Verbal Fluency in Parkinson's disease: neuroanatomical correlates and functional networks modulated by noninvasive brain stimulation

Joana Braga Pereira
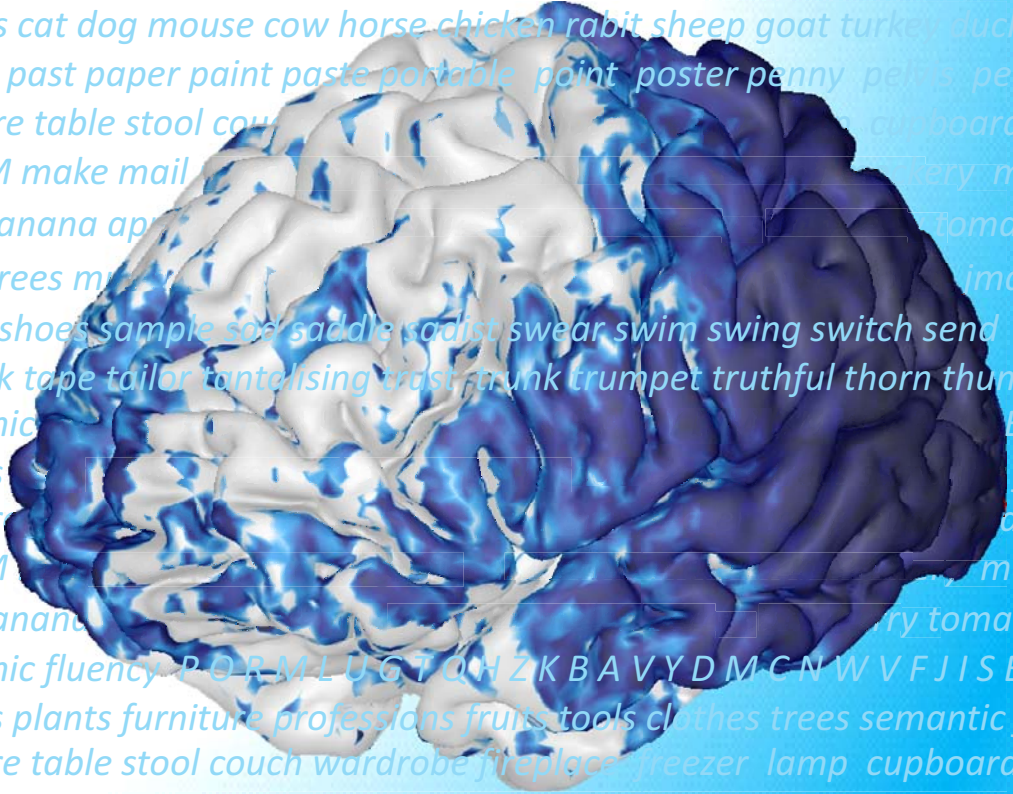
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semantic fluency animals plants furniture professions fruits tools clothes trees
P O R M L U G T Q H Z K B A V Y D M C N W V F J I S E C O P phonemic fluency
animals cat dog mouse cow horse chicken rabit sheep goat turkey duck goose
letter P past paper paint paste portable point poster penny pelvis pentagon
furniture table stool couch wardrobe fireplace freezer lamp cupboard stove
letter M make mail martyr magnificent morbid more mob mockery monster
fruits banana apple orange watermelon melon berry strawberry tomato kiwi
drinks trees m materials
letter S shoes sample soil saddle sadist swear swim swing switch send   sweat
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Joana Braga Pereira
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Verbal Fluency in Parkinson's disease: neuroanatomical correlates and functional networks modulated by noninvasive brain stimulation

Presented by Joana Braga Pereira

Supervised by Carme Junqué i Plaja and David Bartrés-Faz

Thesis submitted for the Degree of Doctor in Biomedicine

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Professor Carme Junqué i Plaja, University of Barcelona

and **Professor David Bartrés-Faz,** University of Barcelona,

declare and confirm that they have supervised and guided the PhD thesis entitled**:**

Verbal Fluency in Parkinson's disease: neuroanatomical correlates and functional networks modulated by noninvasive brain stimulation, presented by **Joana Braga Pereira.**

They hereby assert this thesis fulfills the requirements to be defended for the European Degree of Doctor in Biomedicine.

Signature,

Prof. Carme Junqué i Plaja   **Dr. David Bartrés-Faz**

University of Barcelona   University of Barcelona

Barcelona, June, 2012

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INDEX

I. Foreword

This dissertation presented to obtain the European Degree of Doctor in Biomedicine by the University of Barcelona is the result of three studies performed at the Department of Psychiatry and Clinical Psychobiology, Faculty of Medicine, University of Barcelona.

The following articles have been published in international journals as a result of the work performed:

"Structural brain correlates of verbal fluency in Parkinson's disease."

JB Pereira, C Junqué, MJ Martí, B Ramírez-Ruiz, D Bartrés-Faz, E Tolosa.

Neuroreport 2009; 20 (8): 741-4.

Impact Factor (2009) = 1.81.

Quartile in Category: 3.

Journal Rank in Category: 174/237 (Neurosciences area).

"Modulation of verbal fluency networks by transcranial direct current stimulation in Parkinson's disease."

JB Pereira, R Sala-Llonch, D Bartrés-Faz, C Junqué, MJ Martí, Y Compta, C Falcó, E Tolosa.

Brain Stimulation 2012; Accepted.

Impact factor (2011) = 4.964.

Quartile in Category: 1

Journal Rank in Category: 19/185 (Clinical Neurology area); 41/239 (Neurosciences area).

"Assessment of cortical degeneration in patients with Parkinson's disease by voxel-based morphometry, cortical folding, and cortical thickness."

JB Pereira, N Ibarretxe-Bilbao, MJ Martí, Y Compta, C Junqué, N Bargalló, E Tolosa.

Human Brain Mapping 2011; in press.

Impact factor (2011) = 5.107.

Quartile in Category: 1

Journal Rank in Category: 2/14 (Neuroimaging area); 38/239 (Neurosciences area).

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II. Glossary of abbreviations

AD, Alzheimer's disease

BOLD, blood oxygen level dependent

CBZ, carmazepine

DLB, Dementia with Lewy Bodies

DLPFC, dorsolateral prefrontal cortex

DMN, default-mode network

DMO, destromethorphan

EEG, electroencephalography

FDR, false-discovery rate

fMRI, functional Magnetic Resonance Imaging

fNIRS, functional near-infrared spectroscopy

FWE, family wise error rate

GM, Gray Matter

HY, Hoehn and Yahr

LB, Lewy Bodies

LN, Lewy Neurites

LTP, long-term potentiation

MCI, Mild Cognitive Impairment

MMSE, Mini-Mental State Examination

MRI, Magnetic Resonance Imaging

MSA, Multiple System Atrophy

NMDA, N-methyl-D-aspartate

PD, Parkinson's disease

PDD, Parkinson's disease with Dementia

PET, Positron Emission Tomography

PSP, Progressive Supranuclear Palsy

REM, Rapid Eye Movement

ROI, region of interest

SPM, Statistical Parametric Mapping

STN, subthalamic nucleus

tDCS, transcranial Direct Current Stimulation

TMS, transcranial magnetic stimulation

TPC, Temporo-Parietal Cortex

UPDRS, Unified Parkinson's Disease Rating Scale

VBM, Voxel-Based Morphometry

VH, Visual Hallucinations

WM, White Matter

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Introduction

Parkinson's disease (PD) is currently the second most common neurodegenerative disorder after Alzheimer's disease (AD), affecting 100.000 people in Spain and more than 4 million people worldwide. The devastating impact of this disease is shown by the fact that PD patients present a risk of mortality that is two to five times higher compared to normal individuals (Louis et al., 1997).

The social and economical burden of PD on society is expected to increase in the coming decades with the aging of the worldwide population (de Lau and Breteler, 2006). In fact, together with other neurodegenerative disorders, it has been projected to exceed cancer among the elderly by the year 2040 (Lilienfeld and Perl, 1993).

Current medical and treatment strategies have greatly improved the length and quality of patients with this disease. However, despite of these advances, PD still progresses to decreased responsiveness to dopamine replacement medication and to development of dyskinesias (Leverenz et al., 2009).

Being a movement disorder, impairment of motor functions is considered to be the hallmark symptom of PD. However, cognitive dysfunction is now recognized as a common feature (Emre et al., 2007), being present since early disease stages and affecting the majority of patients as the disease progresses. Cognitive impairment in PD includes executive, visuospatial and memory deficits that play a relevant role in determining the functional outcome in these patients (Kehagia et al. 2010). In line with this, patients with PD present an increased risk to develop clinical dementia (Aarsland et al., 2001), which is associated with decreased quality of life (Schrag et al., 2000) and increased caregiver distress (Aarsland et al., 1999).

Although there are still no established biomarkers for PD (Maetzler et al., 2009), neuroimaging methods offer the possibility of mapping the neurobiological substrates of motor and cognitive impairment in these patients. Amongst the available neuroimaging techniques, structural and functional magnetic resonance imaging (MRI, fMRI) produces images of the brain that provide quantitative values of cerebral atrophy and brain dysfunction, respectively. These techniques are relevant because they shed light into neurodegeneration processes occurring in PD compared to normal aging as well as those pathological processes that specifically underlie

cognitive decline in these patients. In addition to neuroimaging, another method that allows studying brain networks and their disruption in PD is noninvasive brain stimulation, which, in addition to modulating functional connectivity, provides a tool for cognitive and motor rehabilitation (Fregni and Pascual-Leone et al., 2007).

The goal of the current thesis was twofold. First of all, this work represents an attempt to characterize the brain's structural and functional correlates of semantic and phonemic fluency cognitive deficits in patients with PD using MRI, fMRI and noninvasive brain stimulation methods. Secondly, given the lack of a comparison of the relative contribution of different existing MRI-based techniques to characterize cortical degeneration in PD, specific changes in different characteristics of the cortical gray matter (GM) layer were assessed to determine whether brain atrophy in PD can be attributed to changes in cortical thickness, cortical folding or GM volume.

This thesis starts by providing the reader with a review of the literature related to PD, verbal fluency and transcranial direct current stimulation (tDCS), the method of noninvasive stimulation used in this work. Then, a brief description of the main hypotheses and methods of each of the three studies will be provided. Finally, the results, general discussion and conclusions derived from these three studies will complete and conclude the thesis.

Chapter 1.
State of the Art

1. Parkinson's disease

1.1 Diagnosis and motor symptoms

The diagnosis of PD is currently made on the basis of clinical criteria consisting of four cardinal motor symptoms: *bradykinesia, tremor, rigidity and postural instability*.

Although it can also be observed in depression and other diseases, *bradykinesia* is the most characteristic clinical feature of patients with PD and refers to slowness of movement. Being a hallmark of basal ganglia disorders, this symptom comprises problems with planning, initiating and performing motor actions, especially in repetitive, simultaneous and sequential tasks (Berardelli et al., 2001). There are certain symptoms that have been described as being associated with bradykinesia such as akinesia or inability to initiate movements and hypokinesia or decreased amplitude of movements. Other manifestations of bradykinesia include monotonic and hypophonic disartria, loss of facial expression (hypomimia) and reduced arm swing while walking (for review, see Jankovic et al., 2008).

Rest tremor is the most frequent and easily recognized symptom of PD, being evident in James Parkinson's initial description of this illness as the "shaking palsy" (Parkinson, 1987). In PD patients, tremors usually start in an extremity, being unilateral and occurring at a frequency between 4 and 6 Hz (for review, see Jankovic et al., 2008). Classically, rest tremor disappears with action and during sleep in PD. In addition, some patients also report an "internal" shaking that is not associated with a visible tremor (Shulman et al., 1996).

Rigidity refers to an increased tone or stiffness in the muscles that are resistant to passive movement. This symptom may occur proximally in the neck or shoulders, as well as distally in the wrists and ankles (for review, see Jankovic et al., 2008). In addition, it may be associated with pain, with painful shoulder being one of the most common initial manifestations of PD, although it is frequently misdiagnosed (Stamey et al., 2008). When rigidity of the neck and trunk occurs (axial rigidity) patients may present abnormal axial postures and posture deformities (Doherty et al., 2011).

Of the fours cardinal symptoms, *postural instability* is the most potentially dangerous because it can result in falls and subsequent fractures. This symptom usually occurs after the onset of other clinical symptoms, at later stages of PD. It is commonly described as a tendency to lose balance with propulsion and retropulsion, being assessed with the pull test in which the patient is quickly pulled backward or forward by the shoulders. In this test, taking more than two steps backwards or the absence of postural response usually indicates postural abnormalities. Combined with freezing of gait, also referred to as motor blocks or loss of movement, postural instability is the most frequent cause of hip fractures (for review, see Jankovic et al., 2008).

The onset of these four motor symptoms in PD is typically asymmetrical, affecting preferentially one side. At present, the diagnosis of PD involves three steps as shown in Table 1 (Daniel and Lees, 1993):

- Step 1) Identifying cardinal motor features typical of PD;
- Step 2) Excluding possible alternative causes and signs of atypical parkinsonisms;
- Step 3) Detecting supportive prospective positive criteria that confirm PD and allow establishing the definite diagnosis (three or more are required).

Table 1. United Kingdom Parkinson's Disease Society Brain Bank's clinical criteria for the diagnosis of probable Parkinson's disease

Step 1

- Bradykinesia
 - At least one of the following criteria:
     - Rigidity
     - 4-6 Hz Rest tremor
     - Postural instability not cause by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Step 2

- Exclude other causes of Parkinsonism:
    - History of repeated strokes with stepwise progression of parkinsonian features
    - History of repeated head injury
    - History of definite encephalitis
    - Neuroleptic treatment at onset of symptoms
    - >1 affected relatives
    - Sustained remission
    - Strictly unilateral features after 3 years
    - Supranuclear gaze palsy
    - Cerebellar signs
    - Early severe autonomic involvement
    - Early severe dementia with disturbances of memory, language and praxis
    - Babinski's sign
    - Presence of a cerebral tumor or communicating hydrocephalus on computed tomography scan
    - Negative response to large doses of levodopa (if malabsorption excluded)
    - MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) exposure

Step 3

- At least three of the following supportive (prospective) criteria:
    - Unilateral onset
    - Rest tremor
    - Progressive disorder
    - Persistent asymmetry primarily affecting side of onset
    - Excellent response (70-100%) to levodopa
    - Severe levodopa induced chorea (dyskinesia)
    - Levodopa response for 5 years or more
    - Clinical course of 10 years or more

Source: Daniel and Lees (1993).

1.2. Nonmotor symptoms

Despite of the emphasis on motor symptomatology, various studies have shown that PD is also associated with a number of relevant nonmotor symptoms that play an important role in this disorder and have greater significance when assessed by quality of life measures (Schrag et al., 2000). Most of these symptoms correlate with increasing age and disease severity, although some nonmotor symptoms such as depression, olfactory deficits, rapid eye movement disorder and constipation can occur early in the course of the disease (Chauduri et al., 2005; 2006). Common neuropsychiatric symptoms in PD comprise depression, apathy, anxiety, anhedonia, hallucinations and obsessional behavior. In addition, sleep disturbances are a source of disability in PD (Stacy et al., 2002) and can give place to insomnia and excessive daytime sleepiness. A wide range of autonomic disorders has also been frequently reported such as urinary urgency, sweating, orthostatic hypotension, constipation, nausea and dysphagia. Finally, sensory changes including decreased olfaction, pain or other symptoms such as fatigue have also been consistently observed in these patients (Chaudhuri et al., 2006). Below a Table can be found that provides a brief description of nonmotor symptoms in PD.

Table 2. Nonmotor symptoms in Parkinson's disease

• **Psychiatric symptoms**
- Depression, apathy, anxiety
- Hallucinations, illusions, delusions
- Obsessional behavior (usually drug induced), repetitive behavior
- Confusion
- Delirium (could be drug induced)
- Panic attacks
• **Sleep disorders**
- Restless legs and periodic limb movements
- Rapid eye movement (REM) sleep behavior disorder and REM loss of atonia
- Non-REM-sleep related movement disorders
- Excessive daytime somnolence
- Vivid dreaming
- Insomnia
- Sleep disorder breathing

Autonomic symptoms
- Bladder disturbances (urgency, nocturia, frequency)
- Sweating
- Osthostatic hypotension (falls related to orthostatic hypotension, coat-langer pain)
- Sweating
- Sexual dysfunction (hypersexuallity, erectile dysfunction)
- Dry eyes (xerostomia)

Gastrointestinal symptoms
- Dribbling of saliva
- Ageusia
- Disphagia and choking
- Reflux, vomiting
- Nausea
- Constipation
- Unsatisfactory voiding of bowel
- Faecal incontinence

Sensory symptoms
- Pain
- Paraesthesia
- Olfactory disturbance

Other symptoms
- Fatigue
- Diplopia
- Blurred vision
- Seborrhoea
- Weight loss
- Weight gain (possibly drug induced)

Source: Chaudhuri et al. (2006).

1.3. Cognitive symptoms

Contrary to James Parkinson's initial thoughts that the senses and intellects are uninjured in PD (Parkinson, 1987), this disorder is nowadays characterized by a significant and disabling impairment of several cognitive functions. In line with this, the concept of mild cognitive impairment (MCI), which is commonly used to define the transitional state between normal cognitive ageing and Alzheimer's disease, is now used and applied in PD to describe the executive, memory and visuospatial deficits occurring in these patients (for review, see Kehagia et al., 2010). Regarding the prevalence of cognitive impairment, this has been reported to occur up to 60% approximately in patients with no signs of dementia and even within the first years of the disease (Janvin et al., 2006; Williams-Gray et al., 2007; Caviness et al., 2007). Moreover, the presence of cognitive deficits has shown to increase the risk of developing psychiatric symptoms, more rapid motor decline and progression to dementia (for review, see Kehagia et al., 2010).

Executive deficits

Executive functions, which include the ability to plan, organize and regulate goal-directed behavior, are compromised in PD, being regarded as the main symptom of cognitive decline in this disease (Zgaljardic et al., 2003). Patients with PD have been reported to display significant deficits in working memory (Owen et al., 1997), generating strategies to solve problems (Van Spaendonck et al., 1996), trial-and-error learning (Postle et al., 1997), set-shifting processing (Richards et al., 1993) and in the use of internal attentional cues (Brown & Marsden, 1988), which are all abilities that rely on executive functions. These impairments have been compared to those seen in patients with frontal lesions (Owen, 1993), being thought to indicate a dysfunction within the fronto-striatal neuronal circuitry (Jahanshahi et al., 2002), in which the dorsolateral prefrontal cortex plays a relevant role. One of the most commonly used tests to assess executive functions in PD is verbal fluency that usually comprises both semantic and phonemic fluency tasks (Henry and Crawford, 2004).

Memory deficits

Memory functions require the ability to acquire, retain and retrieve knowledge intentionally. A number of studies have shown impairment in immediate and delayed recall in patients with PD as well as temporal ordering and conditional associative learning (Zgaljardic et al., 2003). Some

studies suggest that these deficits could be the consequence of retrieval problems and can be solved by providing patients with external cues (Pillon et al., 1993; Aarsland et al., 2003). These findings suggest that memory deficits may be due to executive dysfunction (Higginson et al., 2003), although not all studies support this hypothesis (Portin et al., 2000; Beatty et al., 2003; Higginson et al., 2005). Other evidence suggests that some patients with PD, in addition to having deficits in verbal recall, also present a significant impairment in recognition, similarly to patients with AD (Weintraub et al., 2004).

Attention deficits

Difficulties in the ability to focus and maintain attention has also been associated with executive dysfunction in PD, being reported in shifting and sustained attention tasks (Lewis et al., 2005). PD patients have shown to be more vulnerable to distracters in tasks that require attention compared to healthy elders (Vingerhoets et al., 2005). Significant deficits have been found on attentional tasks that require speeded cognitive processing or that need the patient to internally guide attentional resources (Pahwa et al., 1998; Ridenour et al., 1999). In cases with dementia, attentional problems consisting of both reduced and fluctuating performance are particularly prominent (Ballard et al., 2002), being more severe than in AD (Emre et al., 2007).

Visuospatial deficits

There is substantial evidence in favor of visuospatial dysfunction in PD. Previous studies have shown these patients present deficits in unifactorial measures of visuospatial ability in these patients such as in tests of line orientation (Alegret et al., 2001a; Green et al., 2002; Uc et al., 2005) in addition to deficits in multifactorial tasks such as mental rotation (Crucian et al., 2003). Moreover, significant visuospatial deficits have been found in memory for spatial location (Pillon et al., 1996) and visual form discrimination (Pereira et al., 2009). Some studies have suggested that these deficits are related to impairment in other cognitive functions such as working memory and attention (Kemps et al., 2005), while other studies have shown that visuospatial deficits are rather specific of PD and unrelated to executive abilities (Cronin-Golomb and Braun, 1997; Janvin et al., 2003).

Visuoperceptive deficits

Visuoperceptive impairment has also been found in patients with PD in a range of tests that involve object detection, categorization of visual stimuli (Laatu et al., 2004) and face recognition (Kida et al., 2007; Pereira et al., 2009). In those cases with clinical dementia, a significantly worse performance has been found in face recognition tasks as well as form and space perception compared both to nondemented patients and healthy individuals (Laatu et al., 2004; Mosimann et al., 2004). The pattern of visuoperceptive deficits was suggested to be similar to that found in dementia with LB (DLB) but different from AD (Mosimann et al., 2004).

Language deficits

Previous studies have shown that PD patients present deficits in linguistic abilities such as reduced confrontation naming performance compared to healthy elder individuals (Goldman et al., 1998; Green et al., 2002). In addition, these patients also appear to have difficulties in tasks requiring complex comprehension and grammar knowledge, possibly due to deficits in information speed processing (Grossman et al., 2002) and grammatical processing (Ullman et al., 1997). Finally, a significant impairment in sentence processing has also been found in PD (Grossman et al., 1999), which has been attributed to dysfunctional attentional mechanisms (Grossman et al., 1992).

1.4. Dementia in Parkinson's disease

According to Aarsland et al. (2001), patients with PD present a six fold increased risk to develop dementia compared to cognitively normal healthy subjects. In community-based studies, an incidence rate of dementia between 9.5% and 11.2% per year has been reported, indicating that each year 10% of PD patients will develop dementia (Aarsland et al., 2009). Regarding cumulative prevalence rates, a previous study based on a strictly epidemiological cohort showed that following an 8-year period, the prevalence of dementia in initially nondemented patients at moderate stages of PD was 78% (Aarsland et al., 2003).

The most consistent risk factors that predict development of dementia in PD are older age at onset (de Lau et al., 2005; Williams-Gray et al., 2009), more severe axial symptoms (Locascio et al., 2003), such as rigidity, postural instability and gait disturbance (Verbaan et al., 2007) and mild cognitive impairment at baseline (Janvin et al., 2006). In addition, visual hallucinations

(Aarsland et al., 2003) and greater disease duration (Locascio et al., 2003) have also been regarded as important predictive factors.

1.5. Neuropathological studies

PD affects multiple neuronal systems, being the result of pathological changes occurring in a few susceptible types of nerve cells at specific regions of the human peripheral, enteric and central nervous system (Braak et al., 2003; Braak et al., 2006a). It has been shown that these susceptible neuronal types belong to a particular class of projection neurons, which generate an axon disproportionately long and thin in relation to the size of the cell soma, and that is unmielinated or poorly mielinated (Braak et al., 2004).

During the pathological process of PD these vulnerable cells develop intraneural aggregations of a misfolded protein called α-synuclein as spindle-like lewy neurites (LN) and in the form of LB (Pollanen et al., 1993; Forno et al., 1996) which are not a normal concomitant of healthy aging (Thal et al., 2004).

The disease usually progresses slowly, but relentlessly, and requires several years to reach its full extent. In line with this, neuronal damage occurring in PD has been reported to start before the initial symptoms even appear (Del Tredici et al., 2002) and, if not interrupted by death, leads to the full manifestation of the disease.
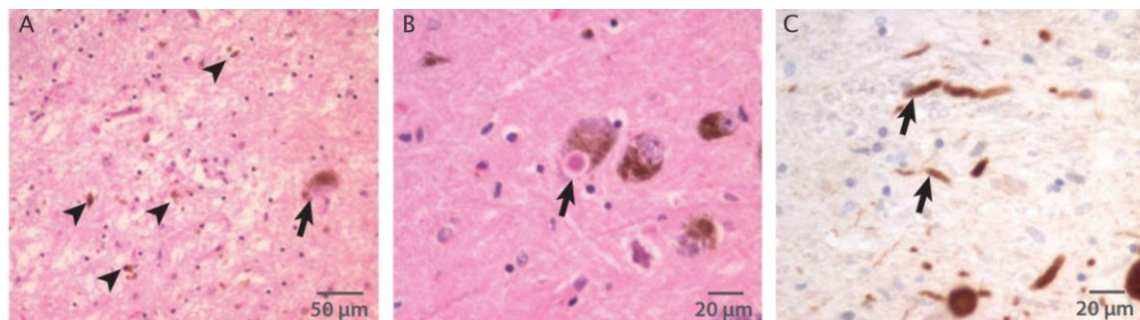
Figure 1. LB and LN pathology in PD. A) View of the substantia nigra showing marked depletion of dopaminergic neurons (arrow, remaining neuron), reactive gliosis and neuromelanin present in phagocytic cells (arrowheads). B) Typical brain-stem LB pathology (LB, arrow) in a pigmented dopaminergic neuron. The LB has a dense eosinophilic core and surrounding paler halo. C) Lewy neuritis (arrows). Source: Shulman et al. (2011).

Lesions to specific nuclei of the substantia nigra pars compacta with severe obliteration of their neuromelanineladen projection neurons is considered to be the core feature of PD (Damier et al., 1999). This degeneration depletes dopamine available to the caudate and putamen, giving place to the typical motor symptomatology of PD (Przedborski, 2007). By the time patients begin expressing motor symptoms, approximately 50-70% of the dopaminergic cells in the substantia nigra have already been lost (Fearnley and Lees, 1991).

With time, the disease progresses and LB and LN expand beyond the substantia nigra into much of the neuroaxis (Braak and Del Tredici, 2008). α-Synuclein has been described in the peripheral cutaneous nerves, autonomic and enteric nervous systems, spinal cord, lower brainstem (dorsal motor nucleus of the vagus), limbic structures (amygdala and hippocampus) and neocortex. The vulnerable cell populations to the progression of the disease include several nondopaminergic cell types, such as noradrenergic neurons of the locus coeruleus, serotoninergic projections from raphe nuclei, and acetylcholinergic cells of the basal forebrain in the nucleus of Meynert (Shulman et al., 2011).

On the basis of a postmortem analysis, Braak et al. (2003) have proposed a staging system for PD pathology consisting of six neuropathological stages. This staging procedure rests on the assumption that Lewy Body pathology is the first step along a disease continuum. Below, a Figure showing the areas that are compromised by the disease in each stage is provided.
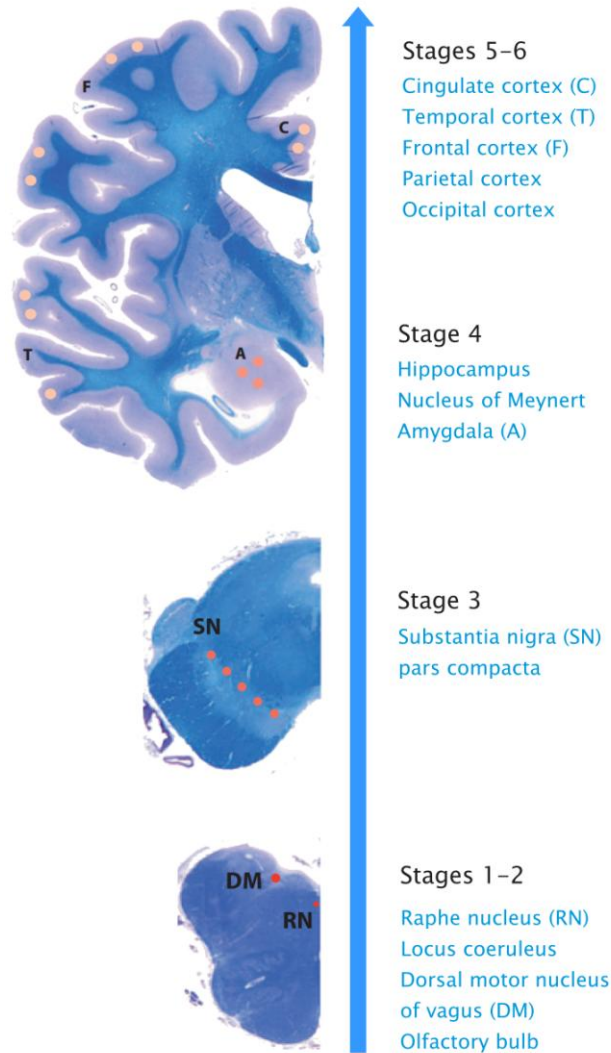
Figure 2. Pathological changes associated with Parkinson's disease. This figure represents a scheme depicting the major stages of PD pathology as proposed by Braak et al. (2003). Source: Shulman et al. (2011).

The first two stages refer to incidental LB disease, with LB in the medulla oblongata, particularly in the dorsal motor nucleus IX/X and/or intermediate reticular zone, caudal raphe nuclei, gigantocellular reticular nucleus, the coeruleus-subcoeruleus complex and the olfactory bulb. Around stage 3, these specific inclusions reach the midbrain, in particular the substantia nigra pars compacta. At this point, patients arrive at and cross the threshold from a subclinical or presymptomatic disease phase and start manifesting motor symptoms. When patients reach stage 4, the lesions expand to the temporal mesocortex (transentorhinal region), the nucleus of Meynert as well as limbic regions such as the cornus ammonis 2 (CA2) of the hippocampus and the amygdala. Stage 5 is characterized by expansion of LB to neocortical areas, particularly high

order sensory areas such as the insula, anterior cingulate and prefrontal cortex and finally, on stage 6, the lesions compromise first order sensory areas of the neocortex and premotor areas, occasionally affecting primary sensory areas and the primary motor field. The damage in important limbic structures and extensive neocortical areas occurring during stages 5 and 6 is considered to be associated with cognitive impairment in PD (Braak et al., 2003).
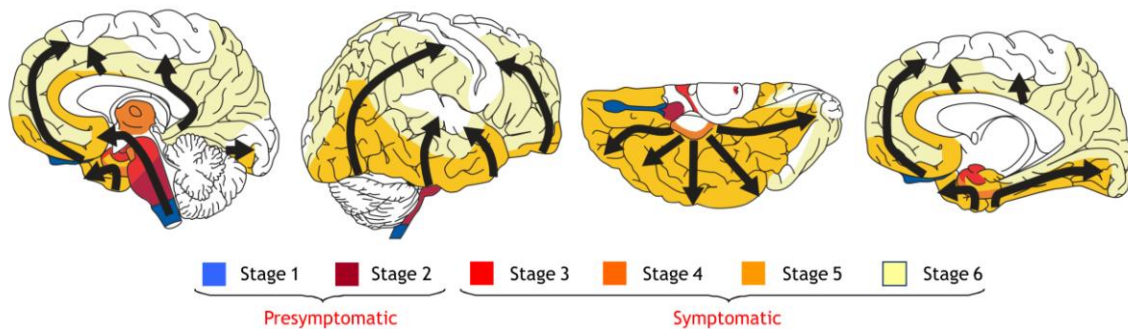
Figure 3. Progressive involvement of central nervous system structures by LB pathology in PD, according to Braak et al. (2003). The first two stages correspond to the prodromal or presymptomatic phase of PD. When patients reach Stage 3, they start manifesting motor symptoms, beginning with the symptomatic phase. Source: Farlow et al. (2008).

