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Longitudinal assessment of neural activity in Parkinson's disease with mild cognitive impairment using task based fMRI

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Longitudinal assessment of neural activities in Parkinson's disease mild cognitive impairment using task based fMRI

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Résumé

La maladie de Parkinson (PD) a été uniquement considérée pour ses endommagements sur les circuits moteurs dans le cerveau. Il est maintenant considéré comme un trouble multisystèmique, avec aspects multiples non moteurs y compris les dommages intérêts pour les circuits cognitifs. La présence d'un trouble léger de la cognition (TCL) de PD a été liée avec des changements structurels de la matière grise, matière blanche ainsi que des changements fonctionnels du cerveau. En particulier, une activité significativement réduite a été observée dans la boucle corticostriatale 'cognitive' chez des patients atteints de PD-TCL vs. PD non-TCL en utilisant IRMf. On sait peu de cours de ces modèles fonctionnels au fil du temps. Dans cette étude, nous présentons un suivi longitudinal de 24 patients de PD non démente qui a subi une enquête neuropsychologique, et ont été séparés en deux groupes - avec et sans TCL (TCL n = 11, non-TCL n = 13) en fonction du niveau 2 des recommandations de la Movement Disrders Society pour le diagnostic de PD-TCL. Ensuite, chaque participant a subi une IRMf en effectuant la tâche de Wisconsin pendant deux sessions, 19 mois d'intervalle. Nos résultats longitudinaux montrent qu'au cours de la planification de période de la tâche, les patients PD non-TCL engageant les ressources normales du cortex mais ils ont activé en plus les zones corticales qui sont liés à la prise de décision tel que cortex médial préfrontal (PFC), lobe pariétal et le PFC supérieure, tandis que les PD-TCL ont échoué pour engager ces zones en temps 2. Le striatum n'était pas engagé pour les deux groupes en temps 1 et pour le groupe TCL en temps 2. En outre, les structures médiales du lobe temporal étaient au fil du temps sous recrutés pour TCL et Non-TCL et étaient positivement corrélés avec les scores de MoCA. Le cortex pariétal, PFC antérieur, PFC supérieure et putamen postérieur étaient négativement corrélés avec les scores de MoCA en fil du temps. Ces résultats révèlent une altération fonctionnelle pour l'axe ganglial-thalamo-corticale au début de PD, ainsi que des niveaux différents de participation corticale pendant

une déficience cognitive. Cette différence de recrutement corticale des ressources pourrait refléter longitudinalement des circuits déficients distincts de trouble cognitive légère dans PD.

Mots-clé: la maladie de Parkinson, fMRI, WCST, trouble léger de la cognition

Abstract

PD was traditionally thought of as purely a movement disorder, now it is considered a multisystem disorder, with multiple non-motor aspects including damages to the cognitive circuits. Mild cognitive impairment (MCI) in PD has been linked with structural gray matter, white matter as well as functional brain changes. Specifically, significantly reduced activity was observed in the 'cognitive' corticostriatal loop in patients with PD-MCI vs. PD non-MCI using fMRI. Little is known regarding the course of these functional patterns over time. In this study we present longitudinal follow up of 24 non-demented PD who underwent neuropsychological investigation and were separated in two groups - with and without MCI (MCI n=11, Non-MCI n=13) according to the MDS level 2 recommendation for diagnosis of PD-MCI. Afterwards, each participant underwent an fMRI investigation by performing the Wisconsin Card Sorting Task over two sessions, 19 months apart. Our longitudinal results show that during planning set-shift period of the task, PD Non-MCI patients were engaging the normal cortical resources but they also activated more cortical areas at time 2 that are related to decision-making such as the medial prefrontal cortex (PFC), parietal lobe and the superior PFC, whilst the patients with MCI failed to engage these areas at both time points. The striatum was not engaged for both groups at time 2 and for MCI group at time 1. Furthermore, medial temporal lobe structures (MTLS) were under-recruited overtime for both the MCI and Non-MCI PD patients, and were positively correlated with MoCA scores over time. Parietal cortex, anterior PFC, superior PFC, and posterior putamen were negatively correlated with MoCA scores. These results reveal functional alteration along the basal ganglial-thalamo-cortical axis in early PD, as well as different cortical involvement levels along the course cognitive impairment. This discrepancy in cortical resources recruitment over time might reflect deficient circuitry distinct to cognitive impairment in Parkinson's disease.

Keywords: Parkinson's disease, fMRI, WCST, mild cognitive impairment

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List of abbreviations

AD – Alzheimer's Disease

ANOVA – Analysis of Variance

CSF – Cerebrospinal Fluid

DLPFC – Dorsolateral Prefrontal Cortex

DTI – Diffusion Tensor Imaging

H&Y – Hoehn and Yahr

MCI – Mild Cognitive Impairment

MMSE – Mini-Mental State Examination

MNI – Montreal Neurological Institute

MoCA – Montreal Cognitive Assessment

MRI – Magnetic Resonance Imaging

fMRI – Functional Magnetic Resonance Imaging

MTLS – Medial Temporal Lobe Structures

PD – Parkinson's Disease

PFC – Prefrontal Cortex

SMA – Supplementary Motor Area

SMC – Superior Motor Cortex

SPECT – Single Photon Emission Computed Tomography

UPDRS – Unified Parkinson's Disease Rating Scale

VBM – Voxel Based Morphometry

VLPFC – Ventrolateral prefrontal cortex

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« The dream was marvelous but the horror was great; we must treasure the dream whatever the horror; for the dream has shown that misery comes at last to the healthy man, the end of his life is sorrow. »

Enkidu's death, Tablet VII

« O Mighty King, remember now that only Gods stay in eternal watch. Humans come then go, that is the way fate decreed on the Tablets of Destiny. So someday you will depart, but till that distant day Sing, and dance. Eat your fill of warm cooked food and cool jugs of beer. Cherish the children your love gave life. Bathe away life's dirt in warm drawn waters. Pass the time in joy with your chosen wife. On the Tablets of Destiny it is decreed For you to enjoy short pleasures for your short days. «

Siduri to Gilgamesh, Tablet X

-The Epic of Gilgamesh.
Mesopotamia, Iraq. Circa 1800 B.C.

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CHAPTER 1

General introduction

1.1. Parkinson's disease historical background

Ever since first described in 1817 by James Parkinson in his classic publication "an essay on the shaking palsy", Parkinson's disease has been primarily recognized as a motor disorder. At the time, James Parkinson reported six cases of the disease, three of which were not actually examined by him, but rather casually observed in London's streets. Detailed observations of the patients' asymmetrical motor symptoms, the insidious onset and the long duration of disease were noted. Parkinson also noted the progression of disease; increase immobility, disturbances of sleep, speech and bodily functions. Though interestingly enough he stated "the senses and the intellects being uninjured".

Nearly 50 years later, Charcot suggested the name "Parkinson's disease," He classified the disorder as "névrose", meaning a neurologic disorder without a known pathologic lesion. Charcot found little benefit from therapies available at the time, including belladonna and ergot products (Goetz 1986). But it was not until 1913, when the pathognomic feature of the disease "Lewy bodies" that the disease was first described. Yet, no progress in dopaminergic treatment was made until the 1960's (Goetz 2000) when Birkmayer and Hornykiewicz's published their observations of the Levodopa's antikinetic effects on PD patients:

"Bed-ridden patients who were unable to sit up, patients who could not stand up when seated, and patients who when standing could not start walking performed all these activities with ease after L-dopa [levodopa]. They walked around with normal associated movements and they could even run and jump. The voiceless, aphonic speech, blurred by pallilalia and unclear articulation became forceful and clear as in a normal person" (Birkmayer and Hornykiewicz 1961).

These discoveries opened the chances for series of subsequent open-label and double-blinded placebo controlled levodopa trials. These trials came only to confirm both short and long-term benefits (Barbeau 1969; Cotzias et al., 1969; Yahr et al., 1969). While cognitive profile of other neurodegenerative diseases such as Alzheimer's disease were heavily investigated, it was only many years later when researchers have started to look into the cognitive decline in PD and eventually recognize it as an early component of the disease (Foltynie et al 2004).

Now, PD is now regarded as multisystem brain disease in which predisposed neuronal types in specific regions of the peripheral, enteric and central nervous systems become progressively involved by presenting neuronal loss, Lewy bodies and Lewy neuritis (Del Tredici et al., 2002) in the substantia nigra pars impacta which project to the dorsal striatum (McGeer et al., 2004), this neuronal involvement has a widespread and heterogeneous effects on the nervous system resulting in various clinical motor and non-motor expressions (Foltynie et al., 2002). Despite recent advances, much is yet unknown regarding the pathogenesis, characteristics and prognosis of the cognitive impairment in PD.

1.2 Etiology

It is unknown why the loss of nerve cells associated with Parkinson's disease occurs. PD is characterized by the loss of specific subsets of dopaminergic neurons in the substantia nigra pars compacta which project to the dorsal striatum (McGeer et al., 2004). However, PD is considered a multisystemic disorder in which predisposed neuronal types in specific regions of the peripheral, enteric and central nervous systems become progressively involved by presenting neuronal loss, Lewy bodies and Lewy neuritis (Del Tredici et al., 2002). The

neuropathology of PD is associated with alpha-synuclein-containing Lewy-Bodies (Sabbagh et al., 2009). Nevertheless, it has now become a fact that PD is much more than just the loss of nigro-striatal neurons, this morphological feature being only one aspect in the whole picture of the disease (Tolosa et al., 2009). A small proportion of cases can be due to known genetic factors such as in familial Parkinson's disease. Many experts think that the disease is caused by a combination of genetic, endogenous risk factors and environmental factors, which may vary from a patient to another. Yet, the interactions between these factors with their triggering to susceptible genes are yet to be discovered (De Lau et al., 2006).

1.2.1. Environmental factors

Epidemiological researchers have identified several environmental factors such as; exposure to certain toxins or injury, rural living, well water, industrial pollution, manganese, smoking, saturated fatty acid rich diet and pesticides might increase the risk of developing PD, however, cause-effect relationship is yet to be identified. In 2009, the US Department of Veterans Affairs added PD to a list of diseases possibly associated with exposure to a synthetic neurotoxin agent called Agent Orange or MPTP (an agent used in studying laboratory models of PD) which can also cause immediate and permanent Parkinsonism. There is a chemical resemblance between MPTP and some of herbicides and insecticides.

This resemblance suggested that an MPTP-like environmental toxin might be a cause of environmental cases of Parkinson disease, but no specific agent has been yet identified. Nonetheless, it was found that mitochondrial complex I activity is reduced in Parkinson disease, suggesting a common pathway with MPTP-induced Parkinsonism. Thus, environmental etiology in MPTP exposure can be attributed to the dopaminergic loss as in

well water study (Gatto et al., 2009). Luckily, cases of MPTP-induced Parkinson's in the general population are very rare. It is also noted that a simple exposure to an environmental toxin is never enough to cause Parkinson's. There is an inverse association between smoking and PD, and coffee consumption seems to decrease the risk of PD (Liu et al., 2012). Dietary factors such as diet rich in polyunsaturated fatty acid and low in saturated fatty acid might lower the risk of developing PD; however consistent results are still missing (Kamel et al., 2013).

1.2.2. Genetic factors

PD has been traditionally considered a non-genetic disorder. However, around 15% of individuals with PD have a first-degree relative who has the disease (Samii et al., 2004). At least 5% of people are now known to have forms of the disease that occur because of a mutation of one of several specific genes (Lesage et al., 2009). Our understanding of genetics in PD is limited by several factors; the penetrance of mutations is often unknown, clinical and pathological expressions are variable, and presence of a genetic mutation indicates a risk for developing PD. Furthermore, genetic research though advancing has not been able to establish estimates about timing of disease onset (Stephenson et al., 2009).

Nevertheless, in the last two decades there have been some discoveries in understanding the genetic causality and association with PD. The Contursi kindred family showed for the first time that PD could indeed be inherited (Golbe et al., 1990). Six generation of large family in Iowa with autosomal dominant Parkinson's disease were studied. The 'Iowa kindred' or 'Spellman-Muenter kindred' family study (Devine et al., 2011) provided good insight regarding the genetic risk factors predisposing to Parkinson's disease.

The genetic causality of Parkinson's disease can be outlined by categorizing the genes into two major categories; causal and PD-associated genes. An example of causal genes is alpha-synuclein, which is located on chromosome 4. Normally, the chromosome carries only a single copy of the alpha-synuclein gene, but members of Iowa kindred family with Parkinson's carried three copies of the gene. This extra dose of alpha-synuclein caused certain family members to develop Parkinson's at a young age. This study proved the important role that the alpha-synuclein gene plays in PD because the alpha-synuclein protein is the main component of Lewy bodies (Lesage et al., 2009).

1.3. Epidemiology

Following Alzheimer's disease, idiopathic PD is the second most frequent neurodegenerative disorder (Rijk et al., 1997). Studies have shown that PD has increasing prevalence with age, with about 1 % of the population over the age of 60, and about 4 % of people in the highest age groups being affected by PD (De Lau et al., 2006). Furthermore, PD also affects 10 percent of people older than 80 years of age. This disease affects over 4 million people over age 50, and the rates in 2005 were expected to double over the following 2 decades (Dorsey et al., 2007). As a general estimation, PD affects around 1-4 % of the general population more than 60 years of age (De Lau et al., 2006). PD is about 1.5 times more common in men than in women.

Gilberto Levy proposed a model for the relationship between PD and aging; he also noted an interaction between the effects of age and disease on non-dopaminergic structures (Levy et al., 2007); stating that advancing age, rather than disease duration, is the most important determinant of clinical progression (Levy et al., 2007).

The Parkinson's disease society in Canada estimates that more than 100,000 Canadians are thought to have Parkinson's disease. Due to the aging baby boomer population, this number is expected to rise dramatically. The population aged 65 and over is predicted to rise over 30 years from 11.6% to 23.6% (Parkinson Society Canada fact Sheet, April 2014). The age onset of PD is quite variable; yet, the majority of cases are being diagnosed as late as age of 50 those diagnosed with Parkinson's under the age of 40 is referred to as "Young Onset." It has been recently suggested that the age related Alzheimer's type pathology and the age at which the disease symptoms onset are the two major factors for the PD pathology progression (Halliday et al., 2010).

1.4. Neuropathology and anatomy

Histologically, PD is characterized by the presence of intracellular alpha-synuclein positive inclusions containing Lewy-bodies and Lewy neuritis (Sabbagh et al., 2009). It is also characterized by a subsequent reduction of dopaminergic cells in the substantia nigra pars compacta (Fearnley et al., 1991) and a resultant dopamine deficiency in specific nuclei of the basal ganglia.

The mechanism by which this dopaminergic cellular loss occurs has not yet been well understood. There is speculation of several mechanisms by which the brain cells could be lost (Obeso et al., 2010). However, animal models have shown that the injection of synthetic α-synuclein fibrils in mice induced Lewy body like pathology, progressive dopaminergic cell loss in the substantia nigra, and motor impairments. It has been also suggested that the abnormal accumulation of alpha-synuclein that bound to ubiquitin intracellularily might provide an explanation for the dopaminergic cellular loss, the accumulated insoluble protein

forming Lewy bodies throughout subcortical and cortical brain regions (Davie 2008; Schulz-Schaeffer 2010). There are other researchers who have suggested cell-death mechanisms including protosomal and lysosomal system dysfunction and reduced mitochondrial activity. However, none of these studies has been confirmed yet (Obeso et al., 2010). Regardless of the different suggested mechanisms, the resulting dopaminergic deficiency subsequently explains the motor and cognitive dysfunction. Arguably, this explanation does not account for the full clinical picture seen in patients with PD (Rodriguez-Oroz et al., 2009).

