	6	4.08	920
	(47/12) R	–	–	–	–	–	–	–	–	–	–	46	12	0	3.99	1064
	(47/12) L	–	–	–	–	–	–	–	–	–	–	−26	12	12	3.57*	112
SMA	(6) R	–	–	–	–	–	6	20	50	4.19	216	4	22	50	3.64	248
Sensory	(2) R	–	–	–	–	–	–	–	–	–	–	62	−22	30	3.87	248
PPC	(40) L	–	–	–	–	–	–	–	–	–	–	−34	−46	38	3.75	368
	R	–	–	–	–	–	–	–	–	–	–	48	−30	36	3.74	240
Visual	(18) L	−8	−84	−14	4.18	288	–	–	–	–	–	–	–	–	–	–
	(19) L	−30	−74	−6	3.58	280	–	–	–	–	–	–	–	–	–	–
Caudate	R	–	–	–	–	–	–	–	–	–	–	16	2	16	3.57*	120
Putamen	L	–	–	–	–	–	–	–	–	–	–	−24	4	−6	4.55	952
OFF>HC																
Anterior cingulate	(32) L	−2	22	38	3.41*	72	–	–	–	–	–	–	–	–	–	–
DLPFC	(46,9) R	36	34	26	3.45*	48	–	–	–	–	–	–	–	–	–	–
Cingulate	(24) R	2	−6	38	4.29	304	4	−6	38	3.64*	96	–	–	–	–	–
Temporal	(21) R	54	−6	−2	4.02	464	–	–	–	–	–	–	–	–	–	–
Posterior insula	(13) R	40	−12	−4	3.36*	32	42	−12	−2	3.34*	64	–	–	–	–	–
Visual	(31)	–	–	–	–	–	0	−62	28	3.64*	136	–	–	–	–	–
HC>ON																
aPFC	(10) R	–	–	–	–	–	–	–	–	–	–	44	38	−2	4.31	264
SMA	(6) R	–	–	–	–	–	6	20	50	3.86*	104	0	22	50	4.05	1176
DLPFC	(46,10) L	–	–	–	–	–	–	–	–	–	–	−34	40	32	3.47*	168
VLPFC	(47/12) L	–	–	–	–	–	–	–	–	–	–	−52	10	2	4.44	2264
	R	–	–	–	–	–	–	–	–	–	–	46	10	−2	3.92	368
	(45) L	–	–	–	–	–	–	–	–	–	–	−30	24	10	4.06	1480
PPC	(40) L	–	–	–	–	–	–	–	–	–	–	−58	−36	30	4.48	3560
Visual	(18) L	−12	−84	−10	4.33	2880	−12	−86	−10	3.79	768	–	–	–	–	–
	(19) L	−32	−82	18	4.13	528	−30	−82	22	4.11	1672	–	–	–	–	–
	(37) L	–	–	–	–	–	−50	−58	2	3.96	816	−56	−64	2	5.14	1176
	R	–	–	–	–	–	50	−68	2	3.83	240	–	–	–	–	–
ON>HC																
aPFC	(10) R	46	42	−2	4.14	376	–	–	–	–	–	–	–	–	–	–
DLPFC	(46, 9) L	–	–	–	–	–	−32	22	30	3.72*	184	–	–	–	–	–
	R	40	36	26	3.37*	64	–	–	–	–	–	–	–	–	–	–
	(9) R	32	34	32	3.78*	192	–	–	–	–	–	–	–	–	–	–
	(9) L	–	–	–	–	–	–	–	–	–	–	−30	14	32	3.96	192
	(46) L	−46	36	8	3.49*	64	–	–	–	–	–	–	–	–	–	–
PMC	(6) R	28	24	58	4.22	360	–	–	–	–	–	–	–	–	–	–
SMA	(6) L	−2	20	40	4.59	632	–	–	–	–	–	–	–	–	–	–
	(6) R	2	24	60	4.02	400	–	–	–	–	–	–	–	–	–	–
Cingulate	(29) R	–	–	–	–	–	–	–	–	–	–	12	−50	8	3.86	296
Temporal	(36) L	–	–	–	–	–	−22	−6	−28	4.11	320	–	–	–	–	–
	(22) R	54	−6	−2	3.99	544	56	−6	2	3.84	296	–	–	–	–	–
Posterior insula	(13) R	40	−14	−4	3.44*	64	–	–	–	–	–	–	–	–	–	–
ON>OFF																
aPFC	(10) R	46	42	0	3.47*	96	30	54	6	3.21*	16	–	–	–	–	–
OFF>ON																
Visual	(19) L	−10	−74	30	3.32*	24	–	–	–	–	–	–	–	–	–	–

Abbreviations as in Table II.

Chapter 4: Levodopa, disease asymmetry and hand proficiency

The focus of the next chapter is the interaction between the effects of levodopa, left and right hand movements and disease asymmetry. Based on the results of left and right hand movements from healthy young adults, we wanted to look more closely at the differences in the activation patterns of regions involved in the cortico-striatal circuits when patients with PD perform left and right hand movements. In our previous study we had demonstrated that activity of the putamen plateaued for movements of the left hand, whereas when participants used their right hand, activity in the putamen increased incrementally for control, ET, and SI movements, respectively (Francois-Brosseau *et al.*, 2009). We had suggested that these differences were related to hand proficiency. The goal of the following section was to examine the effect of levodopa on the differences between right and left hand movements, with a specific emphasis on disease asymmetry. As will be explained in the following paragraphs, we show that levodopa has an asymmetrical effect on the cortico-striatal circuit regions during SI and ET movements. Although the patients that participated in our protocol were right handed and affected more severely on their left side, we provide intriguing results that suggest a relationship between the asymmetrical effect of levodopa and disease asymmetry and/or hand proficiency.

Differential effects of levodopa on neural activation patterns underlying movements of right and left hands in Parkinson's disease

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Will be submitted shortly to *Movement Disorders*.

Abstract

PD is a neurodegenerative illness often characterized by asymmetrical symptoms. However, the cerebral correlates underlying symptom asymmetry are still not well understood and the effect of levodopa on the cerebral correlates of disease asymmetry have

not been investigated. In this study, right-handed PD patients performed SI, ET and repetitive control (CTL) finger movements with both their right and left hands during fMRI to investigate asymmetrical effects of levodopa on the hemodynamic correlates of finger movements. Patients completed two experimental sessions (with a minimum of 12h levodopa withdrawal): OFF and ON medication (regular dose of levodopa 1h prior to testing). We compared the effect of levodopa on the neural activation patterns underlying the execution of both more affected and less affected hand for SI and ET movements. Our results show that there were significant increases in activity after levodopa administration in regions of the motor cortico-striatal network when patients perform SI and ET movements with their left hand. When patients use their right hand, significant increases were observed between ON and OFF, only in the cerebellum during SI movements. As our patients were mainly affected more severely on their left side, levodopa may help provide additional dopaminergic input for left hand movements perhaps because it was more affected in this sample. These results suggest that the impact of reduced dopamine in the cortico-striatal system and the action of levodopa treatment is not symmetrical in the treatment of PD symptoms.

Introduction

PD is a neurodegenerative illness whose cardinal symptoms are rigidity, tremor and bradykinesia. Symptoms often manifest more severely on one side of the body, and this lateralization persists throughout the duration of the disease (Hoehn & Yahr, 1967; Djaldetti *et al.*, 2006). It has been suggested that symptoms begin (and remain more pronounced) more frequently on the dominant side of the body (Uitti *et al.*, 2005; Yust-Katz *et al.*, 2008; van der Hoorn *et al.*, 2011). The underlying physiological and functional cerebral substrates of disease asymmetry in PD are not well understood. Importantly, the interaction of levodopa with the hand being used and symptom asymmetry has yet to be fully understood. Here we used SI and ET movements during fMRI to investigate the effect of levodopa on the neural patterns underlying movements of asymmetrically affected dominant and non-dominant hands.

The involvement of cortical regions and the basal ganglia in movement has long been documented (Deecke *et al.*, 1969; Romo *et al.*, 1992; Schultz & Romo, 1992; Jenkins *et al.*, 2000). For right-handed individuals, movements of the left hand lead to greater increases in activity in motor areas than right hand movements (Mattay *et al.*, 1998), and cortical, subcortical and cerebellar task-related activity has been shown to decrease with automaticity (Wu *et al.*, 2004). Although patients with PD can also reach movement automaticity, they show greater increases in cortical and cerebellar activity than healthy controls when doing so (Wu & Hallett, 2005). We have previously shown that regions implicated in the motor cortico-striatal circuit (putamen, thalamus and PMC) are involved in both SI and ET movements (Francois-Brosseau *et al.*, 2009; Martinu *et al.*, 2012). More specifically, in young healthy adults, we have shown that activity of the putamen increases during repetitive control, ET and SI movements performed with the right hand. When using the non-dominant (left hand), however, activity of the putamen plateaued for both ET and SI movements. We suggested that the gradual involvement of the putamen during right hand movements is masked by the lack of proficiency of the non-dominant hand (Francois-Brosseau *et al.*, 2009).

When dopamine levels are deficient, such as in PD, dopamine replacement therapy such as levodopa and apomorphine can restore motor-related activity (Jenkins *et al.*, 1992; Haslinger *et al.*, 2001; Feigin *et al.*, 2002). We have previously shown that the effect of levodopa in PD leads to an increase in activity in the putamen whether movements are SI or ET performed with the dominant hand in right-handed PD patients (Martinu *et al.*, 2012). We did not, however, investigate the effect of levodopa on the neural patterns linked to the non-dominant hand.

The goal of the present study was to examine the effect of levodopa on the neural activation patterns underlying asymmetrically affected left and right hand movements. We hypothesized that levodopa may lead to an increase in activity in the motor cortico-striatal network during more affected-side hand movements. Consistent with our previous work, we further hypothesized that this effect would be equivalent for both SI and ET movements (i.e., not task-specific). In right-handed patients with more pronounced symptoms on the non-dominant side, this would imply that levodopa might selectively act on movements of the

left hand, perhaps compensating for symptom severity. Understanding the interaction between levodopa and disease asymmetry would allow for new perspectives on levodopa mechanisms and subsequent research and treatment of asymmetrical symptoms.

Methods

Participants

Informed consent was obtained from all participants. The protocol was approved by the Joint Ethics Committee of the "Regroupement Neuroimagerie Quebec (RNQ)", following the guidelines of the Tri-Council Policy Statement of Canada, the Civil Code of Quebec, the Declaration of Helsinki and the code of Nuremberg.

Twelve right-handed patients diagnosed with PD [mean age 62.89±6.70 (SD), 6 women] participated (Table 1). All PD participants met the UK brain bank criteria (Hughes *et al.*, 1992) for the diagnosis of idiopathic PD. Motor disability of patients with PD was mild to moderate severity, according to the Hoehn and Yahr staging criteria (Hoehn & Yahr, 1967). Patients presenting any other neurological or psychiatric disorder were excluded. Handedness was assessed with the Edinburgh Handedness Inventory (mean 91.57±14.47), early signs of dementia were assessed using the MoCA (Nasreddine *et al.*, 2005) (mean OFF 27.55±1.51, ON 26.92±1.88), and symptoms of depression in all participants was measured using the BDI-II (mean 12.58±11.74). At each session, the motor symptoms were measured with the UPDRS-III (OFF: 31.17±4.87 and ON: 23.42±6.95, score out of 156; the UPRDS form used for these evaluations is included in Appendix III). Left and right subsections were separated to give left and right UPDRS scores (average OFF: 10.9L/9.9R and ON: 9.0L/7.0R). In addition to levodopa, some patients also regularly took other anti-parkinsonian drugs such as COMT inhibitors (n=5), MAO-B inhibitors (n=6), dopamine agonists (n=3) and others (n=3). Patients remained off these other medications for both the ON and OFF sessions.

Procedure

All patients came for two counterbalanced scanning sessions (one OFF medication, one ON levodopa), and were asked to withdraw from all anti-parkinsonian medications for a minimum of 12 hours prior to each appointment. Participants remained off medications for the OFF session. For the ON session, participants took their usual dose of levodopa 1 hour prior to the beginning of MRI acquisitions. All participants practiced three blocks of the finger-movement task (for a total of 9 repetitions of each condition) prior to the scanning session to ensure they were comfortable performing it in the scanner.

Task

Participants performed SI, ET and CTL finger movements using left and right hands separately during functional MRI acquisitions in a pseudo-randomised order across runs, in both ON and OFF conditions. This task was identical to that previously described (Martinu *et al.*, 2012). Each block began with written instructions, displayed for 2.5s, followed by the appearance of five squares oriented in a horizontal row on the screen, each corresponding to a button on the response box. Participants used all fingers except for the little finger (where 1 was the thumb and 4, the ring finger); the square corresponding to the little finger was displayed for hand positioning, but remained inactive. The squares displayed on the screen turned green to indicate when a particular button should be pressed, and turned yellow for the duration of the button press. In the control condition, participants were instructed to repeatedly press a single button chosen at random for the duration of the block. In the ET condition, participants followed a randomly generated sequence. Finally, in the SI condition, participants generated their own sequences of finger movements. Participants were instructed to avoid pressing the same button consecutively in the SI task (this was considered an error), and to refrain from automatic (e.g., 1-2-3-4 or 4-3-2-1) or repeated sequences. For all tasks, participants were instructed to keep a comfortable, regular pace. Task conditions alternated at random after 20 button presses. An incorrect selection resulted in an error, and the corresponding square turned red to provide feedback.

fMRI

Data acquisition. Participants were scanned using a 3T Siemens TIM Trio MRI scanner at the Functional Neuroimaging Unit (UNF) of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM). Each scanning session (ON and OFF) comprised a T1-weighted three-dimensional volume acquisition (voxel size $1mm^3$) for anatomical localization, followed by four T2*-weighted functional echoplanar acquisitions with BOLD contrast. Each run consisted of 146 frames of 43 slices (matrix size 128x128, voxel size 2.34 x 2.34 x 3mm) acquired at a repetition time of 3.5 seconds.