There is still significant debate on the relationship between Braak's staging of PD and clinical data, with some studies reporting an acceptable correlation between pathological findings and symptom severity (Halliday et al., 2008), while others show no association between LB pathology and clinical severity or dementia (Jellinger, 2009a; 2009b). For instance, in a previous study Braak et al. (2006b) found that the neuropathological stages of PD correlated with the Mini-Mental State Examination (MMSE) scores, showing a linear trend. However, in that study two thirds of the patients with stage 4 pathology were moderately or severely demented, suggesting that, contrary to previously thought, cognitive decline may take place in the presence of relatively few cortical LB and LN. In addition, two patients on stage 5 did not fulfill criteria for dementia according to the MMSE, although there were abundant cortical LB and LN in these cases.

Other neuropathological studies have confirmed that the staging based on LB pathology is barely applicable to cognitive impairment and dementia occurring in PD (Ferrer, 2011). For instance, Parkkinen et al. (2009) showed that only a percentage of clinical cases showed an

association between cognitive decline and dementia with cortical LBs. These studies suggest that other factors rather than LBs might be playing a role in cognitive decline observed in PD.

In line with this, a role of the cholinergic system has been proposed as early cholinergic alterations are observed since early stages of the disease that increase with development of dementia, suggesting a correlation between cognitive impairment and impaired cholinergic innervation in the cerebral cortex in PD (Bohnen et al., 2009, 2011; Shimada et al., 2009). Indeed, significant loss of cholinergic forebrain neurons in the nucleus basalis of Meynert had been previously reported in PD brains (Candy et al., 1983; Whitehouse et al., 1983; Tagliavini et al., 1984), with one study finding even greater forebrain neuronal loss in late stage PD than in AD (Arendt et al., 1983).

Although less consistently, deficits in other ascending monoaminergic systems have also been proposed to play a part in cognitive impairment in PD (Calabresi et al., 2006). These deficits include reduction of cortical and forebrain concentrations of noradrenaline and serotonin as well as neuronal cell loss in the locus coeruleus and in the raphe nuclei (Scatton et al., 1983).

Finally, a synergistic interaction between α-synuclein and protein aggregates of AD such as amyloid-β and tau has also been proposed as a critical determinant of dementia in PD (Masliah et al., 2001; Apaydin et al., 2002; Pletnikova et al., 2005; Lashley et al., 2008; Clinton et al., 2010), with some studies even suggesting a link between concomitant AD pathology and faster progression to dementia (Ballard et al., 2006; Sabbagh et al., 2009). Recently, it was shown that a combined high burden of LB, amyloid-β and tau pathologies is the best neuropathological correlate of dementia in PD, being present in several cortical areas in PDD patients compared to those without dementia (Compta et al., 2011). Moreover, in that study, cortical amyloid-β scores and Braak's tau stages, by contrast to LB scores or Braak α-synuclein stages, significantly correlated with scores on the MMSE, which is frequently used to assess dementia in PD and other neurodegenerative disorders.

1.6. MRI studies

In the past few years, the detection of structural cortical and subcortical changes on magnetic resonance imaging (MRI) scans has become increasingly important for clinical research. In particular, MRI has proven to be of great utility in the study of neurological diseases, providing sensitive biomarkers that can aid in the early diagnosis and track disease progression.

Many pathological processes that occur in the brain result in morphological changes and atrophy of brain tissue, which can be identified by MRI. In line with this, particular patterns of atrophy are associated with specific neurodegenerative diseases.

Until recently, the traditional techniques that were used to assess brain atrophy on MRI included visual assessment by expert radiologists and manual measurements of regions of interest. However, thanks to great advances in neuroimaging, automatic methods of analysis are now available that permit evaluating large samples of subjects without requiring time-consuming manual and subjective measurements (Whitwell, 2009).

1.6.1. Voxel-based Morphometry (VBM)

Voxel-based morphometry (VBM) is an example of an automated neuroimaging technique that has gained increasing popularity since it was first introduced (Wright et al., 1995; Ashburner and Friston, 2000) given that it provides results that are biologically plausible (Whitwell, 2009). Usually this technique uses T1-weighted images and performs statistical tests at every voxel in the image in order to detect significant differences of tissue volume or density between groups of subjects or to assess the neuroanatomical correlates of cognitive and behavioral impairments (Whitwell, 2009). Several studies have compared results from VBM with manual and visual measurements of brain structures, finding a good correspondence between these two methods (Good et al., 2002; Giuliani et al., 2005; Whitwell et al., 2005; Davies et al., 2009).

In order to carry out statistical analyses across MRI scans of different subjects with VBM, a number of pre-processing steps must be applied to the images (Ashburner and Friston, 2000; Whitwell, 2009). According to the Statistical Parametric Mapping (SPM) toolbox (http://www.fil.ion.ucl.ac.uk/spm/), which was the first software to implement VBM analyses, these steps (Figure 4) consist of:

1) Spatial normalization of the images in a way that a specific location in one subject's MRI corresponds to the same location in another subject's MRI. This involves registering all the images of a study onto the same template image so that they are all normalized to the same space.

2) Image segmentation of the spatially normalized images into different brain compartments: GM, white matter (WM) and cerebrospinal fluid. The VBM analyses will be carried out separately on gray or white matter, depending on the study's specific hypotheses. Two types of image output can be selected: modulated images that provide information on brain volume or unmodulated images that provide information on brain density. Nowadays, it is generally recommended to use DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) (Ashburner et al., 2007), which is a more sophisticated registration model that alternates between computing a template based on the average tissue probability maps from all subjects, and then warping all subject's tissue maps into increasingly good alignment with the template (Ashburner et al., 2009).

3) Smoothing of the images, by which the intensity of each voxel is replaced by the weighted average of the surrounding voxels, which blurs the segmented images (Kiebel et al., 1999). The number of voxels averaged at each point is established by the size of the smoothing kernel.
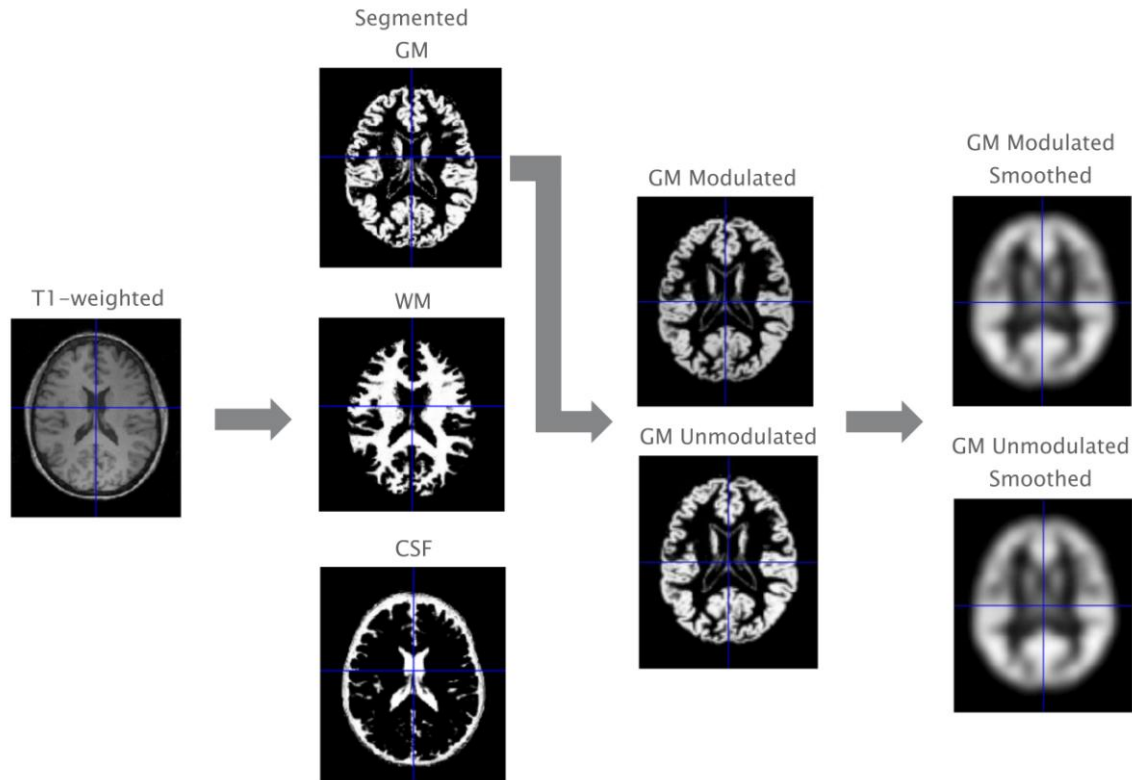
Figure 4. Standard preprossessing steps applied during VBM analyses using SPM.

Once these steps have been completed, images are prepared for statistical analyses, which provide results in terms of parametric brain maps that depict differences in brain regions between groups or brain regions that are significantly associated with performance in a particular test. In addition, region of interest (ROI) analyses focusing on single brain structures can also be performed. Since the maps from the statistical analyses include the results for multiple statistical tests at every voxel (for the whole brain or within a ROI), then correction for multiple comparisons is considered appropriate by means of false-discovery rate (FDR) or family wise error rate (FWE) corrections. These correction techniques are both associated with advantages and pitfalls. Essentially, while FDR is less restrictive and provides a poor control of false positives, FWE is considered to be too conservative and is associated with a risk of eliminating true positives. In response to these limitations, a new type of correction has been recently introduced called topological FDR, which is more sensitive than FWE control with minimal cost in terms of false positives (Chumbley et al., 2010).

According to Mechelli et al. (2005), VBM analyses are associated with a number of limitations and potential confounds. On one hand, this technique is especially sensitive to misregistration problems and movement artifacts on MRI, giving place to systematic classification differences between subjects that can be incorrectly identified as significant brain atrophy. Moreover, studying brains with severe pathologies may also be problematic with VBM due to difficulties in spatial normalization and segmentation of atypical brains. Another disadvantage is that it uses a relatively imprecise image registration. The parametric procedures of VBM are only valid if the residuals, after fitting the model, are normally distributed, raising the possibility that non-normality in the error terms can make statistical inferences invalid in some studies. Finally, the nature of the gray matter and white matter changes is poorly understood, especially in healthy subjects as to whether they are related to changes in the neuropil, neuronal size or to dendritic or axonal arborization. In addition, cortical assessment by VBM merges information about morphology, size, and position (Ashburner and Friston, 2001) and the final measures include a mixture of thickness and cortical folding (Park et al., 2009; Voets et al., 2008), being therefore unspecific.

Despite of these limitations, several studies have used VBM to assess atrophy in the whole brain or within ROIs in patients with PD. On Table 3 (see Page 45), a brief summary on the methodological details of such studies is provided.

Overall, in patients without dementia, most consistent findings indicate significant GM reductions in frontal areas (Burton et al., 2004; Nagano-Saito et al., 2005; Nishio et al., 2010; Biundo et al., 2011; Melzer et al., 2012; Song et al., 2011), including the superior, inferior and medial portions. In addition, a number of studies have found significant GM atrophy in temporal lobe structures such as the superior temporal gyrus and insula (Summerfield et al., 2005; Beyer et al., 2007a; Nishio et al., 2010; Melzer et al., 2011; Song et al., 2011), in addition to the anterior cingulate (Kostic et al., 2010) (Figure 5), which is known to be particularly vulnerable to LB inclusions in PD (Hurtig et al., 2000; Hishikawa et al., 2003).
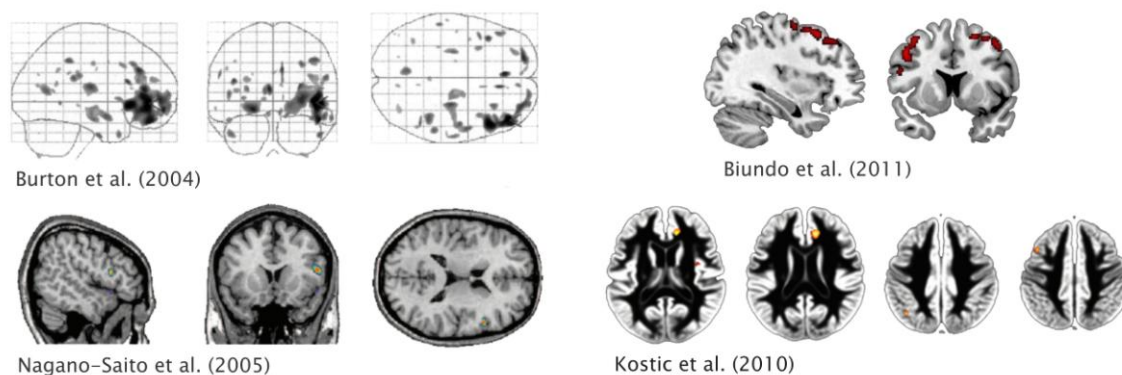
Figure 5. GM reductions in frontal, temporal, insular areas and the anterior cingulate in PD patients compared to controls. Adapted from: Burton et al. (2004), Nagano-Saito et al. (2005), Biundo et al. (2011) and Kostic et al. (2010).

However, within patients without dementia there seem to be differences between those that are considered to be cognitively intact and those with mild cognitive impairment (Figure 6). For instance, Beyer et al. (2007a) showed that PD patients with MCI had reduced gray matter density in the left middle frontal gyrus, precentral gyrus, left superior temporal lobe and right inferior temporal lobe compared to cognitively intact PD patients. In addition, Nishio et al. (2010) found that, while GM loss occurred in limited parts of the cerebral cortex in patients that were at a stage without cognitive deficits, in cognitively impaired patients without dementia GM atrophy extended into widespread cortical and limbic regions. In a subsequent study, Melzer et al. (2012), found that compared to controls, no GM differences were found in cognitively normal PD patients, by contrast to PD with MCI, which exhibited GM atrophy in temporal, frontal, parietal areas, in addition to the hippocampus, amygdala and right putamen.
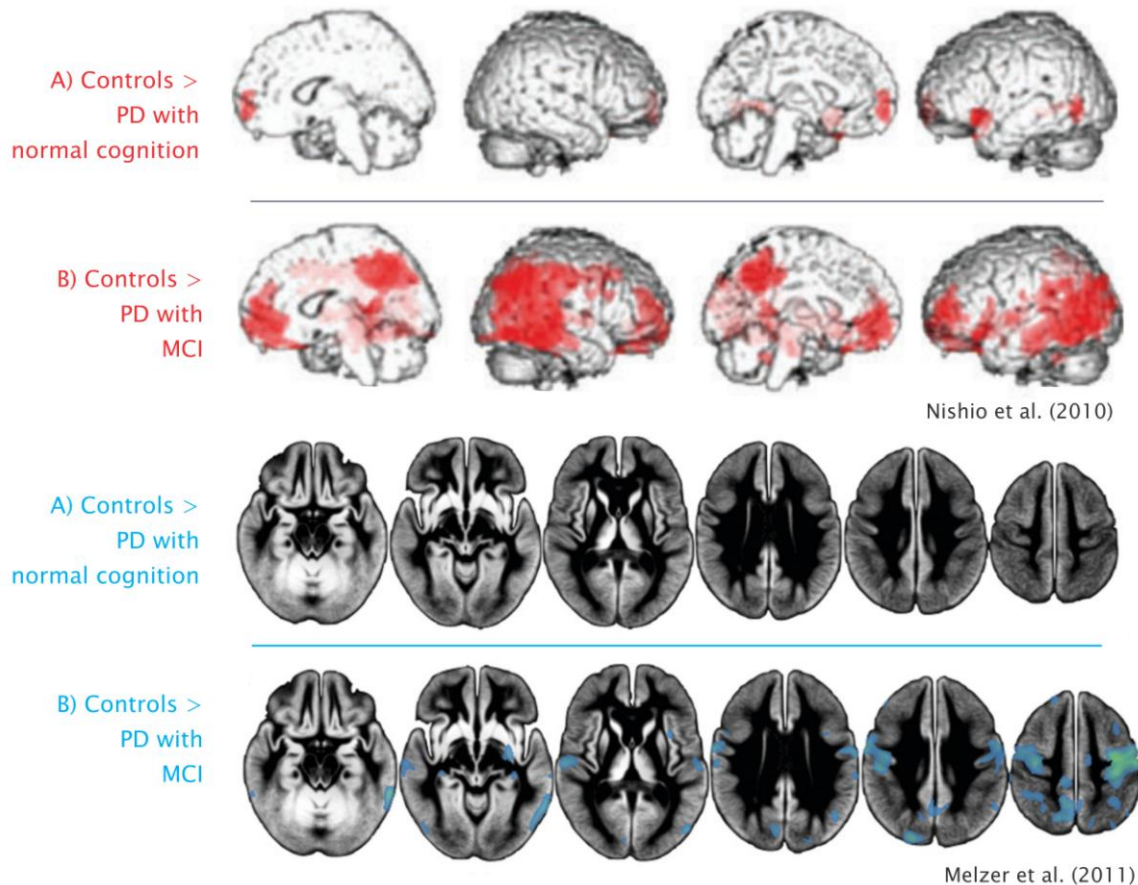
Figure 6. GM reductions in (A) PD patients without cognitive deficits compared to controls and (B) patients with MCI compared with controls (B). Adapted from Nishio et al. (2010) and Melzer et al. (2012).

Hence, these studies seem to suggest that cognitive impairment could be responsible for GM atrophy occurring in PD patients and that those cases without cognitive decline are very likely to have no or very mild GM loss.

In patients with visual hallucinations (VH) but without dementia, greater GM volume decreases have been found compared to nonhallucinating patients in parietal and occipital areas (Ramirez-Ruiz et al., 2007a). Occipital regions are known to play an important role in color perception, visual discrimination and visual attention (Gallant et al., 2000; Lee et al., 2000), while parietal regions have been involved in visuospatial working memory (Newman et al., 2003), mental imagery (Lambert et al., 2004), and together with the frontal lobe, participate in processing information in visuospatial attention tasks (Kastner et al., 1999). In a study using a ROI approach to assess hippocampal volumes, significant reductions were found in the hippocampal head in

patients with visual hallucinations, which extended to all hippocampal subregions in patients with dementia, compared to controls (Ibarretxe-Bilbao et al., 2008). In addition, Janzen et al., (2011) found volume reductions in the pedunculopontine nucleus and thalamic nuclei in hallucinating patients compared to PD without hallucinations, suggesting that these regions are involved in the pathophysiology of visual hallucinations in PD. However, findings from studies assessing regional atrophy in hallucinating patients have not always been consistent, with one study reporting no GM differences between hallucinating and nonhallucinating PD patients (Meppelink et al., 2011).

In PD patients with dementia (PDD), far more extensive GM atrophy has been observed compared with cognitively intact PD and PD with mild cognitive impairment in large areas of the temporal lobe, intracalcarine and lingual gyri, frontal regions and bilateral caudate and hippocampi (Melzer et al., 2011). Indeed, these patients present widespread GM changes in various cortical and subcortical regions (Beyer et al., 2007b; Song et al., 2011), including the hippocampus and anterior cingulate (Summerfield et al., 2005), although not as extensive as those observed in patients with AD (Burton et al., 2004) and patients with DLB (Beyer et al., 2007b; Lee et al., 2010; Sanchez-Castañeda et al., 2010).

Longitudinal studies assessing GM changes at baseline and follow-up in patients with PD have also been performed. In one study, VBM revealed significant GM loss in limbic and paralimbic regions in nondemented patients after 25 months, while in demented patients neocortical volume reductions was the most relevant finding, suggesting the neocortex could be a substrate for dementia in PD (Ramirez-Ruiz et al., 2005). In another study (Ibarretxe-Bilbao et al., 2010), patients with VH showed widespread limbic, paralimbic and neocortical GM loss, whereas in patients without VH GM loss was restricted to the frontal cortex and cerebellum at follow-up, which was 30 months later.

Although most VBM studies have assessed atrophy in GM, a few have also analyzed WM volume in PD patients at early disease stages, showing significant brain stem (Jubault et al., 2009), right fusiform and superior temporal gyri (Martin et al., 2009) WM volume decreases with respect to healthy controls.

Finally, several studies have assessed whole brain GM differences between subgroups of PD patients, finding that those patients with excessive daytime sleepiness (Kato et al., 2011), that developed MCI or dementia earlier in the course of the disease (Lee et al., 2012; Beyer et al., 2008), that had depression (Kostic et al., 2010) or rest tremor (Benninger et al., 2009) presented greater GM or WM atrophy compared to patients without these characteristics, with one study reporting GM increases in patients with levodopa-induced dyskinesias compared to those without dyskinesias (Cerasa et al., 2011).

At a subcortical level, using different methods than VBM that were either automated or semi-automated, others have found that nondemented patients show hippocampal atrophy (Camicioli et al., 2003; Bouchard et al., 2008; Apostolova et al., 2011), in addition to amygdalar (Bouchard et al., 2008), caudate, thalamic reductions (Lee et al., 2011) and a significant ventricular enlargement (Apostolova et al., 2010; Dalaker et al., 2011). Using visual assessment scales, Bruck et al. (2004) also found significantly smaller hippocampal volumes in patients with PD; Tam et al. (2005) showed medial temporal lobe atrophy both in demented and nondemented patients; and Junqué et al. (2005) found significant amygdalar and hippocampal reductions in patients with dementia. These findings agree well with results from VBM studies and further validate the use of this technique.

In summary, the majority of VBM studies assessing atrophy in the whole brain have reported GM loss restricted to frontal and temporal areas in nondemented stages of PD, which further extend to neocortical areas with disease progression and development of dementia. It should be noted that a few studies using VBM have also found no GM reductions in PD patients compared to controls (Price et al., 2004; Feldmann et al., 2008), suggesting that differences in methodology, clinical variables and sample sizes might be playing a role in the nature of these discrepancies and should be controlled for in future studies.

The use of structural MRI, particularly through VBM analysis methods, has proved very useful to assess the neuroanatomical correlates of cognitive dysfunction in PD (Figure 7). For instance, regarding executive functions, Nagano-Saito et al. (2005) showed that dorsolateral prefrontal volume reductions were associated with executive deficits on the Raven Colored Progressive Matrices test in patients with PD. In addition, Ibarretxe-Bilbao et al. (2009) found a significant

correlation between GM of the orbitofrontal cortex and performance on the Iowa Gambling test that also assesses executive processes such as decision-making, while Camicioli et al. (2009) found that temporal, parahippocampal, caudate, precuneal and cerebelar regions were associated with an executive index that included the stroop interference, trail-making and digit ordering tests in PD patients. Concerning memory deficits, several studies have shown that hippocampal measures correlate with learning (Junqué et al., 2005; Ibarretxe-Bilbao et al., 2008), recall (Bouchard et al., 2007) or recognition impairment (Camicioli et al., 2003) in PD. In addition, impairment on a test that involved recognizing facial expressions of emotions was also found to correlate with GM volume in the bilateral orbitofrontal cortex in these patients (Ibarretxe-Bilbao et al., 2009). Finally, correlations with visuospatial and visuoperceptive functions have also been performed in PD (Pereira et al., 2009). In that study, performance in a visual form discrimination spatial task was found to correlate with GM reductions in dorsal parietal areas, while scores on a facial perception task correlated with areas of the ventral occipitotemporal cortex. Overall, the areas of reduced volume or density reported by these studies were interpreted in light of the role they play in the cognitive processes they were found to correlate with, suggesting that GM loss in these areas might be contributing to the observed cognitive deficits in PD patients.

A) Correlations with verbal learning
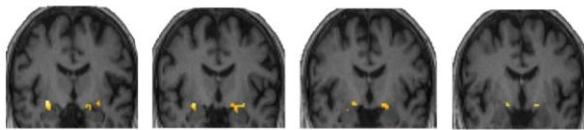
Ibarretxe-Bilbao et al., (2008)

B) Correlations with executive functions
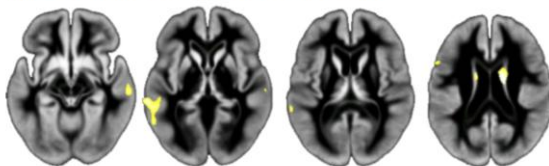
Camicioli et al., (2009)

C) Correlations with emotion recognition
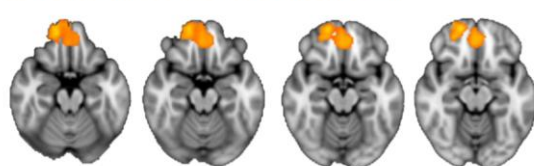
Ibarretxe-Bilbao et al., (2009)

D) Correlations with facial recognition
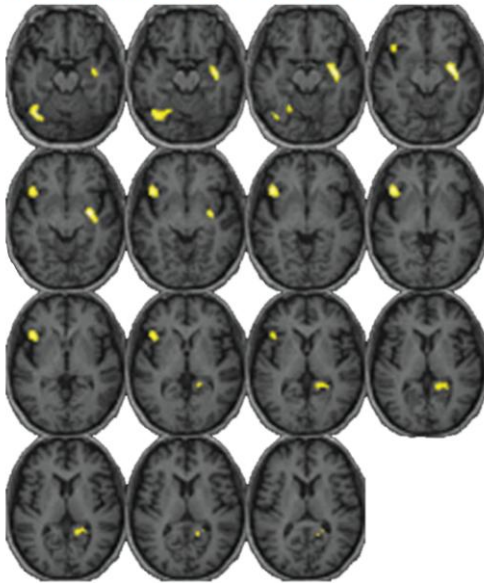
E) Correlations with visual form discrimination
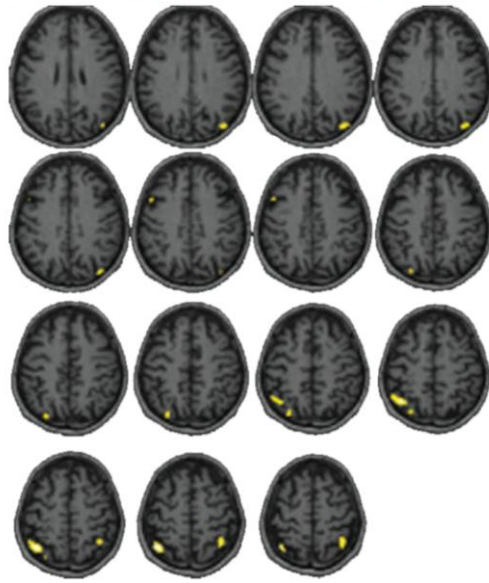
Pereira et al., (2009)

Pereira et al., (2009)

Figure 7. Significant correlations between GM volume or density and performance in a verbal learning task of the Rey's Auditory Verbal Learning Test (A), in an executive index that involved the stroop interference, trail-making and ordering tests (B), in a task of recognition of emotions from the Ekman test (C), in Benton's facial recognition test (D) and in a visual form discrimination task (E). Adapted from Ibarretxe-Bilbao et al. (2008, 2009), Camicioli et al. (2009) and Pereira et al. (2009).

Despite of being an area of increasing interest, there is still scarce literature on the brain structural correlates of neuropsychological impairment in PD. As such, there are several neuropsychological functions whose neuroanatomical substrates in PD are still unknown.