Heiko Braak presented a theory, suggesting that the distribution pattern of alpha-synuclein develops in a topographically predictable sequence in six stages, during which Lewy bodies first appear in the olfactory bulb, medullar oblongata and pontine tegmentum in the first 3 stages, with individuals at these stages being asymptomatic. As the disease progresses, Lewy bodies develop in amygdalda and thalamus. According to the Braak model, in the final stages (Braak V-VI) areas in the basal ganglia are affected and the pathological process might reach the sensory association cortex, prefrontal cortex and finally the entire neocortex (Braak et al., 2004; Braak et al., 2006). There are conflicting opinions about this model and it has been criticized because it does not provide convincing evidences for the caudal to rostral temporal progression of the disease and for the possibility of a beginning of the deficits in non-dopaminergic system of the brainstem (Burke et al., 2008). Nevertheless, Braak's model has been globally confirmed and validated by other investigators (Parkkinen et al., 2008). Furthermore, the neuropathology of synuclein has shown a potentiality to better understand the pathogenesis of PD.

Others suggested that in the earlier stages of PD, dopamine depletion is restricted to the putamen and dorsal caudate nucleus, originating from substantia nigra, and only later progresses to the more ventral parts of the striatum and the mesocorticolimbic dopaminergic, this results in decreased inhibition of the internal globus palidus via direct pathway and increased excitation of the internal globus palidus via the indirect pathway. In turn, this results in increased inhibition of the thalamus and reduced excitation or inhibition of the cortex, depends on the task performed (Rosvold 1972; Kish et al., 1988; Swainson et al., 2000; Cools et al., 2001). This explanation can account for the dopamine depletion evolving in a spatiotemporal pattern within the striatum and the terminal distribution of its cortical afferents to explain the cognitive impairment in PD (Monchi et al., 2010).

1.5. Clinical Features

1.5.1. Motor signs and symptoms

The clinical presentation of PD is quite variable (Weiner 2008). The major clinical motor signs of PD are resting tremor, bradykinesia, rigidity, and postural instability (Gelb et al., 1999). These signs are typically unilateral in early PD. The cardinal resting tremor sign is the most common motor symptom in PD occurring in approximately 70% of patients (Jankovic et al., 1990). Tremor in the upper extremity usually starts in the fingers or thumb, as the disease progresses, tremor may spread to lower extremity on the same side or the other upper extremity before it gets generalized, albeit, it remains asymmetrical. PD clinical presentation is very heterogeneous and even presents different motor subtypes according to the pathology and the pattern of disease progression. It has been also found that tremor-dominant patients have a slower rate of progression and better prognosis than akinetic, or

non–tremor-dominant patients (Rajput et al., 1993). On the other hand, Postural gait instability is usually observed in later stages of the disease, it is poorly responsive to treatment and represents a common source of impaired balance and frequent falls (Yao et al., 2013) and a poor prognostic factor (Foltynie et al., 2002).

1.5.2. Non-motor signs and symptoms

As discussed earlier, according to Braak's model PD begins its progression at the base of the brainstem long before it is detected (Braak et al., 2004). By the time patients visit the neurologist clinic for the first time, PD is on an already ongoing progression. The motor deficits present after a 40-60% of dopaminergic neuron loss in the striatum (Obeso et al., 2000). There has been a growing notion that many non-motor symptoms might present earlier than the cardinal motor symptoms. The non-motor symptoms that are thought to be present in early stage of PD are: olfactory dysfunction, autonomic dysfunction such as constipation and bladder dysfunction, sleep disturbances, mood changes and cognitive dysfunction. Many of these could be explained by the Braak hypothesis and give rise to investigate possible signs of pre-symptomatic PD (Tolosa et al., 2009).

Non-motor symptoms are common in PD. In fact, more than 50% of PD patients experience olfactory dysfunction such as anosmia, 35% of patients have severe hyposmia and 14% of patients have moderate hyposmia (Hawkes et al., 1977; Muller et al., 2002). Depression is highly frequent in PD, occurring in up to 45% of cases (Burn 2002). In a longitudinal study, it was suggested that there was an increased risk of developing PD in subjects suffering from depression as compared to not depressed ones (Schuurman et al., 2002). Furthermore, the great majority of PD patients develop sleep disruption, and there is evidence that the process usually starts at early stages of the disease (Chaudhri 2003).

Virtually all PD patients suffer from autonomic dysfunction represented by constipation (Magerkurth et al., 2005). Subtle autonomic disturbances that can at least partly be related to the degeneration of the vagal nerve are an early and frequent sign in PD (Micieli et al., 2003). Presence of these "pre-motor" signs and symptoms implicate a possibility of early detection, which might help in early treatment, control of debilitating prognosis and decrease morbidity. However, having screening tools that are cost effective added to the lack of effective therapeutic regimes and knowledge of course PD pathology (Stephenson et al 2009) are what complicate our approach to PD.

Although long-term studies in PD have demonstrated that most patients will eventually develop dementia, the time of onset of dementia and the less sever cognitive deficits is variable (Pedersen et al., 2013). Through the usage and the interpretation of neuroimaging techniques, this research aims at recognizing patterns of neural activation using functional magnetic resonance imaging in order to better characterize and predict cognitive dysfunction. By providing an overview of neuroimaging findings specific to MCI, this research hopes to delineate a better understanding of the course of the disease at early stages. In addition, methodological issues involved in studying this heterogeneous population and future directions to continue to improve our understanding of the clinical subtypes cognitive dysfunction will also be highlighted and discussed. Due to the relevance of understanding cognitive dysfunction in PD, a separate section of this thesis is going to be dedicated to discuss it in depth.

1.6. Diagnosis

Diagnosis of Parkinson's disease relies primarily on clinical history and neurological examination. The diagnosis of idiopathic PD is often challenging because the symptoms are generally insidious, and a list of differential diagnosis might be extensive, including other Parkinsonism producing disorders such as AD, Lewy-body dementia, progressive supranuclear palsy and parkinsonian 'plus' disorders such as Multiple System Atrophy and Progressive Supranuclear Palsy. On the other hand, as the disease takes its chronic course, the progress might reveal misdiagnosis. For that reason some authorities recommend that the diagnosis be periodically reviewed (National Collaboration Centre for Chronic Conditions in Great Britain 2006).

There are several suggested diagnostic criteria by different authorities; based on the apparent motor signs and the response to dopaminergic treatment. However, this research has adopted the United Kingdom PD society brain bank criteria to diagnose participants in the study. These criteria require presence of slowness of movement as well as resting tremor or rigidity or postural instability. The other differential causes for these symptoms -if present- need to be ruled out as well. The UK PD society criteria also require that more than two of the following are identified during the onset or along the course of the disease; unilateral onset, tremor at rest, progression in time, asymmetric motor symptoms, response to levodopa for at least five years, clinical course of at least ten years and appearance of dyskinesia induced by the intake of excessive levodopa. (Jankovic et al., 2008) The accuracy of diagnostic criteria valuated at autopsy is 75–90%, with specialists such as neurologists having the highest diagnosis rates of accuracy (Jankovic et al., 2008).

One of the clinical tools to evaluate the severity of PD and follow its clinical progression longitudinally is known as the Unified Parkinson's Disease Rating Scale (UPDRS). Following the UPDRS scores over time provides insight into the patient's disease progression. Hoehn and Yahr (H&R) scale is another scaling system that defines PD into five basic stages according to the severity of symptoms. There is a little role of neuroimaging for PD diagnosis; anatomical MRI and CT scans used in clinical settings of PD patients usually appear normal. However, MRI and CT scan may be used to rule out disorders that could have similar symptoms and they considered the corner stone in the research field of PD.

1.7. Treatment

Treatment of PD is not therapeutic. It provides symptomatic relief. It encompasses medications that are useful for the motor symptoms. Dopamine replacement therapy such as Levodopa, several dopamine agonists, Monoamine oxidase (MAO) inhibitors, deep brain stimulation and surgery are examples of PD treatment options. The group of medication chosen to administer relies on the stage of the disease. For example, if the patient presents with initial disabilities that require medical intervention, agents such as MAO-B inhibitors or dopamine agonists are of choice since they provide a good symptoms control with minimal side effects as compared to Levodopa, Levodopa use will be delayed as much as possible. Nonetheless, if the patient presents with motor symptoms, and was already administered Levodopa, and experienced medication side effects such as wearing off and dyskinesia, the treatment will aim to control the dose fluctuation by using multiple regimes. Ultimately, for PD patients suffering from uncontrolled predominantly motor symptoms, surgical options including deep brain stimulation can be used.

Further studies have also indicated that Cholinesterase inhibitors might be useful for PD patients with cognitive dysfunction, agents such as Donepezil was associated with improvements in memory monitoring (Leroi et al., 2004). Recent studies have documented benefits from MAO inhibitors. MAO inhibitors have demonstrated potential neuroprotective effects that might slow the progression of the disease, in addition to increase dopamine levels in the brain. Rasagiline, a selective MAO type-B inhibitor, to PD-MCI patients may exert beneficial effects on certain aspects of attention and executive functions for non-demented PD (Hanagasi et al., 2011) and might be beneficial for the with dementia as well (Emre et al., 2004).

1.8. Cognitive Dysfunction

1.8.1. Dementia

Dementia is a common late feature of PD. A person with PD has two to six times the risk of dementia compared to the general population with a dramatic impact on the quality of life and it is considered a risk factor to place PD patients in nursing homes facilities (Aarsland et al., 2001; Caballol et al., 2007). It usually occurs at late stages of the disease and the prevalence of dementia increases with duration of the disease (Caballol et al., 2007). Histologically, PD-dementia has shown a more generalized pattern of Lewy body distribution and an Alzheimer's like pattern of neurofibrillary triangles and senile plaques (Dickson DV 2007). Typically PD-dementia has an insidious onset, and a slow progression; developing within the context of an already diagnosed PD. PD-dementia usually involves different cognitive domains such as attention, memory, visuospatial, constructional and executive domains.

The diagnosis of PD-dementia is clinical. It relies on medical history, neurological and mental examination. It is important to differentiate PD-dementia from other neurodegenerative disorders such as dementia with Lowy bodies, the latter typical presents with dementia, vivid visual hallucinations and Parkinsonism. This might be quite challenging given the shared features of the two diseases, therefore, some authorities suggest periodic re-evaluations for diagnosis. Dementia is associated with a reduced quality of life in people with PD and their caregivers, increased mortality, and a higher probability of needing nursing home care (Carballo et al., 2007).

1.8.2. Mild Cognitive Impairment (MCI)

MCI was originally a term used for description of the transitional stage between normal cognitive functioning and AD (Petersen 2004). Later on; it has been implemented to categorize non-demented PD patients with cognitive dysfunction that –unlike dementia- does not intervene with their life style. One major challenge when attempting to understand the nature and source of this deficit, is the marked cognitive heterogeneity that exists amongst PD patients. Furthermore, Even among PD-patients presenting significant cognitive deficits, there is great variability with respect to which cognitive domain is affected. This variability can be partially explained by the inhomogeneous dopamine decrease in the basal ganglia and the related circuits (Lewis and Barker 2009; Sawamato et al., 2008). Some of the cognitive domains that are typically affected in PD include; fronto-executive functions (e.g. planning and set-shifting), memory, non-frontal lobe derived dysfunctions such as visuospatial and language function difficulties (Janvin et al., 2003; Mamikonyan et al., 2009).

Single domain impairment is more common than multiple domains and within a single domain; nonamnestic impairment is more common than isolated amnestic deficits (Litvan et al., 2011). Although increasing age is associated with cognitive dysfunction in PD patients, this variable alone, does not account for the higher prevalence of dementia in PD patients compared to the general population (Janvin et al., 2006).

MCI can be diagnosed using neuropsychological assessment tests. However, unified comprehensive neuropsychological testing tools were lacking. For that reason, the movement disorder society (MDS) initiated a task force that included guidelines to diagnose MCI. These guidelines also provide examples of appropriate neuropsychological testing for each cognitive domain (Litvan et al., 2012). The guidelines consist of two main categories of criteria; level II and I.

Level I category of the MDS task force is based on an abbreviated cognitive assessment to detect a possible PD-MCI. The requirements for level I are impairment on a scale of global cognitive abilities validated for use in PD or impairment on a limited battery of neuropsychological tests each assessing a domain such as attention and working memory as well as executive, language, memory, and visuospatial functions. Impairment must be present on at least two tests to diagnose PD-MCI by level I criteria. Level I criteria do not allow complete subtyping of PD-MCI and they provide less diagnostic certainty than level II. (Litvan et al., 2012). However, they are more suitable for clinical practice as well as for large-scale studies (Pedersen et al., 2013) when the comprehensive neuropsychological testing is not practical or unavailable.

By level II criteria, the (MDS) task force recommends formal, comprehensive neuropsychological testing that encompasses at least two tests for each of the five cognitive domains previously listed. Impairment should be present on at least two tests, either within a single cognitive domain or across different cognitive domains. The use of two tests in each cognitive domain (minimum of 10 tests) for the level II category addresses all cognitive domains equally, can increase sensitivity, and allow full subtyping of PD-MCI (Litvan et al., 2012).

Some of the validated tests of global cognitive ability in PD are the Montreal Cognitive Assessment, the Parkinson's Disease-Cognitive Rating scale, Scales of Outcomes of Parkinson's disease-Cognition and the Blessed Dementia Rating Scale.

1.9. Biomarkers for MCI

Early interventions have the potential to exhibit better outcomes if taken place early enough in the course of PD. Therefore, early detection of MCI can be critical not only in treating but also in initiating a clinical diagnostic design to help predicting the future occurrence of PD dementia as early as possible. Biomarkers for PD-MCI including Cerebrospinal fluid, neurophysiology, genetics and neuroimaging are currently under study, their use in combination, or separately to incorporate them in PD-MCI criteria is to be determined.

1.9.1. Cerebrospinal fluid (CSF)

Proposed CSF biomarkers for PD-MCI include those which have been incorporated into researching criteria for AD-MCI in an effort for early detection and interventions (i.e., low beta-amyloid -42 peptide and elevated total tau or phosphorylated tau levels), because these might be components of an inflammatory or oxidative stress process subsequent to the degenerative disease (Albert et al., 2011). While some suggested that CSF beta-amyloid -42 and tau predict cognitive decline in PD as well (Alves et al., 2010; Montine et al., 2010; Shi et al., 2010; Siderowf et al., 2010); others proposed that progression from very mild MCI to more pronounced MCI was not reflected by these biomarkers deviations (Wallin et al., 2011). It is also concerning that variability between testing laboratories for CSF may limit the utility of these techniques in clinical practice (Zhang et al., 2007). Therefore, whether CSF biomarkers are useful in early stage PD requires further research.

1.9.2. Genetics

Genetic biomarkers that have been identified in PD patients with cognitive dysfunction encompassed polymorphisms related to dopamine regulating enzyme in the prefrontal cortex [catechol-O-methyl transferase gene (COMT Val158Met)], which affect executive function tasks (Foltynie 2004) and microtubule-associated protein tau gene (MAPT) H1/H1 genotype. An inversion polymorphism in the latter was found to be a risk factor for dementia PD patients as compared to normal control (Goris et al., 2007; Seto-Salvia et al., 2011) and associated with greater posterior cortical cognitive impairments (Williams-Gray et al., 2009). These findings tend to support the hypothesis that posterior as compared to frontostriatal cortical cognitive deficit may have a higher risk for developing dementia in PD patients (Ekman et al., 2014). Recent study in our laboratory revealed that VNTR DAT 1 porlymorphism has shown to play a role in cortico-striatal activation and cognition Habak et al., (in press). Yet, more research needs to be conducted to specify the importance genetic markers on the early prediction of dementia in PD.

1.9.3. Neurophysiology

It was reported that there were increases in slow wave activity, and a decreased alpha and fast wave activities at the frontal pole, frontal location specifically in patients with executive dysfunction also increases in the absolute and relative posterior theta amplitude have been reported (Fonseca et al., 2009).

These quantitative electroencephalogram characteristics in PD-MCI might represent an intermediate electrophysiological state along the disrupted cognitive spectrum that could complement neuropsychological testing to detect MCI; however, it does not elaborate on the underlying pathophysiology of the disease. These biomarker findings merit replication in larger samples, with

particular attention to PD-MCI longitudinal follow-up of the patients to establish risks of cognitive decline.