Data analysis. Data analysis was performed using fmristat software and minctools (Worsley *et al.*, 2002) using a similar analysis strategy to our previous studies (Francois-Brosseau *et al.*, 2009; Martinu *et al.*, 2012), and was based on a linear model with correlated errors. After discarding the first three frames, all images were realigned to the fourth frame for motion correction and smoothed using a 6 mm full width half-maximum (FWHM) isotropic Gaussian kernel. The design matrix of the linear model was first convolved with a difference of two gamma hemodynamic response functions timed to coincide with the acquisition of each slice. The linear model was then re-estimated using least squares to produce estimates of effects and their standard errors. The resulting effect and standard effect images as well as anatomical images were spatially normalized using the ICBM152 atlas (Collins *et al.*, 1994; Zijdenbos *et al.*, 2002). In a second step, runs and subjects were analyzed using a mixed-effects linear model. A random-effects analysis was performed by first estimating the ratio of the random-effects variance to the fixed-effects variance, and then regularizing this ratio using spatial smoothing with a Gaussian filter. The amount of smoothing was chosen to achieve 100 effective degrees of freedom (Worsley, 2005). Within-session analyses (SI vs. CTL, ET vs. CTL, SI vs. ET) were performed by direct comparison using the effects and standard deviation images; all peaks at a significance of $p < 0.05$ corrected and $p < 0.001$ uncorrected (marked by an asterisk) are reported in the supplemental material. Between-session analyses (ON vs. OFF) were performed by direct comparisons using the effects and standard deviations images of all participants in both

drug conditions. All peaks at a significance of $p < 0.001$ uncorrected with a cluster size > $100mm^3$ are reported in tables VIII and IX.

Results

Clinical scores:

There was no significant effect of session order and no statistical differences between MoCA scores ON and OFF. There were no significant correlations between MoCA or BDI-II scores and behavioral performance during the finger-movement task. Patients had significantly lower UPDRS scores ON than OFF ($p = 0.005$). Only one patient was more affected on the right side of the body, the other 11 patients were either left side asymmetrical or approximately even (Table VI). Levodopa did not affect symptom asymmetry.

Behavioral performance during scanning:

Reaction times. The mean reaction times for SI, ET and CTL tasks ON and OFF for the left and right hand are reported in Table VII. A 3-way repeated measures ANOVA comparing drug condition (ON/OFF), hand (left/right) and task (SI/ET/CTL) revealed a 3-way interaction ($p = 0.034$). A paired-sample t-test analysis showed that there were no statistical differences between ON and OFF sessions for either task (SI, ET or CTL movements) for the left or right hands. Patients ON medication had significantly longer reaction times for the left hand compared with the right hand in the CTL task ($p = 0.017$).

Errors. The percentages of errors in SI, ET and CTL tasks ON and OFF for the left and right hands are reported in Table VII. A 3-way repeated measures ANOVA comparing drug condition, hand and task revealed an effect of task ($p = 0.018$) with more errors in the ET condition, but no effect of drug condition, hand or any significant interactions.

fMRI results:

SI movements. When comparing patients ON and OFF levodopa administration (ON – OFF) for the SI vs. CTL subtraction (Figure 23, Table VIII), patients showed significantly increased activity in the right anterior prefrontal cortex (aPFC), left PMC, bilateral motor cortex, left superior temporal gyrus (STG) and anterior cingulate cortex in the ON condition when using the left hand. Significant subcortical increases in activity were also observed in the left putamen, bilateral thalamus and right cerebellum. For the right hand, patients ON showed significantly increased activity the right cerebellum only. Compared with the ON condition (OFF – ON), patients OFF showed significantly greater activity than ON only in the left aPFC when using the right hand. Within-session results for SI movements are reported in the supplemental material.

ET movements. For the ET vs. CTL contrast, patients ON showed significantly greater activity than OFF in the left PMC, bilateral motor cortex and SMA, left STG and PPC, left putamen and right thalamus when using their left hand (Figure 23, Table IX). No significant activations were observed when using the right hand. Compared to the ON condition (OFF – ON contrast), patients OFF had significant increases in activity in the left aPFC and motor cortex when using their right hand, and no significant differences in activity for the left hand. All significant within-session peaks for ET movements are reported in the supplemental material.

Discussion

The goal of this study was to examine the effect of levodopa on the neural patterns underlying asymmetrically affected dominant and non-dominant hand movements in patients with PD. To our knowledge, this is the first direct evaluation of the impact of levodopa administration on behavioral and cerebral laterality. We found that regions involved in the motor cortico-striatal network (motor and pre-motor cortex, SMA, putamen and thalamus) and the cerebellum showed significant increases in activity ON vs. OFF

when participants used their left hand (Figure 23). In contrast, only the cerebellum showed significant differences ON vs. OFF when participants used their right hand. Our results suggest that levodopa does not affect brain activity symmetrically, but rather that it has a greater effect on the more affected non-dominant side. Although literature suggests that PD patients tend to be more affected on their dominant side (Uitti *et al.*, 2005; Yust-Katz *et al.*, 2008; van der Hoorn *et al.*, 2011), the patients that participated in this study were mainly affected on the left non-dominant side of the body. There are two possible interpretations that are not necessarily mutually exclusive. First, as non-dominant hand movements are less automatic than dominant hand movements (Mattay *et al.*, 1998), levodopa may provide additional resources necessary to execute the less automatic left hand movements. Alternatively, levodopa may have a stronger effect on left hand movements because it was the most affected side in our patient cohort.

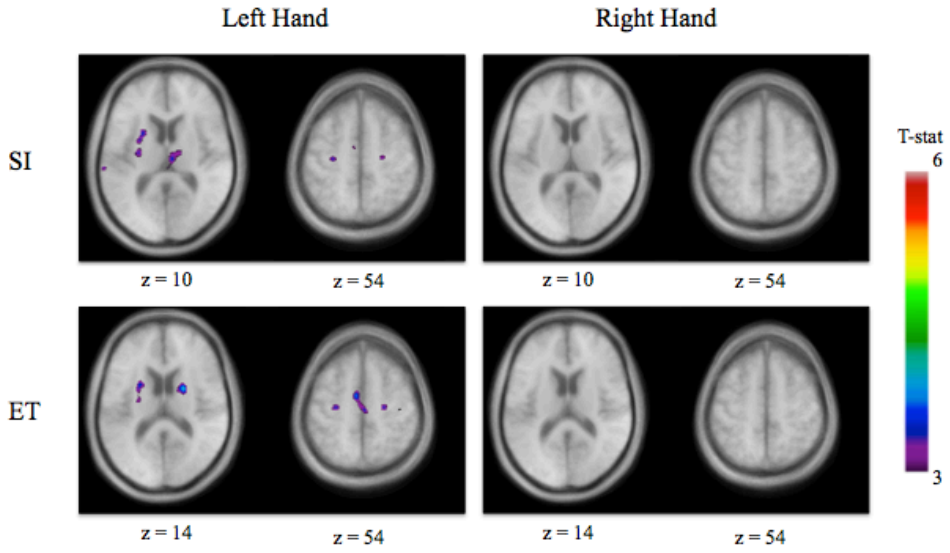

Figure 23: Location of peaks for SI – CTL (top) and ET – CTL (bottom) movements for sessions ON vs. OFF

Anatomical images shown are the average of the T1 acquisitions of all patients transformed into stereotaxic space. The functional peaks are shown for t-stat values between 3 and 6.

Levodopa has been shown to have an effect on the amplitude of the BOLD signal as well as a "focusing effect" of the spatial distribution of activity (Ng *et al.*, 2010). The

authors suggested that levodopa would help normalize the spatial distribution of activity observed in PD patients to that of control participants, possibly through an increase in signal-to-noise ratio by dopamine (Winterer, 2006). In relation with this focusing theory, we speculate that dopamine facilitates the activation of brain regions necessary for the generation of movements with the non-dominant or more affected limb. Asymmetrical effects after levodopa administration have been previously observed by PET at rest; Feigin *et al.* (2001) showed that levodopa decreased the PDRP of brain metabolism by suppressing metabolic activity in the left motor cortex, putamen, right thalamus, and bilateral cerebellum. Laterality effects were partially attributed to low statistical power, but the authors speculated that the least affected side might have preferentially responded to levodopa because the nigrostriatal dopaminergic terminals of that side were less degenerated. The discrepancy between this study and our results likely stems from the comparison between the effect of levodopa on brain metabolism at rest and during the performance of a motor task. Another group recently investigated the effect of a single dose of levodopa on a unimanual and bimanual grip task during fMRI in PD patients and healthy controls (Kraft *et al.*, 2009). Levodopa significantly increased activity in the thalamus and putamen during bimanual movements. Although left side movements additionally recruited the ventrolateral thalamus, no significant differences between ON and OFF conditions were observed between the two hands. Although gripping movements may solicit different neural processes, these results strongly suggest that the effect of levodopa on dominant and non-dominant hand movements is not symmetrical.

Asymmetrical degeneration of dopaminergic neurons in the substantia nigra underlies symptom asymmetry in PD (Kempster *et al.*, 1989). It has been shown that the lateral ventricle contralateral to the more symptomatic side is enlarged in PD patients with asymmetrical symptoms (Lewis *et al.*, 2009), and cognitive disruption often is consistent with the symptomatic hemisphere (Verreyt *et al.*, 2011). For example, left motor dysfunction and a smaller substantia nigra volume have been shown to be associated with poorer spatial memory (Foster *et al.*, 2008). Furthermore, responses to levodopa have been shown to vary throughout the course of the disease. More specifically, responses tend to be mild and long-lasting in the early stages of PD, followed by greater responses with shorter

duration times in the later stages, and ending in abrupt on and off switches (Duvoisin, 1989). This can be further applied to the asymmetry of the disease between the two hemispheres; asymmetrically affected hemispheres represent different stages of the disease, suggesting that the response to levodopa on the left and right sides of the body will vary depending on the patients' asymmetry. Using four different tapping tasks, one study demonstrated that the more affected side showed reduced response latency, greater magnitude of improvement and shorter response duration to an infusion of levodopa (Rodriguez *et al.*, 1994). In addition, another study showed the more affected side to have a delayed response onset after oral levodopa administration (Kumar *et al.*, 2003). Based on the timing of our fMRI acquisitions (1h after levodopa administration), it is possible that the effect observed between ON and OFF is related to the differences in levodopa response of the more and less affected hemispheres. Taken together, the asymmetrical effect of levodopa observed in our study could reflect the different disease stages between the two hemispheres.

Because most patients in our protocol are more severely affected on their non-dominant side, asymmetrical effects of levodopa could also be due to hand proficiency. Using SI, ET and control movements in a study with young healthy right-handed participants, we have shown that non-dominant (left hand) movements recruit the putamen to a greater extent than right hand movements, suggesting that greater recruitment is necessary to compensate for a lack of automaticity (Francois-Brosseau *et al.*, 2009). Based on these previous results, we proposed that in healthy individuals, the increase in putamen activity reached a plateau when using the left non-dominant hand, whereas gradual increases in activity could be observed from control to ET to SI movements when using the right hand. In patients with PD performing the same tasks with their right hand only, we have previously shown that differences in putamen activity between control, ET and SI tasks were reduced compared with older healthy controls, and that levodopa led to non-task-specific increases in cortico-striatal activity (Martinu *et al.*, 2012). This was in accordance with a study investigating arm-reaching movements during PET imaging that showed that levodopa increased motor task-related activity (Feigin *et al.*, 2002). Taken together, the significant differences in activity observed when patients use their left hand could also

suggest that levodopa increases cortical and subcortical activity in the left hand condition due an increase in difficulty when using the non-dominant hand.

Although we cannot conclusively attribute the effect of levodopa to the hand used and/or disease asymmetry, the fact that levodopa has different effects on movements of the left and right hand has important implications for understanding the mechanisms underlying levodopa function and the treatment of asymmetrical PD symptoms. Follow-up studies with a full cross-over design including left- and right-handed patients with left- and right-asymmetry will be necessary to further disentangle the relationship between levodopa's effect on movements as a factor of handedness and symptom and cerebral lateralization.

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Table VI: Demographics for the twelve patients with PD

Patient	Gender	Age	Dur.	Meds	BDI-II	Hand	MoCA (On/Off)	UPDRS scores Total (On/Off)	Left/Right (On)	Left/Right (Off)
1	F	69	2	1, 2	0	100	27/27	33.5/39.5	14/15	13/15
2	F	51	5	1, 4	12	58	27/27	18.5/31	7.5/5	11.5/7
3	M	67	2	1, 3	6	68.5	24/27	26/29	10/5.5	10.5/8
4	M	69	9	1, 4, 5	27	89	28/25	23/34.5	7/7.5	11/10.5
5	M	58	2	1, 2, 3	16	100	26/30	16.5/21.5	7/3.5	9/5
6	M	54	5	1, 2, 3,	6	83.3	30/30	25.5/36	12/6.5	16.5/11.5
7	M	68	3	1	6	100	27/28	26.5/27.5	9/8.5	9/7
8	F	62	5	1, 3, 4	12	100	29/28	19.5/31.5	8/5	14/10.5
9	F	68	11	1, 3, 5	15	100	26/27	25/31.5	8/7.5	9.5/10.5
10	F	68	1	1, 2	42	100	24/-	21.5/27	5.5/11.5	4.5/14
11	F	65	1	1, 2	3	100	29/26	26/36	13/6.5	13/11
12	M	55	2	1, 3	6	100	26/28	12.5/29	7.5/2	9.5/8.5
Mean		62.8	4		12.6	91.5	26.9/27.5	23.42/31.17	9.0/7.0	10.9/9.9
SD		6.6	3.2		11.7	14.5	1.9/1.5	6.9/4.9	2.6/3.5	3.1/2.9

Dur., years since illness onset; Med., parkinsonian medication (1, levodopa; 2, COMT inhibitor; 3, MAO-B inhibitor; 4, dopamine agonist; 5, other).