Table 3. Methodological details of VBM studies performed in PD

N	Study	Subjects	Age	UPDRS III or HY*	Duration in years	Scanner	Software	VBM processes	Statistical threshold	Smoothing
1	Brenneis et al. (2003)	12 PD 12 MSA 12 C	63 (10.8) 62(6.6) Matched for age.	34(15-42) 42(31-61) -	6 (3.1) 2.8(1.1) -	1.5 T General Electric Signa scanner	SPM99	Modulation. MNI template.	P < 0.05 corrected.	10 mm
2	Burton et al. (2004)	31 PD 26 PDD 28 AD 17 DLB 36 C	75.2 (5.2) 72.3 (5.2) 77.9(5.4) 75.5(7.2) 75.1 (6.6)	25.8(11) 36.4 (11) 4(3.8) 26.8(16.9) -	3.6 (2.9) 6.8 (5.1) 2.7(1.4) 2.4(1.4) -	1.5 T GE Signa scanner	SPM99	Modulation. Study specific GM templates. Covariate: ITV.	P < 0.001 uncorrected.	8 mm
3	Price et al. (2004)	12 PD 12 PSP 12 C	65.4 (9.2) 65.3(5.8) 67.4 (4.6)	16.7 (5.1) 20.4(8.7) -	13.3(6.7) 4.8(1.7) -	1.5 T General Electric Signa scanner	SPM99	Modulation. SPM T1 template. Covariates: GM,age,gender.	P < 0.05 corrected.	8 mm
4	Cordato et al. (2005)	17 PD 21 PSP 23 C	67.7 (6.7) 70.3(6.4) 71.5 (7.2)	18.9 (7.4) 23.1(10.1) 0.3(0.5)	7.9 (3) 4(2.8) -	1.5 T Siemens Magnetom Vision	SPM99	Modulation. MNI template. Covariates: age, gender, global voxel intensity.	P < 0.05 corrected.	12 mm
5	Nagano-Saito et al. (2005)	39 PD 9 PDD 31 C	61.8 (8.1) 67.3 (5.4) 63.5 (8.8)	25.5 (16.1) 45.7 (10.9) -	3.5 (3.4) 9.3 (5.4) -	1.5 T Visart MRI scanner	-	Modulation. MNI template.	P < 0.001 uncorrected.	8 mm
6	Summerfield et al. (2005)	13 PD 16 PDD 13 C	72.8 (4.9) 70.1 (7.9) 70.1 (7.2)	24.5 (12) 36.3 (13.8) -	10.6 (7.4) 12.9 (5.4) -	1.5 T General Electric scanner	SPM99	Modulation. Study specific GM templates.	P < 0.001 uncorrected.	-
7	Beyer et al. (2007)	20 PD 16 PDD 20 C	72.5 (8.5) 73.5 (6.5) 73.3 (6.3)	2.4 (0.6)* 3.0 (0.6)* -	12 (6.3) 12.3 (7.5) -	1.5 T Philips Gyroscan intra release 8.1	SPM2	No Modulation. Study specific GM templates.	P < 0.001 uncorrected.	12 mm
8	Ramirez-Ruiz et al. (2007)	20 PD 18 PD VH	Age matched.	24.5 (14) 29.3 (11.7)	10.6 (4.3) 12.6 (5.6)	1.5 T General Electric	SPM2	Modulation. Study specific GM	P < 0.001 uncorrected.	12 mm

No	Reference	Subjects	Age (years)			Scanner	Software	Method	Threshold	Smoothing
		21 C		-	-	scanner		templates. Covariates: ITV, MMSE,Hamilton HY scores.		
9	Feldmann et al. (2008)	27 PD 23 PD with depression 16 C	62.3 (7.5) 61.1 (7.7) 54.3(10.4)	33.6 (8.8) 35.1 (9.3) -	11.2 (5.9) 9.9 (5.2) -	1.0 T Siemens Harmony Expert scanner	SPM2	No modulation. SPM T1 template. Covariates: age, gender.	P < 0.05 FDR.	8 mm
10	Kendi et al. (2008)	12 PD 13 C	62.1(12.7) 58(7.3)	43 (13.8)	5.8 (4.5)	3 T Trio Siemens scanner	SPM2	Modulation. Study specific GM template.	P < 0.05 corrected.	10 mm
11	Ibarretxe-Bilbao et al. (2008)	19 PD 16 PD VH 9 PDD 56 C	72.5 (5.8) 73.5 (5.1) 69.8 (9.5) 73 (6.7)	24.7 (14.3) 29.7 (12.8) 42.8 (17.4)	10.9 (4.2) 12.9 (5.9) 13.1 (5.4)	1.5 T General Electrics scanner	SPM2	ROI hippocampus. No modulation.	P < 0.05 corrected.	6 mm
12	Camicioli et al. (2009)	43 PD 43 C	70.7 (4) 71 (4.5)	16.7 (8.1) 1.9 (2.5)	8.3 (4.5) -	1.5 T Siemens Sonata scanner	SPM5	Modulation. Covariates: age, ITV.	P < 0.05 FDR.	12 mm
13	Jubault et al. (2009)	23 PD 18 C	64 (5.5) 62.2 (5.4)	29.1 (9) -	6.3 (3.9) -	3 T Siemens Trio scanner	SPM5	Modulation. MNI template. Covariates: age, gender, GM or WM volume.	P < 0.05 FDR.	12 mm
14	Martin et al. (2009)	26 PD 14 C	59.8 (7.7) 56.8 (7.8)	15.8 (6.9) -	3 (1.7) -	1.5 T Siemens Sonata scanner	SPM5	Covariates: ITV, age.	P < 0.05 FDR.	12 mm
15	Sanchez-Castañeda et al. (2009)	16 PDD 16 C	71.2 (7.2) 71.8 (7.6)	35.5 (13.5) -	4.4 (2.3) -	1.5 T Philips Intera scanner	SPM5	Modulation. Covariates: years education.	P < 0.05 FWE.	8 mm
16	Tir et al. (2009)	19 PD 14 C	61.6 (7.6) 59.2 (7.6)	21 (9) -	6.6 (2.5) -	1.5 T Philips Achieva scanner	SPM2	No Modulation. Study specific GM template.	P < 0.05 corrected.	12 mm
17	Lee et al. (2010a)	20 PDD 18 DLB Controls	71.9(5.9) 73.2(7.1) -	30.3(15) 16.7(1) -	6.2(5) 1.4(1) -	3.0 T Philips Intera scanner	SPM8	Modulation with DARTEL	P < 0.001 uncorrected.	6 mm

#	Author	Participants				Scanner	Software	Method	Threshold	Smoothing
18	Lee et al. (2010b)	41 PD MCI 78 MCI Controls	71.3(6.3) 70.5(8) -	- - -	1.7(1.6) 1.9(1.5) -	3.0 T Philips Intera scanner	SPM8	Modulation with DARTEL. Covariates: age, MMSE.	P < 0.001 uncorrected.	6 mm
19	Nishio et al. (2010)	27 PD 13 PD CI 13 C	65.6 (5.2) 67.6 (5.5) 63 (4.6)	18.3 (8) 22.4 (6.4) -	3.7 (2.9) 6.1 (5.8) -	1.5 T General Electric Signa scanner	SPM5	Modulation. Covariates: age, sex, ITV.	P < 0.001 uncorrected.	12 mm
20	Dalaker et al. (2010)	31 PD 11 PD MCI 37 C	63.5 (9.6) 67.5 (9.3) 63.9 (9.5)	22.9 (9.3) 28.8 (10.1) -	2.6 (2) 2.4 (1.6) -	1.5 T	SPM5	Modulation. Covariate: ITV.	P < 0.05 FDR.	8 mm
21	Kostic et al. (2010)	24 PD 16 PD with depression 26 C	65(54-79) 66(50-78) -	19(10-35) 23(4-36) -	5 (1-9) 6 (1-14) -	1.5 T Siemens Avanto scanner	SPM5	Modulation with DARTEL. Covariates: age, gender, ITV.	P < 0.001 uncorrected.	8 mm
22	Melzer et al. (2011)	57 PD 23 PD MCI 16 PDD 34 C	64.3 (8.7) 70.8 (8) 73.3 (7) 69.6 (9.2)	25.9 (14.2) 35.7 (18.7) 48.9 (15.7) -	3.8 (3.3) 7.2 (5) 12.9 (8.8) -	3 T General Electric HDx scanner	SPM5	No modulation. Covariates: age, gender, ITV, years education.	P < 0.05 FDR.	10 mm
23	Kato et al. (2011)	13 PD 9 PD EDS 22 C	63.6(10.3) 62.2(9.6) 63.4 (6.1)	28.6 (19.9) 24.8 (17.6) -	10 (4) 8.2 (5.8) -	3 T Trio Siemens scanner	SPM5	Modulation. Covariates: age, gender, ITV.	P < 0.05 FDR.	12 mm
24	Biundo et al. (2011)	24 PD 33 PD ICD 22 C	70.4(6.8) 61.3(10.2) -	32.3 (12.8) 30.2 (13.2) -	8.9 (5.4) 8.8 (4.8) -	1.5 T Philips Achieva scanner	SPM8	Modulation. Covariates: age, gender, ITV, years education.	P < 0.01 FWE.	8 mm
25	Meppelink et al. (2011)	13 PD 11 PD VH 14 C	64.6 (7.8) 61.2 (8.2) 58.5 (7.5)	20.4 (7.3) 21.4 (7) -	8.7 (4.7) 8.1 (5) -	3 T Philips scanner	SPM5	Modulation. Covariate: ITV.	P < 0.001 uncorrected.	10 mm
26	Cerasa et al. (2011)	36 PD 36 PD Dys 32 C	60.9(10.2) 61.5 (9.5) 65.1 (8.2)	23.5(12-37) 20(10-50) -	6.4 (2.8) 7.6 (3.9) -	1.5 T Signa General Electric	SPM8	Modulation with DARTEL. Covariate: ITV.	P < 0.05 FWE.	8 mm
27	Janzen et al. (2011)	16 PD 13 PD VH 13 PDD VH 11 DLB	64.3(8) 66(6.9) 67.7(7.1) 62.6(6.5)	23.6(11.5) 29.1(8.4) 45.7(15.9) -	3.1(3.6) 11.5(5.2) 10.9(5.5) 4.6(4.5)	3.0 T General Electric Signa HDxt scanner	SPM8	Modulation with DARTEL. Study specific template.	P < 0.001 uncorrected.	8 mm

								Covariates: age, ITV.		
28	Lee et al. (2011)	23 PD E-MCI 19 PD L-MCI	71.1(5.4) 70.2(6.2)	20.6(12.4) 25.2(20.2)	1.3(0.6) 6.9(4.8)	3.0 T Philips Intera scanner	SPM8	Modulation with DARTEL. Covariates: age, duration of disease, GM volume.	P < 0.001 uncorrected.	6 mm
29	Song et al. (2011)	23 PD 27 PD MCI 18 PDD 20 C	69.1(6.1) 71.3(6) 72(6) 71.2(6.5)	16.9(11.8) 18.6(10.9) 32.1(10.9) -	1.4(1.2) 3.9(5.3) 4.7(3.4) -	3.0 T Philips Intera scanner	SPM8	Modulation with DARTEL. Covariates: age, years education; GM volume.	P < 0.001 uncorrected.	6 mm

MSA, Multiple System Atrophy; C, Controls; PSP, Progressive Supranuclear Palsy; VH, Visual Hallucinations; CI, Cognitively Intact; EDS, Excessive Daytime Sleepiness; ICD, Impulse

Control Disorder; Dys, Dyskinesias; E-MCI, Early Mild Cognitive Impairment; L-MCI, Late Mild Cognitive Impairment.

1.6.2. Cortical thickness

The human cerebral cortex is a highly folded sheet of neurons, the thickness of which has been reported to vary between 1 and 4.5 mm, depending on the cortical area and cortical layer. The cortical thickness of the brain is of great interest in both normal development as well as a wide range of disorders (Fischl and Dale, 2000). Changes in cortical thickness have been found to occur in normal aging (Fjell et al., 2009; Tamnes et al., 2010), AD (Du et al., 2007; Dickerson et al., 2009), Huntington's disease (Rosas et al., 2008; Nopoulos et al., 2010), frontotemporal lobar degeneration (Rohrer et al., 2009) and multiple sclerosis (Calabrese et al., 2010), amongst other diseases. The cortical thinning is usually regionally specific and the progress of atrophy can therefore reveal much about the evolution and causative factors of a disease (Fischl and Dale, 2000).

To date, several neuroimaging methods have been developed that allow measuring the cortical thickness of the brain. One such method that has gained increasing interest over the past years is FreeSurfer (http://surfer.nmr.harvard.edu; Fischl and Dale, 2000; Fischl et al., 1999b), which generates highly accurate models of both the gray/white and pial surfaces and measures cortical thickness as the distance between these two surfaces (Figure 8). Compared to VBM methods, cortical thickness offers a number of advantages in that it differentiates between cortices of opposing sulcal walls within the same sulcal bed, enabling more precise measurement in deep sulci (Lerch and Evans, 2005). Moreover, cortical thickness measures allow for subvoxel precision because thickness values are assigned to individual vertices instead of voxels (Fischl and Dale, 2000).
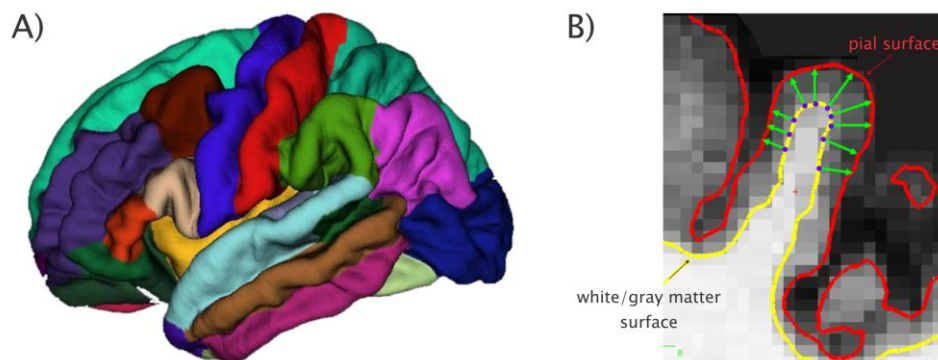
Figure 8. Cortical reconstruction and automatic labeling of brain regions using FreeSurfer (A). In FreeSurfer, cortical thickness is measured as the distance between the white/gray matter boundary and the pial surface (B).

Previous reports of cortical thickness in AD have shown that cortical thinning mirrors pathological changes identified with histology (Lerch et al., 2005; Singh et al., 2006; Seo et al., 2007). For instance, Lerch et al. (2005) found that AD patients presented greater thinning in the medial temporal lobes, posterior cingulate, parietal and orbitofrontal cortices, in agreement with progression of senile plaques and neurofibrillary tangles of Braak's staging for AD (Braak et and Braak, 1991; Braak et al., 1996). Cortical thickness is related to neuronal structural complexity features such as neuronal size, presynaptic terminals, and complexity of dendritic arborizations. In postmortem studies, frontal and temporal neocortical regions show evidence of cortical thinning with increasing age in the absence of neuronal number loss (Freeman et al., 2008). Hence, changes in cortical thickness could be occurring much before than neuronal death takes place, indicating preclinical stages of a disease as suggested by Fennema-Notestine et al. (2009).

Similarly to VBM and other neuroimaging methods, FreeSurfer applies several pre-processing steps to structural MRI scans prior to the statistical analyses. Briefly, these steps consist of removing nonbrain tissue, transformation to the Talairach reference space, segmentation into GM and WM (Dale et al., 1999), correction of topological defects (Fischl et al., 2001), intensity normalization (Dale et al., 1999), and subvoxel representation of the GM/WM boundary and pial surfaces (Dale et al., 1999; Fischl et al., 1999). As mentioned before, cortical thickness is calculated as the shortest distance between the previous surfaces at each vertex across the cortical mantle. The cortical maps are finally smoothed using a circularly symmetric Gaussian kernel across the surface and averaged across subjects. In order to correct for multiple comparisons, Monte Carlo simulations and FDR corrections can be carried out to identify significant vertex-wise group cluster differences between groups or correlations with neuropsychological, clinical and behavioral measures.

In PD, a few studies have been performed that assessed changes in cortical thickness occurring in these patients. For instance, Lyoo et al. (2010) showed that, in a sample of 48 PD patients without dementia, widespread cortical thinning could be observed in the inferior parietal, rostral frontal and orbitofrontal cortices, with predominance in the temporal cortex compared to age-matched healthy controls. The topographical distribution of cortical thinning found in

that study overlapped with the area where Lewy bodies and Lewy neurites are found in these patients at advanced stages of the disease (Braak et al., 2003), suggesting that cortical thinning occurs early in the clinical course of PD. In a posterior study, Tinaz et al. (2011) found that, at moderate stages of the disease, PD patients showed focal cortical thinning in several frontal and occipital areas such as the inferior frontal gyrus, lingual gyrus, cuneus and the fusiform gyrus, with respect to controls (Figure 9).
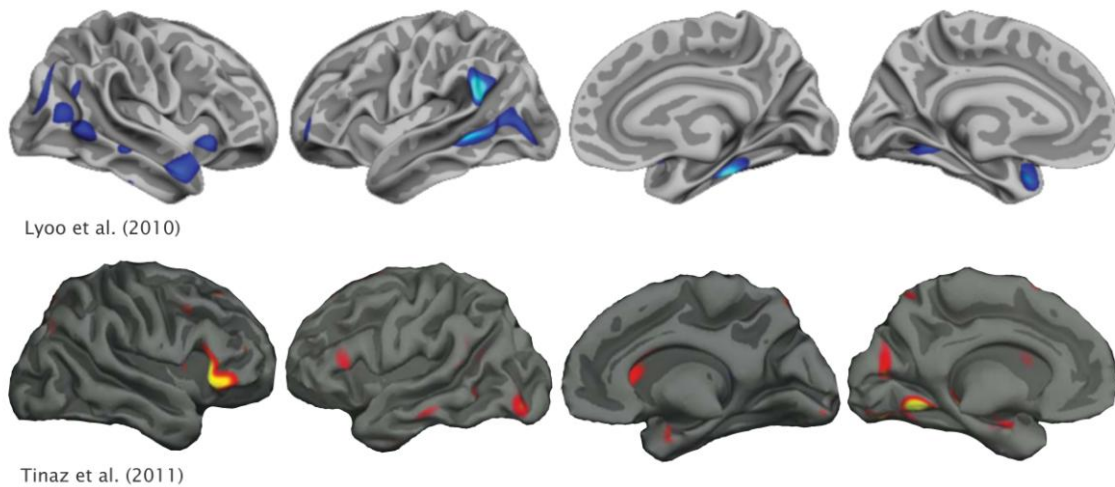
Figure 9. Cortical thinning (blue and hot colors) in PD patients without dementia compared with controls, at an uncorrected statistical level (p < 0.05). Adapted from Lyoo et al. (2010) and Tinaz et al. (2011).

Whereas the studies by Lyoo et al. (2010) and Tinaz et al. (2011) reported results at an uncorrected statistical level, in Pellicano et al. (2011) Bonferroni corrections were applied to correct for multiple comparisons and significant cortical thinning was shown in the fusiform gyrus, in addition to the middle temporal area, which was specifically associated with verbal memory performance in PD patients. Regarding regression analyses between cortical thickness and clinical motor measures, Lyoo et al. (2011) found that cortical thickness of the parieto-temporal cortex, including the inferior parietal and posterior parietal areas, was negatively correlated with disease duration and the UPDRS subscores for bradykinesia as well as axial motor deficits in a large group of 142 patients with PD, suggesting the role of these areas in the exacerbation of specific motor symptoms in PD.

Finally, using a different method to measure cortical thickness called SurfStat (http://www.math.mcgill.ca/keith/surfstat), Jubault et al. (2011) found thinning in the

supplementary motor area of PD patients compared to controls, in addition to a significant association between thickness in the precuneus with age and a significant correlation of disease duration with temporal cortical thinning in the patient group.

1.6.3. Cortical folding

Sulcal folds are the main surface landmarks of the human cerebral cortex, exhibiting structurally complex patterns that describe the burying of the cortex, a concept known as cortical folding (Cachia et al., 2003, 2008). Variations in cortical folding morphology offer another approach to study changes in brain anatomy and have received recent interest following the development of sophisticated 3D-based image processing techniques. One technique that has made considerable contributions to sulcal measurements is BrainVisa (http://brainvisa.info/; Mangin et al., 2004) which consists of applying several preprocessing steps to the MRI scans such as removal of nonbrain tissue, registration to a reference space like the Talairach frame, inhomogeneity correction, brain tissue partial volume segmentation, sulcal extraction (Figure 10) and labeling.
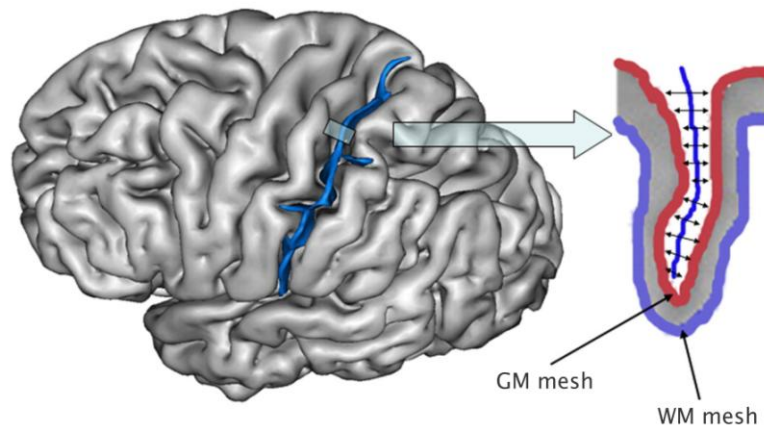
Figure 10. Measurement of the central sulcus using BrainVisa. Source: Liu et al., (2010).

Using BrainVisa or similar methods, previous studies have shown that widening of cortical sulci and decreases of sulcal depth are associated with normal aging (Kochunov et al., 2005, 2008; Liu et al., 2010), MCI (Im et al., 2008), and AD (Bastos-Leite et al., 2006; Im et al., 2008). Although the nature of these changes is yet unknown, it is thought that the atrophy of the underlying WM and GM results in reduction of gyral thickness and causes dilation of cortical sulci (Magnotta et al., 1999; Jernigan et al., 2001).

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In healthy subjects, the collateral fissure and parieto-occipital sulcus have been shown to exhibit the most significant changes with increasing age (Kochunov et al., 2005), while in MCI patients, these abnormalities particularly affect the frontal, temporal and parietal lobes and in AD spread through the entire cortex (Im et al., 2008). Brain sulci and cortical folding have also been associated to cognitive decline of specific neuropsychological functions. For instance, measures of sulcal widening in the anterior cingulate and superior frontal sulci have been related to executive dysfunction in senescing subjects (Kochunov et al., 2009), whereas sulcal indices of the cingulate and calcarine sulci have shown to correlate with deficits on verbal fluency and visuospatial tasks respectively in patients with AD (Mega et al., 1998).

In patients with PD, only two studies have analyzed changes in sulcal morphology. These studies used visually guided methods to measure the depth of the olfactory sulcus and explored its relationship with olfactory deficits (Kim et al., 2007; Wang et al., 2011). In one study (Kim et al., 2007), no sulcal differences were found between patients and controls and correlation analyses did not reveal any association between impairment of olfactory functions in patients with PD and the depth of the olfactory sulcus, suggesting that olfactory loss may not be a primary consequence of sulcal damage. By contrast, in a subsequent study Wang et al. (2011) observed that PD patients presented significant reductions both in the volume of the olfactory bulb and olfactory sulcus depth. However, only volume measures correlated with olfactory deficits, indicating that olfactory GM atrophy, but not sulcus atrophy, might be contributing to olfactory impairment.

1.7. Functional connectivity studies

To date, the majority of studies using fMRI have used a standard model-based approach, which determines regional changes in brain function by creating a model of the expected BOLD response (Ibarretxe-Bilbao et al., 2011). However, thanks to new advances in neuroimaging, model-independent approaches can now be implemented, which allow assessing functional connectivity. Here, a brief description of functional connectivity studies in PD will be provided.

1.7.1. Resting state studies

Resting state functional connectivity is a relatively novel technique that allows studying large scale functional networks in the brain based on the temporal correlation of spontaneous,

intrinsic and non-task related blood oxygen level dependent (BOLD) fluctuations in a very low frequency range (Fox and Raichle, 2007; Vincent et al., 2007). These fluctuations are thought to reflect the hemodynamic consequences of slow variations in transient neuronal dynamics that propagate through anatomically connected networks (Ghosh et al., 2008). The huge metabolic load of these intrinsic fluctuations suggests that they are functionally relevant (Fox and Raichle, 2007), possibly by normalizing or consolidating synaptic weights within a cerebral network (Pinsk and Kastner, 2007; Balduzzi et al., 2008). In addition, it has been shown that alterations in these fluctuations can be used as a marker of network dysfunction (Greicius et al., 2004; Sheline et al., 2009).

The resting state network, commonly referred to as the default mode network (DMN), encompasses the medial prefrontal cortex, posterior cingulate cortex, precuneus, lateral parietal and temporal cortices. When a cognitive task is performed, the areas of the DMN show themselves in a state of deactivation. According to leading hypotheses, deactivation of these areas could signal a reduction in inhibitory processes but also the ability to redirect attentional processes from self-reflection to goal-directed behavior (Raichle et al., 2001; Raichle and Snyder, 2007).

So far, a few studies have applied this technique to investigate network characteristics in PD. For instance, van Eimeren et al. (2009) found that, compared to controls, patients with PD not only failed to deactivate areas of the DMN to a normal extent (Figure 11) but also showed a reversed pattern of activation and deactivation, in addition to a functional disconnection between the medial prefrontal cortex and the rostral ventromedial caudate nucleus.
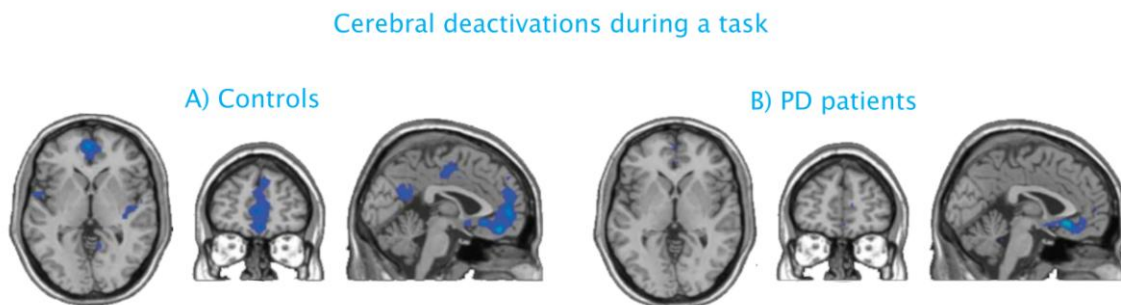
Figure 11. Brain deactivations in controls and PD patients during an executive task. Controls showed deactivation of the medial prefrontal cortex, posterior cingulate and precuneus (A), while patients with PD only showed deactivation of the medial prefrontal cortex. Adapted from Eimeren et al. (2009).

In another study, Helmich et al. (2010) showed that PD patients presented a decreased functional connectivity between the posterior putamen and inferior parietal cortex during resting-state, suggesting these alterations may underlie abnormal sensoriomotor integration in PD.

An association between deactivation of the areas of the DMN and levodopa intake in patients with PD has been proposed. For example, Delaveau et al. (2010) evaluated brain deactivations during a facial recognition task and showed that PD patients failed to deactivate the posterior midline and lateral parts of the DMN while off medication. In that study, after levodopa administration, the DMN was restored together with a significant improvement of motor deficits in PD patients. In another study assessing mild to moderate patients with PD, Kwak et al. (2010) observed an overall increase in the strength of cortico-striatal functional connectivity in patients in the off state of dopaminergic medication compared to controls. However, this enhanced connectivity was down-regulated by levodopa intake shown by an overall decrease in connectivity strength, particularly within motor regions. Wu et al. (2009a) also came to similar findings showing that the administration of levodopa relatively normalizes the pattern of functional connectivity in PD patients and that the change in neural activity in the resting state is secondary to dopamine deficiency and related with the severity of the disease (Wu et al., 2009b). Further confirming these findings, Krajcovicova et al. (2012) showed that the strength in functional connectivity within the DMN was positively correlated with the magnitude of levodopa equivalent doses.

In a recent study by Wu et al. (2011) it was found that connectivity changes occurring in PD were associated with only a few specific networks as greater connectivity changes in networks related to motor preparation and initiation were found compared to networks of motor execution, which may be partially responsible for the difficulties in initiating movements observed in PD. In addition, there are also differences amongst PD patients as those patients without tremor show greater increases in functional connectivity between the subthalamic nucleus and midline cortical motor areas compared to patients with tremor, suggesting that overactivity in the motor cortical-subthalamic pathway might play a role in the pathophysiology of PD (Baudrexel et al., 2011).

1.7.2. Cognitive studies

To date, most studies assessing functional connectivity changes occurring in patients with PD during a specific task have used motor paradigms. However, there is one study by Ibarretxe-Bilbao et al. (2011) that used a facial recognition task and showed that PD patients presented decreased task-related activations in areas involved in the recognition memory network in addition to decreased task-related deactivations in the DMN, compared with healthy controls (Figure 12). In that study, PD patients were at initial stages of the disease and did not present recognition memory deficits, suggesting that functional connectivity analyses can detect early network dysfunctions prior to a clear evidence of cognitive impairment.
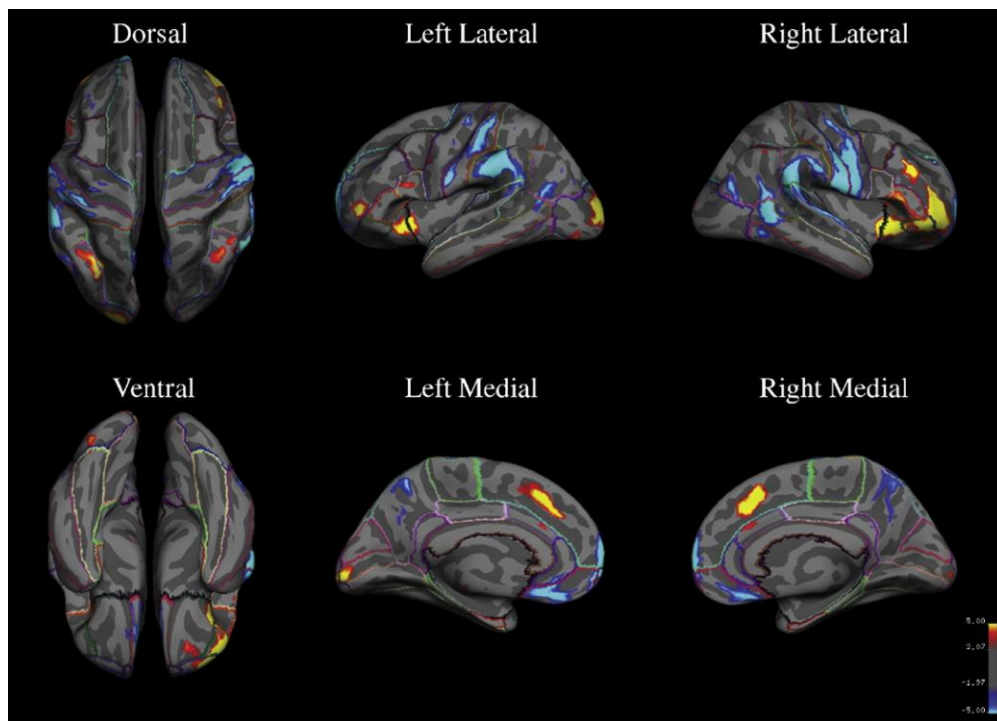
Figure 12. Areas showing decreased activations (in yellow) during a recognition memory task in PD patients compared with healthy controls. These areas correspond to the orbitofrontal cortex, paracingulate, angular and occipital gyri. The areas in blue show decreased task-related deactivations in the DMN in the PD group compared to controls. Source: Ibarretxe-Bilbao et al., (2011).

2. Verbal fluency

2.1 Introduction

Verbal fluency is a classical neuropsychological test of word production that is commonly measured by the amount of words generated in response to a letter or a category within a time limit. Tests of verbal fluency provide a means of assessing how well individuals organize their knowledge. To be successful on these tests one must have a good ability to organize output in terms of clusters of meaningfully related words as well as short-term memory in keeping track of the words that have already been said (Estes, 1974).

Phonemic fluency tests involve generation of words according to an initial letter (for example, salute, savage) and give the greatest scope to subjects seeking a strategy for guiding the search of words.

Semantic fluency tests call for items in a category such as names of animals or plants, providing the structure lacking in those asking for words by initial letter. Notwithstanding, producing words within a category involves a search through conceptual or semantic memory and, even within categories, one will often develop subcategories to organize recall (for example, the category animals can be addressed in terms of domestic animals, farm animals, wild animals, birds, fish, amongst others) (Lezak et al., 2004).

2.2. Studies of verbal fluency in patients with brain lesions

Several studies in patients with focal brain lesions have tried to define the brain areas associated with phonemic and semantic fluency. However, these studies have provided somewhat mixed results regarding the dissociation between phonemic and semantic fluency performance.