1.9.4. Neuroimaging

This chapter will briefly describe the principles behind different examples of neuroimaging techniques and discuss the role of such imaging in assessing the cognitive dysfunction in PD. Neuroimaging shed the lights on the global consequences of the nigro-striatal dopaminergic degeneration. Functional imaging in the resting state as well as task-based paradigms has been applied to the study of cognitive dysfunction in PD because they offer a unique possibility to evaluate physiological responses in relation to cognitive dysfunction in PD patients.

Functional Magnetic Resonance Imaging fMRI is considered a corner stone for research publications and its use increasingly overtook other modalities such as Single Photon Emission Computed Tomography (SPECT) in the research field. Albeit, efforts have been made to incorporate neuroimaging in clinical practice as diagnostic tool for PD, and may eventually assist to develop and assess of new therapies. Structural and metabolic neuroimaging may provide another potential biomarker for PD-MCI.

1.9.4.1. Structural MRI

When a patient's head is in the MRI scanner, it is being subjected to a strong and a uniform magnetic field. Subsequently, the hydrogen atom of H2O molecules in the tissue spins around itself, creating a small magnetic field called the magnetic moment. When subjected to the strong uniform larger magnetic field, the atoms align themselves along the large magnetic field, ultimately; each atom will spin with a certain frequency called the Larmor frequency. This spinning will be either parallel or anti-parallel to the large magnetic field.

Energy is applied at a certain radiofrequency pulse, which in turn leads to the excitation hydrogen atoms, flipping them out of their axis and they eventually returns, back to equibilirium state. The difference between the energy levels of the two states, create a signal correspondent to an area within the tissue investigated, this recovery from the applied magnetization is necessary to create the T1-weighted image.

Applying a radiofrequency pulse also leads the incoherent atoms to dephase themselves on the transverse plane, when the radiofrequency pulse is removed, the atoms loses energy to "relax" and go back to be phased, the difference in decay of the different amount of magnetization create the T2-weighted image.

In T1 weighted image, the T1 relaxation time reflects a better image quality when the spinning is at Larmor frequency and the protons are bound to their surroundings. This leads to a short T1 relaxation time, which in turn allows for some structures to look bright (white matter). Whilst the T1 relaxation time is long in a tissue where the hydrogen protons are free from their surroundings, such as in fluid, leading to some other structures to look dark in color as in cerebrospinal fluid (CSF).

Thus, T1-weighted images are optimal to visualize the gray matter as it appears with intermediate gray signal.

By contrast, in T2 weighted image, the protons can move freely and remain phased for a long time in fluid as in CSF, resulting in a strong signal and that's why it appears bright. Whilst in solid tissue, the T2 relaxation happens fast; leading to a darker image, for that reason the gray matter appears with a dark signal. T2-weighted images are optimal for visualizing abnormalities in the white matter.

Various techniques have been adopted to analyze structural MRI images including volumetric, Voxel-based densometry (VBM) and white matter density. Volumetric MRI acquisitions rely basically on dividing a region of interest (ROI) into voxels (3-dimentional slices usually as low as 1 millimeter cubic), it provides a high resolution, yet it has a high signal to noise ratio. By contrast, the VBM is a method used to assess density and atrophy local grey and white matter density over the whole brain.

Using VBM, reduced gray matter in the left frontal and bilateral temporal lobe regions, compared to PD without MCI was noted (Beyer et al. 2007); however, sample size was small and these differences were not significant after corrections for multiple comparisons. Volumetric MRI, even in non-medicated patients with early PD, has been able to identify some correlations between focal regions of atrophy and specific cognitive impairments (Brück et al. 2004). Left hippocampal atrophy was found to be associated with impaired memory, whereas prefrontal cortex atrophy was associated with sustained attention (Brück et al., 2004).

Early work using ROI methods and visual rating showed that parkinsonian patients (including both PD-MCI and Lewy-body dementia) demonstrated frontal, temporal lobe and hippocampal atrophy in addition to frontal horn ventricular enlargement when compared to normal control (Meyer et al., 2007). However, the sample included those with Lewy body dementia.

Some studies reported medial temporal lobe atrophy in PD-MCI and non-PD MCI using various imaging methods (Lerch and Evans 2005; Jubault et al., 2011) in fact; cognitive impairment in PD was associated with structural cortical and striatal atrophy (Camicioli et al., 2009).

It is established that cortical atrophy does not occur in PD without a comorbid cognitive impairment as PD-MCI displays atrophy different from to that with PD with normal cognition, which is characterized by atrophy of the hippocampus, prefrontal cortex gray and white matter, occipital lobe gray and white matter, and parietal lobe white matter (Weintraub et al., 2011), this effect was stronger for patients with dementia. These findings were replicated later using cortical thickness measures. Atrophy in SMA, medial occipital lobe and temporal lobe were identified and merited to be considered in the future as markers of cognitive decline in PD patients (Hanganu et al., 2013). Albeit, other researchers were unable to find neither regional grey matter atrophy in newly diagnosed PD patients nor any association between grey matter atrophy and cognitive impairment (Dalaker et al., 2011). All these conflicting findings asserted the urgency to initiate a prospective study to evaluate structural MRI as biomarker for MCI.

A recent longitudinal study in our laboratory showed that the early presence of mild cognitive impairment in patients with Parkinson's disease was associated with a faster rate of grey matter thinning in various cortical regions as well as a significant diminishment of limbic subcortical structures (Hanganu et al., 2014).

Structural ventricular changes have been also reported in PD-MCI such as posterior ventricular enlargement (Apostolova et al., 2010) as well as enlarged left inferior lateral ventricle and third ventricles (Dalaker et al., 2011) compared to PD without MCI and healthy controls; fourth ventricle size was highly correlated with memory in PD-MCI patients (Dalaker et al., 2011).

1.9.4.2. Single photon emission computed tomography (SPECT) and Positron emission topography (PET)

PET and SPECT imaging use a number of radiotracers for in vivo to assess brain function. These techniques have been extensively used to study the dopamine system in PD. Radiolabeled water or glucose can used to trace the cerebral blood flow and glucose metabolism. Although not specifically addressing the evolution of PD-MCI early on, SPECT and PET has demonstrated a potential to identify preclinical metabolic changes in PD. Reduced striatal uptake of the ipsilateral as well as the expected contralateral affected side was discovered in PD (Schwarz et al., 2000). It also estimated that approximately 50% reduction in dopaminergic nigro-striatal cells is required before clinical expression of the motor symptoms takes place (Schwarz et al., 2000; Marek et al., 2001).

Executive dysfunction in PD was found to be correlated with dopamine levels in striatal and cortical regions utilizing fluorodopa PET imaging (Rinne et al., 2000). Studies showed impaired metabolism in posterior cortical regions, similar to regions that are frequently abnormal in PD-Dementia patients (Goldman et al., 2011). These findings have opened the chances for researchers to investigate the underlying changes in brain activation and integrity associated with MCI using metabolic studies.

Using 18F-flurodeoxyglucose (FDG) PET scans has shown that PD-MCI patients with multiple domains impaired had patterns of decreased glucose metabolism in prefrontal and parietal areas compared to PD non-MCI; those with a single domain affected had a similar pattern but to a lesser degree than in the multiple domain PD-MCI (Huang et al., 2008). In another study the PD-MCI group demonstrated relative hypometabolism in bilateral posterior parietal lobe and right occipital lobe compared to healthy controls and parietal, temporal, and occipital hypoperfusion compared PD non-MCI. Interestingly, compared to the amnestic MCI patients (without PD), the PD-MCI had greater hypoperfusion in parieto-occipital regions, whereas the amnestic MCI patients had greater hypoperfusion in medial temporal lobe regions (Nobili et al., 2009). These studies though had promising findings; they were only conducted in small cohorts with no longitudinal assessments.

SPECT was used to assess presynaptic dopamine integrity in a recent prospective cohort study, it was discovered that PD-MCI had significantly reduced presynaptic uptake of dopamine in the striatum (right caudate) compared to PD non-MCI (Ekman et al. 2012). SPECT can offer insight about various underlying reasons behind consequent pathological changes and the related altered activation patterns in a way that cannot be achieved with the use other neuroimaging modalities. However, the use of radiation, the lower spatial and temporal resolution as compared to other imaging modalities and cost effectiveness, impose limits on the number of scans that can be performed, thus on the clinical application of this technique.

1.9.4.3. Diffusion tensor imagine (DTI)

DTI measures the magnitude and direction of diffusion of H2O molecules within the brain. This technique can be used to infer the integrity of neuronal fiber tracts. Although not specifically

addressing PD-MCI, studies have shown that a reproducible pattern of degeneration in the microstructure of substantia nigra, thalamus, motor, premotor and supplementary motor areas with a positive correlation between the fractional anisotropy within the somatosensory cortex and the severity of Parkinson's Disease (Zhang et al., 2011).

1.9.4.4. Functional Magnetic Resonance Imaging (fMRI)

fMRI takes advantage of the difference between magnetization of oxygenated and deoxygenated hemoglobin in order to create a signal that represents a dynamic change in neuronal activity related to a correspondent local blood supply increase. The neuronal activity is paired with a hemodynamic process, through which an increase in the blood flow takes place due to a regional increase in demand. This process results in a relative decrease in deoxyhemoglobin, and a subsequent magnetization difference that can be detected. This difference represents a Blood Oxygenation Level-Dependent (BOLD) signal in a way that more neuronal activity leads to a higher increase in blood flow demand, which consequently leads to a more detected signal. Different tasks elicit different neuronal activities at different regions within the operative brain.

Resting-state fMRI by contrast, has emerged with a potentiality to resolve the complicated functional brain networking (Fox and Raichle 2007). It measures patterns of spontaneous fluctuations in the hemodynamic activity “at rest” when no task is performed. It relies on functional connectivity (the regional correlation between temporal activities of distant brain regions). The hemodynamic fluctuations from a selected (a priori) seed region of interest are correlated to all other brain regions using multivariate techniques. Only few studies have looked at resting-state PD (Wu et al., 2009; Helmich et al., 2010).

There is little research conducted using resting-state fMRI to look into PD-MCI. However, cross correlation connectivity analysis has revealed a loss of integrity in the functional connectivity between paracingulate gyrus and precuneus as well as between the right middle frontal gyrus and the bilateral superior parietal lobes (Segura et al., 2013). Functional connectivity profiling of the subthalamic nucleus in PD patients at rest through the use of fMRI has revealed an increased activation of circuits between the subthalamic nucleus and cortical motor areas (Baudrexel et al., 2011). This is believed to be a result of reduced dopaminergic input from the striatum via both direct and indirect feedback loops (Alexander et al. 1990).

1.9.4.4.1. Task-based fMRI

Tasks linked to various cognitive processes were utilized with fMRI to implicate different neural mechanisms early PD patients, however, we will concentrate here on memory and executive tasks (involving set shifting and decision making) these are the two cognitive domains the most affected in early PD (Sollinger et al., 2010; Zakharov et al., 2001).

1.9.4.4.1.1. Memory task

Memory Impairment begins to manifest at the early stages of Parkinson's disease and presents as several types of dysfunction as the disease progresses (Aarsland et al., 2008). It is associated with nigro-striatal (Rinne et al., 2000; Cools 2006; Ekman et al., 2012) and meso-cortical (Mattay et al., 2002; Monchi et al., 2007) dopaminergic dysfunction. Therefore, memory tasks were useful to evaluate the cognitive impairment in early PD.

Delayed recall and Learning are affected early on whilst recognition memory decline is not apparent until the later stages of PD (Higgenson et al., 2005). By using a recognition memory

paradigm, a decreased deactivation of the paracingulate gyrus and precuneus were found to be characteristic of patients with early PD (Segura et al., 2013). And using the Free and Cued Selective Reminding paradigm (Buschke et al. 1997), it was recognized that in amnestic PD-MCI, episodic memory impairment was related to frontal-related retrieval rather than to temporal-mesial consolidation failure suggesting that memory deficits might be due to altered frontal-related executive functioning (Costa et al., 2014).

Longitudinal studies should be performed to verify the sensitivity of the above paradigms in predicting dementia in PD-MCI patients.

Using a working memory paradigm, a significant signal intensity reduction in specific striatal and frontal lobe sites in PD patients with cognitive impairment (with selective executive dysfunction) compared with those patients who were not cognitively unimpaired (Lewis et al., 2003). Further research revealed under-recruitment in the right dorsal caudate nucleus and the bilateral anterior cingulate cortices during working memory tasks in PD-MCI compared to healthy control individuals (Ekman et al., 2012) areas that were interestingly also shown to be significantly hypoactivated in PD patients during olfactory tasks (Hummel et al., 2010).

A recent longitudinal study assessed changes in working-memory related brain responses in PD with and without MCI. It proposed that posterior cortical changes across time might be more pronounced than fronto-striatal changes in patients with PD and MCI, reflecting progression toward prodromal PD-dementia (Ekman et al. 2014). This was in line with previous hypothesis that cognitive decline might be related to neural dysfunction with posterior rather than front-striatal circuit process (Huange et al., 2007; Williams-Gray et al., 2007).

1.9.4.4.1.2. Executive task

Another example of the task-based fMRI is that using executive tasks to elucidate a desired neuronal reaction in relation to planning and execution of taking decisions. fMRI was found to useful early on to identify the neural locus of the selective executive deficit in a subgroup of patients with early PD (Lewis et al., 2003). An event-related fMRI protocol using Wisconsin Card Sorting Task (Monchi et al. 2000) investigated activation during distinct stages of the task in healthy young adults, it showed implication of two cortico-striatal loops including the ventrolateral PFC, the caudate nucleus, and the thalamus during planning of a set-shift, and of another including posterior PFC and the putamen during the execution of a set-shift (Monchi et al., 2004).

Using the same protocol in early-stage PD (off-medication), (Monchi et al., 2004) found a decrease in the activity of the VLPFC and the posterior PFC as compared to healthy age-matched controls who had both these regions co-activated when the striatum is needed in this task.

Although these cross-sectional studies have shed the lights on the anatomical and neurochemical bases of PD-MCI, arguably, only one longitudinal cohort used task-based brain responses to evaluate the underlying mechanisms and the evolution of PD-MCI (Ekman et al., 2014). Therefore, longitudinal cohorts studies are essential in order to better understand underlying mechanisms (Monchi and Stoessl 2012; Ekman et al. 2012).

Considering the aforementioned work highlighting the relevance of MCI as a potential prodromal phase of dementia, and the limited longitudinal research on specific functional neuroimaging cognitive profiles in early PD; the major goal of this thesis is to longitudinally analyze the patterns of neural activation in early PD patients with respect to cognitive impairment, which can be most predictive for the future occurrence of dementia in PD. We expect that PD-MCI and PD non-MCI to differ with respect to their patterns of activations observed with our WCST fMRI protocol at each time points as well as longitudinally.

To provide direct empirical findings to support this general hypothesis, we carried out a longitudinal cohort of PD-MCI and PD non-MCI patients. Their cognitive profiles were evaluated using a neuropsychological evaluation that was in line with the MDS task force recommendation for level II assessment. Participants were followed longitudinally at two time points, baseline and after 18-months. To identify predictive markers that can distinguish between the two groups we used fMRI during the performance of the Wisconsin Card Sorting Task. The protocol is described in Chapter 2 as part of an article soon to be submitted.

To our knowledge, this is one of the first studies that longitudinally analyze PD-MCI and PD non-MCI patients according to their cognitive profiles using fMRI while performing an executive function task. We speculate that this research has the potential to yield markers allowing for an early prediction of dementia in the disease. This will ultimately yield intervention and treatment strategies tailored to different patient cognitive profile.

CHAPTER 2

The entitled article

Evolution patterns of neural activity linked to cognitive process in Parkinson's disease**,** a longitudinal fMRI study*

By

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Evolution patterns of neural activity linked to cognitive process in Parkinson's disease, a longitudinal fMRI study

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Abstract

Introduction: Mild cognitive impairment in Parkinson's disease has been linked with extensive structural gray matter, white matter as well as functional brain changes. Previously we showed different involvement patterns of the cognitive corticostriatal loop in patients with Parkinson's disease who additionally had mild cognitive impairment. Specifically, decreased activity has been shown in the ventrolateral prefrontal cortex and caudate nucleus during the planning of a set-shift. However, we have not to date investigated the longitudinal effect of the early presence of mild cognitive impairment in PD on neural patterns of activity.