Table VII: Mean reaction times (SD) and percent errors for SI, ET and CTL movements for left and right hand movements of patients OFF and ON medication

		Mean RT (SD) in ms			Errors (%)		
		SI	ET	CTL	SI	ET	CTL
OFF	LH	845 (122)	1107 (220)	713 (122)	3.38	8.78	0.64
	RH	842 (168)	1106 (303)	717 (118)	2.87	8.92	0.76
ON	LH	872 (116)	1138 (136)	787 (133)	2.62	8.16	1.55
	RH	870 (150)	1149 (171)	746 (168)	2.55	10.96	1.48

Table VIII: Activation peaks between patients ON and OFF performing SI compared with CTL movements

		Left hand						Right hand				
Anatomical area	BA	R/L	x	y	z	t	cluster	x	y	z	t	cl.
ON > OFF												
aPFC	46/10	R	44	48	16	3.50	104	-	-	-	-	-
PMC	6	L	-56	2	40	4.00	432	-	-	-	-	-
Motor	6	L	-28	-18	54	3.52	112	-	-	-	-	-
		R	24	-14	72	3.76	232	-	-	-	-	-
STG	42	L	-64	-28	12	3.44	104	-	-	-	-	-
Cingulate	32	L	-14	10	36	3.55	128	-	-	-	-	-
		R	16	12	36	3.97	152	-	-	-	-	-
Putamen		L	-24	10	10	3.57	312	-	-	-	-	-
			-28	-18	4	3.83	752	-	-	-	-	-
Thalamus		L	-18	-18	-4	3.60	112	-	-	-	-	-
		R	6	-18	10	3.52	448	-	-	-	-	-
Cerebellum		R	40	-78	-28	4.01	392	30	-54	-58	4.54	304
OFF > ON												
aPFC	10	L	-	-	-	-	-	-12	48	16	3.71	112

The coordinates (x,y,z) in standard Montreal Neurological Institute stereotaxic space for all significant activation peaks for SI compared with CTL movements. Cluster sizes are in mm^3. BA, Brodmann area; R/L, right/left; aPFC, anterior prefrontal cortex; PMC, pre-motor cortex; STG, superior temporal gyrus.

Table IX: Activation peaks between patients ON and OFF performing ET compared with CTL movements

			Left hand					Right hand				
Anatomical area	BA	R/L	x	y	z	t	cluster	x	y	z	t	cluster
ON > OFF												
PMC	6	L	-58	4	32	3.58	128	-	-	-	-	-
Motor	6	L	-28	-18	54	3.59	248	-	-	-	-	-
		R	24	-18	54	3.55	128	-	-	-	-	-
SMA	6	L	-6	-6	54	3.82	928	-	-	-	-	-
		R	4	-22	52	3.74	928	-	-	-	-	-
STG	42	L	-64	-28	10	3.76	104	-	-	-	-	-
PPC	40	L	-46	-44	46	3.57	112	-	-	-	-	-
Putamen		L	-24	6	12	3.59	264	-	-	-	-	-
Thalamus		R	8	-14	8	3.80	312	-	-	-	-	-
OFF > ON												
aPFC	10	L	-	-	-	-	-	-12	50	16	3.70	168
Motor	6	L	-	-	-	-	-	-20	-8	68	4.58	312

The coordinates (x,y,z) in standard Montreal Neurological Institute stereotaxic space for all significant activation peaks for SI compared with CTL movements. Cluster sizes are in mm^3. BA, Brodmann area; R/L, right/left; PMC, pre-motor cortex; SMA, supplementary motor area; STG, superior temporal gyrus; PPC: posterior parietal cortex; aPFC: anterior prefrontal cortex.

Chapter 5: Discussion

In this thesis, we have described the effect of levodopa on the patterns of brain activity during SI and ET movements of the left and right hands. Globally, our results imply that (1) the effect of levodopa on the putamen's activity does not seem specific to SI and ET movements, (2) patterns of hyper-activity observed in PD patients are not improved by levodopa, and may rather be related to long-term levodopa treatment (3) that levodopa has different effects on left and right hand movements, related to hand proficiency and/or disease asymmetry, and we have argued that (4) the increases in activity often observed in the cerebellum of PD patients using neuroimaging techniques cannot be conclusively attributed to compensatory mechanisms. These results have important implications for the treatment of PD; they suggest that although levodopa has unquestionable benefits for motor symptoms, reflected by the improvement of UPDRS scores and its effect on the activity of regions involved in the motor cortico-striatal circuit, it has no beneficial effect on cognitive processes. Levodopa may in fact even promote unwanted increases in activity in regions such as the VLPFC and the cerebellum, contributing to the eventual development of side effects such as dyskinesias.

Several topics warrant further discussion. The first is a discrepancy between the cortico-striatal and cortico-cerebellar involvement in SI and ET movements in our protocols; one model in particular suggests that the processes underlying SI and ET movements are more separate. Secondly, we have investigated whether there are any correlations between cerebral activity and performance. We are also in the process of performing additional analyses, such as the functional connectivity between regions of the cortico-striatal and cortico-cerebellar circuits. We will finally present some drawbacks to the protocols described in this thesis, as well as different avenues for future research.

First of all, there is a discrepancy with some models of basal ganglia and cerebellar activity in SI and ET movements, mainly due to the differences between tasks. One study in particular examined internally guided and externally guided movements performed by a set of twins discrepant for PD (Lewis *et al.*, 2007). The proposed model for the involvement of the basal ganglia and cerebellum in their internally guided and externally guided tasks differs significantly from our observations. More specifically, the authors suggest that

externally guided movements are primarily controlled by the cerebellar circuits, whereas internally guided movements are mainly controlled by the cortico-striatal circuits. Changes in activity in selected regions of interest (ROIs) suggest that the PD-affected twin is mainly impaired on the internally guided task. In contrast, we have shown that the basal ganglia, more specifically the putamen, are involved in both SI and ET movements, although the involvement is more substantial for SI movements. In our protocols, patients with PD show significant cortico-striatal decreases in activity during both SI and ET tasks. It is important to note, however, the differences in the tasks being performed. In our protocol, the SI and ET properties apply to every individual button press. This means that during the ET task, each button is pressed according to the display, one by one. The SI task is a pseudo-random set of button-presses chosen by the participant, again one by one. On the other hand, the IG and EG tasks used in Lewis *et al.* are a sequence of a series of four finger-to-thumb movements and wrist opening and closing, and it is the start of this sequence that is cued either internally or externally. Another important consideration is the contrast used during analyses. Whereas we compared SI and ET movements to a repetitive button-repeat control task, the IG and EG movements described are compared to rest. In general, then, although our results seem to be in contradiction, the discrepancies can be explained by a difference in task. Nonetheless, if the task suggested by Lewis *et al.* can truly dissociate between cortico-striatal and cortico-cerebellar circuits, it provides potential an additional framework that could be used with TMS, as suggested in chapter 2, to test whether activity in the cerebellum is compensatory or pathophysiological.

We have performed additional analyses correlating the brain activity patterns during SI and ET movements of the left and right hand with reaction times as a correlate; these analyses have not been included in the articles because results did not lead to any consistent findings. Although speed was not the purpose of our task, there were no significant differences in reaction times between patients ON and OFF. Additionally, there was no evidence that the VLPFC/insula region would consistently correlate positively or negatively with reaction times. Only when patients OFF medication performed SI movements with their left hand was there a small cluster with a peak of $t = 2.8$ in the right VLPFC (Figure 24). One possible analysis that would address this issue more specifically would be to select

a ROI that encompasses the peaks observed in chapter 3, and correlate the BOLD activity of this ROI not only with performance on the three tasks, but the number of errors as well. The number of errors performed overall was not high enough to give significant results on a whole-brain analysis, but could lead to interesting results when focusing on a single ROI such as the VLPFC/insula. The lack of consistent significant correlation between reaction times and cerebral activity before and after drug administration argues against the compensatory roles of regions such as the VLPFC and the cerebellum in our protocol.

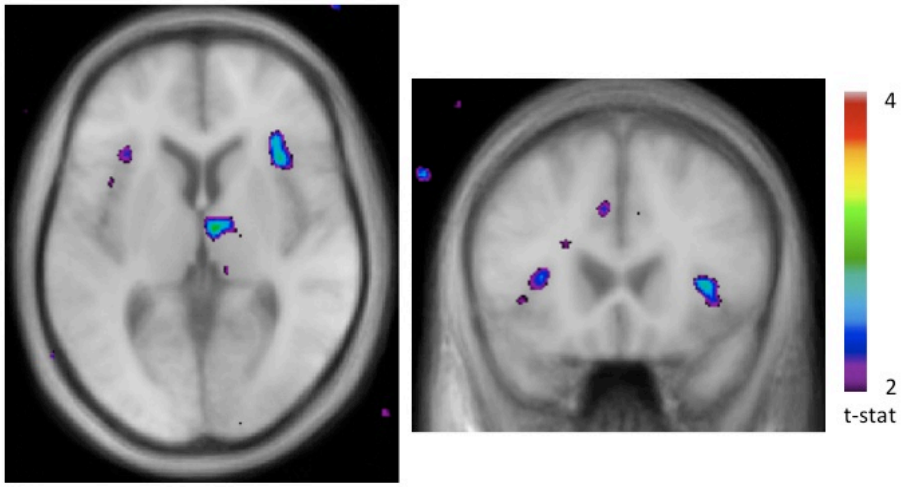

Figure 24: fMRI BOLD activity correlating with performance in patients OFF medication performing SI vs. CTL movements

Other methods than the comparisons of BOLD signal amplitudes could provide additional information. First, one could have also looked at the differences in spatial extent of activity between healthy participants and patients, but also between patients on and off levodopa. For example, Ng *et al.* (2009) have described changes in spatial variance after levodopa administration, suggesting that levodopa has a focusing effect on cerebral activity. Other types of methods include analyses of the changes in connectivity between regions. We are currently running a functional connectivity analysis using the putamen and the cerebellum as seeds. We are hoping that, along with the knowledge of anatomical connections between the cortico-striatal and cortico-cerebellar circuits, we can show strong functional connectivity between the cerebellum and regions of the motor cortico-striatal circuit. Firstly, we expect decreases in connectivity between regions of the cortico-striatal

and cortico-cerebellar loops in patients with PD compared with control participants. The main question, however, revolves around the effect of levodopa on this connectivity. Would levodopa help re-establish the functional connectivity between regions of the cortico-striatal and cortico-cerebellar loop, or will it have no effect? Using structural equation modeling and multivariate autoregressive modeling, Palmer *et al.* (2009b) suggest that levodopa would at least partially restore some effective connectivity and temporal patterns in PD.

One of the major drawbacks of the studies presented here is the limited sample size. We would have ideally recruited an additional 12 to 14 patients with a more equilibrated symptom lateralization (i.e. about half the patients with left and half with right side asymmetry) to be able to draw proper conclusions from the left vs. right study (chapter 4). A larger sample size could have allowed us to properly dissociate between hand proficiency and the effect of disease asymmetry. More specifically, four distinct groups of right-handed and left-handed patients affected on the left and right side would be ideal to fully dissociate hand proficiency from disease asymmetry. A sample of *de novo* patients would also allow the distinction between actual disease pathophysiology, and changes related to the long-term use of dopaminergic medication. Another limitation of our studies and patient-oriented fMRI studies in general is the comparison of populations with possibly quite different hemodynamic properties. Dopamine receptors, for example, play different roles in cerebral vasculature; whereas D1-like receptors elicit vasodilation and hyperperfusion, D2-like receptors lead to vasoconstriction and hypoperfusion (Choi *et al.*, 2006). Using arterial spin labeling (ASL), Fernandez-Seara *et al.* (2012) have shown that PD is characterized by cortical hypoperfusion. This is consistent with the global decrease in BOLD amplitude and cluster sizes in patients with PD reported in chapter 3. Levodopa also seems to have effects on the cardiovascular system that could lead to changes in CBF as well as blood-brain barrier permeability (Ohlin *et al.*, 2012). Looking at cerebral vasoreactivity in PD, however, Krainik *et al.* (2012) suggest that there are no major hemodynamic differences between patients with PD before and after levodopa.

Several avenues of future research can be explored based on the projects described in this thesis. First, it would be interesting to disentangle the pathophysiological and compensatory roles of the cerebellum. For this, as briefly mentioned in chapter 2, one could

stimulate the cerebellum with excitatory and inhibitory TBS sequences before participants perform tasks that are known to specifically involve the basal ganglia and the cerebellum. With the motor learning model described by Doyon *et al.* (2003, 2009), if patients with PD have reached a sufficient level of performance, sequence learning tasks will selectively recruit the basal ganglia, whereas motor adaptation tasks will selectively recruit the cerebellum. If the cerebellum has a strong compensatory role, patients with PD would become impaired on sequence learning tasks after inhibitory TBS stimulation of the cerebellum. It must be noted that the cerebellum does not function uniformly; pathophysiology and compensation are most likely working together, and different regions of the cerebellum may have different roles to play in each of these. Second, another idea would be to further explore the relationship between levodopa, handedness and disease asymmetry. Although many studies suggest that there is a tendency for symptoms to develop on the dominant side of the body (Uitti *et al.*, 2005; van der Hoorn *et al.,* 2011; Yust-Katz *et al.*, 2008), results have not proven to be very robust. Ideally, one would recruit a large number of PD patients that are left and right handed, and asymmetrically affected on the right and left side, as mentioned above, to be able to separate them into four groups of a sufficient size. A large dataset would also allow for more powerful correlation analyses between disease asymmetry, brain activity patterns and performance. Finally, adding acquisitions such as resting state BOLD, DTI and ASL would allow a further understanding of the mechanisms involved in PD pathophysiology. Resting state fMRI analyses could shed light on the difference in network activity between healthy participants and patients with PD. DTI would, in turn, allow us to compare white matter integrity of cortico-striatal and cortico-cerebellar circuits in these patients. Arterial spin labeling, finally, would give us information on the differences in cerebral blood flow and metabolism between healthy participants and patients with PD, allowing us to compare more accurately the differences in cerebral activations measured with BOLD fMRI in both populations.

In conclusion, we present results in this thesis that suggest that despite levodopa's clear helpful effect on motor symptoms, it has no beneficial effect on cognitive processes, and that it may instead promote unwanted increases in activity cortical and cerebellar regions, which are possible related to the development of side effects.

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Appendix I

Supplementary material:

Differential effects of levodopa on neural activation patterns underlying movements of right and left hands in Parkinson's disease

Martinu, K., Nagano-Saito, A., Fogel, S., Monchi, O.

Supplementary tables X – XIII list the all statistically significant in intra-session comparisons described in chapter 4. The statistical threshold was set to $p < 0.05$ correcting for multiple comparisons ($t > 4.3$ for a single voxel or a cluster size >550 mm^3). Peaks within the basal ganglia, thalamus, and PFC that were observed in our previous studies (Francois-Brosseau *et al.*, 2009, Martinu *et al.*, 2012) were considered predicted and are reported at a significance of $p < 0.001$ uncorrected [indicated by an asterisk (*)].