On one hand, some studies have shown that phonemic fluency is proportionately affected in patients with frontal and anterior lesions, while semantic fluency is compromised in those patients with temporal lobe and posterior lesions (Janowsky et al., 1989; Monsch et al., 1994). For instance, Baldo et al. (2006) used a quantitative technique, called voxel-based lesion symptom mapping (VLCM), to analyze lesion data in stroke patients with left hemispheric lesions. This relevant study was designed to explore the relative contribution of the left frontal cortex and the left temporal cortex to verbal fluency performance by generating statistical maps

of brain regions contributing to behavioral performance in these tasks. The authors found that phonemic fluency was associated with damage to more anterior regions including the left frontal cortex, while semantic fluency was associated with lesions in more posterior regions, primarily in the left temporal cortex, as depicted on Figure 13.
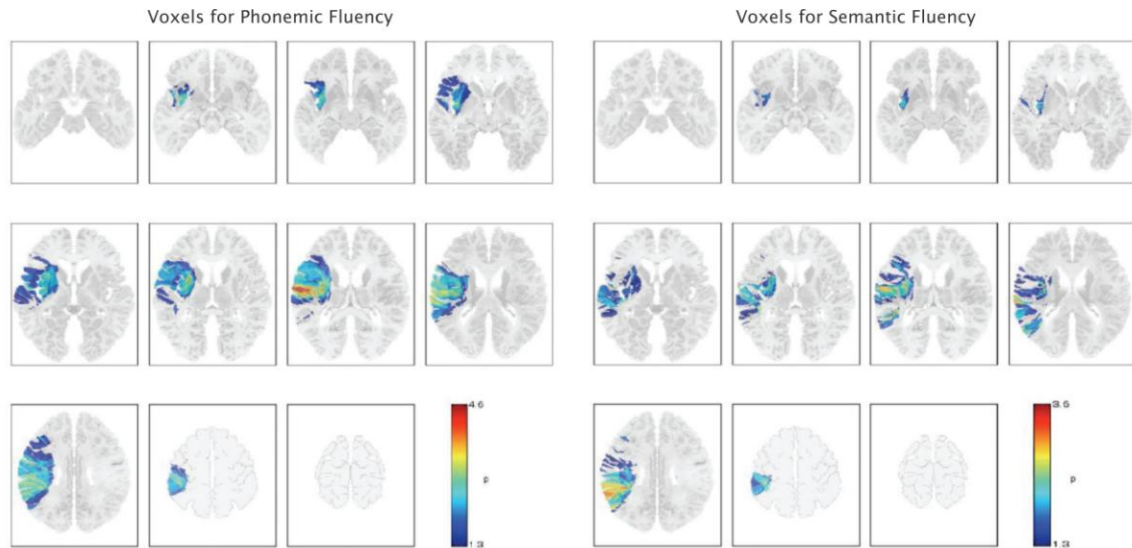
Figure 13. Maps from voxel-based symptom mapping showing p values of all significant voxels for phonemic fluency (left) and semantic fluency (right). All p values are in –log10. Source: Baldo et al. (2006).

In particular, they showed that phonemic fluency engaged frontal circuits, involving Brodmann's Areas 4, 6, and 44, in addition to parietal areas, the insula, putamen and also the anterior temporal cortex. On the other hand, semantic fluency relied mainly on temporal areas, concretely BA 22, 37, 41 and 42, in addition to parietal areas, the insula and putamen, similarly to phonemic fluency. To visualize those regions specific to phonemic versus semantic fluency performance, subtraction maps were also computed in the study for phonemic minus semantic fluency and for semantic minus phonemic fluency as can be observed on Figure 14. In this analysis, they found that phonemic fluency was more related to frontal and parietal areas than semantic fluency, while semantic fluency was more related posterior regions mainly in the temporal lobe.
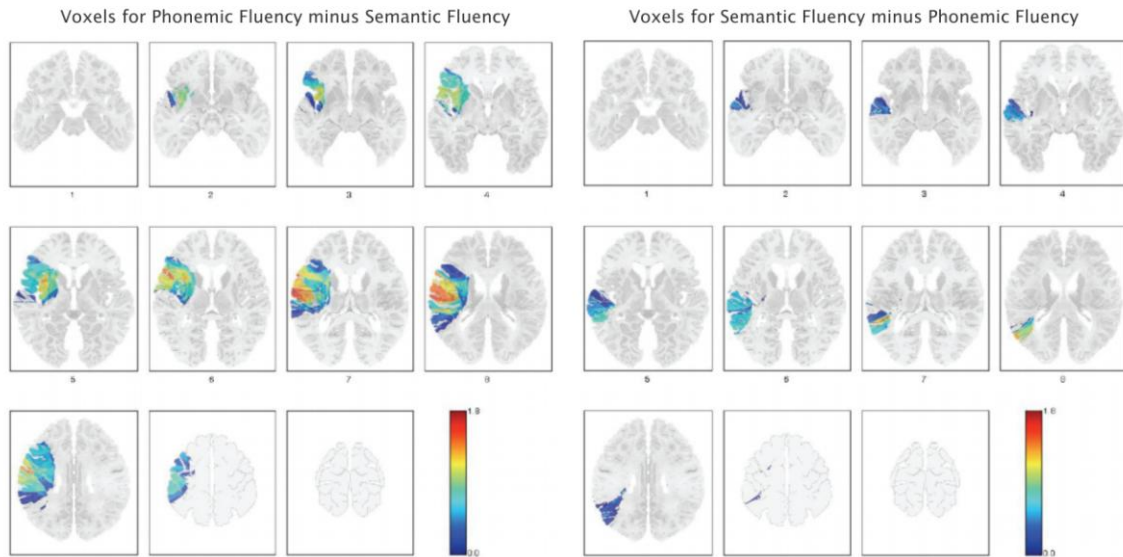
Figure 14. Subtraction maps based on the t statistics for phonemic minus semantic fluency (left) and semantic minus phonemic fluency (right). Source: Baldo et al. (2006).

The authors concluded that letter-based word retrieval depends on the frontal cortex due to its role in strategic retrieval of word forms, while category-based word retrieval relies more heavily on the temporal cortex due to its role in accessing lexical-semantic networks.

On the other hand, regarding the neural correlates of verbal fluency, other studies have reported that both phonemic and semantic fluency are similarly impaired in patients with frontal lesions (Baldo and Shimamura, 1998; Schwartz and Baldo, 2001). These findings have been associated with the impaired ability of frontal patients to make strategic and effective strategies through memory, whether that search is phonemically or semantically driven (Troyer et al., 1998). Such an explanation is consistent with other deficits in these patients, such as impaired free recall and long-term memory retrieval (Gershberg and Shimamura, 1995; Mangels et al., 1996). In a study performed in patients with focal frontal lobe lesions and age/education matched control participants, Baldo et al. (2001) observed that patients with lesions in the left frontal lobe performed worse on both fluency tasks compared to both controls and patients with other lesions. Figure 15 displays the location of the left frontal lesions in these patients.
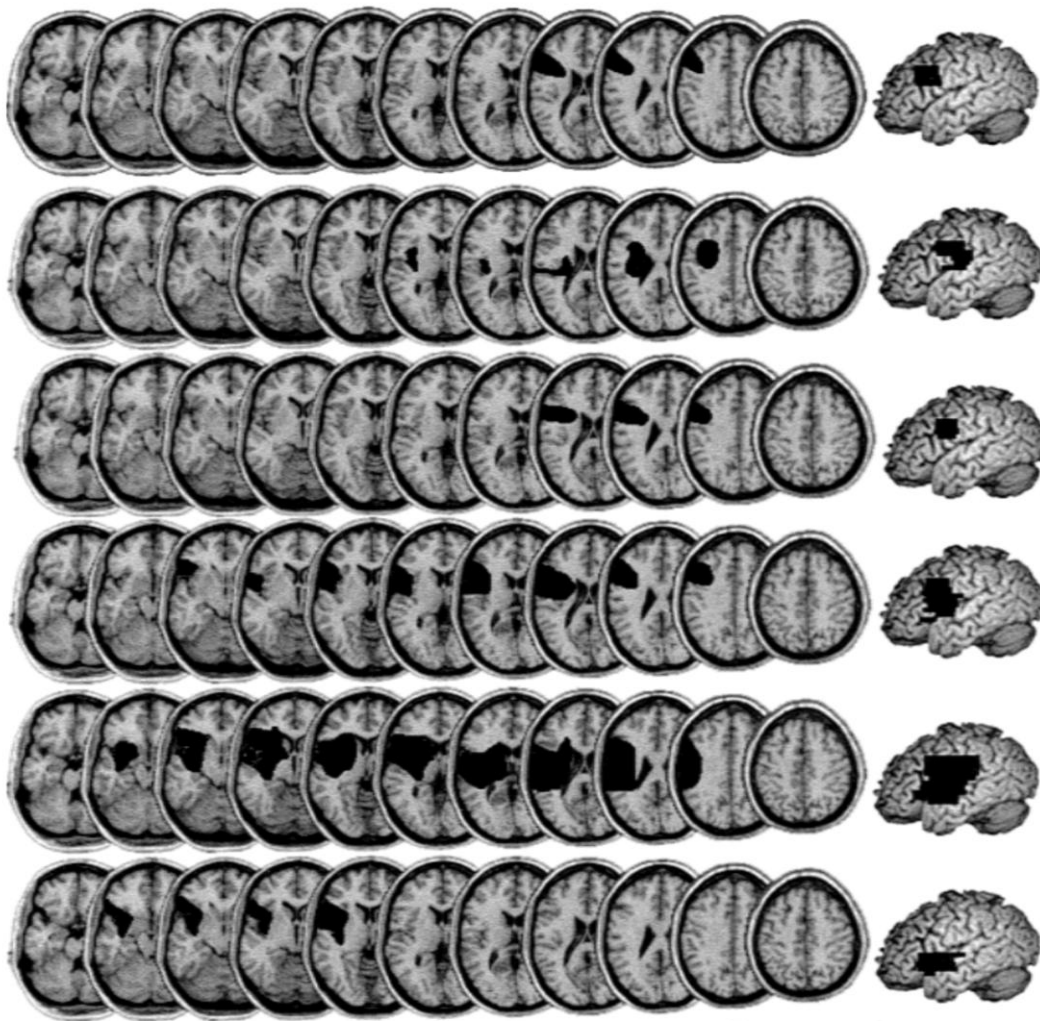
Figure 15. Lesion reconstructions, based on computed tomography and/or magnetic resonance scans, onto a standard brain template. Source: Baldo et al. (2001).

Moreover, a meta-analysis of 31 studies with 1.791 participants, including patients with focal cortical lesions, came to a similar conclusion, namely, that frontal patients are comparably impaired on phonemic and semantic measures (Henry and Crawford, 2004). The results from this meta-analysis demonstrated that the two types of fluency were equivalent in sensitivity to frontal dysfunction, consistent with other evidence showing that semantic fluency, like phonemic fluency, does tap executive processes such as initiation, efficient organization of verbal retrieval and recall, and self-monitoring. However, in this meta-analysis, in addition to being sensitive to frontal damage, semantic fluency was also found to be sensitive to temporal lesions. Concretely, patients with temporal damage were found to display worse performance

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on semantic tasks compared to frontal patients, although this difference did not achieve statistical significance. Moreover, temporal patients were significantly more impaired on semantic fluency than phonemic fluency, suggesting that a compromised semantic system is also an important determinant of impaired semantic performance. Therefore, these results provide strong evidence that, with respect to phonemic fluency, tests based on semantic criteria are equally sensitive to frontal insult and are comparable in this aspect. In addition, semantic fluency performance might also be compromised by damage to the semantic system and temporal brain structures.

Motivated by studies in patients with focal brain lesions, verbal fluency tasks are being increasingly used to evaluate language and executive control processes in several non-focal brain disorders. It is therefore of considerable interest to elucidate the neural systems involved in performing these tasks by patients with different diseases using non-invasive methods.

2.3. Functional magnetic resonance imaging (fMRI) studies of verbal fluency

2.3.1. Preliminary note

To date, most fMRI studies have used paradigms of verbal fluency that considerably diverge from the standard procedures used in the clinical assessment of this cognitive function (Birn et al., 2010). For instance, whereas the standard behavioral paradigm consists of free recall and producing words aloud as fast as possible within a restricted period of time, fMRI studies have typically required either covert word generation (Gurd et al., 2002; Perani et al., 2003a, 2003b; Hirshorn and Thompson-Schill, 2006) or overt but experimenter-paced single word production (Phelps et al., 1997; Abrahams et al., 2003) to decrease motion artifacts associated with the task (Birn et al., 2010). The problem of covert word generation is that it does not have a behavioral correlate and the results are thus complicated to interpret and validate, especially when assessing patient groups. In addition, paced overt single word production tasks are also problematic because they decrease the cognitive demands relative to the behavioral task by allowing subjects more time to inhibit responses (Basho et al., 2007; Birn et al., 2010).

Fortunately, paradigms that allow self-paced overt responses have been recently introduced. In this section a brief description of such studies is provided.

2.3.2. Self-paced overt fMRI studies

One of the most relevant studies is the one by Basho et al. (2007), which investigated semantic fluency in an overt self-paced paradigm in healthy subjects. In that study, when compared to an overt speech baseline control condition, significant left-hemispheric activations in the inferior frontal cortex, left middle frontal gyrus, left lingual gyrus, left cingulate gyrus and the thalamus were found during category-driven word generation. Activation in frontal areas was linked to previous studies showing the role of these areas in word retrieval and working memory, while activation in the anterior cingulate was interpreted as reflecting the attentional demands of fluency tasks.

In another study, Heim et al. (2008) also explored the patterns of brain activity not only related to semantic fluency like Basho et al. (2007) but also to phonemic fluency tasks. They found that both fluencies recruited similar areas such as left frontal Brodmann's areas 44 and 45, the postcentral gyrus, middle and inferior temporal gyri, fusiform, caudate nucleus and insula. However, when the fluency conditions were compared to each other, phonemic fluency was associated with greater left frontal and parietal cortical activity, while semantic fluency was related to greater left temporal activation as shown in Figure 16.
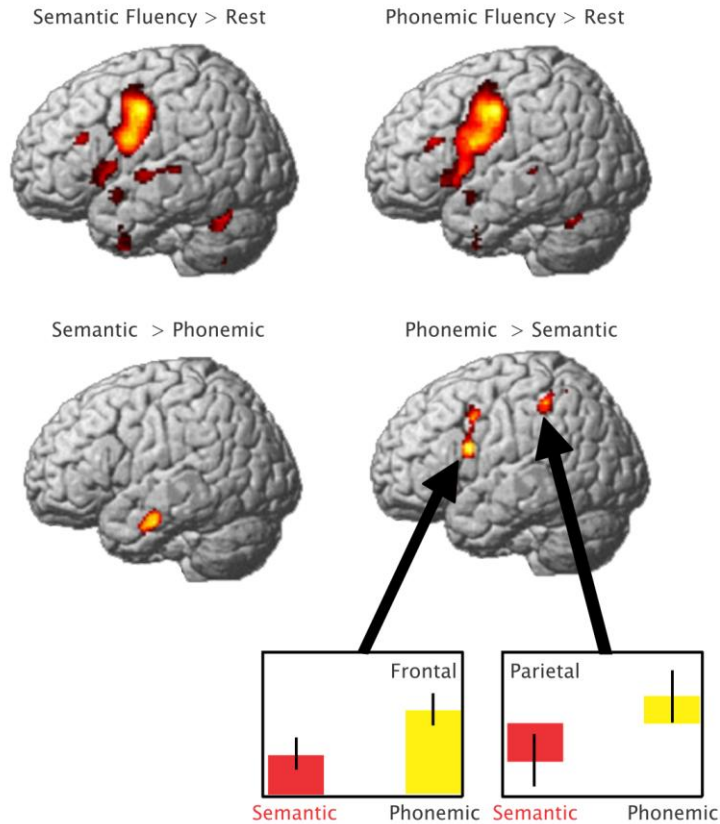
Figure 16. Top: Surface renderings of brain activation of semantic and phonemic fluency compared to the resting baseline (free generation task of nouns without a predefined criterion). Bottom: Differential fMRI effects of semantic > phonemic fluency and phonemic > semantic fluency. All clusters were corrected with FWE rate at the whole brain level. Adapted from: Heim et al., (2008).

Similarly to Heim et al. (2008), Birn et al. (2010) also studied brain activity during semantic and phonemic fluency in healthy subjects. In this study, both fluencies induced activation of left frontal, occipito-temporal, left parietal and supplementary motor areas as well as the thalamus, compared to a control condition (repeating months of the year in chronological order). In addition, differences between fluency task conditions were also found. Relative to semantic fluency, phonemic fluency yielded greater activity in the left inferior frontal gyrus, bilateral parietal cortex and in the bilateral ventral occipito-temporal cortex centered on the occipital sulcus. By contrast, relative to phonemic fluency, semantic cues produced greater activity in the occipital cortex, left fusiform gyrus and left middle frontal gyrus. The fact that phonemic fluency enhanced responses in the left inferior frontal cortex was associated with its role in selecting and retrieving information based on spelling, whereas the enhancement of fusiform activity by semantic fluency was related with the more posterior basis of this task and the greater demands

it poses on conceptual knowledge stores. Figure 17 depicts these areas showing increased activation during verbal fluency tasks and the control condition.
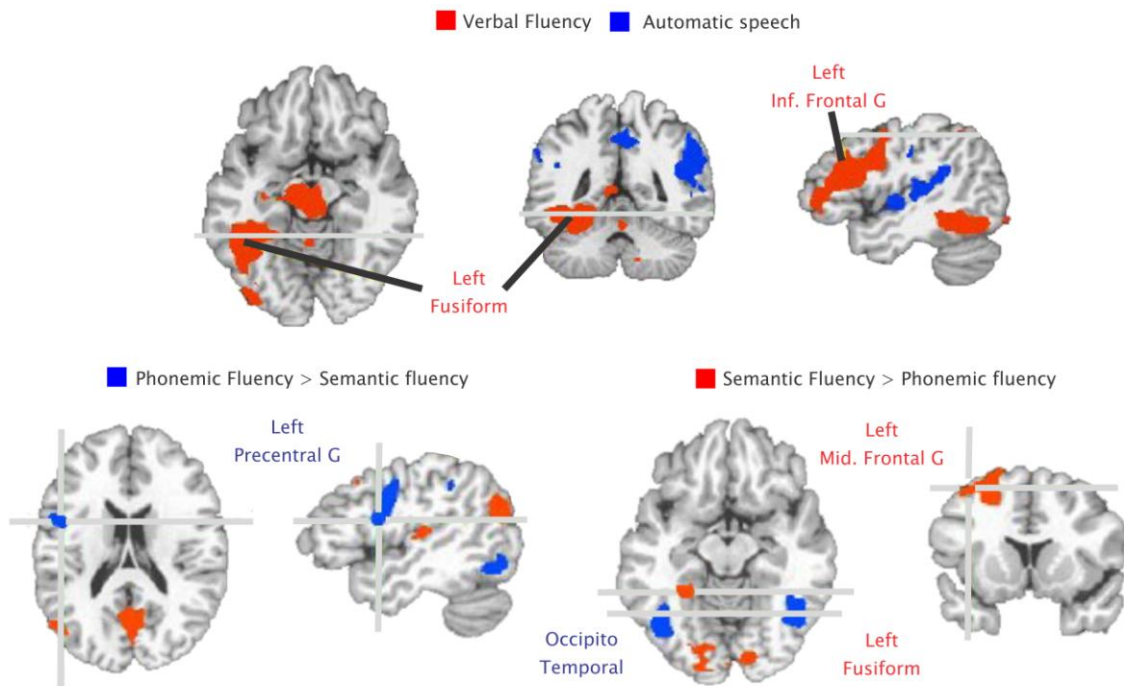
Figure 17. Top: Red areas indicate regions with a greater activation during the fluency tasks, while blue areas indicate regions with a greater activation during the automatic speech condition. Bottom: Semantic vs Phonemic fluency. Regions with greater activation during the semantic task are shown in red, while regions with greater activation during the phonemic task are shown in blue. All activations were thresholded at $p < 0.05$, corrected for multiple comparisons. Adapted from: Birn et al., (2010).

Finally, a number of studies have also assessed the patterns of functional brain connectivity related to verbal fluency. For instance, Vitali et al. (2005) studied effective functional connectivity associated with semantic fluency with structural equation modeling analysis, a method that evaluates the inter-regional covariance and task-related changes in the coupling among brain areas activated during tasks. In that study, a significant pattern of connectivity between the fusiform gyrus, superior occipital and middle occipital gyri was found, while subjects performed the semantic task. The increased coupling found between lateral medial occipital and temporal regions suggests the involvement of a visualization strategy during semantic tasks and have been previously found in studies that require encoding of episodic memory (Fletcher et al., 1995) or mental imagery (Kosslyn et al., 1994). Using a similar method, Fu et al. (2006) studied functional connectivity associated with a phonemic task in healthy

subjects. In that study, they found significant increases in functional coupling between the left middle frontal gyrus, precuneus and the anterior cingulate. The middle frontal gyrus has been proposed to have a particular role in the manipulation of items (Fletcher and Henson, 2001), while the precuneus has been previously shown to be involved in directing attention to items that are self-generated (Cabeza et al., 2003). In addition, the anterior cingulate has been reported to have a role in selective attention processes (Devinsky et al., 1995), more specifically in response selection (Mesulam et al., 2001) and monitoring the conflict that arises from the generation of multiple responses (Carter et al., 1998).

Finally, a different type of functional connectivity associated with verbal fluency has also been studied using dynamic causal modeling, a technique used to find a causal model of the underlying neuronal interactions, which may explain the pattern of brain activation. Using this method, Heim et al. (2009) found that the best model that explained brain activity during phonemic and semantic fluency tasks was a model in which BA 45 supported word retrieval processes, while BA44 was involved in processing phonological information during word generation.

2.4 Verbal fluency in Parkinson's disease

2.4.1. Cross-sectional studies

Several studies have shown that PD is associated with verbal fluency deficits, which have been thought to result from executive dysfunction occurring in these patients (Henry and Crawford, 2004). Executive functions are responsible for the highest level of behavioral organization, including the capacity to elaborate a new plan of action or strategy, the maintenance of this new representation using working memory, and the inhibition of incorrect responses (Goldman-Rakic et al., 1996; Robbins, 1996). The anatomical substrates of these processes have been attributed to regions of the prefrontal cortex, particularly the dorsolateral frontal areas (Robins, 1996).

Several studies have shown that PD is associated with specific executive deficits, involving effortful processing, the use of internal attentional cues and cognitive set-shifting (Henry and Crawford, 2004). These deficits might be related to neuropathological changes occurring in PD in the basal ganglia and in many of the cortical fields and subcortical nuclei that are connected to them (Braak and Braak, 2000). Given the anatomical relationships between the basal ganglia and

the prefrontal cortex (Alexander et al., 1986), it comes to no surprise that many neuropsychological studies have reported impaired performance of PD patients on tests thought to be sensitive to executive frontal functions such as verbal fluency tasks. In fact, performance in frontally mediated tasks has been shown to be influenced by both levodopa therapy (Owen et al., 1995; Cools et al. 2001) and functional polymorphisms in genes involved in dopamine regulation (Foltynie et al., 2004a), supporting the notion that executive deficits reflect dopaminergic dysfunction in frontostriatal networks. Hence, executive impairment may arise in PD from frontal lobe dysfunction caused by disruption of fronto-striatal circuitry (Owen et al., 1998; Rinne et al., 2000).

Many cross-sectional studies have shown impairment of verbal fluency, reflecting deficiencies in executive search and retrieval processes, in patients with PD compared to normal controls (Williams-Gray et al., 2007). Significant reductions in both semantic and phonemic fluency have been found in early nondemented patients and patients with advanced PD compared with normal controls, in the absence of clinical depression (Bouquet et al., 2003; Fine et al., 2011; McDowd et al., 2011). In addition, a few studies using large samples of patients have shown that these deficits can become apparent in very early stages of the disease. For instance, Muslimovic et al. (2005) found that newly diagnosed patients with PD already presented mild executive deficits in several tasks, including semantic fluency, although with a small effect size. Subsequently, Aarsland et al. (2009) further confirmed these findings in a sample of 196 newly diagnosed and unmedicated patients that had significant deficits in semantic fluency compared to a large group of cognitively normal controls.

In those patients with PD and visual hallucinations, a greater reduction in semantic and phonemic fluencies is observed compared with nonhallucinating patients with similar motor symptom severity (Grossi et al., 2005; Ramirez Ruiz et al. 2006), with one study suggesting that executive dysfunction in frontally-mediated tasks might be considered a risk factor for the development of hallucinations in nondemented PD patients (Grossi et al., 2005).

Finally, studies comparing fluency performance in PD patients with diagnosed dementia to patients without dementia show that dementia is associated with more severe impairment in semantic and phonemic fluency (Piatt et al., 1999; Biasio et al., 2012).

For further details, please refer to Table 4 (see Page 71), in which a summary of the neuropsychological studies of verbal fluency in patients with PD is provided.

In general, these neuropsychological studies in PD have provided evidence in favor of a degree of overlap in terms of the underlying neurobiological basis of phonemic and semantic fluency deficits, with both relying on frontally-based executive strategies. For instance, a previous study performed in a large cohort of PD patients recruited in the United Kingdom (Foltynie et al., 2004) divided the patient's sample into four subgroups on the basis of cognitive ability evaluated with the MMSE, Tower of London test and a pattern recognition task: cognitively intact, frontostriatal deficits, temporal lobe type deficits and frontostriatal and temporal lobe type deficits. PD patients with frontostriatal impairment and patients with both fronstriatal and temporal impairment were found to have significant deficits in both phonemic and semantic fluencies, while the subgroup with temporal lobe deficits did not show statistical differences in these tasks compared to the cognitively intact patients, suggesting that frontostriatal dysfunction is likely to subserve processes that are crucial for both phonemic and semantic fluencies.

Finally, regarding the prevalence of phonemic and semantic deficits in PD, a large meta-analysis of 68 studies with a total of 4644 participants (Henry and Crawford, 2004) demonstrated that PD patients are more impaired on tests of semantic than phonemic fluency. In this study, the authors suggested that pathology in the temporal lobe might contribute to the observed fluency impairment, in agreement with the view that phonemic and semantic fluencies have a different neural correlate relying on the frontal and temporal cortex, respectively. However, this assumption greatly contrasts with the studies described above showing that both fluencies share a common correlate, the frontal cortex. Hence, future studies in patients with PD are needed in order to shed some light into these discrepancies.

2.4.2. Longitudinal studies

Previous studies have assessed longitudinal changes in verbal fluency in patients with PD. For example, Azuma et al. (2003) followed a sample of nondemented patients and healthy controls to assess cognitive changes specifically related to PD and to determine whether performance in

any measures predicted cognitive decline in these patients. Importantly, in this study, the authors found that among the various neuropsychological tests performed by the patients, only semantic and phonemic fluency significantly declined at follow-up, which was two years later. Interestingly, they also found that the control group declined in phonemic fluency, suggesting that semantic fluency might be more sensitive to specific deficits arising from PD.

These findings agree with those of two subsequent studies assessing larger samples of patients. For instance, Williams-Gray et al. (2007) reported that, in a group of 126 PD patients, following correction for age the most important clinical predictors of cognitive decline had a posterior cortical basis and included semantic fluency and the ability to copy and intersecting pentagon figure, which would be reflecting non-dopaminergic cortical LB pathology. In addition, in a posterior study, similar results showing a significant decline in semantic but not phonemic fluency were found (Elgh et al., 2009) four years after baseline in 88 PD patients compared to 30 matched controls. In patients with visual hallucinations that became demented at follow-up, semantic fluency was also found to show a greater decline compared to phonemic fluency (Ibarretxe-Bilbao et al., 2010).

These findings do not agree with those of a very early study (Jacobs et al., 1995), in which baseline performance on both phonemic and semantic verbal fluency were significantly and independently associated with incident dementia, indicating that both of these tests might be used as surrogate markers of the preclinical phase of dementia in PD. Similarly, in a longitudinal study, patients with visual hallucinations were found to be similarly impaired on both fluencies at follow-up (Ramirez-Ruiz et al., 2007b).

Moreover, they highly contrast with the results of several other studies (Mahieux et al., 1998; Levy et al., 2002) showing that in samples of initially nondemented PD patients, phonemic but not semantic fluency predicted subsequent dementia. In patients with visual hallucinations, Santangelo et al. (2007) found that, although a significant decline on both semantic and phonemic fluency performance was observed, only poor phonemic fluency independently predicted development of generalized cognitive impairment at follow-up. In addition to verbal fluency, other tests assessing executive functions were impaired in hallucinating patients in this study, suggesting a link between frontal lobe dysfunction and visual hallucinations.

The discrepancy observed between findings of different studies could be related to sample sizes, clinical characteristics of the patients, controlling for confounding variables such as age and the inclusion of a control group. Studies showing semantic fluency as a better predictor of dementia compared to phonemic fluency have generally included a greater number of patients (Williams-Gray et al., 2007, Elgh et al., 2009) in addition to controls (Azuma et al. 2002; Williams-Gray et al., 2007, Elgh et al., 2009) and also corrected for the effects of age (Williams-Gray et al., 2007) or cognitive status at baseline (Ibarretxe-Bilbao et al., 2010).

2.4.3. Deep brain stimulation studies

Deep brain stimulation (DBS) in PD consists of administering high-frequency continuous electrical stimulation to subcortical areas through a surgically implanted device in order to relieve motor symptoms. DBS can be applied to different cortical subtargets such as the subthalamic nucleus, the globus pallidum internus, or the thalamus. In particular DBS of the subthalamic nucleus (STN) has been recognized as an effective therapy for PD (Krack et al., 2002), improving motor functions (Alegret et al., 2001b) and reducing dyskinesias for up to five years (Krack et al., 2003).

However, although considerable symptomatic benefits are observed following STN DBS, certain side effects on cognitive functions related to this surgical intervention have been consistently reported such as a significant decline in verbal fluency. The majority of DBS studies that included measures of verbal fluency reported a significant postsurgical reduction in phonemic and semantic fluency scores (Woods et al., 2002). This decline in verbal fluency does not seem to be associated with changes in psychomotor speed given that most of the patients participating in a previous study showed improvement in the performance on speeded word-reading tasks following DBS (Jahanshahi et al., 2000).

The underlying neural mechanisms of DBS in patients with PD are still under study. Imaging studies of DBS to the subthalamic nucleus have shown activation of brain areas related to word production such as the inferior frontal gyrus, perhaps indicating that stimulation of this nucleus may directly or indirectly affect this region by influencing striato-thalamo-cortical circuits (Saint-Cyr et al., 2000). It is also possible that the reductions of verbal fluency are associated with the

influence the stimulation might exert on the surrounding neural pathways, implying that a more widespread impact on functional connectivity could be responsible for the verbal fluency decline.

A few studies have assessed the impact of STN DBS on brain activity during verbal fluency tasks in PD patients. For instance, Shroeder et al. (2003) used positron emission tomography (PET) to measure changes in regional blood flow induced by the stimulation in eight patients with PD. In that study, they showed that worsening in phonemic fluency during STN stimulation was accompanied by decreased blood flow in the right orbitofrontal cortex, the left inferior temporal gyrus, the left inferior frontal gyrus and the insular cortex, as can be observed on Figure 18.
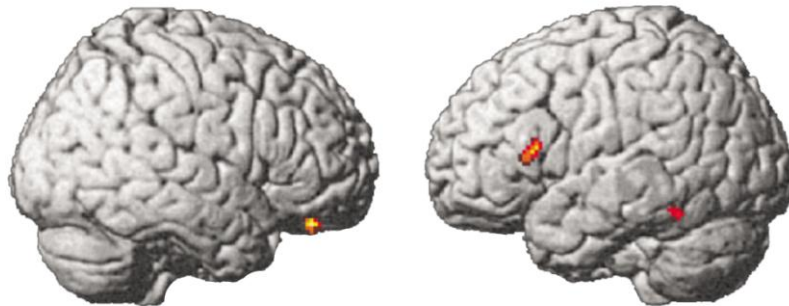
Figure 18. Regions of decreased activation following STN stimulation compared with the OFF state during a phonemic fluency task. All voxels are p < 0.001 uncorrected. Adapted from: Shroeder et al., (2003).