Material and Methods: Twenty one non-demented patients with Parkinson's disease underwent a neuropsychological investigation according with level II MDS recommendation, and were separated in two groups - with and without mild cognitive impairment. After that, each participant underwent an fMRI investigation by performing the Wisconsin Card Sorting Task. The fMRI task was performed twice 19 months apart.

Results: When planning the set shift, patients who were cognitively intact were using the normal cognitive resources (by engaging the cognitive loop), but they also activated more cortical areas that are related to decision making over time such as the medial prefrontal cortex, parietal lobe (BA 40, 7) and the superior prefrontal cortex, whilst the group of patients with cognitive impairment failed to engage these areas during planning the set shift.

Discussion: Our results reveal functional alteration along the basal ganglia-thalamo-cortical axis in early PD. The discrepancy in cortical resources recruitment over time between cognitively intact and impaired patients might reflect deficient circuitry specific to cognitive impairment and evolution in Parkinson's disease.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by its motor symptoms (McGeer & McGeer, 2004). However, cognitive deficits are present early in the course of disease development (Foltynie, Brayne, Robbins, & Barker, 2004). The scope and intensity of these deficits can worsen with disease progression (Muslimović, Post, Speelman, & Schmand, 2005; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). Mild cognitive impairment (MCI) has been described recently in PD patients (Litvan et al., 2011) as a stage that would precede the development of dementia. It has been reported that up to 40% of patients with PD have MCI (Aarsland & Kurz, 2010). Furthermore, it has been reported that patients with PD and MCI have a higher risk of developing dementia compared with patients who do not have MCI (Emre et al., 2007; Kehagia, Barker, & Robbins, 2010; Williams-Gray et al., 2007).

Previous studies reported structural grey matter (Hanganu et al., 2013; Melzer et al., 2012; Song et al., 2011), white matter (Agosta et al., 2013) as well as functional (Atsuko Nagano-Saito et al., 2014) suggesting that PD-MCI is associated with specific functional and anatomical brain abnormalities. Nevertheless, the neural mechanisms of cognitive impairment in PD patients with MCI are not well understood. We recently reported that PD patients with MCI exhibit reduced activity in the cognitive corticostriatal loop, which includes the caudate nucleus while planning a shift during the performance of Wisconsin Card Sorting Test (WCST) (Atsuko Nagano-Saito et al., 2014). Applying the same methods, we found that PD patients who did not receive dopaminergic medication revealed a significant decrease of activation in the ventrolateral prefrontal cortex and caudate nucleus while planning a shift, and in the posterior prefrontal cortex, premotor cortex and putamen when executing the set shift (Monchi et al., 2004). Additionally, levodopa medication was shown to partially restore the activity in the motor loop but not the cognitive corticostriatal loop

(Jubault et al., 2009). However, a longitudinal study was necessary to establish the functional changes in these loops over time and its association with MCI.

In the present study we applied the WCST fMRI protocol in PD patients with MCI in a group of PD patients at two time points. Due to the fact that PD patient with MCI has been shown to express faster cognitive decline that those with intact cognition, and PD patients have been shown to recruit new cortical connections with the cortex when compared to healthy controls (Palmer, Li, Wang, & McKeown, 2010), we expected that certain cortical areas recruitment present in PD-non-MCI patients might not be present in those with MCI.

Materials and Methods

Subjects

Twenty-four non-demented PD participants (mean age, 62.86 years; 11 males and 13 females) at stages I and II of Hoehn and Yahr were recruited for the study. All participants were diagnosed by movement disorders neurologists in Montreal and met the UK brain bank criteria for idiopathic PD (Hughes, Daniel, Kilford, & Lees, 1992) as assessed by the movement disorders neurologist (A-LL., SC., VS.). All patients were responsive to dopamine medication and we excluded patients with other comorbidities. Participants were studied twice at 19,8±2,7 months apart. In each session (at baseline, Time 1 and follow-up at Time 2) they underwent a functional magnetic resonance imaging (fMRI) during which they performed a computerized version of Wisconsin Card Sorting Task (WCST) (Monchi et al., 2004; Monchi, Petrides, Petre, Worsley, & Dagher, 2001).

Participants were also asked not to take any dopaminergic medication at least 12 hours prior to the sessions. We chose the off-medication period due to several reasons: previous studies reported that dopamine loss in the ventral striatum is less severe than in the putamen and dorsal striatum

(Kish, Shannak, & Hornykiewicz, 1988), Levodopa medication withdrawal has a detrimental effect on the cognitive loop between the dorsolateral prefrontal cortex and the dorsal caudate nucleus, specifically with task-set switching (Cools, Barker, Sahakian, & Robbins, 2001), thus we argue that during WCST task PD patients will use the normal potential of the cognitive loop. All participants provided informed consent, which was approved by the Research Ethics Committee of the Regroupement Neuroimagerie Quebec. Participants received a standardized and validated neuropsychological assessment within two weeks of each session of fMRI scans.

At baseline, participants were divided in two groups: those with MCI (PD-MCI, n=11) and those cognitively intact (PD non-MCI, n=13) based on the neuropsychological scores. The cognitive performance reevaluation at Time 2 revealed that two PD-MCI patients converted to non-MCI so they were excluded from the analysis (for a total of n=9 PD-MCI and n=15 PD non-MCI patients). One PD-MCI patient was excluded from the study because he could not stay off-medication for the necessary 12-hours period at Time 2 (for a total of n=8 PD-MCI patients).

MCI is defined as a cognitive deficit commonly quantified as a performance level 1 to 2 standard deviations below the population mean in one or more cognitive domains (Litvan et al., 2012). Inclusion criteria for MCI, both for Parkinson's disease and healthy controls, were: (i) objective evidence of cognitive decline: performance >1.5 standard deviations below standardized mean on two or more subtests within a cognitive domain; (ii) subjective complaint of cognitive decline by the patient or accompanying person [the neuropsychologist assessed the presence of various symptoms including those used by other studies (Singh-Manoux et al., 2013): forgetfulness in daily activities, difficulty recalling memories, difficulty retaining new information, difficulty in mental calculation, language difficulties, orientation difficulties]; (iii) absence of significant decline in daily living activities (based on clinical observations of the referring neurologists and neuropsychologist); (iv) absence of dementia as diagnosed by the evaluating neuropsychologist

[based on the Movement Disorder Society Task Force guidelines (Level I testing) for the diagnosis of dementia in Parkinson's disease (Dubois et al., 2007)]; and (v) evidence of cognitive abnormalities that cannot be attributed to age. These criteria are consistent with the newly proposed guidelines (Level II, comprehensive assessment) for the diagnosis of MCI in patients with Parkinson's disease by the Movement Disorder Society Task Force (Litvan et al., 2012). No significant differences were observed between the groups with respect to sex, age and education. Similarly, no significant differences existed between the groups with respect to time since diagnosis or disease advancement as measured by the motor part of the Unified Parkinson's Disease Rating Scale at Time 1 (Table 2).

Neuropsychological Assessment

The comprehensive neuropsychological assessment battery was the same as previously used by (Hanganu et al., 2014; Jubault et al., 2009; A. Nagano-Saito et al., 2014). The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) was administered as a screening test before the first scanning session in case participants must be excluded based on their cognitive profile. The comprehensive neuropsychological evaluation, performed by a licensed neuropsychologist (Dr. BMC) was based on the five relevant cognitive domains suggested previously by the Movement Disorders Society Task-Force (Litvan et al., 2012): attention and working memory; executive function; language; memory; visuospatial functions (Table 1).

Symptoms and signs of depression and anxiety were measured using the Beck Depression Inventory II BDI-II and Beck Anxiety Inventory (BAI) because both depression and anxiety often occur in PD (Gallagher & Schrag, 2012), depression and anxiety could influence cognitive performance and even interact with evolution of cognitive performance in a way that higher rate of apathy and anxiety in PD than in the general population may reflect a direct consequence of

the damage to the frontostriatal system and its cortical connections, resulting in both neuropsychiatric and neurocognitive deficits (Bogdanova & Cronin-Golomb, 2011).

Finally, Unified Parkinson's Disease Rating Scale (UPDRS) on PD patients at each session. We related the UPDRS motor subscale score, a measure of motor disease severity to our cognitive measures.

Table 1. Neuropsychological test battery according to cognitive domain.

MEC, Montreal Evaluation of Communication protocol; MoCA, Montreal Cognitive Assessment Scale.

Cognitive domain	Test
Attention and working memory	Trail Making Test Part A (Reitan & Wolfson, 1985)
	Digit span test (Wechsler, 1997)
	Stroop color-word test, reading and color naming parts (Golden & Freshwater, 1998)
	Tower of London (Culbertson & Zillmer, 2005)
	Brixton (Burgess & Shallice, 1997)
Executive function	MEC, orthographic verbal fluency subtest (Joanette, Ska, & Côté, 2004)
	Trail Making Test Part B (Reitan & Wolfson, 1985)
	Stroop color-word test, interference part (Golden & Freshwater, 1998)
Language	Wechsler Abbreviated Scale of Intelligence, vocabulary subtest (Wechsler, 1999)
	Boston Naming (Kaplan, Goodglass, & Weintraub, 1983)
	MEC, semantic verbal fluency subtest (Joanette et al., 2004)
Memory	Rey Auditory Verbal Learning Test (Schmidt, 1996)
	Wechsler Memory Scale 3rd ed., logical memory subtest (immediate and delayed recalls) (Wechsler, 1997)
Visuo-spatial function	Hooper Visual Organization Test (Hooper, 1958)
	Clock-drawing subtest of the MoCA, evaluated by scores of Schulman et al. (Nasreddine et al., 2005; Shulman, 2000; Shulman, Pushkar Gold, Cohen, & Zucchero, 1993)

Cognitive task during fMRI

A computerized version of the Wisconsin Card Sorting Task (WCST) (Monchi et al., 2004; Monchi et al., 2001) was administered using stimulus presentation software. The participants were fully trained on the task prior to the scanning sessions. On each trial of the task, participants have to match a new test card to one of the four fixed reference cards (presented in a row on the upper part of the screen) based either on the color, shape or the number of the stimuli in each reference card. Participants used a 2-button response-box with their right hand. The index button moved a cursor along the four reference cards, and the middle finger confirmed the choice. On each test trial, a new card was presented.

The classification rule was not given to the participant and s/he had to find it using feedback (positive or negative) that followed each trial. On each experimental trial, participants had to find the proper classification rule and apply it as long as a positive feedback followed their response. A bright screen indicates a correct classification. A dark screen indicates an incorrect classification. On each control trial, the test card was identical to one of the four reference cards, therefore participants only had to select the twin reference card. On the control trails the screen maintains its original brightness throughout the feedback period.

The first period of each trial starts with the presentation of a new test card at which point the participant chooses one of the four reference cards. The second period of each trial starts as soon as the subject makes a selection and consists of feedback conveyed through a change in screen brightness lasting 2300 msec.

In the WCST blocks six consecutive correct matching responses need to be completed before a change in classification rule occurs. Each functional MRI run contained blocks of each of the four trial classification (color, shape, number, and control) presented in random order. For experimental WCST trial blocks, six consecutive correct matching responses were required before a change in

classification rule could occur. Control blocks contained eight trials. Patients were trained on the task before scanning until they reached a peak in performance.

To evaluate the pattern of activation during the different stages of the WCST, four experimental and two controls time periods were defined as follows: (1) Receiving negative feedback (RNF): the screen darkens indicating an incorrect response: a set-shift is therefore required and must be planned; (2) Matching after negative feedback (MNF): execution of the set-shift; (3) Receiving positive feedback (RPF): screen brightens: the current matching criterion must continue; (4) Matching after positive feedback (MPF): selection using the same classification rule as the previous trial; (5) Receiving control feedback (RCF): original screen brightness maintained; (6) Matching with control feedback (MCF): select reference card identical to test card. Each feedback period lasted 2.3 sec. The length of each matching period depended on participant response time, which during scanning, averaged 2.86 secs across all participants.

fMRI scanning

Participants were scanned using the Siemens Tim Trio 3.0 T scanner at the Unité de Neuroimagerie Fonctionnelle of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal. Sessions began with high-resolution, T1-weighted, 3D volume acquisition for anatomical localization (repetition time, 2300 ms; echo time 2.91 ms; inversion time, 900 ms; flip angle, 90^{o}; 160 slices, flied of view, 256 x 240 mm; matrix 256 x 240; voxel size, 1 x 1 x 1 mm; 12-channel coil), followed by echoplanar T2*-weighted image acquisitions with blood oxygenation level-dependent (BOLD) contrast (echo time 30 ms; flip angle 90°). Functional images were acquired over five runs in a single session. Volumes were acquired continuously every 2.5 s, for a total 155 volumes within runs, and contained 36 slices (matrix size, 64 x 64 pixels; voxel size, 3.7 x 3.7 x 3.7 mm3).

MRI data analysis

Contrast analyses

Data analysis, using fmristat (Worsley et al., 2002), was similar to previously reported contrast analyses (Jubault et al., 2009; Monchi et al., 2004; Monchi et al., 2001; A. Nagano-Saito et al., 2013; Atsuko Nagano-Saito et al., 2014). Images from each run were realigned to the third frame of the first run and smoothed using a 6 mm full-width half-maximum kernel. Statistical analysis was based on a linear model with correlated errors, where the design matrix was first convolved with a hemodynamic response timed to coincide with each slice (Glover, 1999). Temporal drift was removed by adding a cubic spline in the frame timed to the design matrix, and spatial drift, by adding a covariate to the whole volume average. The linear model was then re-estimated using least squares on the whitened data, to produce estimates of effects and their SDs at each voxel.

The following contrasts were computed: 1. RNF vs. RPF reflecting planning a set-shift, MNF vs. MPF reflecting executing the set-shift, RPF vs. RCF reflecting maintaining set, and MPF vs. MCF reflecting matching according to the same rule. The resulting effects and SD images were then non-linearly transformed into standard proportional stereotaxic space (ICBM152 template) using anatomical MRI to template transformation parameters, using a feature-matching algorithm (Collins, Neelin, Peters, & Evans, 1994; Zijdenbos, Forghani, & Evans, 2002).

In the second step, runs and subjects were combined using a mixed-effects linear model that was performed by first, estimating the ratio of the random-effects variance to the fixed-effects variance, and then regularizing this ratio by spatial smoothing with a Gaussian filter. Both intra-group (Time 1, Time 2) and inter-group comparisons were generated.

Statistical maps threshold was set at $p<0.05$ correcting for multiple comparisons using the minimum between a Bonferroni correction and random field theory in the single and intergroup

analysis, yielding a threshold of $t > 4.82$ for a single voxel. Predicted peaks reaching $p < 0.0001$ ($t > 3.87$) with a cluster size +- 40 mm3 assessed on the spatial extent of contiguous voxels, are also reported and identified with an asterisk (*) in the tables. A region was predicted if it had been identified in our previous work using this task (Jubault et al., 2009; Monchi et al., 2004; Monchi et al., 2001; A. Nagano-Saito et al., 2013; Atsuko Nagano-Saito et al., 2014). For group comparisons, predicted peaks reaching $p < 0.001$ ($t > 3.18$) with a cluster size +- 40 mm3 are also reported with 2 asterisks (**) in the tables.

To evaluate the effect of performance on the imaging measure over the follow-up period for the MCI relative to the non-MCI and for the two groups separately overtime. We focused on comparing MCI to non-MCI, then group MCI in both time points, group non-MCI in both time points.

Correlation analysis

While our sample size of PD patients with MCI did not allow us to compare impairment arising from a predominance of memory or executive problems, we wanted to address how individual ability on a cognitive performance, separately, affects patterns of activation during the various stages of the WCST. To do this we performed correlation analyses on the BOLD data while performing the WCST, using cognitive scores of Montreal Cognitive Assessment test (MoCA) (Nasreddine et al., 2005) at the subject level. MoCA is a validated 12-minutes test for screening MCI and is a sensitive measure of global cognitive profile and evolution.