Patients OFF.

SI movements. Compared with control movements, when patients OFF performed SI movements (Table X) with their left hand, significant increases in activity were observed in the DLPFC, VLPFC/insula, PMC, motor and sensory cortex, SMA and PPC. Subcortical activations included the right putamen and thalamus, as well as the bilateral cerebellum.
When patients OFF performed SI movements with their right hand, there were significant activations in the DLPFC, VLPFC/insula, PMC, motor cortex, SMA, PPC and visual cortex compared with control movements. Additionally, increases in subcortical regions were observed in the bilateral putamen, left thalamus and bilateral cerebellum.

ET movements. Patients OFF performing ET (Table XI) movements with their left hand showed significant increases in activity in the VLPFC/insula, PMC, motor and sensory cortex, PPC, and visual cortex compared with control movements. Subcortical activations included the right putamen and bilateral cerebellum.

During right hand ET movements, patients OFF medication had significant increases in activity in the VLPFC, PMC, PPC and visual cortex compared to control movements, as well as in the bilateral putamen, thalamus and right cerebellum.

Patients ON:

SI movements. Compared with the control task, when patients ON performed SI movements (Table XII) with their left hand, there were significant increases in activity the bilateral aPFC, DLPFC, VLPFC, cingulate cortex, pPFC, inferior frontal gyrus, PMC, sensory cortex, SMA, PPC and visual cortex. Subcortical activations were additionally observed in the bilateral putamen, thalamus, STN and cerebellum.

When patients ON performed the SI task with their right hand, significant increases in activity were observed in the DLPFC, VLPFC/insula, cingulate gyrus, PMC, motor and sensory cortex, SMA, and PPC compared with the control task. Subcortical activations were observed in the bilateral putamen, thalamus and cerebellum.

ET movements. When patients ON performed ET movements (Table XIII) with their left hand, we observed significant increases in activity in the DLPFC, VLPFC/insula, PMC, SMA, sensory cortex, PPC and visual cortex compared to control movements. Additionally, subcortical activations included the bilateral putamen, thalamus, STN and cerebellum.

When patients ON performed the ET task with their right hand, significant increases in activity were observed in the VLPFC/insula, PMC, motor cortex, SMA, PPC and visual cortex compared with the control task. Subcortical activations included the putamen, thalamus and cerebellum.

Table X: Activation peaks for patients OFF performing SI versus CTL movements

			Left hand					Right hand				
Anatomical area	BA	R/L	x	y	z	t	cluster	x	y	z	t	cluster
DLPFC	9,46	L	-32	32	30	4.37	1248	-32	32	32	3.79	720
		R	34	36	28	4.84	1512	34	34	30	4.89	1000
VLPFC/Insula	47/12,13	L	-36	16	6	5.63	2056	-34	18	4	4.77	1304
		R	32	20	6	4.03	2048	34	20	6	3.49	2352
PMC	6	L	-28	-6	64	4.72	8808	-24	-12	58	5.28	10160
			-22	-4	50	4.99	8808	-	-	-	-	-
			-54	-2	40	3.88	728	-	-	-	-	-
		R	28	-4	58	6.64	38968	28	-4	56	6.01	7528
			52	8	24	5.64	4504	54	8	26	4.42	1888
Motor	4	L	-	-	-	-	-	-38	-18	58	5.09	10160
		R	40	-16	64	5.38	38968	-	-	-	-	-
Sensory	3	L	-58	-18	36	3.84	968	-	-	-	-	-
	2	R	56	-18	30	5.69	38968	-	-	-	-	-
SMA	6	L	-6	0	48	4.21	8808	-6	-2	50	4.09	1776
		R	6	-2	48	4.09	664	-	-	-	-	-
PPC	40	L	-42	-38	36	4.55	9576	-42	-32	38	4.95	16616
		R	48	-32	48	6.04	38968	48	-34	44	6.64	13792
			38	-44	48	6.43	38968					
PPC	7	L	-22	-64	60	6.50	9576	-20	-64	60	6.40	16616
			-34	-48	52	4.52	9576	-36	-52	58	4.65	16616
		R	20	-66	60	5.36	38968	20	-68	60	5.39	13792
			26	-58	52	4.82	38968	-	-	-	-	-
Visual	19	R	-	-	-	-	-	32	-80	10	3.77	560
	18	R	-	-	-	-	-	-12	-86	-10	4.70	760
Putamen		L	-	-	-	-	-	-22	4	10	5.56	4936
		R	24	4	6	5.00	2048	24	2	8	4.52	2352
Thalamus		L	-	-	-	-	-	-16	-14	4	4.40	4936
		R	12	-14	2	3.60*	248	-	-	-	-	-
Cerebellum		L	-28	-48	-24	4.70	5168	-30	-68	-22	4.08	920
			-26	-64	-50	4.86	2320	-	-	-	-	-
			-30	-44	-50	4.05	1048	-	-	-	-	-
			-6	-58	-16	3.98	5168	-	-	-	-	-
		R	8	-56	-10	4.00	5168	14	-70	-18	4.16	5232
			30	-54	-26	3.96	1672	30	-54	-26	5.18	5232
			28	-48	-54	4.69	992	-	-	-	-	-

The coordinates (x,y,z) in standard Montreal Neurological Institute stereotaxic space for all significant activation peaks for SI compared with CTL movements. Cluster sizes are in mm3. Sc indicates that the peak is part of the same cluster as the peak listed immediately above it. The following abbreviations are used for Tables 1 – 4.

BA, Brodmann area; R/L, right/left; aPFC, anterior prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; pPFC, posterior prefrontal cortex; IFG, inferior frontal gyrus; PMC, pre-motor cortex; SMA, supplementary motor area; PPC, posterior parietal cortex.

Table XI: Activation peaks for patients OFF performing ET versus CTL movements

			Left hand					Right hand				
Anatomical area	BA	R/L	x	y	z	t	cluster	x	y	z	t	cluster
VLPFC/Insula	47/12,13	L	-36	16	6	4.57	912	-34	18	6	4.37	640
		R	32	20	6	4.16	504	-	-	-	-	-
PMC	6	L	-54	0	42	4.48	1512	-50	-2	42	4.23	968
			-22	-4	50	4.74	2552	-24	-10	54	4.42	4032
		R	28	-4	56	6.48	6184	30	-4	58	5.58	5832
			52	6	34	4.50	3560	50	4	34	4.24	2168
			48	8	22	5.24	3560	44	6	24	4.41	2168
Motor	4	R	40	-16	64	3.81	6184	-	-	-	-	-
Sensory	3	L	-58	-18	36	4.18	824	-	-	-	-	-
		R	48	-22	58	4.14	15624	-	-	-	-	-
	2	R	56	-18	30	4.71	15624	-	-	-	-	-
			-	-	-	-	-	-6	0	50	3.66*	208
PPC	40	L	-36	-38	38	4.35	3032	-42	-34	38	4.77	8264
		R	48	-30	44	5.27	15624	42	-42	56	4.96	9824
			40	-44	56	5.24	15624	-	-	-	-	-
	7	L	-16	-74	54	4.77	2072	-22	-64	60	5.22	8264
			-34	-50	52	3.79	3032	-	-	-	-	-
		R	28	-58	52	5.02	15624	28	-56	50	5.02	9824
Visual	37		-	-	-	-	-	44	-64	-12	4.13	5088
	19	L	-28	-84	-14	4.30	4856	-24	-86	12	4.07	872
		R	34	-84	14	4.48	14032	30	-74	32	3.75	280
			-	-	-	-	-	32	-82	8	4.62	4080
	18	L	-12	-86	-10	4.73	4856	-12	-86	-10	6.00	3424
			-24	-100	6	4.47	4856	-	-	-	-	-
		R	10	-78	-12	4.98	14032	-	-	-	-	-
			26	-94	10	4.50	14032	-	-	-	-	-
	17	R	12	-84	4	3.98	14032	-	-	-	-	-
Putamen			-	-	-	-	-	-22	4	10	3.52	824
		R	24	6	6	4.47	680	24	2	10	3.82	552
Thalamus		L	-	-	-	-	-	-14	-20	12	3.21	824
		R	-	-	-	-	-	14	-12	8	3.29	552
Cerebellum		L	-34	-52	-26	4.27	3208	-	-	-	-	-
			-26	-62	-48	3.92	824	-	-	-	-	-
		R	30	-54	-24	4.06	14032	30	-54	-26	4.48	5088

Abbreviations as in Table X.

Table XII: Activation peaks for patients ON performing SI versus CTL movements

			Left hand					Right hand				
Anatomical area	BA	R/L	x	y	z	t	cluster	x	y	z	t	cluster
aPFC (not A1)	10	L	-	-	-	-	-	-32	52	10	3.84*	144
aPFC	46/10	L	-38	38	20	3.81	3144	-	-	-	-	-
		R	42	48	22	3.79	6328	-	-	-	-	-
DLPFC	9,46	L	-42	32	32	4.72	3144	-42	30	32	4.80	1512
		R	30	36	28	6.40	6328	34	34	32	5.33	2272
VLPFC/Insula	47/12,13	L	-36	16	6	6.65	41128	-34	16	4	5.17	9144
		R	30	20	6	5.23	22096	30	20	4	4.82	6784
Cingulate	32	L	-12	12	38	5.15	82088	-8	10	46	4.83	55440
		R	8	16	38	5.65	82088	-	-	-	-	-
pPFC	44,6	R	58	10	26	6.07	82088	-	-	-	-	-
IFG*?	44	R	50	6	12	4.42	82088	-	-	-	-	-
PMC	6	L	-28	-8	58	6.12	41128	-24	-14	60	5.87	55440
			-54	0	40	6.51	41128	-54	0	42	5.46	1496
		R	26	-4	58	7.03	82088	20	-6	58	6.08	55440
			48	4	34	5.03	82088	52	8	24	5.12	1928
Motor	4	L	-	-	-	-	-	-32	-18	70	5.98	55440
Sensory	2	L	-60	-22	34	5.35	22696	-	-	-	-	-
		R	56	-18	28	5.46	82088	-	-	-	-	-
	3	L	-	-	-	-	-	-42	-18	58	5.81	55440
		R	40	-24	50	7.03	82088	-	-	-	-	-
SMA	6	L	-6	8	48	5.87	82088	-6	-4	54	4.99	55440
			-4	-4	60	4.96	82088	-6	10	48	4.80	55440
		R	8	-4	66	4.29	82088	6	-4	54	4.07	55440
PPC	40	L	-44	-36	40	6.09	22696	-40	-34	52	5.63	55440
			-36	-48	48	5.21	22696	-36	-48	48	5.41	55440
		R	48	-28	46	7.45	82088	48	-30	46	6.45	21280
			36	-44	52	7.50	82088	40	-38	46	6.09	21280
PPC	7	L	-22	-64	60	7.07	22696	-34	-56	62	5.77	55440
			-	-	-	-	-	-22	-66	60	7.27	55440
			-	-	-	-	-	-20	-68	44	5.09	55440
		R	16	-66	50	6.56	82088	18	-70	58	6.93	21280
			-	-	-	-	-	40	-46	60	5.63	21280
Visual	37	R	44	-60	-14	4.62	49984	-	-	-	-	-
			32	-64	-22	4.79	49984	-	-	-	-	-
	18	L	-22	-88	12	4.29	464	-	-	-	-	-
		R	34	-84	4	5.38	49984	32	-84	2	4.23	736
Putamen		L	-24	8	6	6.26	41128	-24	6	6	6.87	9144
			-26	-12	8	5.66	41128	-	-	-	-	-
		R	22	6	6	6.97	22096	22	10	4	6.73	6784
Thalamus		L	-14	-16	10	6.18	41128	-10	-18	0	4.73	9144
		R	14	-16	6	6.67	22096	10	-16	0	5.17	6784
STN		L	-8	-24	-2	4.88	41128	-	-	-	-	-
		R	8	-20	-4	5.49	22096	-	-	-	-	-
Cerebellum		L	-26	-52	-26	6.52	49984	-28	-58	-56	4.17	2392
			-14	-66	-52	4.79	49984	-28	-60	-28	4.36	3048
			-2	-54	-6	5.01	49984	-	-	-	-	-
		R	10	-78	-16	5.12	49984	26	-54	-28	6.77	16392

42	-76	-26	4.60	49984	28	-54	-58	5.81	16392
28	-54	-28	6.91	49984	16	-66	-54	4.34	16392
26	-38	-38	4.18	49984	-	-	-	-	-
26	-52	-58	5.42	49984	-	-	-	-	-

Abbreviations as in Table X.

Table XIII: Activation peaks for patients ON performing ET versus CTL movements

			Left hand					Right hand				
Anatomical area	BA	R/L	x	y	z	t	cluster	x	y	z	t	cluster
DLPFC	9,46	L	-30	34	26	3.76*	360	-	-	-	-	-
		R	30	36	28	5.01	1304	-	-	-	-	-
VLPFC/Insula	47/12,13	L	-34	16	8	5.56	13632	-32	20	6	4.78	768
		R	32	20	8	4.71	1232					
PMC	6	L	-52	0	42	7.25	21280	-52	0	42	5.91	2120
			-26	-8	56	5.82	7424					
		R	58	10	26	4.60	45120	42	2	32	3.86	728
			26	-6	54	6.46	45120	32	-4	58	4.89	3008
			42	2	32	5.52	45120	-	-	-	-	-
Motor	4	L	-	-	-	-	-	-32	-16	72	4.54	2672
SMA	6	L	-6	0	50	5.68	6248	-8	-2	52	4.11	552
Sensory	3	L	-60	-20	36	5.03	21280	-	-	-	-	-
		R	62	-16	34	5.18	45120	-	-	-	-	-
			42	-22	52	5.12	45120	-	-	-	-	-
PPC	40	L	-42	-38	38	5.75	21280	-42	-38	38	4.31	6448
			-36	-50	50	5.00	21280	-34	-50	46	4.34	6448
		R	36	-46	54	7.25	45120	34	-48	54	4.00	3072
			48	-30	48	6.50	45120					
	7	L	-22	-64	60	5.02	21280	-34	-56	62	4.69	6448
			-	-	-	-	-	-22	-66	60	5.39	6448
			-	-	-	-	-	-18	-76	54	4.91	6448
		R	18	-70	58	5.15	45120	20	-70	60	5.11	3072
Visual	19	L	-36	-64	-22	4.53	16152	-	-	-	-	-
		R	26	-72	36	4.31	45120	-	-	-	-	-
	18	L	-24	-88	12	6.05	16152	-	-	-	-	-
			-20	-78	-16	4.62	16152	-	-	-	-	-
		R	34	-84	4	6.39	33856	34	-82	2	5.18	2208
			28	-80	-18	4.75	33856	-	-	-	-	-
	17	L	-10	-92	-12	4.21	16152	-	-	-	-	-
			-6	-86	6	4.15	1184	-	-	-	-	-
		R	12	-82	2	4.95	33856	-	-	-	-	-
Putamen		L	-24	8	8	5.76	13632	-24	6	6	4.34	1392
			-30	-6	2	5.18	13632	-	-	-	-	-
		R	24	2	8	6.05	12304	24	10	4	3.20*	8
			26	2	-4	4.21	12304	-	-	-	-	-
Thalamus		L	-14	-16	4	5.70	13632	-14	-18	0	4.01*	456
		R	14	-14	4	5.30	12304	10	-18	-2	4.22	616
STN		L	-10	-24	-2	4.74	13632	-	-	-	-	-
		R	6	-24	-6	4.71	12304	-	-	-	-	-
Cerebellum		L	-34	-52	-26	4.89	16152	-	-	-	-	-
			-16	-64	-50	4.41	2776	-	-	-	-	-
			-32	-54	-58	4.50	2776	-	-	-	-	-
		R	10	-78	-18	4.78	33856	34	-66	-22	4.28	5736

	28	-52	-26	5.24	33856	26	-54	-30	5.02	5736
	28	-52	-58	5.12	1432	28	-52	-58	5.42	1552

Abbreviations as in Table X.