These regions, particularly the left inferior frontal and temporal gyri, have been consistently implicated in verbal fluency tasks, as previously mentioned in this thesis.

In a subsequent study, Anzak et al. (2011) analyzed local field potential recordings from deep brain stimulation electrodes implanted in the STN of eight patients with PD, during both semantic and phonemic fluency tasks. The authors observed specific power changes during task performance, which were consistent with the involvement of the subthalamic nucleus in switching during verbal fluency tasks. These findings suggest that the inhibition of inappropriate responses while switching between different categories and letters during semantic and phonemic fluency could explain the fluency impairment consistently observed following DBS by previous studies.

Finally, using patient specific DBS computer models, Mikos et al. (2011) showed that stimulating specifically the ventral part of the STN induces significant decreases in phonemic fluency performance.

Table 4. Studies that assessed verbal fluency performance in patients with PD

Study	Sample	Age	UPDRS[1] or HY[2]	Duration of PD	Fluency deficits
Piatt et al. (1999)	59 C	72.9 (7.5)	-	-	Significant reduction in semantic and phonemic fluencies in PDD
	57 PD	70.3 (6.6)	-	-	patients compared to both PD and control groups.
	20 PDD	73.9 (6.4)	-	-	
Green et al. (2002)	61 PD	59.3 (9)	T 70.8 (18) [1]	12.6 (4)	Compared to a normative data set, 30% of patients were impaired on phonemic fluency.
Barnes et al. (2003)	20 C	66.1 (7.5)	-	-	No deficits in phonemic fluency between any of the patient groups.
	20 PD	62.8(10.9)	2.9(0.5) [2]	8.8(4.4)	
	17 PD VH	67.9(5.9)	3.4(0.6) [2]	11.9(4.3)	
Bouquet et al. (2003)	20 C	63.5(10.1)	-	-	Impairment in both semantic and phonemic fluency compared to controls.
	20 PD	66.1(7.6)	1.83(0.4) [2]	10.3(5.8)	
Uekermann et al. (2003)	15 C	54.5(3)	-	-	Depressed PD (DPD) patients showed worse phonemic fluency compared to controls, patients with only depression (DEP) and non-depressed PD patients (NPD). No differences were found for semantic fluency.
	14 DEP	53.1 (7.7)	-	-	
	16 NPD	56.4 (2.9)	25.9 (9.3) [2]	18.6(16.3)	
	12 DPD	57.7 (9.8)	30.4(13.1) [2]	20.8(20.8)	
Foltynie et al. (2004)	92 PD CN	66.5	21.9 [1]	3.1	Patients with frontostriatal (FS) and patients with frontostriatal and temporal lobe deficits (FS+T) were significantly impaired in semantic and phonemic fluencies with respect to cognitively normal (CN) PD patients.
	17 PD FS	74.0	32.6 [1]	2.2	
	12 PD T	70.7	23.3 [1]	2.3	
	21 PD FS+T	76.4	33.8 [1]	2.2	
Grossi et al. (2005)	34 PD	66.9(9)	2.5(0.8) [2]	6.3(4.2)	Phonemic and semantic deficits in hallucinating (PD VH) compared to non-hallucinating patients.
	14 PD VH	67.4(11)	2.8(0.6) [2]	10.38(7.3)	
Muslimovic et al.	70 C	63.7(7.3)	-	-	Mild impairment in phonemic and semantic fluency in patients

(2005)	115 PD	66.2(10.1)	16.8(7.8)[2]	1.6(0.9)	compared to controls.
Ramirez-Ruiz et al. (2006)	21 C	74.7(5.4)	-	-	Deficits in semantic fluency in the 2 patient groups and of phonemic
	21 PD	73.3 (3.4)	24.9(13.7)[2]	10.6(4.3)	fluency in PD patients with visual hallucinations (VH) compared to
	24 PD VH	73 (6.7)	30.6(14.5)[2]	12.6(5.6)	controls.
Ozer et al. (2007)	30 PD	65.5(9.4)	16.5(11.1)[2]	5.9(3.2)	Semantic fluency deficits were found in hallucinating patients (PD VH);
	33 PD VH	67.4(8.3)	21.9 (11.5)[2]	6.8(4.4)	however these had significantly higher scores on UPDRS.
Aarsland et al. (2009)	171 C	67.3(9)	-	-	Semantic fluency deficits in newly diagnosed drug-naive patients
	196 PD	67.6(9)	22.8(11.1)[2]	2.3(1.8)	compared to controls.
Biasio et al. (2011)	155 PD	64.5(8.6)	17 (10)[2]	8.4(5.4)	Demented patients (PDD) performed significantly worse on phonemic
	45 PDD	67.8(6.7)	23.3(10.5)[2]	11(6.3)	fluency compared to nondemented patients.
Fine et al. (2011)	32 C	67(7.2)	-	-	No differences were found in category fluency between patients and
	32 PD	64.4(8.8)	18.2(9.8)[2]	5.2(3.4)	controls.
McDowd et al. (2011)	36 Young C	21.5(3.1)	-	-	Worse performance on phonemic and semantic fluency in PD patients
	30 Old C	72(5.4)	-	-	with respect to controls but not compared to AD patients.
	23 AD	73.8(7.2)	-	-	
	30 PD	71.9(6)	34.3(11.7)[2]*	-	

* In this study, only the total scores on the UPDRS are reported, by contrast to the other studies in which the scores correspond to UPDRS – III motor subscale.

3. Transcranial Direct Current Stimulation

3.1 Non-invasive Brain Stimulation

In the past few years there has been an increasing interest in noninvasive brain stimulation to assess the relationship between brain and behavior as well as treating a wide range of diseases. Applications of this new method are currently being studied to modulate specific cortico-subcortical brain networks, induce controllable manipulations in behavior, assess neuropharmacology delivery and provide novel tools for interventional neurophysiology. In addition, several studies have claimed the therapeutic utility of noninvasive brain stimulation in many neurological diseases, pain syndromes and psychiatric disorders, suggesting that it could help a great deal of patients in vulnerable health conditions (Wagner et al., 2007).

To date, the two most widely used techniques of noninvasive brain stimulation are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Although both techniques have produced very promising results, the underlying principles they use to influence brain activity are quite different.

In TMS, a magnetic coil is placed close to the scalp and electricity is passed through the coil in brief pulses, creating a changing magnetic field perpendicular to the subject's head (Figure 19). This magnetic field passes through the scalp and skull and into the underlying targeted cortical tissue (McKingley et al., 2012) inducing a current, which flows in the opposite direction of the current flow in the coil, in the underlying neural tissue strong enough to raise neuronal membrane potential and force action potentials (Rossi et al., 2009).

On the other hand, tDCS uses a mild electrical current that passes between electrodes on the scalp to modify neuronal membrane resting potential in a polarity dependent manner (Figure 19), increasing or decreasing excitability in a region (Paulus, 2004; Priori, 2003; McKingley et al., 2012).
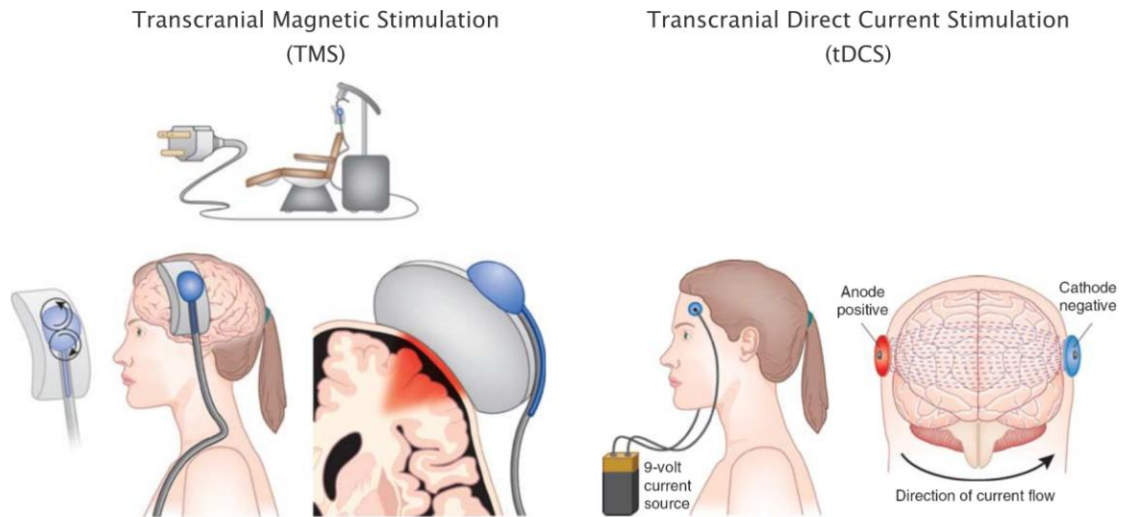
Figure 19. Right: Transcranial magnetic stimulation (TMS). Current is used to charge a bank of large capacitors, which send a pulsing electrical current to the coil that is resting on the scalp. The powerful and brief electrical current in the coil creates a transient magnetic field, which passes unimpeded through the skin and skull and results in electrical pulses in neurons in superficial cortex under the coil. Left: Transcranial direct current stimulation (tDCS). The tDCS device uses an anode and cathode connected to a direct current source much like a 9V battery. The direct current passes through the intervening tissue, with some shunting through the skull but much of it passes through the brain and changes resting electrical charge. Source: George and Aston-Jones, (2010).

Compared to TMS, tDCS offers a number of important advantages: a) on one hand, it is easier to conduct placebo stimulation-controlled studies with tDCS, because, with the exception of slight itching sensation and sensory phenomena, subjects rarely experience sensations with the treatment; b) it is currently less expensive and much more portable; c) and it is very well tolerated and associated with fewer safety concerns (George and Aston-Jones, 2010). Below a more detailed description of tDCS is provided.

3.2 Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) involves passing a weak direct current (usually from 1 to 2 mA) through the brain between two large saline-soaked sponge electrodes: the anode and the cathode (Figure 19). The current enters the brain from the anode, travels through the tissue and exits out the cathode (George and Aston-Jones, 2010). Studies using tDCS refer to this as either anodal or cathodal stimulation and have shown that the effects of this stimulation are dependent on the current direction, with anodal stimulation increasing cortical excitability, while cathodal stimulation decreases it (Boggio et al., 2009).

3.2.1 Parameters

The efficacy of tDCS to induce behavioral and brain activity modulations depends on a number of factors such as **current density, electrode montage and duration of the stimulation** (Nitsche et al., 2008).

Current density can be measured as the quotient of current strength and electrode size, which determines the strength of the induced electrical field (Figure 20). Importantly, increasing current density increases the depth penetration of the electric field in the brain. Generally, it is not recommended to increase current density beyond a certain threshold as it can induce cutaneous pain sensation in the subject and affect different or undesired populations of neurons (Nitsche et al., 2008). On the other hand, some studies have shown that it is necessary to apply enough current strength to observe detectable effects. For instance, Iyer et al. (2005) reported that while a current strength of 2mA successfully produced a behavioral effect, 1 mA did not. The focality of the effects of tDCS is mostly limited by the size of the electrodes. Smaller electrodes increase the focality of this stimulation. Because large electrode sizes are typically used in tDCS, it is possible that this technique also stimulates adjacent cortical areas in addition to the intended area. In addition, a cephalic reference electrode might also stimulate the cortical area beneath it and this electrode is therefore not physiologically inert (Wagner et al., 2007).

0   0.5   1.0
Relative current density magnitude (mA/cm^2)
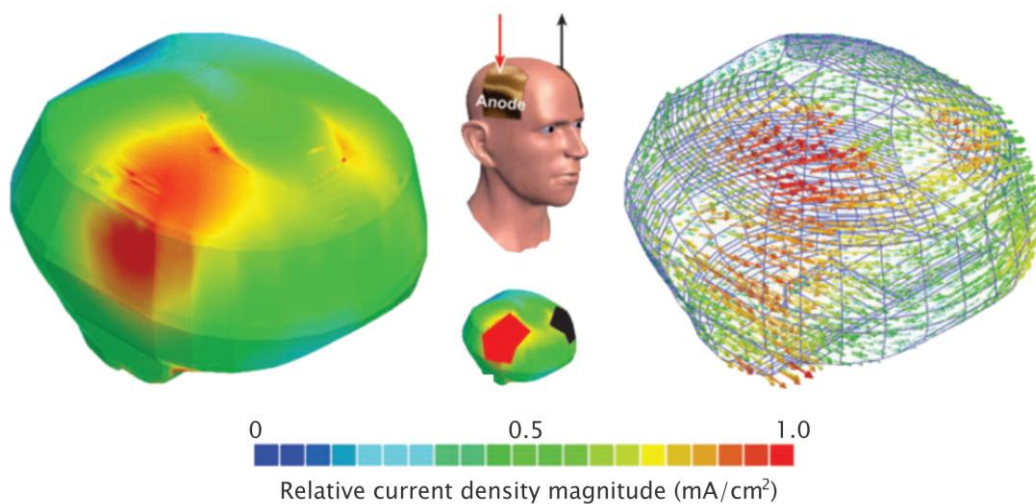
Figure 20. Plot for the current density magnitude on the cortical surface for tDCS. The location of the stimulation source is depicted to the right of the current density magnitude solution, both graphically over the 3D model (left)

and with the source (middle) shown above with the anode (red arrow) and the cathode (black arrow). The current density vector plots on the gray matter surface are also represented (right). This figure shows that both electrodes, the anode and cathode, have an effect on the brain. Adapted from: Wagner et al. (2007).

Another important parameter of tDCS is the **electrode montage**, which is critical to achieve an effective stimulation of the intended brain regions. Several suitable electrode positions have been suggested by different studies. In these montage combinations, the positive electrode or anode is positioned on the desired area so that the resulting current flow allows effective modulation of neuronal activity under this electrode. Previous studies using tDCS placed the electrodes based on the International 10-20 EEG system by Herwig et al. (2003), as shown in the Figure below.
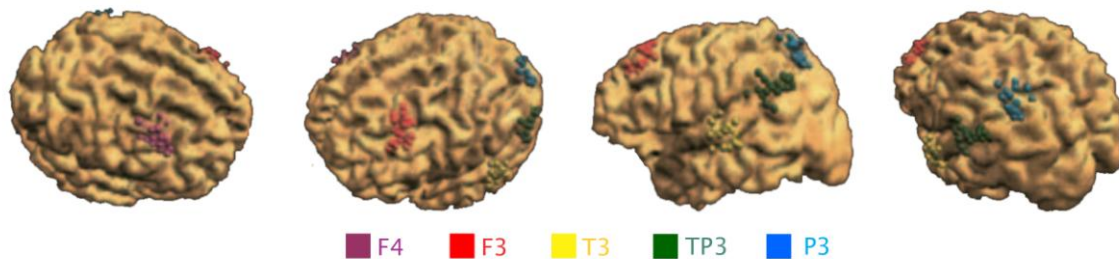
Figure 21. Visualization of the different 10-20 electrode positions on a Talairach-size-transformed and surface-rendered MRI of a subject's brain. The dots indicate the individual electrode positions of 21 subjects relative to the cortex. Violet dots: F4, right dorsolateral prefrontal cortex; red dots: F3, left dorsolateral prefrontal cortex; yellow dots: T3, left superior temporal gyrus; green dots: left temporo-parietal cortex; blue dots: left parietal cortex. Adapted from Herwig et al. (2003).

On the other hand, the **duration of stimulation** is one of the most relevant factors in the lasting effects of tDCS. Previous studies have shown that the residual effects of tDCS strongly rely on the duration of stimulation. For instance, Nitsche and Paulus (2001) and Nitsche et al. (2003) studied the long-lasting effects of tDCS, showing that 9 minutes of stimulation can last for up to half an hour.

3.2.2 Safety issues

A great number of tDCS studies have been carried out both in healthy as well as in pathologic subjects and no serious side effects have been reported (Stagg and Nitsche, 2011). In a minority of cases a mild itching sensation under the electrode, in addition to headache, nausea and

fatigue have been described (Poreisz et al., 2007). Moreover, studies specifically designed to assess the safety of tDCS showed no signs of neuronal damage as assessed by serum neuron-specific enolase after application of a 1mA anodal current for 13 minutes (Nitsche and Paulus, 2001; Nitsche et al., 2003) or MRI measures of edema using contrast-enhanced and diffusion-weighted MRI measures after applying a 1mA current for 13 (anodal) or 9 (cathodal) minutes (Nitsche et al., 2004). With stronger current densities of up to 2 mA for 20 minutes applied to the frontal lobe, no pathological waveforms were observed on EEG and no worsening was seen on neuropsychological measures (Iyer et al., 2005). Finally, no evidence of heating occurred under the electrode during 20 minutes of 2mA tDCS, even with the bore of a 7T MRI scanner (Stagg et al., 2009).

In a study performed in rats using an epicranial electrode montage similar to that used in tDCS, brain lesions only occurred at current densities greater than 1429 mA/cm^2 applied for more than 10 minutes (Liebetanz et al., 2009). In standard tDCS protocols applied in humans, a current density of only 0.05 mA/cm^2 is produced (Stagg and Nitsche, 2011). Hence, applying tDCS to the human brain is considered a safe procedure to modulate cortical-subcortical brain activity.

3.2.3 Underlying mechanisms

Although the exact mechanisms that underlie the effects of tDCS are not completely clear, there is increasing evidence that those effects that occur during stimulation are caused by different mechanisms than those occurring after the stimulation (Nitsche et al., 2003; McKinley et al., 2012). As mentioned before, anodal tDCS produces an elevation in neuron excitability in the area of stimulation, while cathodal tDCS causes a decrease in excitability. These effects are thought to be the result of changes in the resting membrane potential. In a study performed by Liebetanz et al. (2002) it was shown that anodal tDCS effects were abolished using carbamazepine to block sodium channels and that flunarizine, a block of calcium channels, was capable of diminishing anodal tDCS effects. These findings suggest that during stimulation, tDCS influences the activity of sodium and calcium channels.

On the other hand, tDCS has also shown to produce lasting effects that extend beyond the stimulation period and eventually later return to baseline. The duration of these after-effects depends on the number of tDCS sessions as well as the duration of the stimulation. In a previous study by Nitsche and Paulus (2001), 7 minutes of tDCS were found to produce after-effects of 5

minutes, while 9-13 minutes of tDCS produced significantly larger effects of 30 and 90 minutes. In addition, in studies in patients with depression, 20 minutes of 2mA tDCS administered twice a day for many days produced after-effects that lasted at least a month in most patients (Brunoni et al., 2010; Ferrucci et al., 2009).

Several studies have suggested that the long after-effects of tDCS might be associated with the phenomena of long-term potentiation (LTP). There is a possibility that the polarizing effects of tDCS facilitate the removal of the magnesium blockade within NMDA (N-methyl-D-aspartate) receptors, leading to a facilitation of LTP (McKingley et al., 2012). Some of these studies have adopted a pharmacological approach to test the concept of LTP effects through tDCS. For instance, Liebetanz et al. (2002) studied the possible role of sodium channels with the drug carmazepine (CBZ) and NMDA receptors with the drug destromethorphan (DMO), after tDCS. The results showed that CBZ eliminated anodal effects and DMO prevented effects of both anodal and cathodal tDCS, suggesting that tDCS depolarizes the membrane to induce anodal after-effects and NMDA receptors are important for this plasticity induction. Finally Nitsche et al. (2003) demonstrated that the effects during short-duration tDCS are caused by membrane polarization, while long-lasting effects may be the result of improved NMDA receptor function and intracellular calcium levels.

3.3. Studies in healthy subjects

In addition to its potential utility as a treatment for clinical disorders, tDCS has also been investigated for its efficacy in enhancing cognitive performance in healthy individuals. In fact, the majority of studies using tDCS assessed the behavioral effects of stimulating presumably intact cortical areas in healthy young subjects without any pathology. These behavioral effects were tested on tasks assessing motor functions, cognitive skills, social cognition or perception. Given the large amount of studies conducted with tDCS to date (approximately 500 publications can be found in PubMed using "transcranial direct current stimulation" as a keyword) and specially taking into account the purposes of this thesis, a review of those studies focused on cognitive functions in the healthy population is provided here to give an overview of the potential of this stimulation technique.

Regarding cognitive studies, there is a significant amount of works that have assessed the modulatory effects of tDCS on different cognitive tasks, such as learning, social cognition, decision making, working memory, verbal fluency and language. A detailed description of these studies can be found on Table 5 (Page 80).

The majority of them targeted the left DLPFC (F3) (Fregni et al., 2005; Iyer, et al., 2005; Ohn et al., 2008; Cattaneo et al., 2011), the right DLPFC (F4) (Fecteau et al., 2007; Knoch et al., 2008; Cerruti et al., 2009; Cerruti and Schlaug, 2009; Elmer et al., 2009) or bilateral DLPFC (F3 and F4) (Marshall et al., 2004, 2005; Fecteau et al., 2007; Priori et al., 2008) probably due to the important role of this area in high-order cognitive functions such as attention, planning, organization and regulation (Zelazo and Muller, 2002). In addition, a few studies stimulated the right and left anterior temporal lobes (Boggio et al., 2009; Ross et al, 2010; Ross et al., 2011), Wernicke's area (Floel et al., 2008; Sparing et al., 2008; Fiori et al., 2011), the cerebellum (Ferrucci et al., 2008), the anterior prefrontal cortex (FP2) (Karim et al., 2010) or the temporo-parietal cortex (P6-P8) (Tímea et al., 2007).

In most studies, positive results were found after anodal stimulation such as improved learning and memory, higher accuracy (Boggio et al., 2006; Sparing et al., 2008) and in some studies negative effects were shown (Ferrucci et al., 2008; Marshall et al., 2005).

The reference electrode in most of the studies targeting DLPFC was placed over the contralateral orbit (Boggio et al., 2007; Fecteau et al., 2007; Iyer et al, 2005; Knoch et al., 2008; Ohn et al., 2008). In all the studies, sham conditions showed no effect, suggesting the effects of tDCS are genuine.

Table 5. Cognitive studies with tDCS in healthy subjects

Cognitive domain	Studies	tDCS Conditions	Stimulation Electrode Positions	Reference Electrode Position	Parameters (minutes/mA)	Effects
Learning/ memory	Nitsche et al.(2003)	Anodal Cathodal	M1 or hand area	Contr. Orbit	10min/1mA	Anodal tDCS affects performance after motor sequence learning.
	Kincses et al.(2004)	Anodal Cathodal	Fp3	Cz	10min/1mA	Anodal tDCS of Fp3 enhanced probabilistic classification learning.
	Marshall et al.(2004)	Anodal	F3 and F4	Both mastoids	15sec off/ 15sec on during 30min	Anodal tDCS during slow-wave sleep Improves declarative verbal memory
	Floel et al.(2008)	Anodal Cathodal Sham	Cp5	Contr. Orbit	10min/1mA	Anodal tDCS of Cp5 resulted in enhanced language learning
	Boggio et al. (2009)	Anodal Cathodal Sham	L and R anterior temporal lobe	L and R anterior temporal lobe	10min/2mA	Anodal tDCS of the anterior temporal lobes resulted in a decrease of false memories.
	Cerruti & Schlaug (2009)	Anodal Cathodal Sham	F3, F4	Contr. Orbit	20min/1mA	Anodal stimulation of L DLFC (F3) improves complex verbal associations
	Dockery et al.(2009)	Anodal Cathodal Sham	L DLPFC	Contr. Orbit	15min/1mA	Both anodal and cathodal tDCS enhanced performance in a Tower of London task at different learning phases (early: cathodal; later: anodal), that lasted for 12 months.
	Elmer et al.(2009)	Anodal Cathodal	F3, F4	Mastoid	5min/1.5mA	Cathodal tDCS of F3 impaired short-term verbal learning, compared to

	Sham				sham.
Galea et al.(2009)	Anodal Cathodal Sham	M1	Contr. Orbit	30min/1mA	Anodal stimulation increased the magnitude and duration of motor memories.
Reis et al.(2009)	Anodal Cathodal Sham	M1	Contr. Orbit	20min/1mA	Applying anodal tDCS to M1 over 5 consecutive days during motor skill learning increased learning that lasted for 3 months.
Bolognini et al.(2010)	Anodal Sham	P3, P4	Contr. Deltoid muscle	30min/2mA	tDCS of R parietal cortex increases training-induced behavioral improvement of visual exploration in a bimodal visual exploration task.
Chi et al.(2010)	Anodal Cathodal Sham	L, R anterior temporal lobe	L, R anterior temporal lobe	13min/2mA	Cathodal tDCS improved visual memory performance.
Clark et al.(2010)	Anodal	R Inferior Frontal and R Parietal	Contr. Orbit	30min/2mA	Improved learning performance in identifying concealed objects in naturalistic surroundings.
Liuzzi et al.(2010)	Anodal Cathodal Sham	L M1	Contr. Cheek	20min/1mA	Cathodal tDCS impaired learning of action-related words.
Penolazzi et al.(2010)	Anodal Cathodal Sham	Between C3 & F3 or C4 & F4	Contr. Between C3 & F3 or C4 & F4	20min/1mA	R Anodal (between C4 & F4) and L cathodal (between C3 & F3) improved recall of pleasant images, while L anodal and R cathodal improved recall of unpleasant images.

Ross et al.(2010)	Anodal Sham	L or R anterior temporal lobe	Contr. Orbit	15min/1.5mA	R anterior temporal lobe tDCS improved recall of names of people in young adults.
Nitsche et al.(2010)	Anodal Cathodal Sham	F3	Contr. Orbit	15mA/1mA	Anodal tDCS improved motor memory consolidation during REM sleep.
Tecchio et al.(2010)	Anodal Sham	C4	Ipsilateral Arm	15min/1mA	Improvement of early consolidation in a serial finger tapping task induced by anodal stimulation.
De Vries et al.(2010)	Anodal Sham	L BA 44/45	Contr. Cheek	20min/1mA	Anodal tDCS of Broca's area improved detecting syntactic violations while learning an artificial grammar.
Ambrus et al.(2011)	Anodal Cathodal Sham	DLPFC	Cz	10min/1mA	The categorization of prototypes was significantly impaired by anodal tDCS.
Hammer et al.(2011)	Anodal Cathodal Sham	L DLPFC (F3)	Contr. Orbit	30min/1mA	Improved memory performance after errorful learning by cathodal tDCS of L DLPFC.
Ross et al.(2011)	Anodal Sham	L or R anterior temporal lobe	L or R anterior temporal lobe	15min/1.5mA	L anterior temporal lobe tDCS improved picture naming of people in old adults.
Stagg et al.(2011)	Anodal Cathodal Sham	L M1	Contr. Orbit	10min/1mA	Application of anodal tDCS during an explicit sequence-learning task induced faster learning, while cathodal tDCS resulted in slower learning.

Working memory	Fregni et al.(2005)	Anodal Cathodal Sham	L DLPFC or L M1	Contr. Orbit	10min/1mA	Anodal tDCS of L DLPFC enhanced performance on working memory.
	Marshall et al.(2005)	Anodal Cathodal	F3 and F4	Both mastoids	15sec off/ 15sec on during 15min 260 μA	Anodal and cathodal tDCS impaired performance in Sternberg task.
	Ferrucci et al.(2008)	Anodal Cathodal Sham	Cerebellum	R deltoid muscle	15min/2mA	Anodal and cathodal tDCS of cerebellum impairs the practice-dependent proficiency in working memory.
	Ohn et al.(2008)	Anodal Sham	F3	Contr. Orbit	30min/1mA	Anodal tDCS enhanced performance in a 3-back letter task.
	Cerruti et al.(2009)	Anodal Cathodal Sham	F3, F4	Contr. Orbit	20min/1mA	Anodal tDCS of L DLPFC improves performance on a verbal problem-solving task.
	Berryhill et al.(2010)	Anodal Cathodal Sham	P4	L Cheek	10min/1.5mA	Cathodal stimulation of R inferior parietal cortex impaired performance in recognition in working memory task.
Decision-making	Fecteau et al.(2007a)	Anodal Cathodal Sham	L and R DLPFC (F3, F4)	L or R DLPFC (F3, F4)	20min/2mA	Bilateral tDCS of DLPFC with anode on of L or R side resulted in a risk-averse response style compared to sham or unilateral tDCS.
	Fecteau et al.(2007b)	Anodal Cathodal Sham	L and R DLPFC (F3, F4)	L or R DLPFC (F3, F4)	15min/2mA	R anodal/L cathodal tDCS resulted in safer responses.

	Boggio et al.(2010a)	Anodal Cathodal Sham	L and R DLPFC (F3, F4)	L or R DLPFC (F3, F4)	15min/2mA	Anodal tDCS of L DLPFC/Cathodal of R DLPFC resulted in higher risk prospects compared to sham or R Anodal/L Cathodal.
	Hecht et al. (2010)	Anodal Cathodal Sham	R and L DLPFC (F3, F4)	R or L DLPFC (F3, F4)	22min/2mA	Anodal tDCS of L DLPFC and cathodal tDCS of R DLPFC increased how fast subjects guessed the most frequent alternative in a probabilistic task.
Verbal fluency	Iyer et al.(2005)	Anodal Cathodal Sham	L F3 (DLPFC)	Contr. Orbit	20min/2mA	Enhanced phonemic fluency performance by anodal tDCS of L DLPFC.
	Cattaneo et al.(2011)	Anodal Sham	Broca's area	R Supraorbital	20min/2mA	Improved performance in phonemic and semantic fluency after anodal tDCS of Broca compared to sham.
Language	Sparing et al.(2008)	Anodal Cathodal Sham	Cp5	Cz	7min/2mA	Anodal tDCS improved picture naming.
	Fertonani et al.(2010)	Anodal Cathodal Sham	L DLPFC	R shoulder	8-10min/2mA	Stimulation of L DLPFC speeded up verbal reaction times in a naming task after the end of stimulation.
	Fiori et al.(2011)	Anodal Sham	Wernicke's area (Cp5), R occipito-parietal	Contr. Orbit	20min/1mA	Anodal tDCS of Wernicke's area improved accuracy in picture naming task.

Social cognition	Varga et al.(2007)	Anodal Cathodal Sham	Oz or P6-P8	Cz	10min/1mA	Cathodal tDCS of the temporo-parietal cortex (P6-P8) improved facial adaptation.
	Knoch et al.(2008)	Cathodal	R DLPFC (F4)	Contr. Orbit	14min(4min before and 10min during task)/1.5mA	Less propensity to punish unfair behavior.
	Priori et al.(2008)	Anodal Cathodal Sham	Bilateral DLPFC	R Deltoid muscle	10min/1.5mA	Anodal tDCS of DLPFC influences experimental deception.
	Boggio et al.(2009)	Anodal Sham	L M1, DLPFC, or V1	Contr. Orbit	5min/2mA	Anodal tDCS of L DLPFC decreased ratings of unpleasantness and discomfort/pain while viewing images of other humans in pain, compared to sham and baseline.
	Karim et al.(2010)	Anodal Cathodal Sham	FP2 and PO3	FP2 and PO3	13min/1mA	Inhibition of the anterior prefrontal cortex (FP2) with cathodal tDCS improved deceptive behavior: faster reaction times in telling lies.
	Mameli et al.(2010)	Anodal Sham	R and L DLPFC (F3, F4)	R and L DLPFC (F3, F4) (10sec)	15min/2mA	Anodal tDCS decreased reaction times for telling lies about general knowledge.
Attention	Bolognini et al.(2011)	Anodal Sham	P4, O2	Contr. Deltoid muscle	15min/2mA	Anodal tDCS of R posterior parietal cortex improved performance on a multisensory attentional orienting task.