These analyses were performed across all participants combined (i.e. both MCI and non-MCI PD patients grouped) since these measures were used to define the two groups. Only predicted peaks reaching $p < 0.001$ uncorrected are reported. To investigate the evolution of performance on the MoCA and imaging measures over the follow-up period for PD in Time1 and Time2, we performed a Time 1 vs. Time 2 comparison correlated with the difference of MoCA scores between both sessions.

Results

The behavioral results during fMRI

At Time 1 mean error rates on the control condition was 3.2 ± 3.0 % (non-MCI) and 2.0 ± 1.8% (MCI), and those on the WCST were 13.7 ± 8.4% (non-MCI) and 20.5 ± 7.2 % (MCI). A mixed-design repeated measures ANOVA (task x group) indicated that there were main effect of task ($F = 90.2$, $p < 0.001$), but no effect of groups (non-MCI vs. MCI: $F = 2.96$, $p = 0.101$). There was a significant interaction between group and task ($F = 8.58$, $p = 0.008$). Post-hoc t-test showed MCI made more errors in WCST, compared to non-MCI ($t = 2.37$; $p = 0.028$), but no difference in control task ($t = 1.09$; $p = 0.289$).

At the time 2, mean error rates on the control condition were 3.4 ± 2.9 % (non-MCI, with n =15) and 3.1 ± 2.2% (MCI, with n = 7), and those on the WCST were 13.7 ± 8.1% (non-MCI) and 22.2 ± 5.6 % (MCI). A mixed-design repeated measures ANOVA (task x group) indicated that there were main effect of task ($F = 107.2$, $p < 0.001$), and marginal effect of groups (non-MCI vs. MCI: $F = 3.724$, $p = 0.068$). There was a significant interaction between group and task ($F = 9.54$; $p = 0.006$). Post-hoc t-test showed MCI made more errors in WCST, compared to non-MCI ($t = 2.50$; $p = 0.021$), but no difference in control task ($t = 0.227$; $p = 0.829$).

When all the subjects were considered (n = 22), repeated measures ANOVA (task x time) indicated a significant task effect ($F = 91.27$; $p < 0.001$), but no time effect ($F = 0.100$; $p = 0.755$). There is no interaction between them ($F = 0.051$, $p = 0.823$). Additionally, a mixed-design repeated measures ANOVA (task x time x group) indicated main effect of task ($F = 78.2$, $p < 0.001$), and significant interaction of task x groups ($F = 5.571$, $p = 0.35$). No group effect was observed ($F =$

2.125; p = 0.169). No other main effects (including the group effect) or no interaction was observed (p > 0.1).

For the MCI group, a mixed-design repeated measures ANOVA (task x time) indicated no main effect of time (F = 0.547, p = 0.472), and no interaction between the time (F = 0.045, p = 0.834).

Imaging analysis

While all contrasts analysis results were conducted, we selectively report the comparison RNF vs. RPF representing planning the set shift and MNF vs. MPF representing executing the set-shift in the tables. Those two contrasts are the most representative for the whole brain analysis for both PD-MCI, PD non-MCI, similarly the correlation analysis for both groups. Specifically, planning the set shift contrast represents the cognitive loop, while executing the set shift contrast represents the motor loop.

Planning the set-shift (table 3)

When planning the set shift at Time 1, the PD-MCI group demonstrated significant activation peaks in the right dorsolateral PFC and the right posterior occipital cortex. At Time 2 PD-MCI revealed again significant activation peaks in the right dorsolateral PFC, however right ventrolateral PFC and the posterior parietal cortex (Brodmann Area 40, 7) also showed activations. Longitudinal changes in PD MCI group across the two time points (substracting Time 1 minus Time 2), revealed decreased activation peaks over time in cerebellum bilaterally and the right parahippocampal gyrus (BA 35) as well as increased activation peaks over time in the right superior parietal cortex/precuneus area (area 7), right precuneus (BA 7) and the right ventrolateral prefrontal cortex.

By contrast, at Time 1, PD non-MCI group demonstrated significant activity in the dorsolateral PFC bilaterally (PFC; BA 46, 9/46), right ventrolateral PFC (BA 47/12), medial PFC (BA 6, 8, 32, 32/8) bilaterally, posterior left parietal cortex (BA 7, 40), fusiform gyrus/extrastrital cortex (BA 37) bilaterally, left precuneus (BA 7), occipital visual areas bilaterally (BA 17, 18, 19), and in the left cerebellum. The activation observed in the left caudate nucleus was ($t=3.69$) corresponding to $p<0.0001$ non-corrected. At Time 2 PD non-MCI group similarly to Time 1 demonstrated significant activities in the dorsolateral prefrontal cortex bilaterally (PFC; BA 46, 9/46), ventrolateral PFC/insula bilaterally (BA 47/12, 13), medial PFC (BA 6, 8, 32, 32/8), posterior left parietal cortex (BA7, 40), left precuneus (BA 7), occipital visual areas bilaterally (BA 17, 18, 19), and in the right cerebellum. Additionally, at Time 2, PD non-MCI activated medial PFC bilaterally (BA 6, 8, 32, 32/8), left lateral premotor cortex (junction of BA 6, 8 and 44), left superior prefrontal cortex corresponding to the frontal eye field, however, no temporal lobe (BA 37) activation was noticed, and the caudate nucleus did not reach a p value even as low as $p<0.01$ non corrected at Time 2.

Longitudinal changes in PD non-MCI group across the two time points, revealed an decreased fMRI BOLD-signal intensity in postcentral gyrus (BA 3) over time, on the other hand, areas such as the right parietal cortex (BA 40, 7), medial PFC (BA 6, 8, 32, 32/8) bilaterally, and right superior PFC, showed increased BOLD-signal intensity over time.

Executing the set-shift (table 4)

When executing the set shift, at Time 1, PD-MCI group demonstrated positive activation peaks in the left occipital cortex (BA 17, 18, 19) and the cerebellum bilaterally. At Time 2 however, PD-MCI group showed positive activation of peaks in the left parietal lobe on the angular gyrus (BA 39). Longitudinal changes in PD-MCI group across the two time points (substracting Time 1 minus

Time 2) did not reveal any decremented activation peaks over time, however, regions such as cingualate gyrus (BA 31), left cerebellum, showed increased activtiy over time.

By contrast, non-MCI group at Time 1 showed significant activations in the left dorsolateral PFC (BA 46, 9/46), medial PFC (BA 32/8) bilaterally, ventrolateral PFC (BA 47/12) bilaterally, the left parietal cortex (BA 40, 7), anterior PFC (BA 10) bilaterally, the occipital visual areas (BA 17, 18, 19) and the cerebellum bilaterally. At Time 2, PD non-MCI revealed significant activation in the dorsolateral PFC (BA 46, 9/46) bilaterally, precuneus (BA 7) bilaterally, left superior PFC (BA 8). Engagement of putamen and posterior PFC was observed neither in MCI nor in non-MCI at both time points.

Longitudinal changes in PD non-MCI group across the two time points revealed significant decrease in activation over time in hippocampus and parahippocampal gyrus (BA 19, 30) bilaterally, left the superior temporal gyrus (BA 22), right thalamus and left posterior/lateral thalamus. Furthermore, superior parietal cortex/precuneus (BA 7) bilaterally, the declive of the left cerebellum showed significant increased activation over time.

Correlation analysis (table 5)

We performed correlation analysis with MoCA scores for both MCI and non-MCI groups. Areas in the left occipital visual area (BA 18) and the cerebellum bilaterally were positively correlated with MoCA scores across the two time points for all participants . And areas in left ventral pallidum/amygdala, left posterior Putamen/claustrum, right anterior PFC (BA 10), right parietal cortex (BA 40, 7), superior/middle PFC were negatively correlated with MoCA scores across the two time points during planning the set-shift. By contrast, positive peaks in the right hippocampus/parahippocampal gyrus, ventral striatum and right cerebellum were negatively correlated with MoCA scores across the two time points during executing the set-shift.

Discussion

The aim of our study was to longitudinally follow up the brain neural activation of non-demented PD patients with different level of cognitive impairment, undergoing an fMRI while performing the WCST. We predicted that PD-MCI and PD non-MCI would use alternative circuits in the brain to compensate with the cognitive decline. Our results showed that during planning the set shift, PD non-MCI was using the normal cognitive resources (by engaging the cognitive loop), but they also activated more cortical areas that are related to decision making over time such as the medial PFC, parietal lobe (BA 40, 7) and the superior PFC, whilst the PD-MCI group failed to engage these areas during planning the set shift.

Caudate head and body are essential to planning a novel action (DeGutis & D'Esposito, 2007; Monchi et al., 2001; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000). Fronto-striatal activation has been reported to be affected in those with solicited planning deficits as compared to those without in early PD with cognitive impairment and deficit in the dopaminergic system (Cools & D'Esposito, 2011; Ekman et al., 2012; Lewis & Barker, 2009). Using WCST protocol, Monchi and colleagues established the implication of a cognitive cortico-striatal loop including the ventrolateral PFC, the caudate nucleus, and the thalamus during the planning of a set-shift, and of a motor cortico-striatal loop including the posterior PFC and the putamen during the execution of a set-shift in healthy young adults (Monchi et al. 2004). In cross sectional studies, MCI has shown decreased parts of the cognitive loop such as caudate as compared to PD non-MCI (Ekman et al., 2012; Monchi & Stoessl, 2012).

Our results showed that during planning the set shift, activity in the caudate nucleus did not reach statistical significance at Time 2 as compared to Time 1 ($t < 3.87$) for the non-MCI group. The MCI group however, did not activate the caudate nucleus at both time points during planning the set-

shift. On the other hand, there was no involvement of putamen or posterior PFC observed in neither MCI nor non-MCI at both time points during executing the set-shift, both regions recruitments were previously reported in controls (Monchi et al., 2001) and in PD non-MCI (Nagano-Saito et al., 2014) during executing the set-shift. These results are consistent with the longitudinal findings that showed shrinkage over time in the caudate nucleus, putamen, and thalamus in PD (Hanganu et al., 2014). The results collectively illustrate the deterioration of the basal ganglia-thalamic function and deficient cognitive loop overtime for MCI group and to a lesser extent in the non-MCI group.

Longitudinal volumetric results showing that amygdala and nucleus accumbens were the two structures that had a faster cortical thinning in PD-MCI, and the volume loss in these two structures over time correlated with MoCA scores in the non-demented PD and was driven by the PD with MCI group (Hanganu et al., 2014). Our results are in line with these findings, ventral striatum was positively correlated with MoCA scores overtime for the non-demented PD (MCI and non-MCI) during executing the set-shift. We predict that this is probably derived by the longitudinal volumetric changes in this area.

Longitudinally, PD non-MCI revealed during the planning set-shift an increase in activity in multiple cortical areas related to decision making such as the medial prefrontal cortex, lateral premotor cortex and areas related to the frontal eye fields which plays an important role in the control of visual attention and eye movements (Schall, 2004) such as superior prefrontal cortex. These areas did not show an increase in activation overtime in MCI. Furthermore, the anterior and the superior PFC showed a negative correlation with MoCA scores over time during planning the set-shift.

Over-activity of the cortex can be observed in non-demented PD while performing a cognitive task when the striatum is not important for the task (Monchi, Martinu, & Strafella, 2010). Areas such as anterior cingulate gyrus, parietal cortex and PFC have a role in the executive processes (Asari, Konishi, Jimura, & Miyashita, 2005; Banich, 2009; Carter et al., 1998); furthermore, the striatum

receives inputs from various cortical regions (Alexander, DeLong, & Strick, 1986; Parent & Hazrati, 1995), so that nigrostriatal degeneration might virtually alter the activity of many of these regions.

Whether this is reflecting a deterioration of the mesocortical system or even a loss of focus in the cortical neural activity due to a secondary dopamine deficit (Javoy-Agid & Agid, 1980; Sawaguchi & Goldman-Rakic, 1994) or subsequently representing a compensatory mechanism (Dagher, Owen, Boecker, & Brooks, 2001; Samuel et al., 1997); is yet to be determined. Hypo-metabolic cortical areas have been reported in patients with PD and multi-domain MCI compared to PD non-MCI in anterior cingulate gyrus, lateral frontal, parietal, temporal, occipital cortices (Lyoo, Ryu, & Lee, 2010). Longitudinally MCI exhibit higher rate of cortical thinning in the temporal, occipital, parietal and supplementary motor area compared with both cognitively stable patients and healthy controls (Hanganu et al., 2014). Having said that, we speculate that due to sufficient cognitive resources in non-MCI PD patients, compensation can occur in many parts of the cortex. On the other hand, once the cognitive impairment takes place, cortical activations tend to be globally reduced in PD patients as they are undergoing a more extensive dopamine deficit or a mescortical involvement.

Medial temporal lobe structures (MTLS) atrophy including hippocampus is considered a predictor in other non-PD MCI (Apostolova et al., 2010; Apostolova et al., 2006; Sencakova et al., 2001). Postmortem data showed hippocampal involvement in cognitively intact PD patients (Bertrand et al., 2003). MTLS atrophy was found in MCI as compared to non-MCI (Burke, Dauer, & Vonsattel, 2008; Jokinen et al., 2009; Weintraub et al., 2011) with correlation to cognitive function in this group (Jokinen et al., 2009).

Furthermore, Metabolic studies reported increased hippocampal activation while motor planning in non-demented PD (Beauchamp, Dagher, Panisset, & Doyon, 2008; Dagher et al., 2001; Moody, Bookheimer, Vanek, & Knowlton, 2004) and recruitment the hippocampus for working

memory task while failing to engage the striatum (Ekman et al., 2014). It was suggested in a longitudinal PET study that the lack of mid-temporal compensatory activation might be a predictor of PD-dementia (Carbon et al., 2010). Our results came in line with these findings; and with our previous study which showed that activity in the hippocampus, anterior PFC and medial PFC were positively correlated with RALVT scores in non-demented PD (Atsuko Nagano-Saito et al., 2014). In our current study we areas in MTLS decreased in activity over time in MCI group while planning the set-shift and in non-MCI group while executing the set-shift. Areas in the MTLS were positively correlated with MoCA scores while executing the set-shift. It is a possibility that when PD patients are cognitively intact, they tend to recruit the medial temporal lobe structures (MTLS) including the hippocampus, to compensate the fronto-striatal deficit, this explanation can account for the increase in the hippocampal activity in early PD.

In conclusion, our results show important neural changes in PD-MCI patients when compared with PD-non-MCI group. Specifically, PD-MCI failed to engage the areas of medial PFC, parietal lobe (BA 40, 7) and the superior PFC during planning the set shift. Yet more work in this area is definitely warranted. It is important to establish whether functional and anatomical changes medial temporal and cortical structures put the PD non-MCI at increased risk for cognitive decline and PD-MCI at risk of dementia.

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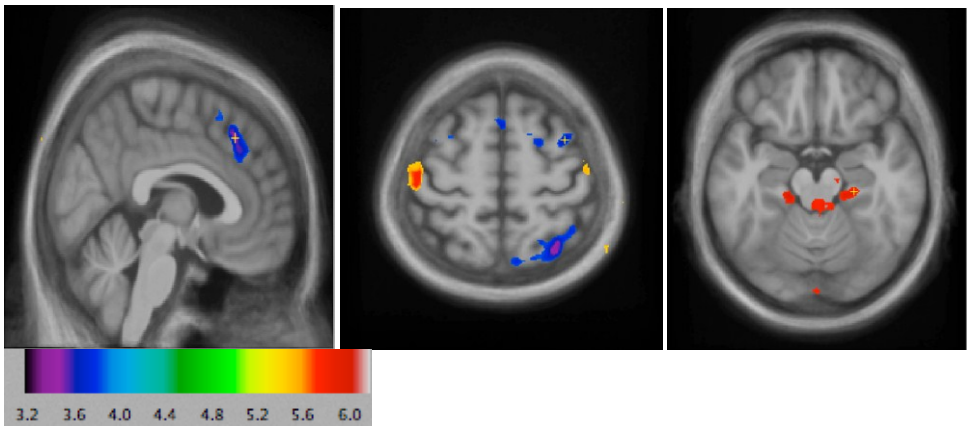
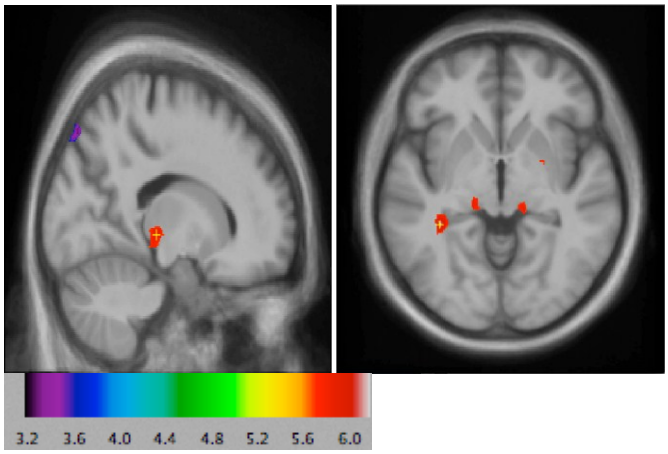
Figures

Figure 1: significant activations in the contrast receiving negative feedback minus control feedback (planning the set-shift) Time 1 vs. Time 2.