Appendix II

Basal ganglia and frontal involvement in self-generated and externally triggered finger movements in the dominant and non-dominant hand.

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Abstract

While there are a number of functional neuroimaging studies that have investigated SI and externally generated movements, data comparing directly right and left hands in this context is very scarce. The goal of this study was to further understand the role of the basal ganglia and the PFC in the realm of SI and ET right and left hand movements. Young healthy right-handed adults performed random, follow and repeat conditions of a finger moving task, with their right and left hands, while being scanned with fMRI. Significant activation of the DLPFC was observed when comparing the SI movements with the repeated control and ET movements when using either hand in agreement with its role in monitoring. The caudate nucleus activation was found during SI conditions compared with the control condition when either hand was used, showing that it is particularly involved when a new movement needs to be planned. Significant putamen activation was observed in all within-hand contrasts except for the ET vs. control condition when using the left hand. Furthermore, greater putamen activation was found for the left vs. the right hand during the control condition, but for the right vs. the left hand subtraction for the SI condition. Our results show that the putamen is particularly involved in the execution of non-routine movements, especially if those are SI. Furthermore, we propose that, for right-handed people performing fine movements, as far as putamen involvement in concerned, the lack of proficiency of the non-dominant hand may prevail over other task demands.

Introduction

Many studies have looked into the differences in organization between SI and ET movements. The first studies in humans reporting significant differences between the two were surface electrode experiments that described the involvement of the SMA in SI, or voluntary, movements (Deecke *et al.* 1969). More recent studies, using fMRI, have explored this issue further. For example, Jenkins *et al.* (2000) found that when comparing SI movements to ET ones in a right hand finger extension task, the rostral SMA and its adjacent cingulate cortex, as well as the DLPFC were significantly activated (Jenkins *et al.* 2000). Another study by Cunnington *et al.* (2002) showed that the basal ganglia were only significantly involved in a SI task, and not in the ET task when using their right hand. In accordance with these results, previous lesion studies in monkeys have shown that lesions to the putamen result in a reduced capacity to execute learned movements in the absence of external cues (Nixon and Passingham, 1998). Some of the first studies to investigate the role of the striatum in SI and ET movements were the single cell studies in monkeys perfomed by Romo *et al.,* 1992 and Schultz and Romo, 1992. These studies found cells in both the caudate nucleus and the putamen with activity prior and during the execution of SI movements. Some of these cells fired only for SI movements while others fired for both SI and ET movements (Romo *et al.,* 1992; Schultz and Romo, 1992).

An important distinction, however, must be made between the movements of the right and left hand in humans. Mattay *et al.* (1998) showed that a simple task with the non-dominant hand induces increased ipsilateral cortical activity, comparable to a more complex task with the dominant hand. Although the more complex task was not performed with the non-dominant hand, these results imply that the non-dominant hand recruits more ipsilateral cortical regions because of its lack of automaticity. Furthermore, a study of left hand movements by Taniwaki *et al.* (2003) showed that the basal ganglia-thalamo-motor loop plays a role in the rate control of SI movements, but not of ET movements. Most of these studies, however, examined only one hand, whether dominant or non-dominant, slightly differential tasks with each hand, or the effect of handedness on movement. Data comparing

the same task with the right and left hand directly, with an emphasis on the role of basal ganglia, however, is scarce. In the present fMRI study, right-handed young healthy adults had to perform a new motor task that included a SI random movement condition, an ET condition, and a repeated movement (control) condition with the left and right hands. The goal of this study was to further determine the specific contributions of the putamen, the caudate nucleus, the STN and the PFC during novel movements when using the dominant (right) and non-dominant (left) hands separately. We predicted that the movements of the left hand would be more driven by the cortex, and the movements of the right hand by the striatum. We also predicted that the differences in task difficulty would play a larger role in the use of the right hand compared to the left because movements of the dominant right hand are more automatic.

Materials and Methods

Subjects. Fourteen completely right-handed healthy subjects participated in the experiment (7 males, 7 females; mean age 22.6 ± 0.5 SD years; range, 22-24). All subjects were free of neurological and psychiatric history and gave informed consent to the protocol, which was reviewed and approved by the Joint Ethics Committee of the Regroupement Neuroimagerie Québec (RNQ). Handedness was assessed with the Edinburgh Handedness Inventory.

Tasks. Three different conditions of a finger movement task for each hand were performed during scanning: a SI random movement condition, an ET follow condition, and an ET repeat condition that was used as a control. During the whole task, the participants saw four blue squares, each square corresponding to a button on either the right or left response box; all fingers were used except for the thumbs, with a total of twenty finger presses per condition. Before each condition, instructions appeared on the screen for 2.5 seconds during which the subject was told which hand to use and which condition to perform.
During the control condition, one of the squares would switch colors from blue to green, which would indicate that the corresponding button must be pressed. For the duration of every button-press, the square would turn yellow to show the subject's response, and then

turn green again to illustrate that it is ready to be pressed again. This continued until the subject made twenty successful button-presses. The button to be pressed during the control task was randomly selected by the computer, and remained the same for the duration of the condition. For this task only a minimal response time was set to 300ms between two button presses so that subjects were forced to press continuously, and did not hold the button down. The ET follow condition began in the same manner as the control task, but the button to be pressed changed every time, and no given sequence of four finger presses was repeated within the same block. The subject therefore had to follow the sequence generated randomly by the computer, as one of the blue squares turned green one by one. Every button-press resulted in the corresponding square turning yellow if it was correctly pressed, or red if it was an incorrect selection.

For the SI random condition, all four squares would turn green, and the subject had to generate his/her own sequence of button presses. Once again, as a feedback, the buttons pressed made the green squares turn yellow, after which the next button was ready to be selected. The program insured that no button was pressed twice in a row, and that no repeated sequence or pattern would occur. More specifically, pressing the same button twice in a row (e.g. 2-2) would be an error, indicated by the equivalent square turning red. We also asked the subjects to refrain from using common sequences such as 1-2-3-4 and 4-3-2-1; or to repeat sequences twice in a row such as of 4-2-3-1-4-2-3-1. Such 4-button sequence was registered as an error.

Functional Magnetic Resonance Imaging Scanning. Subjects were scanned using the Siemens Trio 3-Tesla MRI at the Functional Neuroimaging Unit of the CRIUGM. Each scanning session began with a T1-weighted three-dimensional volume acquisition (voxel size, 1x1x1 mm^3) for anatomical localization, followed by six T2*-weighted functional echoplanar acquisitions. Each run consisted of 80 frames with high spatial resolution based on the acquisition parameters used by Lehericy *et al.*, (2005) in order to allow for good subcortical localization. Each frame contained 45 slices (TR = 4000 ms; FA: 90^o; TE: 30ms; partial Fourier imaging 6/8; matrix, 128*128; voxel size, 2x2x2 mm^3).

Data analysis. The methods for data analysis were the same as those used in our previous studies (Monchi *et al.*, 2001, 2004, 2007) and made use of the fmristat software developed by Worsley *et al.* (2002). The first three frames in each run were discarded. Images from each run were first realigned to the fourth frame for motion correction and smoothed using a 6 mm full width half-maximum (FWHM) isotropic Gaussian kernel. The statistical analysis of the fMRI data was based on a linear model with correlated errors. The design matrix of the linear model was first convolved with a difference of two gamma hemodynamic response functions timed to coincide with the acquisition of each slice. The correlation structure was modeled as an autoregressive process. At each voxel, the autocorrelation parameter was estimated from the least squares residuals, after a bias correction for correlation induced by the linear model. The autocorrelation parameter was first regularized by spatial smoothing and was then used to "whiten" the data and the design matrix. The linear model was re-estimated using least squares on the whitened data to produce estimates of effects and their standard errors. The resulting effects and standard effect files were then spatially normalized by nonlinear transformation into the Montreal Neurological Institute (MNI) standard proportional stereotaxic space, which is based on that of Talairach and Tournoux (1988), using the algorithm of Collins *et al.* (1994). Anatomical images were also normalized to the MNI space using the same transformation. In a second step, runs, sessions and subjects were combined using a mixed effects linear model for the data taken from the previous analysis. A random effects analysis was performed by first estimating the ratio of the random effects variance to the fixed effects variance, then regularizing this ratio by spatial smoothing with a Gaussian filter. The amount of smoothing was chosen to achieve 100 effective degrees of freedom (Worsley *et al.*, 2002, 2005). Statistical maps were thresholded at $p<0.05$ corrected for multiple comparisons for all peaks corresponding to a $t> 4.8$ or a cluster size of $> 800mm^3$ and at $p <0.001$ uncorrected for predicted peaks within the basal ganglia (indicated by a * in the tables).

For each hand, the average BOLD signal obtained during the self-generated movement condition was compared with that of the ET condition and the control condition. Also, the ET condition was compared with the control condition, for a total of six contrasts. Furthermore, in order to investigate more precisely the difference between the two hands

the average BOLD contrast of the left hand vs. the right hand, and the right hand vs. the left hand was compared for each of the three conditions, producing another six contrasts.

Results

Behavioural

Reaction times. In the SI condition, right hand response took an average of 504 ms, s.d. 60 ms while left handed movements took 512 ms, s.d. 67 ms, and in the ET movements, the average reaction time was 739 ms, s.d. 40 ms for the right hand and 771 ms, s.d. 78 ms for the left hand. For both conditions, the right hand was significantly faster than the left hand ($p<0.01$). When considering both hands together, reaction times were significantly slower in the ET condition than in the SI condition ($p<0.0001$).

Percentage of Errors. During the SI movements the participants made on average 0.9±0.4% errors with the right-hand and an average of 1.0±0.8% errors with the left one. During the ET condition, participants made an average of 1.8±1.3% errors with the right hand and an average of 2.1±1.1% errors with the left one. There were significantly less errors in the SI than in the ET condition ($p<0.0001$), but the number of errors were not significantly different between the two hands ($p > 0.1$). It should be noted here that, in the ET condition, there is only one selection possible on each trial (the one indicated), while in the SI condition there is more than one possible selection per trial, as long as it is not part of a repetitive sequence. The error rates for both conditions were very low after training (i.e. during the scanning session). Finally, there were no errors in the control condition with either hand.

fMRI

A summary of the major results for the putamen, the caudate nucleus, the STN and the DLPFC is given in Table XX. It should be noted that while high resolution parameters were used for this study (128*128 matrix resolution, voxel size, 2x2x2 mm^3), it may still be

difficult to determine with certainty whether the activations reported below that encompass the STN are actually focused solely in this nucleus. This is partly due to the fact that a standard normalisation technique was used (Nieto-Castanon *et al.,* 2003). However, the coordinates of the activity clusters observed coincided well with the delimitation of the STN in the Talairach and Tournoux atlas and with those reported in previous fMRI studies focusing on this nucleus (Aron and Poldrack 2006; Monchi *et al.,* 2006; Ray *et al.,* 2008).

1. SI movements compared with the control condition

Right hand. Comparison of SI movements with the control condition when using the right hand demonstrated significantly increased bilateral activity in the mid-dorsolateral PFC (area 9, 46, Figure 28), the SMA (area 6), the PMC (area 6), the primary sensory cortex (areas 1, 3), the motor cingulate cortex (area 24), and the PPC (Brodmann area (BA) 7 and 40), while contralateral significant activations were found in the insula, the motor cortex (area 4), and the adjacent superior parietal lobule (area 5) (Table XIV). Subcortically, significant activation was found bilaterally in the putamen (Figure 26A), the caudate nucleus (Figure 28A), the STN (Figure 27A), as well as the left thalamus.

Left hand. Comparison of SI movements with the control condition when using the left hand showed significant bilateral cortical peaks in the dorsolateral PFC (areas 9, 46, Figure 28), the motor cingulate cortex (area 24), the insula, the SMA (area 6), the PMC (area 6), and the posterior parietal area (areas 7 and 40). Significant increased activity also occurred contralaterally in the primary sensory cortex (areas 1, 3) and the superior parietal lobule adjacent to the motor cortex (area 5) and significant ipsilateral activation was found in the primary motor cortex (PMC) (area 4). As was the case with the right hand, there was a significant increase of subcortical activity bilaterally in the putamen (Figure 26A) and the caudate nucleus (Figure 28A), as well as in the left STN (Figure 27A) (Table XIV).