Jacobson et al.(2011)	Anodal Cathodal	P3, P6	P3 or P6	10min/1mA	Anodal tDCS to L superior parietal cortex and cathodal tDCS to R inferior parietal cortex resulted in a significant improvement in the ability to discriminate studied from unstudied words.

L, left; R, right; Cz, midline adjacent to the precentral gyrus; M1, primary motor cortex; Fp3, ; F3, left dorsolateral prefrontal cortex; F4, right dorsolateral prefrontal cortex; Cp5, Wernicke's area; P3, left posterior parietal cortex; P4, right posterior parietal cortex; C3, left precentral sulcus; C4, right precentral sulcus; Oz, midline adjacent to the occipital sulcus; P6-P8, right temporo-parietal; V1, occipital cortex; FP2, right anterior prefrontal cortex; PO3, left parieto-occipital cortex; P6, right inferior parietal cortex; O2, right occipital cortex.

3.4. Studies in clinical disorders

Several studies have claimed the therapeutic utility of noninvasive brain stimulation for neurological conditions such as stroke (Fregni et al., 2005; Hummel et al., 2005) and Alzheimer's disease (Ferrucci et al., 2008; Boggio et al., 2009), psychiatric indications such as chronic depression (Boggio et al., 2007) and drug cravings (Fregni et al., 2008), and pain conditions such as fibromyalgia (Fregni et al., 2006) and traumatic spinal cord injury (Fregni et al., 2006).

In patients with Alzheimer's disease (AD) in particular, two cognitive cross-sectional studies have been performed to date (Ferrucci et al., 2008; Boggio et al., 2009). In one study, Ferrucci et al. (2008) assessed whether anodal tDCS of the temporoparietal cortex, an area considered to be hypoactive in AD (Remy et al.,2005), can increase cortical function and recognition memory in AD patients. This study showed that while anodal tDCS significantly improved accuracy in recognition memory, cathodal tDCS significantly decreased it. In addition, no effects were observed in a visual attention task, suggesting that the effects of tDCS were specific for recognition memory. In a second study, Boggio et al. (2009) exposed patients with mild to moderate AD to anodal tDCS of the left DLPFC, the left temporal cortex or a session of sham stimulation. Patients were tested during each stimulation session and showed improvement on a visual recognition memory task after DLPFC tDCS as well as temporal tDCS, which could not be attributed to nonspecific attentional processes.

These studies suggest that tDCS can effectively modulate cortical function in neurodegenerative diseases such as AD, resulting in an enhancement of cognitive functions that are typically impaired in these patients.

3.5. Studies in Parkinson's disease

Up to date, only three studies using tDCS have been performed in patients with PD. In the study reported by Fregni et al. (2006) the motor effects of tDCS of the M1 and DLPFC in PD patients were assessed. This study showed that anodal tDCS of the M1 produces a significant motor function enhancement in PD, as indexed by simple reaction times and motor scores of the UPDRS, compared with sham stimulation. These effects were specific for tDCS polarity and site of stimulation as cathodal stimulation of the M1 and anodal stimulation of the DLPFC induced small effects that were not significantly different from sham stimulation. Moreover, tDCS effects

in patients were associated with a polarity-dependent effect on corticospinal motor excitability as assessed by motor evoked potentials: while anodal stimulation produced a robust increase in the M1 excitability, cathodal tDCS slightly decreased it. Moreover, there was a trend towards a significant correlation between M1 excitability after anodal tDCS and motor function improvement.

In another tDCS study performed by the same group (Boggio et al., 2006), working memory on a 3N-back task was evaluated in patients with PD. The results from this study showed a significant improvement in task accuracy after active anodal tDCS of the left DLPFC with 2 mA. The other conditions of stimulation: sham tDCS, anodal tDCS of left DLPFC with 1 mA or anodal tDCS of M1 did not result in a significant change in task performance. These results suggest that tDCS exerts a beneficial effect on working memory in PD patients that is not only site specific but also dose specific (with 2 mA, but not 1 mA).

Finally, in a more recent study performed by Benninger et al. (2010) the efficacy of anodal tDCS (2 mA) to the motor and prefrontal cortices was tested in eight sessions (each target area was stimulated four times) over 2.5 weeks and compared with sham stimulation. Patients were assessed in timed tests of gait and bradikynesia, UPDRS, a serial reaction time task, Beck Depression Inventory, Health Survey and self-assessment of mobility before and after one day, one month and three months from the last tDCS session. The results showed significant improvement in gait tests after one day and in bradykinesia for longer than three months, suggesting the therapeutic potential of tDCS in PD.

3.6. Studies with neuroimaging
According to Fregni and Pascual-Leone (2007), tDCS has the theoretical appeal of being able to specifically and selectively enhance adaptive patterns of brain activity, suppress maladaptative patterns of brain activity and restore the equilibrium to imbalanced neural networks. Indeed, there is considerable evidence from neuroimaging studies that the effects of tDCS are not limited to the directly targeted brain region but spread trans-synaptically to distant cortical and subcortical structures depending on the strength of the anatomical connections and the level of activity across the specific neural networks. Here, a description of those studies that assessed

the *in vivo* effects of tDCS by using different neuroimaging techniques is provided (for a summary, please see Table 6, Page 94).

Using **Positron Emission Tomography (PET)**, a functional neuroimaging technique that measures regional cerebral blood flow in the brain, Lang et al. (2005) assessed the effects of anodal and cathodal tDCS on the left primary motor cortex (M1). In that study, subjects received 10 minutes of stimulation with an intensity of 1mA and then performed a finger movement task inside the PET scanner. Anodal tDCS of M1 resulted in widespread cortical and subcortical regional cerebral blood flow (rCBF) increases, particularly in the left M1, right frontal pole, right primary sensorimotor cortex and posterior brain regions. On the other hand, cathodal stimulation resulted in rCBF decreases of frontal, temporal, occipital and cerebelar areas. The effects of the stimulation remained stable throughout the PET scanning session (50min), showing the long lasting effects of tDCS.

More recently, Zheng et al. (2011) came to similar findings by using MRI-compatible electrodes for anodal or cathodal tDCS of the right motor region during resting-state in healthy subjects. Interestingly, they observed that anodal stimulation induced a decrease of 17.1% in rCBF on the targeted motor area and widespread motor regions during stimulation, which returned to baseline after the current was turned off, but exhibited an increase in rCBF again in a post-stimulation period. On the other hand, cathodal stimulation induced a small decrease of 5.6% during tDCS, a significant decrease compared to baseline and a continued decrease in the post-stimulation period. These findings provide evidence on the after-effects of tDCS and confirm the widespread effects of tDCS on large brain networks.

Using **blood oxygen level dependent (BOLD) fMRI**, Baudewig et al. (2001) assessed modulation of sensorimotor brain activity during a hand finger opposition task by anodal and cathodal tDCS to left M1. They showed that, in response to 1mA cathodal tDCS for 5min, a significant reduction in the number of activated voxels was recorded in the supplementary motor area (SMA) whereas only negligible changes were found in M1. In addition, they showed that, while anodal tDCS produced no significant changes, cathodal tDCS decreased the mean number of activated voxels up to 38% ($p < 0.01$).

In two subsequent fMRI studies performed by the same group, Kwon et al. (2008) and Jang et al. (2009) assessed modulation of motor cortex excitability by anodal tDCS of M1. In Kwon et al. (2008) a protocol of four successive stimulation sessions of 21 seconds each was used, which resulted in increased activity of the targeted M1, supplementary cortex and posterior parietal cortex only in the last session. In Jang et al. (2009), tDCS was performed inside the fMRI scanner while subjects performed a hand motor task and increased activation of the hand sensorimotor, supplementary motor and other motor areas was found compared to sham stimulation.

In another study designed to assess these distant and remote effects of tDCS on cortical motor activity (Stagg et al., 2009a), M1 was targeted by anodal and cathodal stimulation in healthy subjects who, after stimulation, performed a visually cued serial reaction time task inside the scanner. Anodal tDCS of M1 led to activation increases in M1 and supplementary motor area, while cathodal tDCS of M1 produced an increase of activation in the contralateral M1 and dorsal premotor cortex as well as a functional connectivity increase between these areas and the stimulated left M1 during the task and compared to sham tDCS.

In Holland et al. (2011), a novel study in which the effects of tDCS were assessed both at a behavioral and neural level, the authors found that anodal stimulation of the left DPLFC enhanced picture naming, modulated activity in Broca'a area and a positive correlation was found between these two events.

By contrast to previous findings, recently Antal et al. (2011) showed a decrease in BOLD activity in the supplementary motor area, when the M1, during a simple finger tapping movement, was stimulated by anodal, excitatory current flow. The authors interpreted these results in light of the stimulation protocol that was used, which consisted of 20 second blocks of anodal and cathodal tDCS at 1mA, with and without task. Indeed this protocol differs greatly from the ones of previous studies, including the one from Kwon et al. (2008) that consisted of successive sessions of anodal tDCS without task. Hence, this might the reason why their results differ qualitatively from the ones of previous studies.

The effects of tDCS on cortical and subcortical activity have also been analyzed during resting-state. In Peña-Gomez et al. (2011) anodal tDCS of left and right DLPFC led to increases of

functional connectivity between brain areas engaged in focused attention such as prefrontal and parietal areas, in addition to decreases in connectivity between areas of the default-mode network during resting-state. In another study, Polania et al. (2011a) showed that anodal tDCS to left M1 increased functional connectivity between the left somatomotor (SM1) cortex and premotor, superior parietal areas as well as between posterior cingulate and DLPFC regions. Moreover, significant decreases were also found after tDCS between SM1 and topologically distant brain areas. In Keeser et al. (2011a), significant increases in regional brain connectivity were found in the default-mode network in addition to the left/right frontal-parietal networks after DLPFC tDCS, both close to the primary stimulation site and in connected brain regions. These studies provide evidence that tDCS induces neuroplastic alterations that are related to functional connectivity changes in the brain.

Finally, the first case study using fMRI and tDCS was performed in a patient that suffered from hemianopia due to stroke and who benefited from a combined treatment of rehabilitation training and tDCS (Halko et al., 2011). In this study, activation associated with a visual motion perception task was used to characterize changes in brain activity at baseline and after training/tDCS. Using electrical field modeling the authors reproduced the lesion and predicted distortions of current flow in peri-lesional areas. Results of the simulation showed a correlation between the electric field and change in fMRI signal in areas under the electrode and peri-lesional visual areas, which were consistent with the tDCS rehabilitation.

Using **electroencephalography (EEG),** Polania et al. (2011b) assessed changes in functional connectivity induced by anodal tDCS of the left M1 during voluntary hand movements. Similarly to what was found by the above mentioned fMRI studies, the authors found that, during the motor task, tDCS increased functional connectivity in a network that comprised the targeted M1, left premotor and sensoriomotor areas. In another study by Wirth et al. (2011) the electrophysiological effects of tDCS of left DLPFC were examined both during and after the stimulation. During the stimulation they found that semantic interference, a task that reflects language integrity, was reduced and a greater activation of left temporal scalp-electrode sites occurred compared to right electrode sites. After stimulation, there was a reduction in delta activity during picture naming and resting state. These findings suggest that tDCS is capable of enhancing neural processes during and after stimulation.

Using **magnetic resonance spectroscopy (MRS)**, an imaging technique that measures changes in cortical neurotransmitter concentrations within a defined region of interest, Stagg et al. (2009b) showed that anodal tDCS leads to a significant decrease in GABA concentration, which is the neurotransmitter involved in synaptic inhibition, by contrast to glutamate that is excitatory. By contrast, cathodal inhibitory tDCS reduced glutamatergic neuronal activity with a correlated decrease in GABA. In a subsequent study by the same group (Stagg et al., 2011) that involved fMRI in addition to MRS, it was found that GABA decreases in M1 induced by anodal tDCS correlated positively with motor learning and change of fMRI signal within the targeted M1 during learning. All together these findings show that the polarity-specific changes occurring during tDCS are characterized by varying metabolic brain levels of GABA and glutamate and that decreases of GABA induced by anodal tDCS favor motor learning and increase fMRI activity in the brain.

Using **functional near-infrared spectroscopy (fNIRS)**, which measures the regional oxygenation state of hemoglobin in cortical tissue, Mergazora et al. (2009) showed that bilateral prefrontal cortex tDCS led to significant increases in oxyhemoglobine concentration that lasted up to 8-10 minutes after the end of the stimulation. By contrast, cathodal tDCS had a negligible effect. This study provides evidence on the after-effects of stimulation, which were quite restricted in time, vanishing after a period of 10 minutes.

Using **spectral power analysis and standardized low resolution tomography (sLORETA)**, a technique that measures the electrical activity of each voxel in the brain being also called as current density analysis, Keeser et al. (2011b) assessed the neuronal electrical activity changes after 20 min of 2mA anodal tDCS of the left DLPFC. In particular they obtained EEG recordings during resting-state which was followed by a working memory task (n-back). The authors found that prefrontal stimulation influences cortical dynamics in a frontal network with pronounced activation in the medial frontal gyrus, the anterior cingulate and the subgenual cortex. This impact on EEG activity lasted for up to 15 minutes after the end of stimulation. In addition, the n-back task following resting state showed a positive effect of DLPFC tDCS on error rate, reaction time and accuracy.

Finally, using **Doppler sonography**, Vernieri et al. (2011) assessed the effects of tDCS to M1 in cerebral vasomotor reactivity (VMR), which is the ability of blood vessels to dilate in response to hypercapnia. VMR has been described as a risk factor for stroke occurrence. The authors of this study observed that following anodal stimulation, a decrease in VMR occurred by 3.4% bilaterally in addition to a decrease in heart variability, whereas cathodal stimulation increased VMR by 0.8% bilaterally. They concluded that tDCS of M1 induces a bilateral alteration of cerebral VMR on a polarity-specific manner, suggesting the potential use of tDCS to modulate vascular dilation in stroke patients.

Table 6. Neuroimaging studies with tDCS

Neuroimaging technique	Studies	tDCS Conditions	Stimulation Electrode Positions	Reference Electrode Position	Parameters (minutes/mA)	Effects on the brain
PET	Lang et al.(2005)	Anodal Cathodal Sham	L M1	R Frontopolar	10min/1mA	Anodal tDCS increased rCBF in L M1 and widespread cortical/subcortical regions. Cathodal tDCS increased rCBF only in L premotor cortex and decreased rCBF in widespread regions.
	Zheng et al.(2011)	Anodal Cathodal	C4	R Contr. Orbital	1.4mA	Anodal tDCS increased rCBF during and after stimulation, while cathodal tDCS increased rCBF during stimulation and decreased rCBF after tDCS.
fMRI	Baudewig et al.(2001)	Anodal Cathodal	L M1	R Contr. Orbital	5min/1mA	Cathodal tDCS reduced the number of activated voxels in the supplementary motor area. Anodal tDCS did not have any effect.
	Kwon et al.(2008)	Anodal Baseline	L M1	R Supraorbital	4x21sec/1mA	Increased activity of the targeted M1, supplementary cortex and posterior parietal cortex only in the last session of anodal tDCS.
	Jang et al.(2009)	Anodal Sham	L M1	R Supraorbital	20min/1mA	Increased activation of the hand sensorimotor, supplementary motor and other motor areas, compared to sham.
	Stagg et al.(2009a)	Anodal Cathodal Sham	L M1	R Contr. Orbital	10min/1mA	Anodal tDCS increased activation in L M1 and supplementary motor area, while cathodal tDCS increased activation in R M1, dorsal premotor cortex and functional connectivity increases between these areas and the stimulated left M1.

	Antal et al.(2011)	Anodal Cathodal	L M1	R Contr. Orbital	2x20sec/1mA (Anodal alternated with cathodal)	Anodal tDCS resulted in a decrease of activation in supplementary motor area. Cathodal stimulation showed no effect.
	Peña-Gomez et al.(2011)	Anodal Sham	L, R DLPFC (F3, F4)	L, R Supraorbital	20min/2mA	Anodal tDCS to L or R DLPFC increased functional connectivity in the anticorrelated network and decreased connectivity in default-mode network.
	Polania et al.(2011a)	Anodal Sham	L M1	R Frontopolar	10min/1mA	L M1 stimulation increased connectivity between SM1 and premotor, parietal areas; and between posterior cingulate and DLPFC areas. Moreover, it decreased connectivity between SM1 and distant brain areas.
	Halko et al.(2011)	Anodal	Occipital pole (Oz)	Vertex (Cz)	2mA	Electrical field modeling showed increased fMRI signal in areas under the anode and peri-lesional areas in a case of a patient with hemianopia due to stroke.
	Holland et al.(2011)	Anodal Sham	FC5	Contr. Frontopolar	20min/2mA	Improved picture naming and increased activation of Broca's area induced by anodal tDCS. Positive correlation between behavioral performance and brain activation.
	Keeser et al.(2011a)	Anodal	L DLPFC (F3)	R Contr. Orbital	20min/2mA	Anodal stimulation increased functional connectivity in the default-mode network and the left, right fronto-parietal networks.
EEG	Polania et al.(2011b)	Anodal Sham	L M1	R Frontopolar	10min/1mA	tDCS of L M1 increased connectivity between motor, premotor and sensorimotor areas during voluntary hand movements.

	Wirth et al.(2011)	Anodal Sham	L DLPFC	R Shoulder	37min/1.5mA	During tDCS, the semantic interference effect was reduced and left temporal EEG activation increased. After tDCS a reduction in delta activity occurred during picture naming and resting state.
MRS	Stagg et al.(2009b)	Anodal Cathodal	L M1	R Contr. Orbital	10min/1mA	Anodal tDCS reduced GABA levels, while cathodal tDCS reduced glutamate with a correlated reduction of GABA.
	Stagg et al.(2011)	Anodal Sham	L M1	R Contr. Orbital	10min/1mA	GABA decreases induced by anodal tDCS of L M1 showed a positive correlation with motor learning and fMRI signal change during learning.
fNIRS	Mergazora et al.(2010)	Anodal Cathodal Sham	L and R prefrontal (Fp1, Fp2)	L , R prefrontal (Fp1, Fp2)	10min/1mA	Bilateral anodal stimulation induced increase of oxihemoglobine concentration that lasted up to 8-10min after tDCS. Cathodal tDCS showed no effect.
sLORETA	Keeser et al.(2011b)	Anodal Cathodal	L DLPFC	R Supraorbital	20min/2mA	Stimulating L DLPFC by anodal tDCS resulted in pronounced activation of frontal areas during resting-state, which lasted up to 15 min after the end of stimulation.
Doppler sonography	Vernieri et al.(2010)	Anodal Cathodal	L M1	Ipsilateral arm	15min/1mA	Anodal tDCS decreased vasomotor reactivity, whereas cathodal stimulation increased it.

L, left; R, right; M1, primary motor cortex; C4, right precentral sulcus; F3, left dorsolateral prefrontal cortex; F4, right dorsolateral prefrontal cortex; FC5 left inferior frontal cortex; Fp1, left prefrontal cortex; Fp2, right prefrontal cortex.

Chapter 2.
Objectives & Hypotheses

1. Study I: Structural brain correlates of verbal fluency in Parkinson's disease

This study was aimed at determining the cerebral GM areas that underlie impairment on two standard neuropsychological tests of semantic and phonemic fluency in patients with PD without dementia.

Impairment on verbal fluency measures is one of the main features of cognitive decline in PD, being thought to reflect a dysfunction in executive processes, which rely upon frontal lobe structures (Henry and Crawford, 2004).

However, previous studies in patients with focal cerebral lesions have shown that whereas impairment in both semantic and phonemic fluencies is commonly found after frontal lobe damage (Baldo et al., 2001), in the case of semantic fluency, damage to temporal areas also seems play a relevant role, suggesting the specific involvement of search processes through semantic memory in this type of fluency (Baldo et al., 2006).

Based on the importance of verbal fluency deficits in PD and previous evidence on the neural correlates of these cognitive functions in lesion patients, we predicted that:

- Scores on a phonemic fluency test would significantly correlate with GM density in frontal areas, particularly the inferior frontal gyrus, due to its role in executive processes.
- Scores on the semantic fluency test would correlate not only with frontal GM reductions but also significant GM decreases in temporal areas, showing this task relies both on executive functions and semantic memory.

2. Study II: Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease

This second study was aimed at assessing the differential effects of tDCS, one applied to the left dorsolateral prefrontal cortex and the other to the left temporo-parietal area, in semantic and phonemic fluency networks in patients with PD. In particular, we wanted to evaluate not only verbal fluency networks under both types of stimulation but also to characterize the differences

between semantic and phonemic networks so that the dissociation between the two fluencies could be assessed under the effects of tDCS.

On the other hand, another goal was to study the impact of tDCS in the deactivation task-related networks that presented high spatial correspondence with the DMN, since the DMN has been reported to be altered in patients with PD (van Eimeren et al., 2009; Delaveau et al., 2010; Ibarretxe-Bilbao et al., 2011).

Finally, a third goal was to observe the effects the stimulation exerted over verbal fluency performance in terms of the amount of words produced under the influence of frontal or temporo-parietal tDCS.

Taking into account these objectives, we predicted the following:

- There would be differential effects of the type of stimulation in functional connectivity, both in verbal fluency as well as in the deactivation task-related networks.
- Anodal tDCS would induce a significant increase in functional connectivity not only in the underlying stimulated area but also in distant functionally connected brain regions.
- Increased functional coupling would be found in brain areas not only related to the type of stimulation but also associated with the task being performed by the patients.
- Frontal tDCS would increase functional connectivity in both verbal fluency networks, while temporo-parietal tDCS would increase connectivity only in the semantic network.
- Frontal tDCS would additionally have a greater effect on the deactivation task-related network compared to temporo-parietal tDCS.
- There would be differential effects of stimulation condition on verbal fluency performance.
- These different effects in task performance would be coherent with changes in functional connectivity.

3. Study III: Assessment of cortical degeneration in patients with Parkinson's disease by voxel-based morphometry, cortical folding and cortical thickness

This study had a different independent goal with respect to the previous studies. Inspired by the fact that there are currently several neuroimaging techniques that provide information on different characteristics of the cortical GM layer, the aim of this study was to assess the contribution of three of the most commonly used methods to the assessment of cortical degeneration in PD. In particular, GM atrophy in patients with PD was evaluated in terms of changes in cortical thickness, sulcal indices and volume loss compared to healthy age-matched controls.

In addition, another goal was to assess the association between these anatomical measures as well as their relationship with the stage of disease, severity of motor symptoms, general cognitive performance and age in PD patients.

According to previous neuropathological studies in PD by Braak et al. (2000; 2003) LB inclusions progress gradually through six stages in a predictable manner. These stages are characterized by involvement of specific brain regions that start in motor nuclei and limbic structures, which further extend to temporal and paralimbic areas and finally reach the prefrontal lobes and other associative areas.

Given that the patients in this study were at symptomatic stages of PD:

- Significant changes of GM volume, folding and thickness were expected in limbic, temporal, paralimbic and prefrontal areas of the cortex in patients compared with controls.
- A regional correspondence was expected between areas identified as atrophic in PD patients by the three different methods.
- An association between relevant clinical variables and global anatomical measures was also predicted and expected to show a similar pattern.

Chapter 3.
Methods

1. Preliminary note

The current thesis consists of a total of three studies. As mentioned in the Introduction, the first two studies were designed in order to assess the neuroanatomical and neurofunctional basis of phonemic and semantic fluency impairment in patients with PD. By contrast, the third study was performed to evaluate the nature of cortical degeneration occurring in PD as the result of changes in cortical thickness, folding or GM volume.

Each study assessed a different sample of patients with different MRI acquisition procedures. All patients gave their written informed consent to the studies, which were approved by the ethics committee of Hospital Clinic, Barcelona.

Below, a brief description of the main methodological aspects of each study is provided. For further details, please refer to the corresponding publications, which can be found in the Results section.

2. All studies

For all studies, patients were recruited from the Parkinson's Disease and Movement Disorders Unit, Department of Neurology of Hospital Clinic using the following inclusion and exclusion criteria:

Inclusion criteria
- Diagnosis of idiopathic PD according to the UK Parkinson's disease Society Brain Bank criteria (Daniel and Lees, 1993):
    - Bradykinesia
    - At least one of the three motor symptoms: rigidity, postural instability or tremor
    - Good initial response to levodopa or dopamine agonists
    - Unilateral onset
    - Persistent asymmetry affecting mainly the site of onset
    - Lack of evidence of other medical conditions associated with atypical parkinsonism
- Lack of diagnostic criteria for dementia associated with PD

- Absence of clinical depression

Exclusion criteria

- Other disorders apart from PD

- Parkinsonism due to antipsychotics or other drugs

- Suspected dementia with Lewy bodies

    - Signs of cognitive impairment during the first year

    - Transient loss of consciousness

    - Neuroleptic sensitivity

- Delirium

- Confusion

- Amnestic disorder

- Neuropsychiatric diseases

- Severe vascular risk factors

- Vascular lesions

- Past traumatic brain injury on MRI

In addition, all patients were clinically assessed by the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) and the Hoehn and Yahr scale (1967).

3. Study I

Sample: Thirty-two patients with PD participated in this study. This sample was recruited between 2004 and 2006. The data used to investigate the brain structural correlates of phonemic and semantic fluency in this study belonged to an earlier study from which the MRI (Ramirez-Ruiz et al., 2007a) and the global neuropsychological results had already been published (Ramirez-Ruiz et al., 2006; Ramirez-Ruiz et al., 2007b).

All patients were screened for dementia using the mini-mental state examination (MMSE) (Folstein et al., 1975) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-4th Edition). Presence of depression was assessed using the Hamilton Depression Rating Scale (Hamilton, 1960).

Image acquisition: MRI scans were acquired on a GE Signa 1.5 T scanner (GE Medical Systems Co., Milwaukee, Wisconsin, USA) in the axial plane (Inversion recovery preparation spoiled gradient recalled echo sequence; repetition time = 12 ms; echo time = 5 ms; inversion time = 300; 1.5 mm thickness; field of view = 24 cm; matrix 256 x 192; number of excitations = 1; flip angle = 201 and voxel size = 2 x 2 x 2).

Image analysis: Image analysis was performed with MATLAB 6.5 (Mathworks, Natick, Massachusetts, USA) and SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK) (http://www.fil.ion.ucl.ac.uk/spm) using the optimized VBM method (Ashburner and Friston, 2000).

Neuropsychological assessment: All patients performed a phonemic and a semantic fluency task. For the phonemic task they were instructed to generate words starting with the letter 'P', and for the semantic task they had to retrieve words that belonged to the category 'animals'. A time limit of 60 s was placed for both tasks.

Statistical analysis: A multiple regression analysis was performed in this study to assess the correlations between whole-brain GM density and direct scores on phonemic and semantic fluency tests of PD patients. Correlations between whole brain GM and the patient's MMSE scores were also carried out in order to avoid confounding effects because of general cognitive impairment.

4. Study II

Sample: Sixteen patients with PD were recruited during a three month period in 2010. They were screened for dementia and depression using the MMSE (Folstein et al., 1975) and the Geriatric Depression Scale (GDI) (Yesavage et al., 1983), respectively. Moreover, they underwent a neuropsychological test battery that included: the Rey's Auditory Verbal Learning test, the Vocabulary and Letters/Digits subtests of the WAIS, a short version of the Boston Naming test and the Visual Form Discrimination test.

Image acquisition: Scanning was performed on a 3T Siemens Tim Trio MRI System (Erlangen, Germany) equipped for echo-planar imaging with a 12-channel head coil at the Center for Image

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Diagnosis (CDIC) of the Hospital Clinic, Barcelona. Blood oxygenation level-dependent (BOLD) functional imaging was performed using a gradient echo T2-weighted pulse sequence (TR/TE = 2000/29 ms, flip angle = 90°, FOV = 220 x 220 mm, 40 axial slices, slice thickness = 3.75, matrix = 128 x 128). To aid in the localization of functional data, a high resolution T1-weighted MPRAGE sequence was also acquired (TR/TE = 2300/2.98 ms; TI = 900 ms; FOV = 256 x 256 mm; 240 sagittal slices; slice thickness = 1.0 mm; matrix = 256 x 256).

Transcranial direct current stimulation (tDCS): tDCS was delivered via a pair of water-soaked sponge electrodes (35 cm^2 surface), with an intensity of 2 mA during 20 min using a battery-driven, constant current stimulator (Phoresor, Iomed Inc., Salt lake City, UT, USA). The anode electrode was placed over F3 (left DLPFC) or P3-T5 (left TPC) according to the 10-20 international system (Herwig et al., 2003), and in either case the cathodal electrode was placed over the right supraorbital area (R SO).