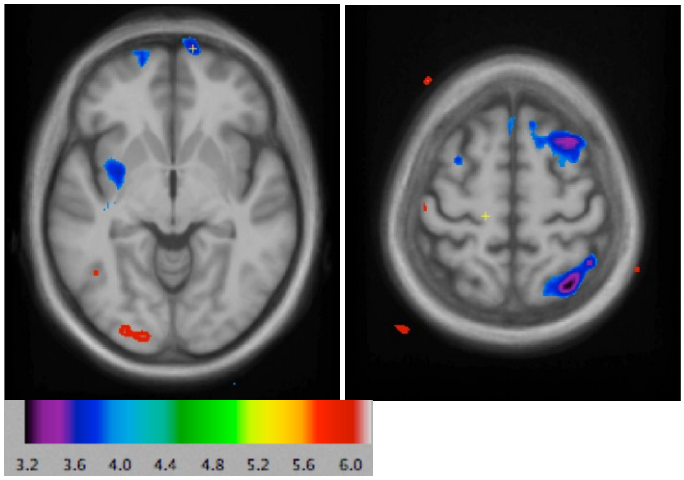
non-MCI x=4 **non-MCI z=56** **MCI z=-18**

Figure 2: significant activations in the contrast of matching after negative feedback minus control matching (Executing the set-shift) Time 1 vs. Time 2.



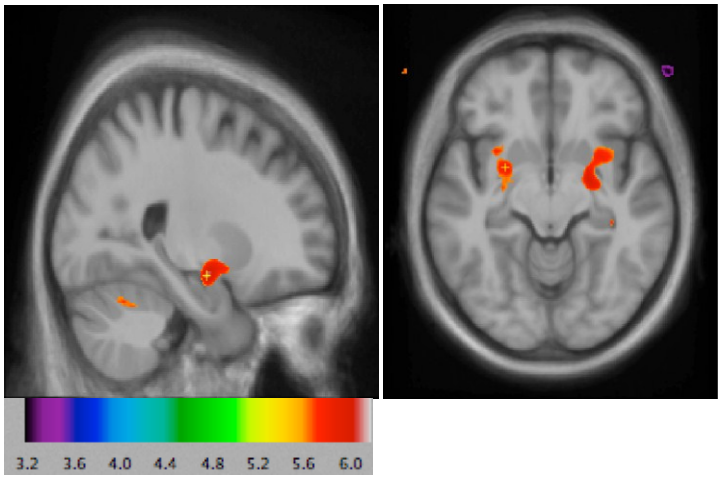
non-MCI x=--16 **non-MCI z=-4**

Figure 3: significant activation peaks with correlation analysis with individual MoCA scores across all patients.



Planing the set-shift

z=-5 **z=58**



Executing the set-shift

X=24 **z=-10**

Tables

Table 2 A. Parkinson's diseasepatient demographics according to cognitive impairment group at both time points for the Non-MCI group.

Non-MCI	Time 1	Time 2	Difference *p value*
N	13	15	
Age *	58,31	60	0.394786451
Male/Female	05/08.	07/08.	0.905221768
Years since diagnosis	4	5,53	0.164780008
Education	13,85	14,07	0.73586451
Hand R/L/A	08/05/00.	10/05/00.	0.045807052
MoCA off *	28,62	28,47	0.786857662
UPDRS off	27,31	29,14	0.685663066
BDI	6,31	6,36	0.316454736
L-Dopa daily	273,08	488,33	0.133354583

Table 2 B. Parkinson's disease patient demographics according to cognitive impairment group at both time points for the MCI group.

MCI	Time 1	Time 2	Difference *p value*
N	11	8	
Age *	62,95	62,13	0.415928228
Male/Female	06/05.	04/04.	0.911176846
Years since diagnosis	5,18	7,31	0.231588867
Education	12,81	12,38	0.823089656
Hand R/L/A	11/00/00.	08/00/00	0.047842523
MoCA off *	27,09	27,13	0.61758505
UPDRS off	28,5	30,56	0.569895373
BDI	10	14,38	0.776957498
L-Dopa daily intake (mg)	368,18	507,14	0.10133261

Table 3: significant activations in the contrast receiving negative feedback minus control feedback (planning the set-shift) in both MCI and Non-MCI patient groups.

Anatomical area	MCI time 1 t-value	x	y	z	cluster size (ml)		Anatomical area	MCI time 2 t-value	x	y	z	cluster size (ml)	
Dorsolateral prefrontal cortex (area 46, 9/46)													
left													
right	4.9	40	28	18	4.864								
							lateral premotor cortex (area6)						
							left	3.97	38	12	30	16	*
Ventolateral prefrontal cortex (area 47/12)													
left								4.17	-32	26	-6	5	*
right								5.07	34	28	-6	3.7	
								4.6	42	26	-8	3.7	*
Parietal cortex (area 40, 7)													
left													
right								4.6	28	-66	58	53	*
Striate/Extrastriate cortex (area 17,18,19)													
right	4.2	42	-82	20	0.664	*							

Anatomical area	MCI time1>MCI time2 t-value	x	y	z	cluster size (ml)		Anatomical area	MCI time2>MCI time1 t-value	x	y	z	cluster size (ml)	
Cerebellum/Culmen													
left	4.4	-18	-30	-20	0.488	*							
right	3.9	14	-34	-22	0.976	*							
	3.9	16	-32	-22	0.976	*							
	3.79	22	-28	-18	0.976	**							
Parahippocampal gyrus (area35)													
right	3.76	24	-26	-18	0.976	**							
							superior Parietal cortex/precuneus (area 7)						
							right	4.29	30	-66	58	12	*
							Precuneus						
							right	4.1	6	-82	50	0.7	*
							VLPFC						
							right	3.97	56	38	-12	0.4	*

Anatomical area	Non-MCI time1 t-value	x	y	z	cluster size (ml)		Anatomical area	Non-MCI time2 t-value	x	y	z	cluster size (ml)	
Lateral Premotor Cortex area 6													
left	4.500	-36.000	12.000	28.000	10.624			5.38	-44	12	32	22	
	4.200	-44.000	4.000	32.000	10.624	*		5.24	-46	14	34	22	
right	4.7	44	8	20	5.808	*		6.17	42	8	26	206	
	4.6	42	8	22	5.808	*		5.4	46	26	20	206	
								5.39	46	12	30	206	
Ventolateral prefrontal cortex (area 47/12)/ Insula area 13													
left								4.46	-38	20	-2	206	*
								4.39	-30	26	-4	206	*
								4.32	-34	22	0	206	*
right	5.8	32	24	-6	6.32			5.88	30	26	-6	206	
Parietal cortex (area 40, 7)													
left	4.4	-32	-50	38	158	*		6.82	34	-62	54	206	
								6.17	32	-60	50	206	
								6.08	32	-62	46	206	
								5.1	-34	-58	46	206	
Precuneus (area 7)													
left	4.5	-8	-74	48	158	*		5.43	-26	-66	40		
Striate/Extrastriate cortex													
left	6.9	-24	-82	-14	158			5.16	-40	-84	10	206	
right	6.4	36	-74	-16	158			5.5	34	-80	26	206	
	6.1	32	-78	26	158								
fusiform gyrus/extrastriatal													
left	7.3	-46	-62	-12	158								
right	6.6	50	-58	-16	158	*							
Cerebellum													
left	7.34	-10	-80	-28	158								
right								5.74	26	-70	-12	206	
Medial prefrontal cortex area 6,8, 32,													
left	4.09	-8	20	42	4.024	*		6.21	-6	22	44	206	
								6.15	-6	26	42	206	
right	3.68	4	18	46	4.024	**		5.45	48	14	32	206	
								5.6	6	24	36	206	
								5.52	6	24	40	206	
								5.36	2	28	42	206	
								5.14	6	32	32	206	
								5.04	30	26	2	206	
Post.prefrontal cortex (junction of area 8, 6 and 44)													
right								5.59	4	16	50	206	
Superior prefrontal cortex													
right								4	22	6	54	206	*
								4.5	38	8	60	206	*

Anatomical area	Non-MCI time1>Non-MCI time2 t-value	x	y	z	cluster size (ml)		Anatomical area	Non-MCI time2>Non-MCI t-value	x	y	z	cluster size (ml)	
Postcentral Gyrus (area 3)													
left	5.53	-40	-24	68	4.416								
	4.8	-34	-26	72	4.416								
	6.073	-48	-20	62	4.416								
right	4.29	52	-12	54	1.208	*							
							Parietal cortex (area 40, 7)						
							right	5.9	34	-64	56	2.7	
							Medial prefrontal cortex area (6,8, 32, 32/8)						
							left	4.37	0	26	48	2.2	*
							right	4.88	4	28	44	2.2	
							Superior prefrontal cortex						
							right	5.2	50	16	34	1.9	
								4.34	42	10	54	1.9	*
								4.16	22	6	54	1.3	*

Findings significant at $p < 0.05$ corrected for multiple comparisons.

∗ Predicted peaks of ≥40 mm3 at $p < 0.0001$ uncorrected.

∗∗ Predicted peaks of ≥40 mm3 at $p < 0.001$ uncorrected.

Table 4: significant activations in the contrast of matching after negative feedback minus control matching (Executing the set-shift) in both MCI and non-MCI groups.

Anatomical area	**MCI time 1** t-value	x	y	z	**cluster size (ml)**	**Anatomical area**	**MCI time 2** t-value	x	y	z	**cluster size**	
Peristriatal cortex (area 17,18,19)												
left	4.83	-28	-84	34	44.112							
						Parietal lobe (area 39)						
						left	4.1967	-34	-60	32	1.34	*
Cerebellum												
left	3.96	-12	-70	-24	6.408	*						
right	4.64	36	-62	-32	6.408	*						

Anatomical area	**MCI time1>MCI time2** t-value	x	y	z	**cluster size (ml)**	**Anatomical area**	**MCI time2>MCI** t-value	x	y	z	**cluster size (ml)**	
NONE						Cingulate gyrus (area 31)						
						left	3.8299	-8	-42	30	0.28	**
						Cerebellum						
						left	3.8205	-20	-98	-24	0.54	**

Anatomical area	Non-MCI time1 t-value	x	y	z	cluster size (ml)		Anatomical area	Non-MCI t-value	x	y	z	cluster size (ml)
Dorsolateral prefrontal cortex (area 46, 9/46)												
left	4.57	-46	26	18	61.048	*		5.0714	-42	36	30	161
	4.35	-54	22	24	61.048	*		4.9935	-40	32	34	161
right								5.1835	46	38	24	161
Ventolateral prefrontal cortex (area 47/12)												
left	4.48	-48	48	-12	61.048	*						
	4.28	-34	26	-8	61.048	*						
right	4.37	40	20	-14	53.712	*						
Parietal cortex (area 40, 7)												
left	4.71	-34	-56	40	15.504	*						
Precuneus (area 7)												
left								5.271	-6	-78	50	127
right								5.1448	32	-74	52	127
								5.1171	44	-72	46	127
Striate/Extrastriate cortex (area 17,18,19)												
left	4.74	-30	-94	0	128.1	*						
right	7.03	34	-92	-2	128.1							
	4.83	28	-80	-6	128.1							
Cerebellum												
left	4.6	-54	-66	-38	128.1	*						
right	4.24	44	-78	-32	128.1	*						
Medial prefrontal cortex (area [illegible])												
left	5.36	-6	26	42	53.712							
	4.45	0	32	40	53.712	*						
	4.4	2	32	38	53.712	*						
right	4.14	4	32	34	53.712	*						
Anterior prefrontal cortex (area 10)												
left	6.04	-36	58	12	61.048							
	4.43	-44	52	-10	61.048	*						
right	4.35	38	58	8	53.712	*						
							sup prefrontal gyrus (area 8)					
							left	5.0476	-42	16	50	161

Table 5: Significant activation peaks with correlation analysis with individual MoCA scores across all patients.

Anatomical area	MCI&Non-MCI time1 >						Anatomical area	MCI&Non-MCI time2>					
	t	x	y	z	cluster size (ml)			x	y	z	t-value	cluster size (ml)	
Correlation to MoCA while Planning the set-shift							**Correlation to MoCA while Planning the set-shift**						
Striatal cortex area 18													
left	4.291	-28	-92	-8	0.85	*							
Cerebellum													
left	3.884	-42	-74	-42	0.73	*							
right	4.071	36	-78	-44	0.78	*							
							Ventral Pallidum/amygdala						
							left	22	-10	6	3.801	19.1	**
							Posterior Putamen/claustrum						
							left	-36	0	-4	4.246	23	*
							Anterior prefrontal cortex (Area10)						
							left	-18	66	-8	6	4.96	
							right	12	72	-6	4.394	6.58	*
							Parietal cortex (area 40, 7)						
							right	32	-66	58	5.701	19.9	
							Superior/middle Prefrontal cortex						
							right	32	18	56	5.188	45.9	

Anatomical area	MCI&Non-MCI time1 >						Anatomical area	MCI&Non-MCI time2>					
	t	x	y	z	cluster size (ml)			x	y	z	t-value	cluster size (ml)	
Correlation to MoCA while Executing the set-shift							**Correlation to MoCA while Executing the set-shift**						
Para hippocampal gyrus/hippocampus													
right	4.596	24	-8	-14	1.61	NONE							
Cerebellum right	3.931	8	-78	-22	1.09	*							
	3.896	10	-76	-24	1.09	*							
Ventral striatum	3.889	-26	2	-10	0.5	*							

Findings significant at $p < 0.05$ corrected for multiple comparisons.

∗ Predicted peaks of ≥40 mm3 at $p < 0.0001$ uncorrected

∗∗ Predicted peaks of ≥40 mm3 at $p < 0.001$ uncorrected

Table 5: Significant activation peaks with correlation analysis with individual MoCA scores across all patients.

Anatomical area	MCI&Non-MCI time1 >					Anatomical area	MCI&Non-MCI time2>					
	t	x	y	z	cluster size (ml)		x	y	z	t-value	cluster size (ml)	
Correlation to MoCA while Planning the set-shift						**Correlation to MoCA while Planning the set-shift**						
Striatal cortex area 18												
left	4.291	-28	-92	-8	0.85	*						
Cerebellum												
left	3.884	-42	-74	-42	0.73	*						
right	4.071	36	-78	-44	0.78	*						
						Ventral Pallidum/amygdala						
						left	22	-10	6	3.801	19.1	**
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						left	-36	0	-4	4.246	23	*
						Anterior prefrontal cortex (Area10)						
						left	-18	66	-8	6	4.96	
						right	12	72	-6	4.394	6.58	*
						Parietal cortex (area 40, 7)						
						right	32	-66	58	5.701	19.9	
						Superior/middle Prefrontal cortex						
						right	32	18	56	5.188	45.9	

Anatomical area	MCI&Non-MCI time1 >					Anatomical area	MCI&Non-MCI time2>					
	t	x	y	z	cluster size (ml)		x	y	z	t-value	cluster size (ml)	
Correlation to MoCA while Executing the set-shift						**Correlation to MoCA while Executing the set-shift**						
Para hippocampal gyrus/hippocampus												
right	4.596	24	-8	-14	1.61	NONE						
Cerebellum right	3.931	8	-78	-22	1.09	*						
	3.896	10	-76	-24	1.09	*						
Ventral striatum	3.889	-26	2	-10	0.5	*						

Findings significant at $p < 0.05$ corrected for multiple comparisons.