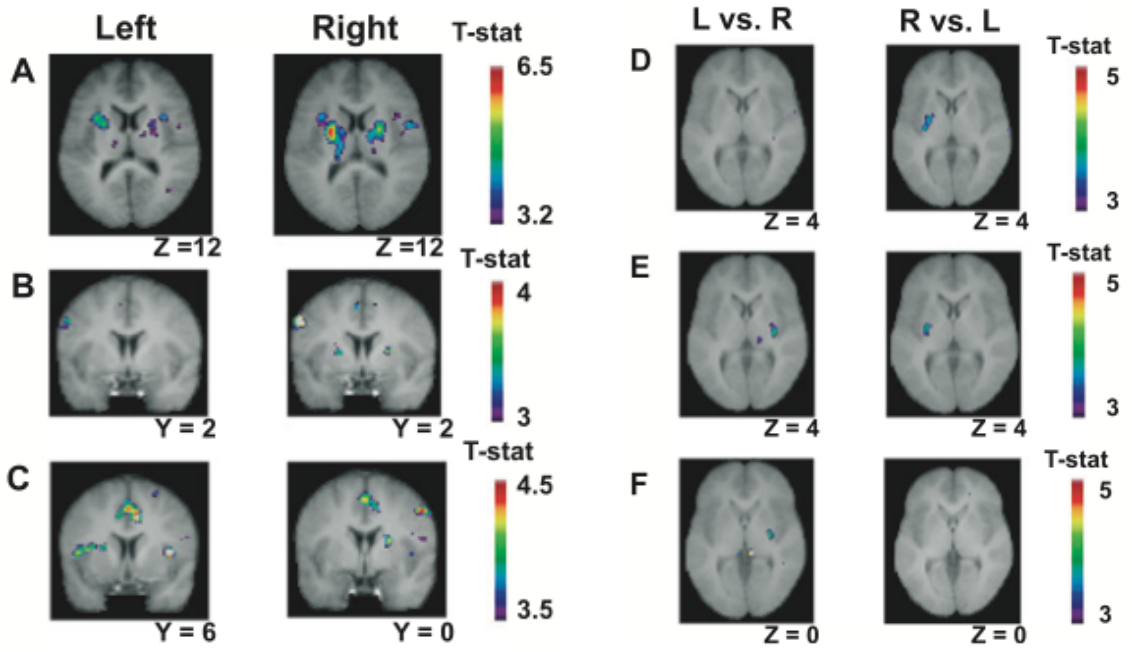

Figure 25: Location of the putamen peaks in the various subtractions.

The anatomical images shown are the average of the T1 acquisitions of all of the participants transformed into stereotaxic space. (A) SI vs. control condition. Significant putamen activation is shown bilaterally for the left hand (left column) and for the right hand (right column). (B) ET vs. control condition. Bilateral significant putamen activation is shown for the right hand but none is observed for the left hand. (C) The location of the contralateral putamen significant activation is shown for each hand in the SI vs. ET condition. (D) For the SI condition, the right column shows the location of the significant left putamen activation in the right vs. the left hand; no significant putamen activation is observed in the left vs. right hand comparison. (E) For the ET condition, the location of the right putamen peak is shown for the left vs. right hand comparison in the left column, similarly for the right putamen peak for the right vs. left hand comparison in the right column. (F) For the control condition, the left column shows the location of the significant right putamen activation in the left vs. the right hand; no significant putamen activation is observed in the right vs. the left hand comparison.

2. ET compared with the control condition

Right hand. In the comparison of ET movements with the control condition when the right hand was used, a significant increase of activity was observed bilaterally in the motor cortex

(area 4), the PPC (area 7), and the motor cortex (area 4). Contralateral significant activation (i.e. on the left) was found in the SMA (area 6), the PMC (area 6), the primary sensory region (areas 1, 2, 3), and the PPC (area 40), (Table XV). Subcortically, significantly increased activity was found in the putamen bilaterally (Figure 26B), but not in the STN even at a low threshold of 0.01 uncorrected (Table XV).

Left hand. For the same comparison in the left hand, significant increased activity was observed bilaterally in the SMA (area 6), the motor cortex (area 4), and the PPC (areas 7 and 40). Significant activations were also observed in the primary sensory areas (areas 1,2,3) contralaterally (i.e. in the right hemisphere), and in the PMC (area 6) ipsilaterally. It should be noted that, unlike for the right hand, no significant activation was found in the putamen (Figure 26B), even at a low threshold corresponding to $p<0.01$ uncorrected.

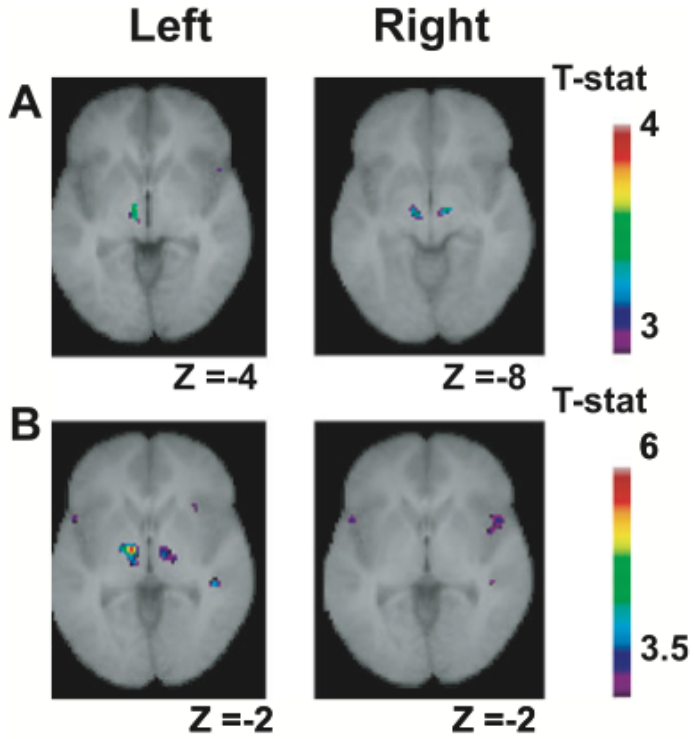

Figure 26: Location of the STN peaks for the left and right hand.

The anatomical images shown are the average of the T1 acquisitions of all of the participants transformed into stereotaxic space. (A) SI vs. control condition. The location of the left significant STN activation is shown for the left hand in the left column and the location of the bilateral STN activation is shown for the right hand in the right column. (B)

SI vs. ET condition. The location of the bilateral STN activation is shown for the left hand in the left column; no such activation in observed when the right hand is used.

3. SI vs. ET movements

Right hand. When comparing the SI with the ET movements, for the right hand, significantly increased activity was found bilaterally in the mid-dorsolateral cortex (areas 9, 46), in the cingulate cortex (at the intersection of areas 24 and 32), in the insula, and the PPC (area 7). In the ipsilateral side (i.e. right hemisphere), significant activition was found in the mid-dorsolateral PFC (area 46), the PPC (area 40), and the putamen (Figure 26C) (Table XVI). No significant activation was found in the STN (Figure 27B) even at a low threshold corresponding to $p<0.01$ uncorrected.

Left hand. When the left hand was used, comparison of the SI with the ET movements demonstrated significantly increased activity bilaterally in the mid-dorsolateral PFC (areas 9, 46), the cingulate cortex (areas 24, 32), the insula (area 13), and the PPC (area 7), as well as on the right PMC (area 6) and the right PPC (area 40). In the subcortical regions, significant activations were found bilaterally in the STN (Figure 27B), and in the thalamus, as well as the left putamen (Figure 26C) (Table XVI).

4. Comparing left and right hands

Self-Initiated movements condition. For the SI movements condition, significantly increased activity was found in the primary sensory region (areas 1, 2, 3), the motor cortex (area 4), the PPC (areas 7 and 40), and the SMA (area 6), all in the right hemisphere, but nowhere in the basal ganglia when comparing the left hand with the right one (Figure 26D) (Table XVII). When the right hand was compared with the left one (the reverse subtraction), significantly increased activity was found in the left hemisphere in the primary sensory region (areas 1, 2, 3), the motor cortex (area 4), the putamen (Figure 26D), and the thalamus, as well as in the right caudate nucleus (Table XVII).

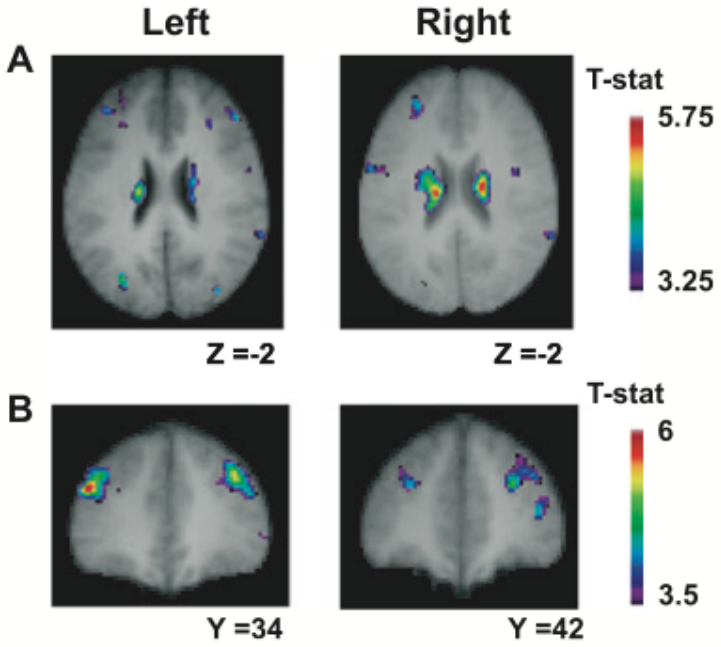

Figure 27: Location of the dorsolateral PFC and caudate nucleus peaks for the left and right hand.

The anatomical images shown are the average of the T1 acquisitions of all of the participants transformed into stereotaxic space. (A) SI vs. control condition. The location of the significant activation of the dorsolateral PFC and caudate nucleus is shown when using the left hand in the left column and when using the right hand in the right column. (B) SI vs. ET condition. The location of the bilateral dorsolateral PFC peaks is shown for each hand.

ET movements condition. When comparing the left hand with the right hand during the ET movements condition, significantly increased activity was found in the right hemisphere in the primary sensory region (areas 1, 2, 3), the motor cortex (area 4), the PPC (area 40), the SMA (area 6), and, subcortically, in the right putamen (Figure 26E) and thalamus (Table XVIII). When the right hand was compared to the left one (the reverse substraction), significantly increased activity was found in the left hemisphere in the primary sensory region (areas 1, 2, 3), the motor cortex (area 4), the putamen (Figure 26E), and the thalamus, and, in the right hemisphere, in the SMA (area 6), and the caudate nucleus.

Control condition. When comparing the left hand with the right hand during the control condition, significantly increased activity was found in the right hemisphere, in the medial

PFC (area 8), the primary sensory region (areas, 1, 2, 3), and the putamen (Figure 26F) (Table XIV). When the right hand was compared to the left one (the reverse subtraction), significantly increased activity was only found in the left primary sensory region (areas 1, 2, 3), and, most importantly, not in the putamen (Figure 26F).

Discussion

The goal of this study was to further investigate the contributions of the putamen, the caudate nucleus, the STN, and the PFC during internally vs. externally generated novel movements when using the dominant and non-dominant hands separately. We will first discuss our results regarding the putamen, followed by the STN, and finally the PFC and caudate nucleus in the context of the dominant and non-dominant hands.

Putamen

We have previously proposed that the putamen plays an important role in the self-execution of non-routine actions (Monchi *et al.*, 2006), which would imply that it is more required for the SI than the ET and control conditions. Several studies are in accord with this hypothesis (Jahanshahi *et al.*, 1995; Jenkins *et al.*, 2000; Weeks *et al.*, 2001; Cunnington *et al.*, 2002; Wiese *et al.*, 2004). Indeed, we observe more putamen activity when comparing the SI and control conditions, as well as the SI and ET conditions. In the comparison of SI versus ET, however, we only obtained ipsilateral putamen activation with each hand as opposed to bilateral activation in SI versus control. In the study by Wiese *et al.* (2004), the authors only used the right hand for SI and ET movements, but they also observed ipsilateral putamen activation in the SI versus ET contrast. It seems, then, that a SI task, compared to the control, requires much more putamen, and therefore recruits them bilaterally. This then appears as an ipsilateral activation in our subtractions. The present results indicate that both the SI and ET movements recruit the putamen, in agreement with previous single-cell recordings in monkeys (Romo et al., 1992; Schultz & Romo, 1992), but that the ipsilateral putamen is even more solicited for a more complex (SI) task. Furthermore, it is interesting to note that for the ET versus control contrast, we only see putaminal activity (bilaterally)

when using the right hand. Our interpretation is that when the left hand is used, the control and the ET conditions have similar putamen requirement, due to a lack of automaticity in this hand, and therefore show no difference when subtracted from each other. This interpretation is substantiated by the fact that significantly more activation was found in the right putamen when comparing the left vs. the right hand but not in the left putamen for the reverse comparison (right vs. left) during the performance of the control condition. Finally, the comparison between the left and the right hand did not generate any significant activation in the right putamen for the SI condition while significant activation was found in the left putamen for the right vs. left hand for the same condition. This result may seem to contradict our initial hypothesis that the putamen is particularly involved in the self generation of a novel action, since this reflects the activity of a non-routine condition using the less proficient hand vs. the more proficient hand. However, it should be noted that significantly increased activity was found bilaterally for each hand separately, when comparing the SI to the control condition. Hence, for the SI condition, the putamen seems significantly recruited for both hands, and a non reported trend was found in the right putamen (t=2.6) when comparing the left to the right hand for the SI condition. These issues show the importance of carrying out additional studies using both hands separately. It may also be that our initial hypothesis needs to be further refined for the left hand.

STN

The STN has been proposed to enhance pallidal inhibition of the thalamus in order to inhibit unwanted (motor) responses (Mink 1996; Nambu *et al.*, 2002). Furthermore, lesions of the STN lead to violent uncontrolled movements called ballism (Hamani *et al.*, 2004). During the performance of a Go/No-Go task, Aron and Poldrack (2006) proposed that the STN is involved in blocking unwanted responses by inhibiting thalamo-cortical output. Furthermore, another study compared differences in stop-signal response time (SSRT) inhibition, and observed increased STN activation in subjects with longer SSRTs (Ray *et al.*, 2008). In the present study, the STN was more involved in the SI condition as compared to the control with both hands, and in the SI condition as compared to the ET condition with the left hand. This would imply that one requires more inhibition for unwanted movements

for the SI task than the other two. In the ET and the control tasks, the computer indicates to the subject with button to press, so there are presumably no movements to inhibit. In the SI task, however, participants need to avoid pressing the same button twice in a row and to repeat simple sequences, both of which requires the more straightforward movements. This explains why the STN is most recruited in the SI condition. When comparing the SI to the ET condition, however, we only observe STN activation when using the left hand. A possible interpretation is that in those individuals, via lifelong training, the right dominant hand is less prone to unwanted errors (such as a repetitions in this task), and for that reason may require less inhibition from the STN.