Experimental protocol:

After performing the baseline phonemic and semantic fluency tests, PD patients were randomized to receive left anodal DLPFC (F3) tDCS and left anodal TPC (P3-T5) tDCS in a counterbalanced order - **(A)** or **(B)** (Figure 22). The cathode electrode was placed over the right supraorbital area (R SO) in both stimulation conditions. After each session of tDCS, which lasted 20 minutes, patients performed an fMRI verbal fluency paradigm inside the scanner, as shown below.
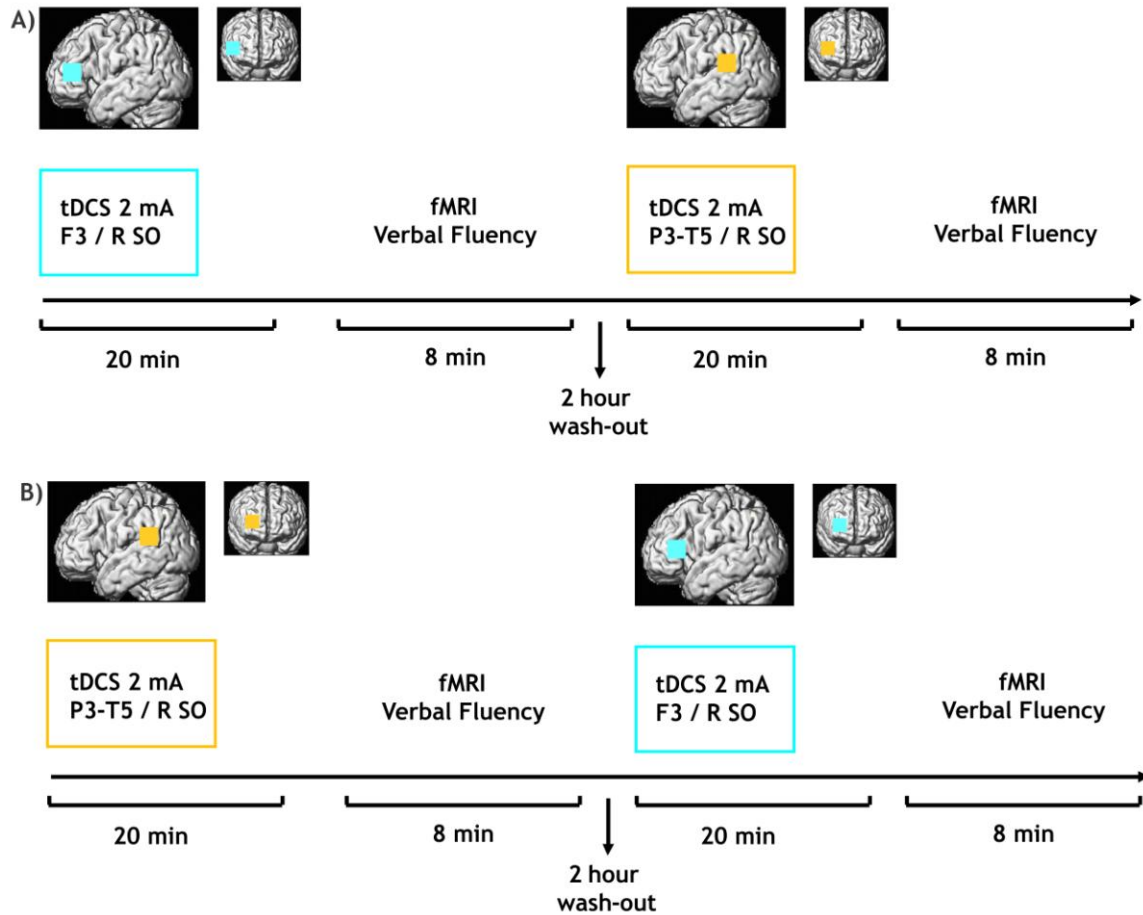
Figure 22. Experimental protocol used in the second study of this thesis.

fMRI task:

The fMRI paradigm consisted of four tasks: cross fixation, repeat continuously the word "mountain", perform a semantic fluency task and perform a phonemic fluency task. Each of these tasks lasted 20 s and was repeated 6 times (once per block) in the first and second fMRI session. The fMRI tasks lasted 8 minutes each (Figure 23).

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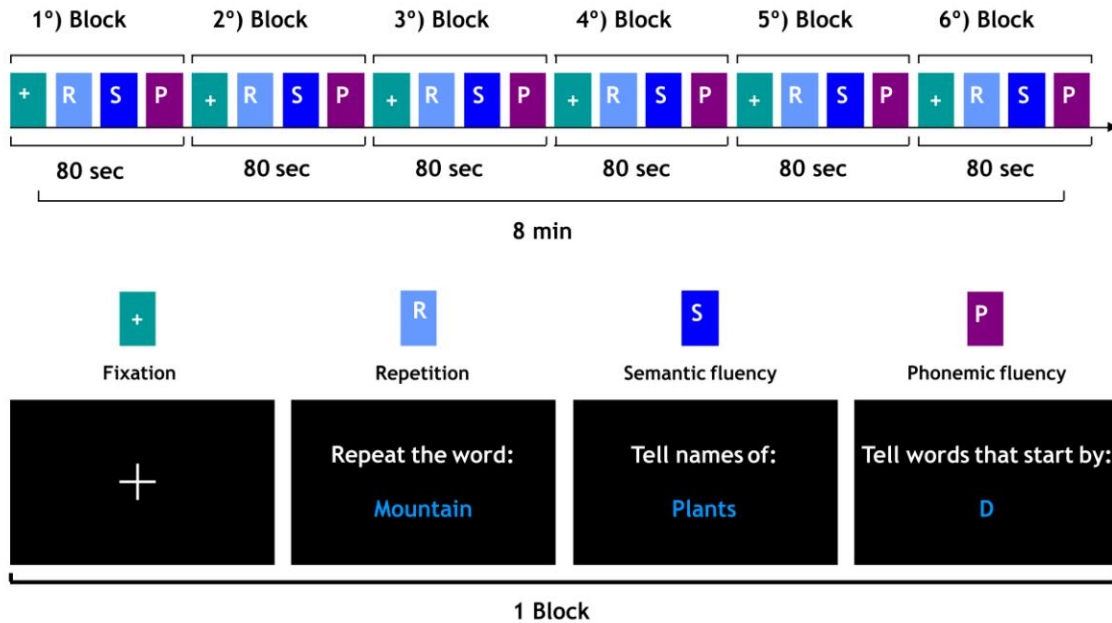
Figure 23. Task performed inside the fMRI scanner by PD patients.

Behavioral analysis: Differences in semantic and phonemic verbal fluency performance after tDCS conditions were tested through a repeated-measures ANOVA with the factors condition (two levels; DLPFC and TPC tDCS) and fluency performance (two levels; phonemic and semantic fluency).

Image analysis: An independent component analysis (ICA) approach using multivariate exploratory linear decomposition into independent components (MELODIC) to study functional connectivity (Beckhmann and Smith, 2005) was applied to fMRI data as implemented in FSL (FMRIB's Software Library, www.fmrib. ox.ac.uk/fsl) (Smith et al., 2004). The independent components showing significant differences between the effects of DLPFC and TPC tDCS in task-related patterns were selected using a repeated-measures ANOVA and the general linear model contrasts: verbal fluency > repetition task, phonemic fluency > semantic fluency and semantic fluency > phonemic fluency. In addition, the differential effects between the two stimulations were also assessed on the deactivation task-related pattern networks with spatial correspondence to the default-mode network by means of the contrast: fixation > verbal fluency. The component for this contrast was selected based on the best cross correlation matching score between the set of ICs and the ones from the large resting-state fMRI dataset of "1000 Functional Connectomes" Project (Biswal et al., 2010).

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5. Study III

Sample: Twenty patients with PD and 20 normal controls were included in this study. This sample was selected from a pool of subjects recruited during a 6-month period. Only subjects with MRI scans that could be preprocessed and analyzed using the three methods employed in this study (VBM, cortical folding, and cortical thickness) were included. In line with this, 12 subjects had to be excluded due to masking, segmentation or sulcus labeling errors during the cortical folding image analysis.

Patients were screened for dementia and depression using the MMSE (Folstein et al., 1975) and the Beck's Depression Inventory (BDI) (Beck et al., 1996), respectively. All participants underwent a neuropsychological test battery that comprised: Semantic and Phonemic Fluency tests, the Rey's Auditory Verbal Learning Test (RAVLT), the Stroop test and the forward and backward Digits subtests from WAIS-III.

Image acquisition: MRI scans were obtained on a 3.0 T Magnetom Trio Tim Siemens (Erlangen, Germany) at the Center of Imaging Diagnosis Clinic (CDIC) of Hospital Clinic, Barcelona. MRI parameters of the three-dimensional MPRAGE Saggital ISO sequence were as follows: repetition time (TR) ¼ 2300 ms; echo time (TE) = 2.98/3.01 ms; inversion time (TI) = 900 ms; 1 mm thickness; field of view (FOV) = 24 x 24 mm; 256 x 256 matrix.

Image analysis: Image preprocessing was performed using three different softwares: the VBM8 toolbox (available at: http://dbm.neuro.uni-jena.de/vbm) implemented in SPM8 (available at: http://www.fil.ion.ucl.ac.uk/spm/) to assess GM volumes; BrainVisa (available at: http://brainvisa.info/) [Mangin et al., 2004] to measure the global sulcal index and the following local sulci based on prior hypotheses: the inferior temporal sulcus, the collateral fissure, the occipitotemporal sulcus, the anterior cingulate sulcus, the anterior sylvian fissure, and the superior frontal sulcus; FreeSurfer (available at: http://surfer.nmr.harvard.edu) to assess cortical thickness.

Statistical analysis: In addition to image analyses, statistical analyses were also performed to assess the relationship between whole brain indices and regional measures derived from the previous three methods as well as their correlation with disease stage, severity of motor

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symptoms, age and global cognitive performance in PD patients, controls and in the entire

sample.

Chapter 4.
Results

Structural brain correlates of verbal fluency in Parkinson's disease

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Verbal fluency tests are often used to assess cognitive dysfunction in Parkinson's disease. These tests have been found to be impaired even in initial stages of this illness. We applied voxel-based morphometry to investigate the neuroanatomic substrates of semantic and phonemic fluency impairment. Correlations between gray matter density and semantic as well as phonemic fluency performance were performed in 32 nondemented Parkinson's disease patients. We found that gray matter of temporal, frontal and cerebellar areas correlated with semantic fluency scores. In contrast, no gray matter correlations were found for phonemic fluency or for general cognitive functions. These results suggest that semantic fluency impairment is reflecting structural gray matter changes in regions involved in language

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Introduction

Impairment in verbal fluency is one of the cognitive changes most frequently observed in Parkinson's disease (PD) and is present even in the early stages of the disease [1–5]. Deficits in phonemic and semantic fluencies are considered secondary to frontal lobe dysfunctions as both types of fluency are impaired in patients with structural frontal lesions [5]. Semantic fluency is, however, more closely related to temporal damage than phonemic fluency [5]. In healthy participants, phonemic fluency activates a network involving mainly the frontal gyrus and anterior cingulate areas [6], whereas semantic fluency, in addition to frontal regions, activates temporal and parietal areas [7].

To date, no studies have investigated the cerebral correlates of phonemic and semantic deficits in PD. The aim of this study was to detect possible cortical gray matter (GM) changes underlying these deficits in a sample of nondemented PD patients by correlating cognitive changes and whole brain GM through voxel-based morphometry (VBM) methods.

Methods
Participants

Thirty-two patients with PD participated in this study. This sample was recruited between 2004 and 2006 from an outpatient Movement Disorders Clinic (Parkinson's Disease and Movement Disorders Unit, Department of

Neurology, Hospital Clinic, Barcelona). The data used to investigate brain-behaviour correlates in this study belongs to an earlier study from which the Magnetic resonance imaging (MRI) [8] and the global neuro-psychological results have already been published [9,10]. In this study, we perform an analysis of correlation between whole brain anatomy and semantic/phonemic alterations. Following the UK Parkinson's Disease Society Brain Bank criteria [11], a diagnosis of idiopathic PD was established for all patients. Clinical assessment was performed by means of the motor subsection of Unified Parkinson's Disease Rating Scale [12] and disease severity was rated according to the Hoehn and Yahr scale [13], while patients were optimally medicated. All patients were screened for dementia using the Mini-Mental State Examination (MMSE) [14] and the *Diagnostic and Statistical Manual of Mental Disorders*, Revised Fourth Edition [15]. Presence of depression was assessed by the Hamilton Depression Rating Scale [16]. Fourteen patients had persistent visual hallucinations. Approval was received from the Ethics Committee of Hospital Clinic and patients gave informed consent. Demographic and clinical characteristics of the patients are shown in Table 1.

Verbal fluency assessment

All patients performed a phonemic and a semantic fluency task. For the phonemic task they were instructed to generate words starting with the letter 'P', and for the

semantic task they had to retrieve words that belonged to the category 'animals'. A time limit of 60 s was placed for both tasks. Results of the tests are shown in Table 1.

Magnetic resonance imaging acquisition and data analysis

MRI scans were acquired on a GE Signa 1.5 T scanner (GE Medical Systems Co., Milwaukee, Wisconsin, USA) in the axial plane (Inversion recovery preparation spoiled gradient recalled echo sequence; repetition time = 12 ms; echo time = 5 ms; inversion time = 300; 1.5 mm thickness; field of view = 24 cm; matrix 256 × 192; number of excitations = 1; flip angle = 20° and voxel size = 2 × 2 × 2). Image analysis was performed with MATLAB 6.5 (Mathworks, Natick, Massachusetts, USA) and SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK) (http://www.fil.ion.ucl.ac.uk/spm) using the optimized VBM method [17]. In brief, the VBM processing was performed as follows: the T1-weighted images were stereotactically transformed into standard Montreal Neurological Institute space using an automated spatial normalization algorithm. Image segmentation into GM, white matter and cerebrospinal fluid and normalization into unmodulated images was carried out. Volumes of these three tissues were obtained and further calculated into intracranial volumes, which are a potential confounding variable in VBM studies. Finally, all images were smoothed using a 12 mm full-width at half maximum isotropic Gaussian kernel.

Statistical comparison

To assess correlations between GM density and performance on the phonemic and semantic fluency tests, we performed a multiple regression analysis, using the direct scores of the patients on those tests. The significance level was set at a P value of less than 0.001 uncorrected across the entire brain. We also performed correlations between whole brain GM and the patient's MMSE scores, to avoid confounding effects because of general cognitive impairment. The Montreal Neurological Institute coordinates of significant clusters were converted

into Talairach coordinates (http://www.cbu.cam.ac.uk/imaging/index.html). The anatomic locations of the peak clusters were found using the Co-Planar Stereotaxic Atlas of the Human Brain and the Talairach Client, version 2.4 (http://www.talairach.org/client.html) [18]. These locations were visually checked using the BrainVoyager Brain Tutor (http://www.brainvoyager.com/BrainTutor.html). To perform group statistics and correlations of fluency performance with clinical variables, we used SPSS version 15 (SPSS Inc., Chicago, Illinois, USA) [19].

Results

We obtained significant correlations between semantic fluency scores and GM density in the inferior and middle frontal gyrus (Brodmann's area 10, 46), several areas in the temporal lobe (Brodmann's area 20, 21, 22, 38) and bilateral hemispheres of the cerebellum (Fig. 1, Table 2). Other significant correlations were also found with the parahippocampus, the caudate and anterior nucleus of the thalamus. We did not find any significant correlation between GM density and phonemic fluency scores. Moreover, no correlations between the patient's MMSE scores and GM density were found.

Performance on both phonemic and semantic fluency test showed a significant correlation with Hoehn and Yahr staging ($r = 0.46$, $P < 0.008$; $r = -0.54$, $P < 0.001$) and MMSE ($r = 0.43$, $P < 0.015$; $r = 0.42$, $P < 0.017$). In addition, phonemic but not semantic fluency correlated with years of education ($r = 0.59$, $P < 0.0001$) and

Fig. 1
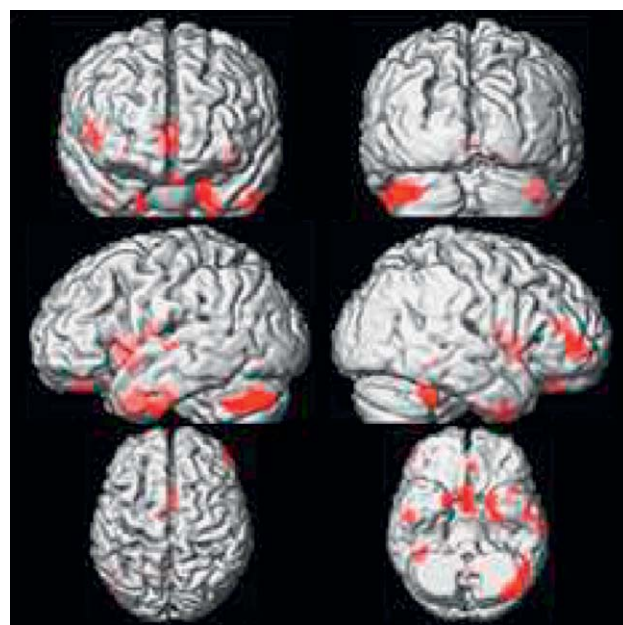
Regions with significant positive correlation with the semantic fluency test.

Table 2 Correlation between gray matter density reductions and scores on the semantic fluency test

Cluster size k (mm³)	Brain region	x	y	z	t value
106	R inferior frontal gyrus (BA10)	50	48	−2	4.37
	R middle frontal gyrus (BA10)	44	56	−8	3.61
	R inferior frontal gyrus (BA46)	52	39	11	3.57
438	L cerebellum	−38	−73	−25	4.32
42	R inferior temporal gyrus (BA20)	50	−12	−38	4.31
68	L inferior temporal gyrus (BA20)	−54	−8	−35	4.19
323	R caudate head	4	10	−2	4.09
	L anterior nucleus of thalamus	−6	−3	9	3.86
	R caudate body	6	2	9	3.65
262	L parahippocampus	−22	1	−27	4.07
		−24	−15	−33	3.95
57	R parahippocampus	18	2	−35	3.84
81	R cerebellum	40	−44	−23	3.81
29	L inferior temporal gyrus (BA20)	−65	−15	−25	3.81
10	L inferior temporal gyrus (BA22)	−69	−17	1	3.73
17	L middle temporal gyrus (BA21)	−44	12	−38	3.69
30	L rectal gyrus (BA11)	−4	34	−25	3.63
28	L superior temporal gyrus (BA38)	−36	5	−10	3.61
14	R culmen	16	−37	−7	3.59
12	L cerebellum	−2	−56	3	3.53

The coordinates x, y and z correspond to the anatomical location, indicating standard stereotactic space as defined by Talairach and Tournoux [18].
BA, Brodmann's area; L, left; R, right.

Unified Parkinson's Disease Rating Scale motor assessment ($r = −0.39$, $P < 0.029$). Finally, a significant correlation between semantic fluency performance and age ($r = −0.38$, $P < 0.03$) was also found.

Discussion

To our knowledge, this is the first VBM study investigating the cerebral correlates of verbal fluency in PD. Our results showed GM loss underlying semantic impairment in temporal and frontal areas, which are part of the semantic brain network described in normal participants. In contrast, no GM reductions were associated with phonemic fluency deficits.

Our results agree with earlier studies carried out in patients with focal brain lesions in which frontal and temporal lobe damage produce impairment in semantic fluency [5]. Similar findings have also been reported in neuroimaging studies. In healthy participants, semantic fluency has been associated with functional MRI activations in the bilateral inferior frontal gyrus, medial temporal lobe and the parahippocampus [7]. The absence of correlations between GM density and MMSE scores found in our study also reinforces these results by indicating that GM regions related with semantic fluency performance are not reflecting a general cognitive impairment.

We did not find any cortical GM regions associated with patient's performance in phonemic fluency tests. Such

lack of correlation gives support to the functional basis rather than structural basis of executive dysfunction proposed for nondemented PD patients [20], which contrasts with the structural basis found for semantic impairment observed in our patients. Moreover, the different patterns of correlation that we have observed between semantic/phonemic fluencies and clinical variables also reinforces the notion that these two tests do not measure the same function. Phonemic but not semantic fluency correlated with motor disabilities and with years of education.

Conclusion

We have shown that impairment in semantic fluency in PD is related to anatomical GM reductions in frontal and temporal regions that have been found to be involved in the verbal semantic fluency network described in normal participants. In contrast, phonemic fluency did not correlate with any cerebral region. These results suggest that semantic fluency tests reflect better cortical dysfunctions in PD than phonemic fluency.

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Original Research

Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease

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ABSTRACT

Background: Verbal fluency relies on the coordinated activity between left frontal and temporal areas. Patients with Parkinson's disease (PD) present phonemic and semantic fluency deficits. Recent studies suggest that transcranial direct current stimulation (tDCS) enhances adaptative patterns of brain activity between functionally connected areas.

Objective: The aim of this study was to assess the differences in the effects induced by tDCS applied to frontal and temporo-parietal areas on phonemic and semantic fluency functional networks in patients with PD.

Method: Sixteen patients were randomized to receive tDCS to left dorsolateral prefrontal cortex (DLPFC) and left temporo-parietal cortex (TPC) in a counterbalanced order. Immediately following stimulation, patients underwent a verbal fluency paradigm inside a fMRI scanner. Changes induced by tDCS in activation and deactivation task-related pattern networks were studied using free-model independent component analyses (ICA).

Results: Functional connectivity in verbal fluency and deactivation task-related networks was significantly more enhanced by tDCS to DLPFC than to TPC. In addition, DLPFC tDCS increased performance on the phonemic fluency task, after adjusting for baseline phonemic performance.

Conclusions: These findings provide evidence that tDCS to specific brain regions induces changes in large scale functional networks that underlay behavioural effects, and suggest that tDCS might be useful to enhance phonemic fluency in PD.

Introduction

Verbal fluency is a classical neuropsychological measure of language production. In particular, phonemic fluency requires individuals to generate lists of words that start with a given letter, while semantic fluency involves generation of words to semantic category cues in a limited period of time [1].

In patients with focal brain lesions, impairment of both phonemic and semantic fluency has been found after frontal lobe damage [2,3]. However, some studies suggest that phonemic fluency relies on a partially different neural network than semantic fluency. For instance, frontal lobe lesions can disproportionately impair phonemic fluency [4–6], while temporal lobe damage impairs semantic fluency to a greater extent [5,7]. Functional neuroimaging studies have generally supported these findings, showing that both verbal fluency tasks are associated with activation of left frontal [8–11] and parietal areas [11,12], while semantic tasks involve additional activation of left temporal regions [11,12].

Parkinson's disease (PD) is associated with phonemic and semantic fluency deficits [13–15]. These deficits have been thought to both be caused by frontal lobe dysfunction in PD [16], but a recent meta-analysis [17] showed that PD patients present greater deficits on tests of semantic than phonemic fluency, implying that pathology in the temporal lobe might contribute to the observed

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fluency impairment. In line with this, gray matter loss in temporal and frontal areas has been found to correlate with semantic fluency deficits in PD patients [18].

Thanks to the development of non-invasive brain stimulation techniques it is now possible to modulate cognitive functions in neurological diseases such as PD. These techniques might provide clinical benefits for the patients as they appear to enhance adaptative patterns of brain activity, suppress maladaptive patterns of activity and restore equilibrium in imbalanced neural networks [19]. For instance, transcranial direct current stimulation (tDCS) can improve cognitive performance in healthy individuals and change cortical excitability in a polarity-dependent manner, with brain excitability being usually increased by anodal tDCS and decreased by cathodal tDCS [20,21]. Recent fMRI studies suggest that anodal tDCS increases brain excitability in the underlying stimulated area and distant presumably connected brain regions, suggesting that tDCS has an effect on brain functional connectivity [22–24]. In patients with PD, anodal tDCS has been shown to improve working memory when targeting the prefrontal cortex [25], and motor functions by increasing motor evoked potential amplitudes over the stimulated motor area [26].

In the current study, our aim was to assess the effects of tDCS on phonemic and semantic fluency functional networks in patients with PD. We hypothesized that tDCS to the left dorsolateral prefrontal cortex (DLPFC) or left temporo-parietal cortex (TPC) would have differential effects on phonemic and semantic verbal fluency and its associated neural networks. We evaluated changes in functional connectivity associated with left frontal and temporo-parietal brain stimulations. In addition, we also assessed the effects of tDCS on deactivation task-related pattern networks that presented high spatial correspondence with the default-mode network, since PD has been recently associated with alterations of the default-mode network [27–29]. We predicted that frontal tDCS would increase functional connectivity in both fluency networks, while temporo-parietal tDCS would increase functional connectivity specifically in the semantic fluency network. Additionally, we predicted that DLPFC tDCS would induce greater increases in functional connectivity of the deactivation network than TPC tDCS, consistent with studies showing significant effects of prefrontal tDCS on the default-mode network [30,31].

Methods

Subjects

Sixteen patients with PD were recruited from an outpatient Movement Disorders Clinic (PD and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona, Spain) during a three month period. Inclusion criteria to participate in this study involved: diagnosis of idiopathic PD according to the UK Parkinson's disease Society Brain Bank criteria [32]; a good initial response to L-dopa or dopamine agonists; lack of diagnostic criteria for dementia associated with Parkinson's disease [33]; and absence of clinical depression. In addition, the following exclusion criteria were applied: other brain disorders apart from PD; parkinsonism due to antipsychotic medications or other drugs; delirium; confusion; amnestic disorder; neuropsychiatric diseases; severe vascular risk factors; vascular lesions; and past traumatic brain injury on MRI. All patients gave their written informed consent to the study, which was approved by the ethics committee of the Hospital Clinic, Barcelona.

Patients were clinically assessed using the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS) [34] and the Hoehn & Yahr scale [35]. They were further screened for dementia and depression using the mini-mental state examination (MMSE) [36] and the Geriatric Depression Scale (GDI) [37], respectively.

Moreover, they underwent a neuropsychological test battery that included: the Rey's Auditory Verbal Learning test, the Vocabulary and Letters/Digits subtests of the WAIS, a short version of the Boston Naming test and the Visual Form Discrimination test. Procedures for neuropsychological assessment are described in Lezak et al. [1]. All patients were studied while treated with levodopa alone or a combination of levodopa and a dopamine-agonist (pramipexole, ropinirole), in addition to rasagiline as monotherapy. In order to take into account the total amount of all dopaminergic drugs the patients were taking, we calculated a levodopa-equivalent dose for each patient according to procedures that have been previously described [38–41]. A detailed description on dopaminergic medication has been provided as supplementary data (Supplementary Table 1). All patients were assessed in the on phase.

Direct current stimulation (tDCS)

tDCS was delivered via a pair of water-soaked sponge electrodes (35 cm^2 surface), with an intensity of 2 mA during 20 min using a battery-driven, constant current stimulator (Phoresor, Iomed Inc., Salt lake City, UT, USA). The anode electrode was placed over F3 (left DLPFC) or P3-T5 (left TPC) according to the 10–20 international system [42], and in either case the cathodal electrode was placed over the right supraorbital area (R SO).

Image acquisition

Scanning was performed on a 3T Siemens Tim Trio MRI System (Erlangen, Germany) equipped for echo-planar imaging with a 12-channel head coil at the Center for Image Diagnosis (CDIC) of the Hospital Clinic, Barcelona. During this scan, subjects remained in the supine position with their heads immobilized by cushioned supports and a forehead strap to minimize head movement. Moreover, they wore earplugs to attenuate MRI gradient noise.

Blood oxygenation level-dependent (BOLD) functional imaging was performed using a gradient echo T2-weighted pulse sequence (TR/TE = 2000/29 ms, flip angle = 90°, FOV = 220 × 220 mm, 40 axial slices, slice thickness = 3.75, matrix = 128 × 128). To aid in the localization of functional data, a high resolution T1-weighted MPRAGE sequence (TR/TE = 2300/2.98 ms; TI = 900 ms; FOV = 256 × 256 mm; 240 sagittal slices; slice thickness = 1.0 mm; matrix = 256 × 256) was also acquired.

Experimental protocol

This study was designed as a cross-over tDCS experiment combined with fMRI. First, baseline performance in phonemic and semantic fluency tasks was assessed in all patients. The phonemic task consisted of generating words beginning with the letter P, while the semantic task consisted of producing as many names of animals as possible. For each task there was a limit of 60 s. Patients were instructed not to provide the same word twice, use the root of a word more than once or use proper nouns.

After these tasks patients were randomized to receive either left DLPFC or left TPC tDCS for 20 min and then immediately asked to perform an overt fMRI paradigm of verbal fluency inside the scanner (Fig. 1). This paradigm consisted of a block design (ABCD) where each block was formed by three periods of activation alternating with one period of rest (fixation task) that lasted 20 s each. Activation conditions consisted of overtly repeating the word "mountain" (repetition task), generating words from a given category (e.g. plants, furniture, colours – semantic fluency task) and generating words beginning with a particular letter (e.g. B, F, T – phonemic fluency task). There were six fMRI blocks and the task lasted for 8 min in total. After completing the task inside the
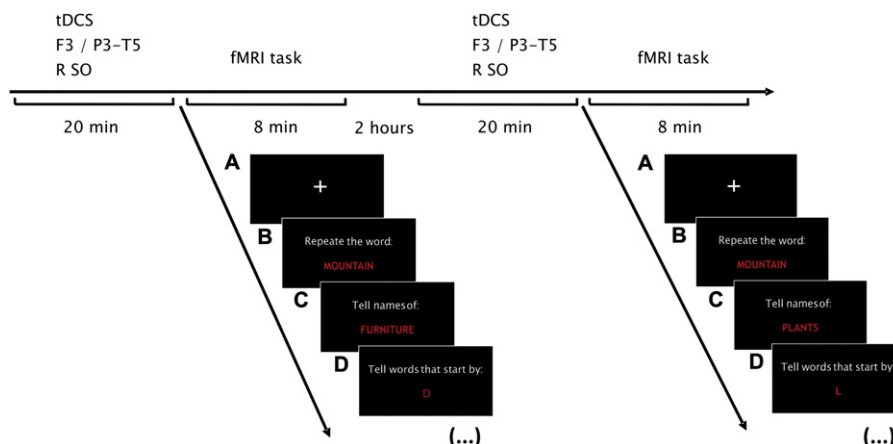
Fig. 1. *Experimental procedure.* After performing the baseline phonemic and semantic fluency tests, PD patients were randomized to receive left anodal DLPFC (F3) tDCS and left anodal TPC (P3-T5) tDCS in a counterbalanced order. The cathode electrode was placed over the right supraorbital area (R SO) in both stimulation conditions. After tDCS, patients performed an fMRI verbal fluency paradigm inside the scanner, which consisted of: A) cross fixation; B) repeat continuously the word "mountain"; C) perform a semantic fluency task; D) perform a phonemic fluency task. Each of these tasks lasted 20 s and was repeated 6 times (once per block) in the first and second fMRI session. The tDCS and fMRI lasted, respectively, 20 and 8 min each.

scanner a 2 h break was given to patients to wash-out any residual tDCS effects.

Once this break was over, patients were asked to repeat the experiment. The second tDCS and fMRI paradigm were counter-balanced with respect to the first so that all patients went through both stimulation conditions and both fMRI sessions of verbal fluency. In order to control the effects of tDCS on motor functions and mood, patients performed the Purdue Pegboard test [43] and self-evaluation visual analogue scales (VAS) assessing different mood domains (nervousness, happiness, sadness, hope or pain) after each stimulation period.

Programming of the verbal fluency paradigms was carried out using the Presentation package software (Neurobehavioral Systems, 2004). Categories and letters for the semantic and phonemic fluency tasks were selected from the Lexesp-Corco database [44] and a review on categories and their rules in the Spanish language [45]. A total of 12 categories and 12 letters were selected and matched according to their difficulty in Spanish language across both fMRI sessions.

The patient's overt responses during the fMRI task were obtained via a MRI-compatible patient response and sound system, which included a microphone attached to headphones worn by the subject during the MRI scanning. Responses were recorded on a computer using Windows Media Player software at a sampling rate of 44.1 kHz. Recordings were subsequently played back for transcription using the same program.

Behavioural statistical analysis

Statistical analyses of behavioural variables were carried out using SPSS software version 16.0 (SPSS Inc., 1989–2007). To correct verbal fluency performance by the patient's articulatory abilities and speed of speech, which have been consistently reported as being impaired in PD [46–49], semantic and phonemic fluency scores were corrected by performance on the repetition task (number of words in phonemic or semantic fluency/number of times they repeated the word "mountain"). Differences in semantic and phonemic verbal fluency performance following tDCS were tested separately by means of two repeated-measures ANOVAs with stimulation condition as the within-subjects factor (two levels; fluency performance after DLPFC and TPC tDCS) and fluency performance (two levels; phonemic and semantic fluency). In this analysis, age and baseline scores on phonemic or semantic fluency

were included as covariates in order to control for possible indi-vidual differences of verbal fluency abilities between patients. In addition, in order to potential order effects of the stimulations we performed ANOVAs with phonemic and semantic performance following tDCS as within-subjects factors and the order of the stimulations as a between-subjects factor. We also performed correlation analyses to assess the relationship between tDCS effects and relevant clinical variables, we performed correlation analyses using Pearson or Spearman coefficients when appropriate between scores of the UPDRS, the HY scale and daily dopaminergic dosis with semantic and phonemic fluency performance after DLPFC and TPC tDCS. Finally, patients were also divided in terms of clinical severity as reflected by the HY scale to assess potential differences of effects of tDCS between less advanced and more advanced disease stages. For all statistical analyses a $P < 0.05$ was established as a criterion for statistical significance.