∗ Predicted peaks of ≥40 mm3 at $p < 0.0001$ uncorrecte

∗∗ Predicted peaks of ≥40 mm3 at $p < 0.001$ uncorrecte

CHAPTER 3

Discussion

Discussion

Little is known regarding the course of the cognitive deterioration over time in PD. The primary objective of this thesis was to longitudinally assess the effect of cognitive decline on the evolution of neural activity in early PD. We predicted that alternative neural circuits are recruited in early PD to compensate with the cognitive decline over time. We aimed to draw an outline of a distinctive pattern of neural circuitry recruitment between PD MCI and PD non-MCI groups with respect to their neuroimaging and neuropsychological measures.

In the previous chapter, we reported results of analysis of PD-MCI group at Time 1 vs. Time 2, PD non-MCI group Time 1 vs. Time 2 and correlation analysis of both groups with MoCA scores across both time points. We conducted other analysis, for the six contrast of the task, reporting them however, was beyond the limits of the article, these analysis include: correlation analysis of PD-MCI group across the two time points with the corresponding difference in MoCA scores for PD-MCI group across the two time points, correlation analysis of PD non-MCI group across the two time points with the corresponding difference in MoCA scores for PD non-MCI group across the two time points correlation analysis of both MCI and non-MCI groups across the two time points with the corresponding difference of RAVLT scores across the two time points, correlation analysis of both MCI and non-MCI groups across the two time points with the error rates of both MCI, non-MCI groups while performing WCST and PD-MCI vs. PD non-MCI at Time 1 and at Time 2 and finally, correlation analysis of the slope of change in MoCA scores with the images of both MCI and non-MCI groups at Time 1. These

unreported contrast analysis generally came in line with the reported analysis in the article and supported our hypothesis.

Caudate head and body are essential in planning a novel action (Rogers et al., 2000; Monchi et al., 2001; DeGutis et al., 2007). Fronto-striatal activation was reported to be affected in those with solicited planning deficits as compared to those without solicited planning deficits in early PD with cognitive impairment and deficit in the dopaminergic system (Lewis et al., 2003; Cools 2011; Ekman et al., 2012). Using the WCST protoco, Monchi and colleagues established the implication of a cognitive cortico-striatal loop including the ventrolateral PFC, the caudate nucleus, and the thalamus during the planning of a set-shift, and of a motor cortico-striatal loop including the posterior PFC and the putamen during the execution of a set-shift in healthy young adults, (Monchi et al. 2004). In cross sectional studies, PD-MCI has shown decreased parts of the cognitive loop such as caudate (Ekman et al., 2012; Monchi et al., 2012) as compared to PD non-MCI. In agreement with these previous studies, our current study showed that areas in the cognitive loop (Caudate and ventrolateral PFC) were positively correlated with RAVLT for both MCI and non-MCI groups across the two time points, in Time 1 and Time 2 during planning the set-shift (unreported data).

Our results reveal that caudate nucleus activity showed a tendency to decrease over time in the non-MCI group, while in the MCI group, caudate activity was not observed at either of the two time points. Likewise, the thalamus was not activated at either time points for both the MCI and the non-MCI group during planning the set shift. On the other hand, there was no involvement of putamen or posterior PFC observed in

neither the MCI nor the non-MCI group at both time points during executing the set-shift. These patterns of neural activity were collectively different from those previously observed in healthy control individuals (Monchi et al., 2004) and may reflect an over time deterioration of the basal gangila-thalamic function and a resultant deficient cognitive loop in early PD.

We observed that PD non-MCI individuals were not only still using some cognitive resources during planning the set-shift (which requires engaging the cognitive loop), but they rather activated more cortical areas that are related to decision making over time such as the medial PFC, parietal lobe (area 40, 7) and the superior PFC. Whilst the MCI group failed to engage these areas during planning the set shift, these areas were negatively correlated with MoCA scores over time across both groups and negatively correlated with RAVLT for both PD-MCI and PD non-MCI at Time 2 during planning the set-shift (unreported data). Interestingly enough, these areas were positively correlated with rate preservative errors participants' committed while performing the task in Time 2 (unreported data). These results are consistent with the hypometabolic cortical areas previously observed in PD-MCI (Lyoo et al., 2010) and with the longitudinally observed thinning of multiple cortical areas in PD-MCI compared to cognitively intact PD patients and healthy controls (Hanganu et al., 2014).

We propose that cognitively intact PD patients engage the aforementioned cortical resources when these cortical areas are still operative to compensate with the functional changes that PD attributes on the structures needed to perform a certain cognitive task,

however, as cognitive impairment become more significant, PD patients tend to fail to recruit these cortical areas.

To conclude our hypothesis, we propose that failure of the PD-MCI group to engage cortical areas that PD non-MCI group recruited over time while performing WCST may draw a distinctive line between the patterns of neural activity observed in PD-MCI and that of PD non-MCI. Furthermore, it may reflect a predictive parameter for a global functional deterioration observed in PD dementia. It will be interesting to observe these cortical neural activation patterns at another stage of follow up (Time 3) to confirm this conclusion.

Medial temporal lobe structures (MTLS) atrophy has been heavily investigated and considered a predictor of dementia in AD patients with mild cognitive impairment (Sencakova et al., 2001; Apostolova et al., 2006b, 2010a,c). Furthermore, studies using structural MRI showed MTLS loss of volume in PD dementia (Nagano-Saito et al., 2005; Burton et al., 2004; Burton et al., 2005; Summerfield et al., 2005; Bouchard et al., 2008, Camicioli et al., 2003, Tam et al., 2005; Junque et al., 2005). However, whether MTLS atrophy can be specific to PD-MCI as opposed to non-MCI has been under debate in earlier studies. Some volumetric studies (Camicioli et al., 2004; Cordato, Duggins, Halliday, Morris, & Pantelis, 2005) did not report hippocampal atrophy in non-demented PD, while others did (Camicioli et al., 2003; Laakso et al., 1996) the discrepancy in these studies findings might be because the age of participants was younger in the studies that did not report hippocampal atrophy as opposed to those reported. Further work reported both structural (Brück et al., 2004; Jokinen et al., 2009; Weintraub et al., 2011) and

metabolic (Dagher et al., 2001; Moody et al., 2004; Beauchamp et al., 2008) alterations in PD-MCI.

It was of our interest to longitudinally analyze any probable implication of cognitive impairment in PD on the neural functional activity of MTLS in PD-MCI and PD non-MCI individuals. We speculated that PD is associated with specific functional alterations of neural activity in the areas of the MTLS over time, which possibly underlies the cognitive deficits related to disease evolution.

Engaging temporal lobe areas while performing a cognitive task to compensate for the compromised frontostriatal dysfunction is possible in early PD, as it has been reported that cognitively intact PD patients tend to activate hippocampus rather than the caudate nucleus while performing a spatial task (Dagher et al., 2001), and that the lack of the compensatory role of the mid-temporal region longitudinally might be a predictor of PD-dementia (Carbon et al., 2010). We propose that this over recruitment tends to cease along the evolution spectrum of the cognitive decline.

Our reported results are in agreement that when correlating change in RAVLT scores over time with image analysis of both MCI and non-MCI groups during executing the set-shift (unreported data), indicating that those who had better memory tend to activate MTLS for this task, and effect probably attributed to the non-MCI group as confirmed by correlating the RALVT scores of non-MCI group with the imaging analysis of non-MCI across the two time points (unreported data). It is a possibility that in early PD when individuals are cognitively intact the MTLS functions are preserved, and these areas can be recruited for the compensation process to take place. However, as the

disease progresses, these structures are less recruited over time. This explanation can account for the alteration in the MTLS neural activity that our participants expressed while performing our cognitive task. The decremented pattern of these alterations however, is consistent with the globally decremented volumetric alterations previously mentioned that the MTLS are experiencing over time in PD.

In the future, we will correlate these functional findings of the MTLS areas with the corresponding volumetric equivalents, in conjunction with the clinical and cognitive measures, to yield anatomo-functional correlates that are distinct for PD-MCI and PD non-MCI. And evaluate how combining these two modalities can predict the occurrence of dementia in PD.

Another possible extension of the present work will be to explore the effect of deep brain structures. Indeed, brain stem damage might be the first identifiable stage of PD neuropathology. This damage accounts for a variety of both dopaminergic and non-dopaminergic dysfunction and that can attribute to the non-motor symptoms in PD. Therefore, an early detection of this damage might be helpful combined with other parameters in establishing a platform of an early diagnose of the disease.

Olfactory bulb, medullar oblongata and pontine tegmentum are the first areas to be affected by Lewy bodies (Braak et al., 2006). Noradrenaline is released from the adrenal medulla and in central nervous system noradrenergic neurons of the locus coeruleus. The locus coeruleues sends projections through the thalamus to cortical areas such as frontal, temporal and parietal areas. Therefore, a degeneration of locus coeruleus

might affect executive processes due to noradrenergic deficit (Vazey and Aston-Jones 2012). Patients with PD commonly demonstrate cortical cholinergic dysfunction that is more pronounced in PD-dementia (Bohnen et al., 2003). In a previous work using VBM, at our laboratory a single cluster in the brainstem was identified, between the pons and the medulla oblongata, which differed significantly between PD and healthy controls (Jubault et al., 2009).

Our results are in line with these findings; we found that activity in the lateral posterior thalamus declined overtime in non-MCI group while executing the set-shift. This provides another evidence for primacy of brainstem structural abnormality in PD.

Areas in the posterior putamen were negatively correlated with MoCA scores during planning the set-shift in for both MCI and non-MCI, and also negatively, this result was replicated when correlating both MCI and non-MCI with the corresponding RAVT scores over time (unreported data). When we performed correlation analysis of MoCA scores with the MCI over time, we found the very same pattern (unreported data), This pattern was absent when correlation analysis was performed for the non-MCI group. Therefore, We expect that this pattern was derived by the MCI group. One possible explanation for this might be due to the anterior to posterior pattern of dopaminergic loss across the striatum, which makes early PD individuals recruit the posterior putamen rather than the caudate for this part of the task, because it might be the only striatal structure preserved as the cognitive decline evolves.

Thus, considering our results, we predict that in cognitively intact PD individuals, the early presence of cognitive deficits accompanied by an under recruitment of MTLS and/or the ventral striatum, with an over recruitment of cortical areas related to decision making such as the medial and posterior PFC, longitudinally detected by fMRI; are more predictive of future cognitive decline than the presence of cognitive deficits alone.

Our research provides an opportunity to understand how cerebral functional changes affect cognition and cognitive decline over time in PD stratified by distinct cognitive profiles. The strength of this research lies in its longitudinal design and collection of numerous neuropsychological measures that helped to reveal consistent results, which collectively promise to yield new markers for the early prediction of dementia in PD.

Yet more work in this area is definitely warranted. It is important to establish in a large multifaceted longitudinal project whether functional and anatomical changes medial temporal and cortical structures put the PD non-MCI at increased risk for cognitive decline and PD-MCI at risk of dementia and to assess the role of dopamine in the suggested compensatory mechanism. All will ultimately improve diagnosis and prognosis of cognitive impairment and dementia in PD. Finally, this will inform interventions and treatment strategies tailored for different cognitive profiles in PD before the occurrence of dementia.

CHAPTER 4

Conclusion and future directions

Our study is part of a PCAN laboratory longitudinal project that aims to enhance our understanding of the nature and evolution of cognitive dysfunction in PD. Combined with other measures, this information has the potential to enhance the use of biomarkers such as neuroimaging clinically and can alter our understanding of the diagnosis and prognosis of cognitive dysfunction in PD; additionally it gives a chance to an early prediction of dementia in PD. This will ultimately yield intervention and treatment strategies tailored to this particular group of patients, targeting improving cognitive impairment and slowing down their deterioration.

Our study was longitudinal follow up of non-demented PD patients, with comprehensive repeated neuropsychological assessments and prospective repeated evaluations of participants with precise inclusive and exclusive criteria. The diagnostic criteria adopted were in line with the recent published PD-MCI diagnostic criteria.

The relatively limited PD-MCI sample was one of our study's limitations considering that we encountered cognitive changes of the participants from cognitively impaired to normal cognition and to dementia. Small sample size affects the ability to generalize the findings to the general PD-population. These conversions however have been Previous reported in other longitudinal studies, 14 to 41 percent conversion of MCI to non-MCI in non-PD population (Boyle et al., 2006; Larrieu et al., 2002; Manly et al., 2008) and in PD populations (Pedersen et al., 2013). Falling in that range, we reported two conversions of MCI to non-MCI across the two time points. We propose that these conversions could possibly be attributed to learning effect of the repeated neuropsychological tests or simply due to a general improvement in the global cognitive

condition of participants after initiation of therapy (Kehagia et al., 2010; Pedersen et al., 2013).

Although the comprehensive neuropsychological tests that were used, allowed the subtyping of the PD-MCI and non-MCI, a larger cohorts would have given a chance to compare different subgroups of PD patients stratified according to their cognitive profiles such as those who suffer amnesic and executive or mixed profiles dysfunction, delineating these different profiles would have shed the lights on the related different outcomes that could reflect different pathological processes predictive of dementia in PD.

Some might argue that age might drive some effects, our MCI group was slightly older than PD Non-MCI group but covarrying the age at time one did not affect the results (Nagano-Saito 2014).

Future work will focus on distinguishing which cognitive MCI subtype are most predictive of dementia in PD, it will also aim to distinguish between the cognitive and neural characteristics that are specific to PD-MCI subjects as opposed to characteristics shared by all MCI subjects whether due to PD or other non-PD etiologies such as AD.

Other longitudinal studies with longer and more repetitive follow up periods are warranted to further examine in a long-term perspective, the prognosis of PD-MCI, their pathological correlates and their influence on developing dementia. Furthermore, combining multiple modalities to assess PD-MCI such as resting state functional connectivity analysis and volumetric studies will aid to draw a bigger picture about the

evolution of the MCI and identify anatomical and functional MRI patterns that can be used in combination with the clinical and cognitive measures for the early prediction of dementia.

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Annexes

Annex I—INFORMED Consent form for Patients with Parkinson's disease participating in a research project
At the Unité de Neuroimagerie Fonctionnelle (UNF) Magnetic Resonance Imaging Unit 3.0 T – Institut universitaire de gériatrie de Montréal (IUGM)

TITLE OF THE RESEARCH PROJECT

Investigation of cognitive and motor impairments evolution in Parkinson's disease

INVESTIGATORS

Principal investigators: *Dr. Oury Monchi, CRIUGM*
Dr. Alain Ptito, MNI

Collaborators : *Dr. Antonio Strafella, University of Toronto*
Dr. Anne-Louise Lafontaine, MNI
Dr. Michel Panisset, Hôtel-Dieu
Dr. Rick Hoge, CRIUGM
Dr. Thomas Jubault, CRIUGM (post doc)
Dr. Laura Monetta, CRIUGM (post doc)

FUNDING ORGANIZATION

CIHR

PREAMBULE

We request your participation in a neuroimaging research project. However, before accepting to participate in this research project, please take the time to read, understand and consider carefully the following information.

The goal of this study is explained to you in this informed consent form; also, the procedures, the advantages, the risks, the inconvenience, as well as the contact information of resource people you can communicate if needed.

The informed consent form may contain words that you will not understand. We invite you to ask any questions to the researcher or members involved in the project, to explain or clarify any words or information.

.1. Presentation of the research project and objective

You are invited to be involved in a research project that seeks to understand the origin and the evolution of cognitive and motor deficits in Parkinson's disease.
This study will last 3 years and include 45 Parkinsonian subjects and 20 controls. The involvement of participants with Parkinson's Disease in this study will last 3 years, and 2 weeks for the control participants.
This research project is divided in two parts. The neuropsychological part will take place at the Montreal Neurological Institute in Dr. Alain Ptito's laboratory. The neuroimaging part will take place at the Unité de Neuroimagerie Fonctionnelle of the Institut Universitaire de Gériatrie de Montréal.