Dominant and non-dominant hands

Many studies focus their attention to right-handed movements only (Jenkins *et al.*, 2000; Cunnington *et al.*, 2002), of left-handed movements only (Taniwaki *et al.*, 2006), or compared the right-handed movements to a simple left-handed movement (Mattay *et al.*, 1998). The main purpose of our study was to investigate the difference when healthy right-handed subjects make equivalent movements with their right as well as their left hands. First, in the SI condition, when the subjects used their right hand (compared to the left), significant activation was observed in the striatum (putamen and caudate nucleus) but not in PFC (Table XVII). Conversely, when they used their left hand (compared to the right), significant activation occurred in the PFC and PPC but not in the striatum. Second, for the ET condition (Table XVIII) we observed putamen activation when subjects use both the right and left hands, and PPC activation only when they use their left hand (as compared to the right). Finally, for the control condition (Table XIX), both medial PFC and putamen activation was observed only when participants used their left hand, but not when they used their right one. Taken together, these results indicate that the right hand requires significantly less cortical processing than the left one across conditions. The left hand, does not produce button presses as automatically as the right hand, and therefore requires more cognitive effort in order to plan, select, and execute movements. One study showed an increase in cortical activations of right-handers during right and left index movements, but this was only in comparison to left-handed subjects, and not within the populations (Kloppel

et al., 2007). It is interesting to note that even in our control condition the PFC was recruited significantly more for the left hand than for the right one. This indicates that even the repetition of simple movements require a fair amount of planning in order to be executed properly with an untrained limb. The fact that both the putamen and the PFC are more solicited for the left hand compared to the right hand in the control condition gives further support to our earlier observation that the control and ET condition are relatively complex for the left hand, and therefore recruit the putamen at similar levels leading to no significant difference in activation between the two conditions. We propose that, with respect to the putamen involvement, variability in task condition is more important for the dominant hand than for the non-dominant hand because the lack of training in the left hand is stronger than the difference between conditions. Furthermore, cortical recruitment is more necessary for the non-dominant hand because of this lack of training.

Recent fMRI studies in humans have suggested that the caudate nucleus is particularly involved when manipulation is required in working memory to plan a novel response (Lewis *et al.*, 2004; Monchi *et al.*, 2006). In the present study, when using the right hand, caudate nucleus activation was found during SI conditions compared with the control condition when either hand was used. Our group has previously observed significant increases in activation in the caudate nucleus when SI retrieval and planning was required to perform a set-shift as opposed to applying the same rule in the context of a card-sorting task (Monchi *et al.*, 2006). SI movements contain some of the same demands as the planning of a set-shift or multiple new moves (considering a distinct button press as a simple action) where the caudate nucleus has been shown to play an important role (Monchi *et al.* 2001, 2006). Furthermore, in the present study, the caudate nucleus was only significantly activated in synchrony with the mid-dorsolateral PFC (Table XX). This is in agreement with the theory that proposes that these two structures are part of the 'cognitive' cortico-striatal loop proposed by Alexander *et al.* (1986). Importantly, a previous Positron Emission Tomography study has shown the involvement of the caudate nucleus together with the dorsolateral PFC in the execution of a complex planning task (Owen *et al.*, 1996). Interestingly, Cunnington et al. (2002) did not report significant activation of the caudate nucleus nor the PFC using fMRI while subjects performed SI finger movements using the

right hand. This is likely due to the fact that, in their task, the sequential finger movements always followed a simple pattern (index-middle-index finger). In the SI condition, then, while participants had to initiate their movements, they did not have to track their previous moves nor plan their next one like those in the present study had to.

Conclusion

First, our results show that the putamen is particularly involved for the execution of non-routine movements for either hand, especially if those are SI, as these require more planning. Furthermore, we propose that, for right-handed people performing fine movements, as far as putamen involvement is concerned, the lack of proficiency of the non-dominant hand may prevail over other task demands. Specifically, the putamen seems to be more required for simple tasks when using the left hand than the right hand, but its activity does not increase as much for the left than the right hand when the tasks get more complex. Second, the patterns of activity observed within the STN provide further evidence of its involvement in movement selection by inhibiting concurring motor events. Finally, the difference of the cortical patterns of activity observed in the left hand compared with the right one indicate that tasks involving cognitive motor control may be harder for the non-dominant hand than for the dominant one and therefore solicit a larger amount of cortical areas. These results raise interesting questions about cortical and subcortical functional interactions during the performance of tasks with both cognitive and motor components, in patients with asymmetrical movement disorders such as PD.

Acknowledgements

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Table XIV: Activity peaks associated with SI movements, compared with the control condition

	Left hand						Right hand					
Anatomical area (BA)	L/R	*x*	*y*	*z*	*t*-value	Cluster	L/R	*x*	*y*	*z*	*t*-value	Cluster
DLPFC (46/9)	R	30	28	28	4.30	2208	R	32	22	32	4.43	928
		48	34	24	4.04	sc						
	L	−40	36	28	4.94	1472	L	−28	46	24	4.68	824
		−32	52	24	3.81	sc						
Insula (13)	L	−34	14	6	5.89	5840	L	−34	12	10	4.77	> 5000
	R	38	18	4	4.66	5488						
Cingulate cortex (24/32)	R	10	10	36	4.87	> 10 000	R	10	6	44	6.27	> 10 000
	L	−8	8	36	3.7*	352	L	−8	6	40	5.43	sc
SMA (6)	R	8	0	50	4.99	> 10 000	R	2	−4	54	5.99	> 10 000
	L	−4	−6	54	5.40	sc	L	−4	−4	52	6.66	sc
Premotor area (6)	R	20	−12	54	5.40	> 10 000	R	26	−8	54	5.73	> 10 000
	L	−24	−8	52	5.62	> 10 000	L	−20	−10	54	5.77	> 10 000
Primary sensory area (1/3)	R	44	−28	62	5.31	> 10 000	L	−34	−20	68	6.57	> 10 000
Primary motor area (4)	L	−30	−22	54	5.03	> 10 000	L	−34	−34	58	5.11	> 10 000
Motor cortex (5)	R	38	−48	60	5.73	> 10 000	L	−44	−38	62	6.65	> 10 000
PPC (40)	R	38	−38	48	6.29	> 10 000	R	38	−42	42	5.39	3944
	L	−34	−42	42	5.32	> 10 000	L	−32	−42	44	6.38	> 10 000
PPC (7)	R	−18	−68	58	6.32	> 10 000	R	38	−50	60	4.61	> 10 000
	L	18	−70	54	5.62	> 10 000	L	−26	−58	60	6.25	> 10 000
Caudate nucleus	R	20	−2	20	4.69	> 3000	R	18	−16	24	5.62	> 5000
	L	−18	−16	24	4.79	> 3000	L	−14	−16	22	5.44	> 5000
Putamen	R	24	4	12	3.95	> 3000	R	22	0	10	5.48	> 5000
	L	−24	4	12	5.18	> 3000	L	−24	−2	12	6.20	> 5000
Thalamus	–	–	–	–	–	–	L	−16	−16	18	5.65	> 5000
STN	–	–	–	–	–	–	R	10	−14	−10	3.65*	104
	L	−10	−10	−2	3.7*	456	L	−10	−16	−8	3.68*	168

*The coordinates (x, y, z) are in standard MNI stereotaxic space. Abbreviations for Tables 1–7: BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; ET, externally triggered (movements); L / R, left / right hemispheres; PMC, premotor cortex; PPC, posterior parietal cortex; sc, same cluster; SI, self-initiated (movements). *P < 0.001 non-corrected for multiple comparisons.*

Table XV: Activity peaks associated with ET movements, compared with the control condition

	Left hand						Right hand					
Anatomical area (BA)	L/R	*x*	*y*	*z*	*t*-value	Cluster	L/R	*x*	*y*	*z*	*t*-value	Cluster
SMA (6)	R	4	−8	52	4.56	3192	–	–	–	–	–	–
	L	−4	−8	56	4.82	sc	L	−4	−6	54	5.69	> 10 000
PMC (6)	L	−52	−2	34	4.78	> 5000	L	−56	−2	38	5.72	> 10 000
Primary motor area (4)	R	24	−14	52	5.63	> 10 000	R	22	−16	54	4.8	2504
	L	−30	−20	68	5.68	7848	L	−32	−20	58	5.81	> 10 000
Primary sensory area (3/1/2)	R	40	−26	64	5.69	> 10 000	L	−44	−34	62	7.84	> 10 000
	–	–	–	–	–	–	–	−26	−56	62	6.87	sc
PPC (40)	R	38	−38	48	5.85	> 10 000	–	–	–	–	–	–
	L	−32	−40	42	4.27	> 5000	L	−40	−40	56	6.51	> 10 000
PPC (7)	R	28	−50	66	5.42	> 10 000	R	20	−68	60	4.4	1760
	L	−20	−64	56	514	> 10 000	L	−20	−58	50	5.23	> 10 000
Putamen	–	–	–	–	–	–	R	22	4	8	3.74*	232
	–	–	–	–	–	–	L	−24	−8	8	4.63	2384

Abbreviations as in table XIV.

Table XVI: Activity peaks associated with SI movements, compared with ET movements

	Left hand						Right hand					
Anatomical area (BA)	L/R	*x*	*y*	*z*	*t*-value	Cluster	L/R	*x*	*y*	*z*	*t*-value	Cluster
DLPFC (9,46)	R	38	34	34	5.33	7136	R	36	34	38	5.6	> 5000
								40	42	10	4.43	> 5000
	L	−44	36	26	6.1	9048	L	−28	44	24	4.31	> 5000
Cingulate cortex (24/32)	R	6	14	40	6.15	> 10 000	R	8	8	40	5.99	> 10 000
	L	−6	16	34	5.09	sc	L	−6	12	44	4.64	sc
Insula (13)	R	42	10	6	5.7	3496	R	36	16	4	4.33	> 5000
	L	−32	14	6	5.54	4464	L	−32	10	12	4.43	1912
PMC (6)	R	20	−2	60	5.62	> 5000	R	50	6	12	5.18	> 5000
								54	0	42	4.41	1728
	L	−24	−8	60	5.2	> 5000	–	–	–	–	–	–
PPC (40)	R	40	−44	44	5.58	> 10 000	R	58	−44	40	6.63	> 10 000
PPC (7)	R	14	−72	54	5.99	3992	R	14	−72	50	4.06	1968
	L	−20	−70	56	5.36	4424	L	−8	−74	58	4.25	2272
Putamen	–	–	–	–	–	–	R	24	0	14	4.24	> 5000
	L	−20	6	12	4.03	4464	–	–	–	–	–	–
Thalamus	R	14	−8	12	4.08	672	–	–	–	–	–	–
	L	−14	−22	2	4.24	1736	–	–	–	–	–	–
STN	R	10	−10	−4	4.56	1144	–	–	–	–	–	–
	L	−12	−10	−2	5.67	1736	–	–	–	–	–	–

Abbreviations as in table XIV.

Table XVII: Activity peaks associated with SI movements, comparing one hand with the other

	Left hand						Right hand					
Anatomical area (BA)	L/R	*x*	*y*	*z*	*t*-value	Cluster	L/R	*x*	*y*	*z*	*t*-value	Cluster
Anterior PFC (46,10)	L	−22	66	20	4.26	562						
Primary sensory area (1/2/3)	R	50	−26	58	8.15	> 10 000	–	–	–	–	–	–
	–	–	–	–	–	–	L	−52	−28	56	6.4	> 10 000
Primary motor area (4)	R	30	−30	72	6.02	> 10 000	L	−30	−32	72	5.82	> 10 000
PPC (40)	R	52	−26	20	4.24	1168	–	–	–	–	–	–
PPC (7)	R	20	−54	64	4.44	> 5000	–	–	–	–	–	–
SMA (6)	R	8	−18	52	3.94	800	–	–	–	–	–	–
Putamen	–	–	–	–	–	–	L	−32	−16	4	4.02	1688
Thalamus	–	–	–	–	–	–	L	−18	−26	10	4	sc
Caudate nucleus	–	–	–	–	–	–	R	12	16	18	4.47	584

Abbreviations as in table XIV.

Table XVIII: Activity peaks associated with ET movements, comparing one hand with the other

	Left hand						Right hand					
Anatomical area (BA)	L/R	*x*	*y*	*z*	*t*-value	Cluster	L/R	*x*	*y*	*z*	*t*-value	Cluster
Primary sensory area (1/2/3)	R	52	−28	60	6.63	> 10 000	–	–	–	–	–	–
	–	–	–	–	–	–	L	−50	−30	60	7.49	> 10 000
Primary motor area (4)	R	44	−30	66	6.42	> 10 000	–	–	–	–	–	–
							L	−32	−34	72	6.97	> 10 000
PPC (40)	R	40	−30	24	5.81	> 10 000	–	–	–	–	–	–
SMA (6)	R	6	−10	52	4.48	1544	R	−6	−22	50	4.63	976
Putamen	R	30	−6	0	4.3	896	L	−30	−8	2	3.96	712
Thalamus	R	16	−24	8	4.05*	472						
Caudate nucleus	–	–	–	–	–	–						

Abbreviations as in table XIV.

Table XIX: Activity peaks associated with control movements, comparing one hand with the other

	Left hand						Right hand					
Anatomical area (BA)	L/R	*x*	*y*	*z*	*t*-value	Cluster	L/R	*x*	*y*	*z*	*t*-value	Cluster
Medial PFC (8)	L	−4	32	52	4.6	1160	–	–	–	–	–	–
Primary sensory area (1/2/3)	R	44	−34	64	6.27	> 10 000	–	–	–	–	–	–
	–	–	–	–	–	–	L	−50	−30	60	7.49	> 10 000
Putamen	R	32	−10	0	4.18	672	–	–	–	–	–	–

Abbreviations as in table XIV.

Table XX: Summary of the major results: (a) left and right hand activations separately, (b) comparing right and left hand activations

(a)

	Left hand				Right hand			
	STN	Putamen	Caudate nucleus	DLPFC	STN	Putamen	Caudate nucleus	DLPFC
SI vs. control	SAL	SBA	SBA	SBA	SBA	SBA	SBA	SBA
ET vs. control	–	–	–	–	–	SBA	–	–
SI vs. ET	SBA	SAL	–	SBA	–	RAL	–	SBA

(b)

	Left hand > right hand		Right hand > left hand	
	Putamen	PFC	Putamen	PFC
SI	–	SAL	SAL	–
ET	RAL	–	SAL	–
Control	RAL	SAL	–	–

SAL, significant activation in the left hemisphere; SAR, significant activation in the right hemisphere; SBA, significant bilateral activation; Other abbreviations as in Table XIV.

Appendix III

In this appendix we have included the UPDRS form used for the symptom evaluation in the chapters of this thesis. Table XXI also lists the individual left and right UPDRS scores for the 12 patients with PD.

To calculate the UPDRS scores for the left and right side of the body (chapter 4), we have used the following subsections of the UPDRS: 3 (tremor at rest), 4 (postural tremor), 5b-e (rigidity), 6 (finger taps), 7 (hand movements), 8 (alternating hand movements), and 9 (leg agility).

Table XXI: Sum of left and right side symptoms for individual patients ON and OFF medication

	ON		OFF	
Patient	Left	Right	Left	Right
1	14	15	13	15
2	7.5	5	11.5	7
3	10	5.5	10.5	8
4	7	7.5	11	10.5
5	7	3.5	9	5
6	12	6.5	16.5	11.5
7	9	8.5	9	7
8	8	5	14	10.5
9	8	7.5	9.5	10.5
10	5.5	11.5	4.5	14
11	13	6.5	13	11
12	7.5	2	9.5	8.5

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NACC Uniform Data Set (UDS) – Initial Visit Packet

Form B3: Evaluation Form – Unified Parkinson's Disease Rating Scale (UPDRS[1]) – Motor Exam

Center: _____ ADC Subject ID:__ __ __ __ __ __ __ __ __ __ Visit Date:__ __/__ __/__ __ __ __

NOTE: This form is to be completed by the clinician. For additional clarification and examples, see UDS Coding Guidebook pages 26–31. Check only one box per question.

ADC Visit #:__ __ __

Examiner's initials:__ __ __

☐ If the clinician completes the UPDRS examination and determines all items are normal, check this box and end form here.

UPDRS MOTOR EXAMINATION

1. Speech
   - ☐ 0 Normal.
   - ☐ 1 Slight loss of expression, diction and/or volume.
   - ☐ 2 Monotone, slurred but understandable; moderately impaired.
   - ☐ 3 Marked impairment, difficult to understand.
   - ☐ 4 Unintelligible.

2. Facial expression
   - ☐ 0 Normal.
   - ☐ 1 Minimal hypomimia, could be normal "poker face".
   - ☐ 2 Slight but definitely abnormal diminution of facial expression.
   - ☐ 3 Moderate hypomimia; lips parted some of the time.
   - ☐ 4 Masked or fixed facies with severe or complete loss of facial expression; lips parted ¼ inch or more.

[1] Fahn S, Elton RL, UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent developments in Parkinson's disease, Vol. 2. Florham Park, NJ: Macmillan Healthcare Information, 1987:153-163, 293-304. Reproduced by permission of the author.

Center: _____ ADC Subject ID:__ __ __ __ __ __ __ __ __ __ Visit Date:__ __/__ __/__ __ __ __

NOTE: This form is to be completed by the clinician. For additional clarification and examples, see UDS Coding Guidebook pages 26–31.
Check only one box per question.

ADC Visit #:__ __ __

Examiner's initials:__ __ __

3a. Tremor at rest – Face, lips, chin

☐ 0 Absent.

☐ 1 Slight and infrequently present.

☐ 2 Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present.

☐ 3 Moderate in amplitude and present most of the time.

☐ 4 Marked in amplitude and present most of the time.

3b. Tremor at rest – Right hand

☐ 0 Absent.

☐ 1 Slight and infrequently present.

☐ 2 Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present.

☐ 3 Moderate in amplitude and present most of the time.

☐ 4 Marked in amplitude and present most of the time.

3c. Tremor at rest – Left hand

☐ 0 Absent.

☐ 1 Slight and infrequently present.

☐ 2 Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present.

☐ 3 Moderate in amplitude and present most of the time.

☐ 4 Marked in amplitude and present most of the time.

3d. Tremor at rest – Right foot

☐ 0 Absent.

☐ 1 Slight and infrequently present.

☐ 2 Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present.

☐ 3 Moderate in amplitude and present most of the time.

☐ 4 Marked in amplitude and present most of the time.

Center: _____ ADC Subject ID:__ __ __ __ __ __ __ __ __ __ Visit Date:__ __/__ __/__ __ __ __

ADC Visit #:__ __ __

NOTE: This form is to be completed by the clinician. For additional clarification and examples, see UDS Coding Guidebook pages 26–31.
Check only one box per question.

Examiner's initials:__ __ __

3e. Tremor at rest – Left foot

☐ 0 Absent.

☐ 1 Slight and infrequently present.

☐ 2 Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present.

☐ 3 Moderate in amplitude and present most of the time.

☐ 4 Marked in amplitude and present most of the time.

4a. Action or postural tremor of hands – Right hand

☐ 0 Absent.

☐ 1 Slight; present with action.

☐ 2 Moderate in amplitude, present with action.

☐ 3 Moderate in amplitude with posture holding as well as action.

☐ 4 Marked in amplitude; interferes with feeding.

4b. Action or postural tremor of hands – Left hand

☐ 0 Absent.

☐ 1 Slight; present with action.

☐ 2 Moderate in amplitude, present with action.

☐ 3 Moderate in amplitude with posture holding as well as action.

☐ 4 Marked in amplitude; interferes with feeding.

5a. Rigidity – Neck (judged on passive movement of major joints with patient relaxed in sitting position; cogwheeling to be ignored)

☐ 0 Absent.

☐ 1 Slight or detectable only when activated by mirror or other movements.

☐ 2 Mild to moderate.

☐ 3 Marked, but full range of motion easily achieved.

☐ 4 Severe; range of motion achieved with difficulty.

Center: _____ ADC Subject ID:__ __ __ __ __ __ __ __ __ __ Visit Date:__ __/__ __/__ __ __ __

ADC Visit #:__ __ __

NOTE: This form is to be completed by the clinician. For additional clarification and examples, see UDS Coding Guidebook pages 26–31.
Check only one box per question.

Examiner's initials:__ __ __

5b. Rigidity – Right upper extremity (judged on passive movement of major joints with patient relaxed in sitting position; cogwheeling to be ignored)

☐ 0 Absent.

☐ 1 Slight or detectable only when activated by mirror or other movements.

☐ 2 Mild to moderate.

☐ 3 Marked, but full range of motion easily achieved.

☐ 4 Severe; range of motion achieved with difficulty.

5c. Rigidity – Left upper extremity (judged on passive movement of major joints with patient relaxed in sitting position; cogwheeling to be ignored)

☐ 0 Absent.

☐ 1 Slight or detectable only when activated by mirror or other movements.

☐ 2 Mild to moderate.

☐ 3 Marked, but full range of motion easily achieved.

☐ 4 Severe; range of motion achieved with difficulty.

5d. Rigidity – Right lower extremity (judged on passive movement of major joints with patient relaxed in sitting position; cogwheeling to be ignored)

☐ 0 Absent.

☐ 1 Slight or detectable only when activated by mirror or other movements.

☐ 2 Mild to moderate.

☐ 3 Marked, but full range of motion easily achieved.

☐ 4 Severe; range of motion achieved with difficulty.

Center: _____ ADC Subject ID:__ __ __ __ __ __ __ __ __ __ Visit Date:__ __/__ __/__ __ __ __

ADC Visit #:__ __ __

NOTE: This form is to be completed by the clinician. For additional clarification and examples, see UDS Coding Guidebook pages 26–31.
Check only one box per question.

Examiner's initials:__ __ __

5e. Rigidity – Left lower extremity (judged on passive movement of major joints with patient relaxed in sitting position; cogwheeling to be ignored)

- ☐ 0 Absent.
- ☐ 1 Slight or detectable only when activated by mirror or other movements.
- ☐ 2 Mild to moderate.
- ☐ 3 Marked, but full range of motion easily achieved.
- ☐ 4 Severe; range of motion achieved with difficulty.

6a. Finger taps – Right hand (patient taps thumb with index finger in rapid succession)

- ☐ 0 Normal.
- ☐ 1 Mild slowing and/or reduction in amplitude.
- ☐ 2 Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.
- ☐ 3 Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.
- ☐ 4 Can barely perform the task.
- ☐ 8 Untestable (specify reason): _____

6b. Finger taps – Left hand (patient taps thumb with index finger in rapid succession)

- ☐ 0 Normal.
- ☐ 1 Mild slowing and/or reduction in amplitude.
- ☐ 2 Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.
- ☐ 3 Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.
- ☐ 4 Can barely perform the task.
- ☐ 8 Untestable (*specify reason*): _____

Center: _____ ADC Subject ID:_ _ _ _ _ _ _ _ _ _ _ _ Visit Date:_ _/_ _/_ _ _ _

NOTE: This form is to be completed by the clinician. For additional clarification and examples, see UDS Coding Guidebook pages 26–31. Check only one box per question.

ADC Visit #:_ _ _

Examiner's initials:_ _ _

7a. Hand movements – Right hand (patient opens and closes hands in rapid succession)

☐ 0 Normal.

☐ 1 Mild slowing and/or reduction in amplitude.

☐ 2 Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.

☐ 3 Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.

☐ 4 Can barely perform the task.

☐ 8 Untestable (*specify reason*): _____

7b. Hand movements – Left hand (patient opens and closes hands in rapid succession)

☐ 0 Normal.

☐ 1 Mild slowing and/or reduction in amplitude.

☐ 2 Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.

☐ 3 Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.

☐ 4 Can barely perform the task.

☐ 8 Untestable (*specify reason*): _____

8a. Rapid alternating movements of hands – Right hand (pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously)

☐ 0 Normal.

☐ 1 Mild slowing and/or reduction in amplitude.

☐ 2 Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.

☐ 3 Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.

☐ 4 Can barely perform the task.

☐ 8 Untestable (*specify reason*): _____

Center: _____ ADC Subject ID:__ __ __ __ __ __ __ __ __ __ Visit Date:__ __/__ __/__ __ __ __

NOTE: This form is to be completed by the clinician. For additional clarification and examples, see UDS Coding Guidebook pages 26–31. Check only one box per question.

ADC Visit #:__ __ __

Examiner's initials:__ __ __

8b. Rapid alternating movements of hands – Left hand (pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously)

- ☐ 0 Normal.
- ☐ 1 Mild slowing and/or reduction in amplitude.
- ☐ 2 Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.
- ☐ 3 Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.
- ☐ 4 Can barely perform the task.
- ☐ 8 Untestable (*specify reason*): _____

9a. Leg agility – Right leg (patient taps heel on the ground in rapid succession, picking up entire leg; amplitude should be at least 3 inches)

- ☐ 0 Normal.
- ☐ 1 Mild slowing and/or reduction in amplitude.
- ☐ 2 Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.
- ☐ 3 Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.
- ☐ 4 Can barely perform the task.
- ☐ 8 Untestable (*specify reason*): _____

9b. Leg agility – Left leg (patient taps heel on the ground in rapid succession, picking up entire leg; amplitude should be at least 3 inches)

- ☐ 0 Normal.
- ☐ 1 Mild slowing and/or reduction in amplitude.
- ☐ 2 Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.
- ☐ 3 Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.
- ☐ 4 Can barely perform the task.
- ☐ 8 Untestable (*specify reason*): _____

Center: _____ ADC Subject ID:__ __ __ __ __ __ __ __ __ __ Visit Date:__ __/__ __/__ __ __ __

NOTE: This form is to be completed by the clinician. For additional clarification and examples, see UDS Coding Guidebook pages 26–31.
Check only one box per question.

ADC Visit #:__ __ __

Examiner's initials:__ __ __

10. Arising from chair (patient attempts to rise from a straight-backed chair, with arms folded across chest)

☐ 0 Normal.

☐ 1 Slow; or may need more than one attempt.

☐ 2 Pushes self up from arms of seat.

☐ 3 Tends to fall back and may have to try more than one time, but can get up without help.

☐ 4 Unable to arise without help.

☐ 8 Untestable (*specify reason*): _____

11. Posture

☐ 0 Normal.

☐ 1 Not quite erect, slightly stooped posture; could be normal for older person.

☐ 2 Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

☐ 3 Severely stooped posture with kyphosis; can be moderately leaning to one side.

☐ 4 Marked flexion with extreme abnormality of posture.

☐ 8 Untestable (*specify reason*): _____

12. Gait

☐ 0 Normal.

☐ 1 Walks slowly; may shuffle with short steps, but no festination (hastening steps) or propulsion.

☐ 2 Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

☐ 3 Severe disturbance of gait requiring assistance.

☐ 4 Cannot walk at all, even with assistance.

☐ 8 Untestable (*specify reason*): _____

Center: _____ ADC Subject ID:__ __ __ __ __ __ __ __ __ __ Visit Date:__ __/__ __/__ __ __ __

NOTE: This form is to be completed by the clinician. For additional clarification and examples, see UDS Coding Guidebook pages 26–31. Check only one box per question.

ADC Visit #:__ __ __

Examiner's initials:__ __ __

13. Posture stability (response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart; patient is prepared)

- ☐ 0 Normal erect.
- ☐ 1 Retropulsion, but recovers unaided.
- ☐ 2 Absence of postural response; would fall if not caught by examiner.
- ☐ 3 Very unstable, tends to lose balance spontaneously.
- ☐ 4 Unable to stand without assistance.
- ☐ 8 Untestable (*specify reason*): _____

14. Body bradykinesia and hypokinesia (combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general)

- ☐ 0 None.
- ☐ 1 Minimal slowness, giving movement a deliberate character; could be normal for some persons; possibly reduced amplitude.
- ☐ 2 Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
- ☐ 3 Moderate slowness, poverty or small amplitude of movement.
- ☐ 4 Marked slowness, poverty or small amplitude of movement.