NATURE AND DURATION OF YOUR PARTICIPATION IN THE RESEARCH PROJECT

In the neuropsychological part of the study, you will be invited to the Montreal Neurological Institute, in Dr. Alain Ptito's laboratory. You will be administered a series of test that will evaluate your language, memory, motor, planning and reasoning performances. These tests will last about 3 hours, and you will be allowed to take a pause.

For these tests, we will ask you to refrain from taking your medication from the night before the session at the Montreal Neurological Institute.

In the neuroimaging part of the research project, you will be invited at the Unité de Neuroimagerie Fonctionelle (UNF) of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM). You will be administrated two MRI exams in the same day.
We will ask you to refrain from taking your medication from the night before the session at the UNF.

Once on the site, you will be trained on a task where you have to classify cards appearing on a video monitor. This training session will last less than 45 minutes.

Following this, you will be administrated the first scanning session. You will execute the task you have been trained on inside the scanner, which will allow us to capture images of you brain while performing the task. The length of this first scanning session will be less than an hour.

You will be then allowed to take your medication, and rest for a one to two hours period.

Finally, you will be administrated another scanning session, which will allow to produce highly detailed images of your brain. You will only have to lay still inside the scanner, and you will not have any task to do. This second scanning session will last less than one hour.
The total duration of your participation in the neuroimaging part of the project will be less than 3 hours.

You will be invited to take the same tests 18 months and 36 months after the beginning of the study.

Since your involvement in the study implies that you do not take your medication during a certain amount of time, we ask you to take a taxi to come to the MNI or the CRIUGM, or that someone drive you on that day.

WHAT IS MAGNETIC RESONANCE IMAGING (MRI)

MRI is a medical technique that produces clear and detailed pictures of the brain and internal organs. It can also perform functional assessments. It is based on a natural force present around us: the magnetism. It uses a strong magnetic field generated by a large big magnet.

MRI allows us to study not only the anatomy but also the function of the brain. In this case, the MRI permits us to see the areas of the brain which activate when a person performs a specific task. The task may involve motor, sensory, or cognitive components. When performing a motor task for example, the participant may be asked to move their fingers. During a cognitive task, a participant may be requested to do some mental calculations, read a word or look at photographs. When the participant is performing the task, there is a local increase in oxygenated blood flow in the brain areas responsible for the task. This local increase in oxygenated blood flow in turn causes a local increase in MR signal over activated brain areas and this increase in MR signal is detected by the MRI machine.

For the MRI, you must lie on a table confined to a small space inside a cylindrical machine, which uses magnetic fields and radio waves to take pictures of your brain. It is extremely important that you do not move during the procedures. The tunnel is open at both ends. The tunnel is well ventilated and well lit. An intercom system allows communication between the participant and the operator. For you comfort, you will be requested to put on an headphone, earplugs will be provided for hearing protection, the MRI makes a loud knocking sound when images are being acquired. It is important that the participant remains still during the imaging session. Positioning cushions will be placed around the head to help the participant maintain the position. No substance will be injected during the imaging session.

ADVANTAGES OF THE PROPOSED STUDY

There are no direct advantages from participating in this research project. However, the knowledge acquired will contribute to a better understanding of the origin and the evolution of motor and cognitive deficits in Parkinson's disease.

INCONVENIENCES OF THE PROPOSED STUDY

As you stop taking the anti-Parkinsonian medication, some symptoms linked to the disease may reappear. Please note than when you will take back your treatment after the first scan, those symptoms will return to their usual level.

The neuropsychological part of the research project requires a large amount of concentration, and you may experience fatigue.

The requirements imposed by the use of magnetic resonance imaging may cause certain discomfort due to the need to remain still during the length of the examination and the noise which is generated by the MRI when images are being acquired. You may also feel a certain sense of stress or anxiety or a sense of claustrophobia.

RISKS ASSOCIATED TO THIS RESEARCH PROJECT

According to the latest knowledge there is no known health risk associated with the use of this technique when all the necessary steps of precaution are taken.

Due to the strong magnetic field emitted by the MRI, it is necessary to take certain precautions. This is why before participating in a MRI session you must complete two detailed screening forms in order to detect any contra-indications before submitting to an examination, for example, a cardiac pacemaker, an aneurysm clip, a metal prostheses or cardiac valve replacement, the presence of metal in an eye or any part of the body, tattoos, body piercing, certain dental work or if you suffer from claustrophobia. Pregnant women and those who are lactating are not permitted to participate in an MRI research study (see annexed questionnaire).

Verification of the presence of the contra-indications will be strictly reinforced by the technologist on duty at the Unité de Neuroimagerie Fonctionnelle.

RISKS ASSOCIATED WITH PREGNANCY

Some recent studies suggest that MRI could entail certain risks for embryo and foetus health.

These risks are attributed to the radiofrequency magnetic field that may cause heating, as well as the gradient fields that can produce a lot of noise from their interaction with the static magnetic field. Consequently, pregnant and breast-feeding women are excluded from the study. Women that could potentially become pregnant must take a pregnancy test before participating in this study.

COMPENSATION IN CASE OF INJURY

In the event of complications resulting from your participation in this research project, you will receive all the necessary medical care, at no cost.

FINANCIAL COMPENSATION

You will receive financial compensation for time and inconvenience: 80 dollars for the neuroimaging part of the research project, and 60 dollars for the neuropsychological part.

REFUSAL OR WITHDRAWAL OF YOUR PARTICIPATION IN THIS RESEARCH PROJECT

It is understood that your participation in this research project is voluntary and that you are free to withdraw from the research project without prejudice. Withdrawing from a research project will not affect, in any fashion, the services, care or treatment you have or will be offered.

TERMINATION OF PROJECT BY THE RESEARCHER

A research project may be interrupted or terminated by a researcher for any reason.

ACCESS TO YOUR MEDICAL FILES

Do you give permission to the individuals responsible, who are associated with this research project, authorization to consult your medical files? Yes ☐ No ☐

INFORMATION RETURN AND AUTHORIZATION TO TRANSMIT THE RESULTS

Research scans are not subject to any medical evaluation and the brain imaging procedures used in this study are neither a diagnostic test nor a treatment. However, the examination of your brain by magnetic resonance could highlight problems that you have not been aware of up until now. In the presence of any particularity of concern at the time of your examination, you will be invited to undergo a new examination with a scanner at 1.5 Tesla for verification. Upon the confirmation for an anomaly, a neurologist will forward these data to your family doctor for follow-up.

I authorize the researcher of the present project to transfer the results of my evaluation to my family physician should there be any incidental findings that require medical attention:

Yes ☐ No ☐

Name and address of the physician: _____

CONFIDENTIALITY

During your involvement in the project, the principal investigator of the project and his collaborators will collect information about you and store it in a research file. Only information necessary to the research project will be collected.

That information can include partial data from your medical file about your past and present health, your life habits as well as the results from the tests, exams and procedures that you will undergo during your involvement in the research project. Your file may also include information such as your name, gender, date of birth and ethnicity.

All information collected in this project will remain confidential in the strict respect of the law. Personal information such as name and address will be coded. All documents will be preserved in locked files at the CRIUGM, in Dr. Oury Monchi's laboratory. Only the members of the research team will have access to these files. MRI data will be anonymized according to standart UNF procedures.

The principal investigator will use the data of the research project in order to meet its scientific purpose as described in this consent form. Personal information will be destroyed 5 years after the completion of the study.

Should the results be published in scientific or medical journals, or shared with peers in scientific meetings, you will not be identified by name. Your identification and personal information will not be released to a third party.

However, for verification purposes, an exception would be made for the Comité mixte d'éthique de la recherche of Regroupement Neuroimagerie/Québec (CMER-RNQ) or the funding organization. Members of these committees seek to respect the requirements for confidentiality.

In order to protect you and to communicate with you, your identification, address, and the dates of your involvement in the research study will be available for one year, in a file stored by the principal investigator or by the research center.

You are allowed to read through your research file in order to check the accuracy of information collected as long as this file is available. However, you will have limited access to this information as the study comes to an end.

LEGAL RIGHTS

By signing this informed consent form, you do not waive any of your legal rights nor do you free the researcher, the sponsor, the funding organization and the establishment where the project takes place of any civil and or professional responsibilities.

SOURCE OF FUNDING FOR THE PROJECT

The researchers were granted with funding from CIHR to conduct the present project.

ACCESS TO THE RESEARCHERS

If you have any questions concerning the research project or if you believe you feel that a health problem related to you participation in it, you are able to communicate with the researchers

responsible for the study: Dr. Oury Monchi, 514 340-3540, extension 4013, and Dr. Alain Ptito, 514 398-8906.

EMERGENCY PROCEDURES

Please note that the Institut universitaire de gériatrie de Montréal is not a hospital that provides short-term care under the supervision of doctors 24 hours per day. Consequently, in case of a medical condition requiring an immediate action, the first care would be offered by the employees on site and, if necessary, actions would be taken in order to transfer you to the emergency service of a nearby hospital.

CONTACT INFORMATION

For all problems concerning the conditions in which the research project you participated in took place, you are able, after having discussed with the person responsible for the project, to communicate your concerns to the person responsible for complaints at the Institut universitaire de gériatrie de Montréal at the following address: The local service quality and complaints commisionner, Institut universitaire de gériatrie de Montréal, 4565, chemin Queen-Mary, Montréal (Québec) H3W 1W5. Tel. : (514) 340-3517

INFORMATON ON ETHICS

The comité mixte d'éthique de la recherche of Regroupement Neuroimagerie/Québec has approved this research project and ensures the rules of ethics will be respected during the entire research project. For more information, you may contact the secretary of the research ethics committee at (514) 340-2800 local 3250.
If you have any questions regarding your rights as a research subject and you wish to discuss them with someone not conducting the study, you may contact the Montreal Neurological Hospital, Patient Ombudsman at 514 934-1934, ext 48306.
If you have any other kind of comments or concerns, or need assistance regarding your participation as a research subject in this project, please contact the MNH Patient's Committee, room 354, tel. 514 398-5358.

PARTICIPANT'S CONSENT

I have read the informed consent form, especially regarding the type of my participation in this research project and the risk related to it. I confirm that the procedures, the advantages and disadvantages as well as the risks associated with the study have been explained to me, that all my questions have been answered to my satisfaction and that I had enough time to make my decision.

I, freely and voluntarily consent to participate in this project. I will receive a signed copy of this informed consent form.

_____ _____

Participant's Name Participant's Signature

RESEARCHER DECLARATION

I, the undersigned _____, certify:

having explained to the participant the terms of the informed consent form and having responded to the questions which have been asked and clearly indicated the terms of participation in this project described here. I will provide a signed copy of the informed consent form to the participant.

_____ _____

Researcher's Name or his representative Signature of the researcher or his representative

Signed at _____, on the_____.

Annex—II: PRELIMINARY SCREENING FOR MAGNETIC RESONANCE IMAGING STUDY (MRI)

Please print

Last name :	First name :
Date of birth : (day/month/year)	Sex : F ❑ M ❑ Weight : ___ kg ___ lbs Height : ___ m ___ pi
Investigator :	Identification number :

In order to ensure the safety of everyone having access to the area of Functional Neuroimaging Unit, it is of the utmost importance that this questionnaire be completed by the subject and investigator

1. Have you ever had any previous operation?

	No	**Yes**	If yes, please specify the type of surgery and the date :
Head			
Chest or heart			
Abdomen			
Arms, hands			
Legs, feet			
Vertebral column			
Eyes			
Others :			

2. Are you carrying any of the following :

Pacemaker?	**No**	**Yes**
Cardiac electrodes?		
Aneurysm clip?		
Cochlear protheses? Hearing aid?		
Vascular filtre or catheter?		
Neurostimulator?		
Electrical stimulator for the bones?		
Prosthetic cardiac valve?		
Metal or metallic fragments in any part of the body? (e.g. bullet, shrapnel or metal silvers)?		
Insulin pump implant?		
Orthopedic prostheses? (e.g.: nail, screw, plate)		
Artificial limb(s)?		
Permanent make-up? Tattoo(s)?		
Body piercing?		

Magnetic or non-magnetic implant(s)?		
Diaphragm or any intra-uterine devise (IUD)?		
Denture or orthodontics devises (e.g. braces)?		
Eye implant(s) or prosthesis?		
Transdermal patches (e.g. nitroglycerin patch)		
Others :		

3. Are you pregnant or do you believe you are? **no** **yes**
4. If any doubt, do you accept to have a pregnancy test? **no** **yes**

5. Do you suffer from claustrophobia? **no** **yes**

6. Have you ever been injured by metal objects **no** **yes**
(e.g: car accident, work accident, war wounds)
If yes, please specify: _____

7. Have you ever had previous magnetic resonance imaging test? **no** **yes**

8. Have you ever been a:
Mechanist? **no** **yes**
Welder? **no** **yes**
Heavy machinary operator? **no** **yes**
Metal worker ? **no** **yes**

9. Do you have any respiratory or motor disorder? **no** **yes**

I fully understand the procedures, advantages and disadvantages of the study using magnetic resonance imaging which have been explained to me. Further, the application safety measures have been fully explained to me and all my questions have been answered to my satisfaction. I certify that all the information provided above are correct and exact to the best of my knowledge and I freely and voluntarily consent to participate in this MRI study.

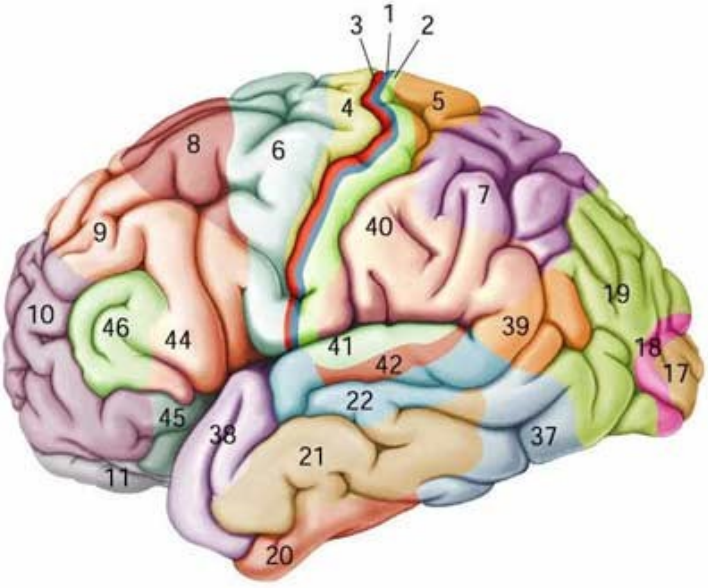
_____ _____
Signature (participant/parent/legal sponsor) Date

_____ _____
Signature (physician/investigator) Date

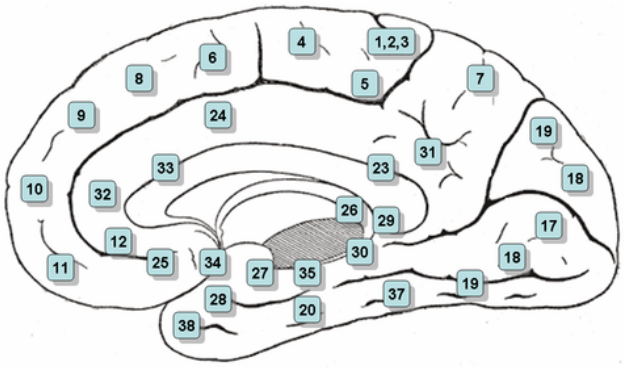
– – – –

Espace réservé
Participation autorisée : non oui
Investigation: non oui

Annex III—Brodmann areas



Source: http://thebrain.mcgill.ca./flash/capsules/images/outil_jaune05_img02.jpg



Source: http://upload.wikimedia.org/wikipedia/commons/thumb/5/58/Gray727-Brodman.png/480px-Gray727-Brodman.png

Annex IV—fMRI Wisconsin Card Sorting Task in young controls