Functional connectivity data analysis

To study functional connectivity we selected an independent component analysis (ICA) approach using multivariate exploratory linear decomposition into independent components (MELODIC) [50] as implemented in FSL (FMRIB's Software Library, www.fmrib. ox.ac.uk/fsl) [51]. ICA is a data-driven method that extracts temporally related signals hidden within sets of random and unrelated variables. It assumes that fMRI data are linear mixtures of independent source signals that represent coherent groupings of BOLD signal change, which are often referred to as component maps and thought to be functionally relevant networks. Using different modules of FSL, the following prestatistics processing was applied to the fMRI data: motion correction [52], non-brain removal [53], spatial smoothing using a Gaussian kernel of FWHM = 8 mm, mean-based intensity normalization of all volumes by the same factor and highpass temporal filtering of 160-s. After preprocessing, images were registered to MNI space using a mean EPI image generated from all subjects and registered to the T1 image [54].

The subject's time series were then temporally concatenated into a single 4D time series and separated in 63 independent components (ICs) with automatic dimensionality estimation (the number of components to extract was determined by MELODIC). One advantage of ICA is that it automatically isolates noise-related signal fluctuations such as head motion, which is especially relevant in studies using overt speech paradigms such as our own.

Table 1
Clinical and neuropsychological data of PD patients.

	PD patients ($n = 16$)
Demographic information	
Gender (M:F)	7:9
Age (years)	61.5 ± 9.9
Education (years)	12.3 ± 6.1
Clinical data	
HY stage	1.6 ± 0.5
UPDRS	13.3 ± 5.6
MMSE	27.7 ± 2.1
GDS	6 ± 3
Dopaminergic dosis (mg)	112 ± 342
Baseline fluency data	
Phonemic	17.1 ± 4.4
Semantic	22.2 ± 4.9
Neuropsychological data	
RAVLT	
Learning	47.5 ± 11.4
Delayed recall	10.6 ± 3.3
Recognition (true positives)	13.8 ± 2.1
BNT	14.4 ± 1.4
Letters & Numbers (WAIS)	9.8 ± 2.9
Vocabulary (WAIS)	45.1 ± 12.9
VFDT	27.6 ± 3.9

Means are followed by standard deviations.
Abbreviations: HY, Hoehn & Yarh scale; UPDRS, Unified Parkinson's disease rating scale; MMSE, Mini-mental state examination; GDS, Geriatric depression scale; RAVLT, Rey's auditory verbal learning test; BNT, Boston naming test; WAIS, Weschler's Adult intelligence scale; VFDT, Visual form discrimination test. Neuropsychological data are expressed as raw scores.

In the final stage of the analysis, post-hoc regression analyses were performed on estimated time courses and session/subjects modes. All final statistical components or spatially relevant maps were thresholded at $z < 2.3$. We selected the ICs showing significant differences between the effects of DLPFC and TPC tDCS in task-related patterns using a repeated-measures ANOVA and the general linear model contrasts: verbal fluency > repetition task, phonemic fluency > semantic fluency and semantic fluency > phonemic fluency. As a secondary analysis, we performed post-hoc regression analyses on estimated time courses and session/subject modes between verbal fluency performance and the spatial maps derived from MELODIC. This analysis was aimed at assessing potential causal relationships between behavioural performance and the functional connectivity networks identified in the repeated-measures ANOVA.

In addition, we also assessed differential effects between the two stimulations on the deactivation task-related pattern networks with spatial correspondence to the default-mode network by means of the contrast: fixation > verbal fluency. The component for this contrast was selected based on the best cross correlation matching score between our set of ICs and the ones from the large resting-state fMRI dataset of "1000 Functional Connectomes" Project, publicly available at http//:www.nitrc.org/projects/fcon_1000 [55].

Results

Behavioural data

Clinical and neuropsychological data of the sample are displayed on Table 1. As expected, we found that patients generated more words in the semantic task compared to the phonemic fluency task ($F_{(1,15)} = 15.660, P < 0.001$) after both stimulation conditions. Moreover, a main effect of age was found ($F_{(1,15)} = 10.217, P < 0.006$), showing that older patients performed more poorly compared to younger ones on both tasks. In order to further investigate this age effect, patients were divided into two groups according to their age.

This analysis showed that older patients only differed significantly from younger ones in semantic fluency performance and not phonemic fluency, independently of the stimulation (semantic fluency after DLPFC tDCS: t = −2.509, $P < 0.025$; semantic fluency after TPC tDCS: t = −2.958, $P < 0.01$; phonemic fluency after DLPFC tDCS: t = −1.321, $P < 0.21$; phonemic fluency after TPC tDCS: t = −0.073, $P < 0.943$).

Regarding the effects of tDCS on verbal fluency, there was a significant main effect of tDCS on phonemic fluency performance ($F_{(1,15)} = 14.079, P < 0.002$), showing that DLPFC stimulation increased the amount of words subjects produced in response to a letter, compared to TPC stimulation, after adjusting for baseline phonemic fluency performance, time of the day of stimulation and levodopa-equivalent doses (DLPFC tDCS: 47 words ± 11; TPC tDCS: 44 words ± 10). Although no significant main effects were found for semantic fluency, we observed that patients produced more words in response to a semantic category cue after DLPFC tDCS compared to TPC stimulation (DLPFC tDCS: 57 words ± 12; TPC tDCS: 55 words ± 10; $F_{(1,15)} = 3.092, P < 0.102$).

In order to confirm that the effect of DLPFC tDCS on the fluency tasks was not an indirect effect of tDCS on patients' speed of speech, we assessed the effect of the stimulations on the repetition task, during which patients had to repeat the word mountain as many times as possible. Results from this analysis showed that DLPFC tDCS did not have a significant effect on word repetition compared to TPC stimulation (DLPFC tDCS: 153.2 ± 32 words, TPC tDCS: 156.6 ± 30 words; $F_{(1,15)} = 1.686, P < 0.215$). In addition there were no significant order effects; performance on verbal fluency tasks did not differ between the first and second session of both stimulations (DLPFC tDCS: $F_{(1,15)} = 0.081, P < 0.781$; TPC tDCS: $F_{(1,15)} = 1.543, P < 0.238$). No significant differences were found between effects of left DLPFC and TPC tDCS in other controls tasks such as Purdue Pegboard test or VAS (Supplementary Table 2).

Finally, there were no significant correlations between phonemic or semantic fluency performance after DLPFC or TPC tDCS and scores on the UPDRS, HY and dopaminergic daily doses in PD patients (Supplementary Table 3). When patients were divided according to clinical severity, no differences were found in fluency performance or demographic variables such as age between groups.

Verbal fluency network analysis

We identified three ICs that were highly correlated with the task (temporally associated with the timing of the block design paradigm for the phonemic and semantic fluency conditions) and included voxels that were positively correlated with the component time course. These task-related ICs depicted significant increases induced by DLPFC tDCS in functional connectivity compared with TPC tDCS.

The first component represented a common neural network for both verbal fluency tasks (general linear model contrast: verbal fluency > repetition) and involved mainly left fronto-parietal areas as well as the fusiform and right frontal regions (Fig. 2A, Table 2). The second component depicted increases in functional connectivity during the phonemic fluency task compared to the semantic task, in a network that involved left frontal regions, the left superior parietal lobule and right insula (Fig. 2B, Table 2). Finally, the third task-related component was associated with functional coupling increases during the semantic with respect to the phonemic task condition, amongst superior temporal, lingual, right frontal and parietal areas (Fig. 2C, Table 2).

The post-hoc regression analyses revealed that phonemic fluency performance correlated positively with the component representing connectivity increases during the phonemic task with respect to the semantic task ($z = 4.31; P < 0.00001$).
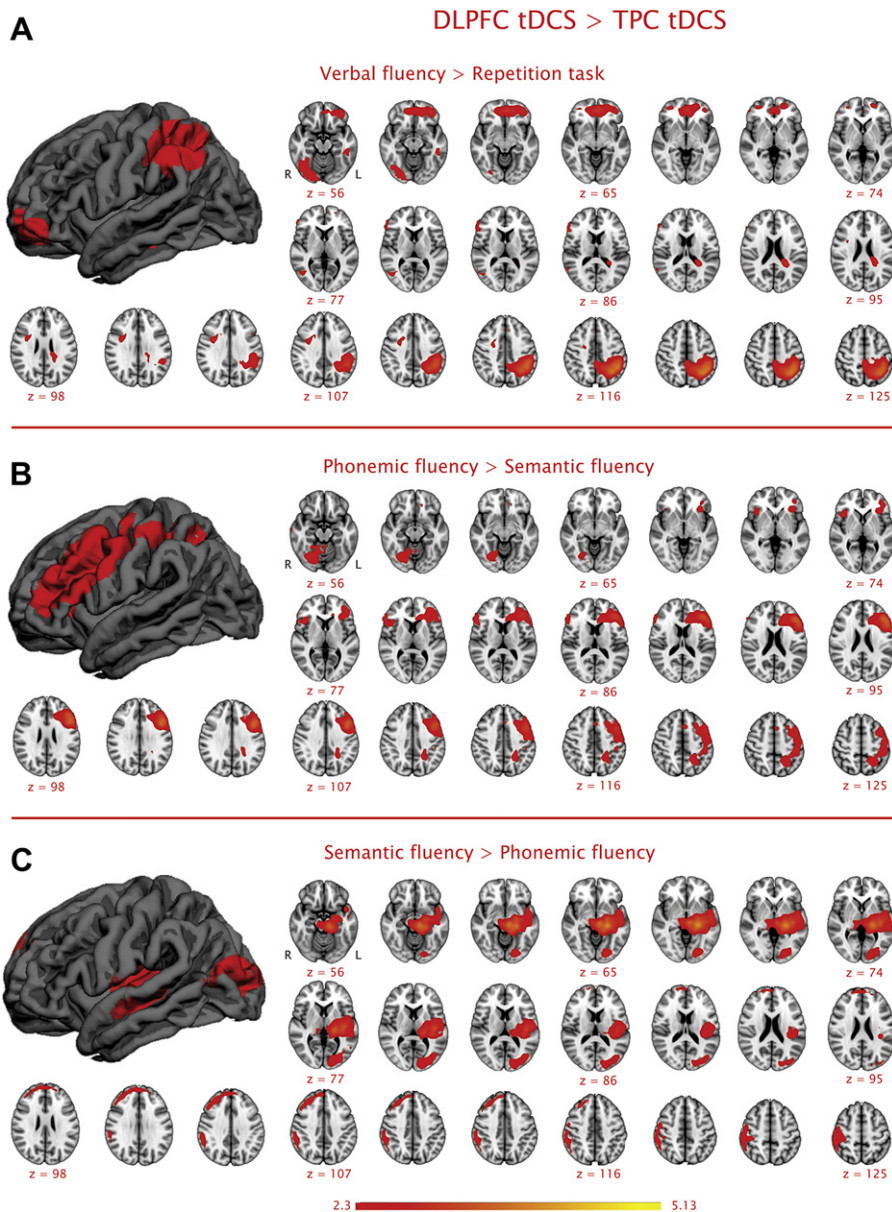
Fig. 2. Functional connectivity increases induced by DLPFC tDCS compared to TPC tDCS in: (A) verbal fluency networks compared to the repetition task, (B) phonemic fluency networks compared to semantic fluency, (C) semantic fluency networks compared to phonemic fluency.

We also observed significant increases induced by DLPFC tDCS compared to TPC tDCS in the deactivation task-related pattern network (general linear model contrast: fixation > verbal fluency). This component showed functional coupling increases between the medial frontal gyrus, posterior cingulate, bilateral parietal lobules, parahippocampus, caudate, cerebellum and inferior frontal gyrus (Fig. 3, Table 3).

No components of increased functional connectivity containing activation or deactivation task-related patterns were identified after TPC tDCS compared to DLPFC stimulation.

Discussion

The main finding of this study is that tDCS enhanced functional connectivity in verbal fluency and deactivation task-related networks significantly more when applied over DLPFC than TPC in PD. In addition, DLPFC tDCS increased performance on the phonemic fluency task. These findings provide evidence of effects of DLPFC tDCS on verbal fluency networks and suggest that this technique might be useful to enhance phonemic fluency functions in patients with PD.

It has been suggested that the effects of tDCS are site specific but not site limited, spreading trans-synaptically to distant cortical structures, depending on the strength and level of activity of brain networks [56]. In this study, we found that DLPFC tDCS increased connectivity in verbal fluency networks involving frontal, parietal and fusiform areas. These findings show agreement with previous studies describing the prefrontal cortex as a crucial area for word comprehension and production [57], and parietal regions in switching between retrieval strategies [58], all processes that are essential for verbal fluency. The fusiform gyrus has also been implicated in word form processing and recognition [59]. Therefore, DLPFC tDCS increased activity in regions that have been previously associated with verbal fluency and language tasks.

Table 2
Significant increases in task-related functional connectivity induced by DLPFC tDCS compared to TPC tDCS.

Brain areas	Cluster size (voxels)	Maximal z-score primary peak	Primary peak location (mm)
Prefrontal tDCS			
Verbal fluency > repetition			
L Inferior Parietal Lobule (BA 40)	39,608	5.1	−39 −53 48
R Fusiform (BA 37)	12,917	3.19	45 −58 −20
L Middle Frontal G (BA 10)	12,409	2.87	−6 46 −4
R Inferior Frontal G (BA 46)	296	2.86	58 34 12
R Middle Frontal G (BA 10)	214	2.3	34 54 −5
L Fusiform (BA 37)	66	2.3	−50 −41 −14
Phonemic > semantic fluency			
L Inferior Frontal G (BA 9)	42,596	5.03	−46 14 28
L Superior Parietal Lobule (BA 7)	3328	3.11	−26 −54 52
R Cerebellum	2380	3.12	26 −66 −12
R Insula (BA 13)	1009	2.81	42 18 4
R Middle Frontal G (BA 46)	470	2.67	54 34 16
L Superior Frontal G (BA 6)	107	2.61	−2 18 48
L Middle Frontal G (BA 6)	76	2.41	−26 6 64
Semantic > phonemic fluency			
L Superior Temporal G (BA 22)	56,055	5.13	−50 −8 −4
R Postcentral (BA 40)	16,786	3.85	46 −31 60
L Lingual G (BA 18)	9982	2.79	−20 −80 −4
R Superior Temporal G (BA 38)	8157	4.3	38 18 −32
R Middle Frontal G (BA 8)	5090	3.1	31 42 36
L Cerebellum	1191	3.12	−14 −74 −28
R Superior Frontal G (BA 10)	25	2.3	5 64 16
R Thalamus	19	2.37	14 −30 4

Coordinates are in MNI space atlas.

Table 3
Significant increases in the deactivation task-related pattern network induced by DLPFC tDCS compared to TPC tDCS.

Brain areas	Cluster size (voxels)	Maximal z-score primary peak	Primary peak location (mm)
Prefrontal tDCS			
Fixation > verbal fluency			
R Medial Frontal G (BA 10)	101,333	7.6	6 66 12
R Caudate	9891	4.35	6 10 0
L Parahippocampal G (BA 30)	4738	2.3	−12 −39 4
R Posterior Cingulate (BA 30)	2456	3.1	8 −49 23
R Superior Parietal Lobule (BA 7)	1935	3.0	42 −66 48
L Superior Parietal Lobule (BA 7)	1346	2.44	−43 −67 45
R Cerebellum	1007	2.79	2 −62 −36
R Inferior Frontal G (BA 47)	355	2.77	34 26 −28

Coordinates are in MNI space atlas.

In addition, under the effects of DLPFC tDCS, we found functional connectivity increases in different brain areas when phonemic fluency was compared to semantic fluency. Specifically, DLPFC tDCS increased functional connectivity in phonemic networks between bilateral frontal areas, the right insula and the left superior parietal cortex. These findings agree with previous studies associating letter fluency with frontal and superior parietal areas [8,11,60]. On the other hand, DLPFC tDCS enhanced connectivity in semantic networks between superior temporal regions, the lingual gyrus and postcentral areas. These results are consistent with studies showing that semantic fluency is more related to activation of posterior cortical areas, especially of the temporal cortex [11,12]. Hence, our findings agree with the dissociation between phonemic and semantic fluency brain areas reported previously [8,11,12,60]. Furthermore, they also agree with the concept of state-dependency, according to which the effects of stimulation depend on the current state of activation of the targeted neurons [61]. For instance, in a previous study performed with transcranial magnetic stimulation [62] it was shown that while subjects were performing an ipsilateral grip motor task, DLPFC stimulation increased brain activity in

the contralateral homologous area as well as in the contralateral primary motor area, whereas stimulation in a no-grip resting condition had the opposite effect. Hence, in the current study, the differential effects of DLPFC tDCS on phonemic and semantic fluency networks suggest that this stimulation increased functional connectivity between brain regions depending on the task that was being performed by the patients and their current state of brain activity.

Although we predicted that stimulation over TPC would increase functional connectivity in the semantic fluency network, our data did not show such effect. In fact, DLPFC tDCS proved to have a greater effect, by increasing functional connectivity in both verbal fluency networks significantly more than TPC stimulation. These results suggest that the left prefrontal cortex is likely to be crucial for both phonemic and semantic fluencies in PD more than temporo-parietal areas, in agreement with previous evidence suggesting that verbal fluency deficits in PD are mainly a consequence of frontal lobe dysfunction [16].

Besides modulating task-related networks, in this study DLPFC tDCS also increased functional connectivity between the medial frontal cortex, the posterior cingulate and lateral parietal areas in the deactivation task-related network, significantly more than TPC stimulation. This finding is consistent with previous studies assessing the effects of tDCS on the default-mode network. For instance, Keeser et al. [30] showed that DLPFC tDCS enhances activation in a network involving the medial frontal gyrus, anterior cingulate and the subgenual cortex during resting-state in healthy subjects. Using functional near-infrared spectroscopy, Merzagora et al. [31] came to similar findings showing oxihemoglobine increases in the prefrontal cortex during resting-state after anodal DLPFC tDCS. Finally, the magnitude of deactivation occurring in the default-mode network has been shown to correlate with better

DLPFC tDCS > TPC tDCS

z = 112   z = 112

2.7 ▭▬▬▬▬▬▬ 7.6
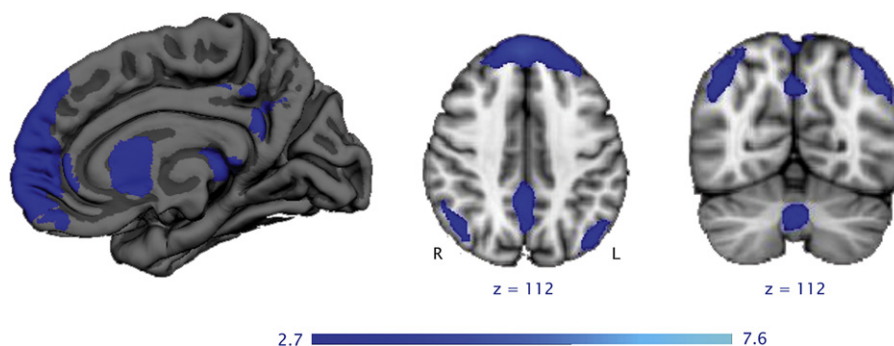
Fig. 3. Functional connectivity increases induced by DLPFC tDCS in the deactivation task-related pattern network compared to TPC tDCS.

working memory performance in healthy young subjects [63]. Recent studies in PD show that these patients present reduced task-related deactivations in the default-mode network compared to healthy controls [22–24]. Hence, our results in PD agree with previous findings in healthy subjects in that anodal tDCS increases excitability of the default-mode network and suggest that these increases might contribute to normalize brain functioning and promote better task performance in PD.

In the current study, patients generated more words in the semantic fluency task than the phonemic task independently of the type of stimulation, consistent with previous studies showing higher performance in semantic compared to phonemic fluency in the general population [64–66]. In addition, we also found a main effect of age, indicating worse fluency performance in older patients compared to younger ones. However, this effect was only statistically significant for semantic fluency. This finding is in agreement with previous studies showing an age-related decline in semantic [67,68] but not phonemic fluency [69,70]. The specific decline in semantic fluency in older adults has been associated with decreases in switching abilities due to increasing deficits in executive functions that occur during aging [71]. Additionally, previous studies have shown that older subjects benefit less from the effects of non-invasive brain stimulation compared to younger ones [72,73]. Hence, the worse semantic fluency performance observed in the present study in older patients might be related to a decline both in specific cognitive functions and tDCS effects over the course of aging.

When the effects of DLPFC tDCS were compared to the ones of TPC stimulation, we found significant increases in phonemic fluency performance, after adjusting for baseline phonemic fluency abilities. This finding agrees with previous studies showing that DLPFC tDCS enhances phonemic fluency performance in healthy subjects [74,75]. In addition, phonemic fluency scores showed a positive correlation with functional connectivity increases in phonemic networks after DLPFC tDCS. This finding indicates a causal relationship between phonemic performance and phonemic network connectivity, suggesting that the functional increases induced by DLPFC stimulation led to the improvement observed on phonemic fluency performance. Although higher scores were found in the semantic task after DLPFC tDCS, this effect did not achieve statistical significance, contrary to previous reports [75]. This discrepancy could be related to a larger variability in fluency scores in our sample compared to the samples of healthy young subjects from previous studies. It is possible that when performing tDCS in neurologically impaired and older subjects, a larger sample is needed in order to observe a statistical effect of tDCS on certain tasks.

A limiting aspect of our study is the small sample size, which could have compromised the statistical power of our findings especially in relation to semantic fluency performance after DLPFC tDCS. In addition, it would have been better to collect measures of word repetition also before the stimulations, in order to further understand the effects of tDCS on more general verbal functions. Another limitation is the lack of control of varying and controlling the active electrode positions. In addition to anodal tDCS of the left DLPFC and TPC, the right supraorbital cortex was also stimulated with cathodal tDCS. Previous studies have shown that cathodal tDCS has a relevant effect on cortical activity. For instance, Lang et al., [76] reported that cathodal stimulation increased the metabolism of the cortex underlying the stimulation electrode, although these increases were much less effective compared to anodal tDCS. More recently, Stagg et al., [22] showed that the effects of cathodal tDCS were not only restricted to the stimulated area but also increased functional connectivity between distant cortical regions. Hence the bipolar electrode positions used in the current study, although consistently used by previous tDCS studies [77], may have

resulted in effective modulation of two brain regions. Furthermore, there is also the possibility that the effects of both stimulations interacted as they were performed on the same day. In a previous study by Monte-Silva et al., [78], it was shown that when a second cathodal stimulation is performed three hours after the first stimulation, there is a prolongation of tDCS-induced excitability decreases, which can last for a period equal or inferior to two hours. Hence, it is possible, that at least part of the behavioural effects observed in the current study, might be reflecting an interaction between the two stimulations or the joint effect of both of them. In addition, it would have been ideal to perform both DLPFC and TPC stimulations at the exact same time of the day in order to assure that dopaminergic concentration was identical as much as possible. Future studies assessing the effects of two active stimulations at the same time of the day and on different days will be required in order to confirm the findings from the current study.

Although previous studies have suggested that tDCS effects on cortical activity can last for 1 h or longer when applied for 10 min [20], recent studies using neuroimaging techniques show that the influences of this stimulation on brain activity are in fact limited to 10 min [30] or 15 min at the most [31], disappearing completely once this time interval has elapsed. Taking into account the above-mentioned studies, the counterbalanced study design, and the fact that we found significant effects of DLPFC tDCS both at a behavioural and functional connectivity level compared to TPC stimulation, we do not think that performing both stimulations on the same day 2 h apart confounded our results. Finally, the fact that we did not include a sham stimulation condition in the current study makes it impossible to exclude an order effect of performance, as compared to baseline values. However, the additional analyses that were carried out showed no significant differences between the first and second sessions on verbal fluency, reducing the probability of a potential order effect in the present findings.

In summary, our study provides the first evidence of tDCS-induced changes in activity in large scale brain networks in patients with PD. Our findings extend previous evidence in healthy subjects showing connectivity increases in activation and deactivation task-related patterns after anodal stimulation of the DLPFC [30,31]. Moreover, our findings suggest that the functional connectivity increases induced by DLPFC stimulation in phonemic fluency networks led to the significant performance increases observed in this task, although future studies would be needed in order to confirm such causal relation between the observed neurobiologic and behavioural effects.

Conflict of interest

None declared.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.brs.2012.01.006.

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Assessment of Cortical Degeneration in Patients With Parkinson's Disease by Voxel-Based Morphometry, Cortical Folding, and Cortical Thickness

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Abstract: Noninvasive brain imaging methods provide useful information on cerebral involution and degenerative processes. Here we assessed cortical degeneration in 20 nondemented patients with Parkinson's disease (PD) and 20 healthy controls using three quantitative neuroanatomical approaches: voxel-based morphometry (VBM), cortical folding (BrainVisa), and cortical thickness (FreeSurfer). We examined the relationship between global and regional gray matter (GM) volumes, sulcal indices, and thickness measures derived from the previous methods as well as their association with cognitive performance, age, severity of motor symptoms, and disease stage. VBM analyses showed GM volume reductions in the left temporal gyrus in patients compared with controls. Cortical folding measures revealed significant decreases in the left frontal and right collateral sulci in patients. Finally, analysis of cortical thickness showed widespread cortical thinning in right lateral occipital, parietal and left temporal, frontal, and premotor regions. We found that, in patients, all global anatomical measures correlated with age, while GM volume and cortical thickness significantly correlated with disease stage. In controls, a significant association was found between global GM volume and cortical folding with age. Overall these results suggest that the three different methods provide complementary and related information on neurodegenerative changes occurring in PD, however, surface-based measures of cortical folding and especially cortical thickness seem to be more sensitive than VBM to identify regional GM changes associated to PD. *Hum Brain Mapp 00:000–000, 2011.*   © 2011 Wiley-Liss, Inc.

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INTRODUCTION

Magnetic resonance imaging (MRI) has been used in the study in vivo of cerebral degeneration occurring in Parkinson's disease (PD) [Whitwell and Josephs, 2007]. There are several methods based on this technique that allow the analysis of global or local volumetric degeneration of the brain. For whole brain volumetric analysis, voxel-based morphometry (VBM) studies have shown gray matter (GM) reductions in frontal, limbic, and paralimbic areas of nondemented PD patients as well as in temporal associative regions [Beyer et al., 2007; Burton et al., 2004; Nagano-Saito et al., 2005; Ramirez-Ruiz et al., 2005; Summerfield et al., 2005]. Moreover, these GM decreases have been related to cognitive impairment in these patients such as visuospatial and visuoperceptual deficits [Pereira et al., 2009].

With the development of powerful three-dimensional-based image-processing techniques, recent studies have proposed sulcal area and cortical folding, a measure that relies on gross anatomical landmarks of the cortical surface describing the burying of the cortex [Cachia et al., 2003, 2008], as new indicators of brain degeneration. Previous studies have shown that widening of cortical sulci and decreases of sulcal depth are associated with normal aging [Kochunov et al., 2005, 2008], mild cognitive impairment (MCI) [Im et al., 2008a], and Alzheimer's disease (AD) [Bastos-Leite et al., 2006; Im et al., 2008a]. Specifically, the collateral fissure and parieto-occipital sulcus suffer the most significant changes during healthy aging [Kochunov et al., 2005], while in MCI patients, these abnormalities particularly affect the frontal, temporal and parietal lobes and in AD spread through the entire cortex [Im et al., 2008a]. Measures of sulcal widening in the anterior cingulate and superior frontal sulci have been related to executive dysfunction in senescing subjects [Kochunov et al., 2009]. Sulcal indices of the cingulate and calcarine sulci have shown to correlate with deficits on verbal fluency and visuospatial tasks respectively in patients with AD [Mega et al., 1998]. In PD, only one study has analyzed sulcal morphological changes using a visually guided method to measure the depth of the olfactory sulcus and its relationship with olfactory deficits [Kim et al., 2007]. In that study no evidences of sulcal alterations were found.

Recently, the width of the cortical GM layer that covers the surface of the brain, referred to as cortical thickness, has been assessed in a variety of disorders. Most consisting findings point to cortical thinning in the lateral and medial temporal lobe of MCI patients [Seo et al., 2007] and to general cortical thinning of the frontal, temporal, parietal and occipital regions in patients with AD [Singh et al.,

2006]. Some studies have shown that cortical thickness is able to detect early stages of preclinical AD [Fennema-Notestine et al., 2009] and is a potential marker to discriminate different clinical diagnosis such as AD and frontotemporal dementia [Du et al., 2007]. Like voxel-based and sulcal morphological measures, cortical thickness has also been associated with performance in neuropsychological tests. In AD patients, cortical thinning of the perirhinal and parahippocampal cortices was related to episodic memory deficits [Dickerson et al., 2009], while in elderly subjects measures of neuroticism and extraversion correlated with prefrontal thickness [Wright et al., 2007]. To our knowledge, only one study has assessed cortical thickness in a sample of PD patients showing cortical thinning of the inferior parietal, frontal and temporal cortices compared with healthy controls [Lyoo et al., 2010].

All together, these studies indicate that GM volume, cortical folding and thickness are useful measures to assess the neuroanatomical patterns associated with aging, neurodegerative diseases such as AD, and very possibly PD. According to neuropathological studies of PD [Braak and Braak, 2000; Braak et al., 2003, 2004], in the earliest disease stages neural degeneration occurs in motor nuclei and limbic areas that propagate to the inferior temporal and paralimbic cortex and further reach associative areas like the prefrontal lobes. At this stage, patients become symptomatic, expressing the typical features of PD. Taking into consideration these studies, we hypothesized that nondemented patients with PD would present GM volume decreases in limbic, temporal, paralimbic, and prefrontal areas of the cortex. Similarly, significant reductions of sulcal indices and cortical thickness within the previous areas were expected, showing a regional correspondence of pathological alterations between volume-based and surface-based measures.

METHODS

Participants

Twenty patients with PD and 20 normal controls were included. This sample was selected from a pool of subjects recruited in an outpatient Movement Disorders Clinic (Parkinson's Disease and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona, Spain) during a 6-month period. Only subjects with MRI scans that could be preprocessed and analyzed using the three methods employed in this study (VBM, cortical folding, and cortical thickness) were included. In line with this, 12 subjects had to be excluded due to masking,

segmentation or sulcus labeling errors during the cortical folding image analysis (see Cortical Folding section).

For PD patients the following inclusion criteria were set: diagnosis of idiopathic PD according to the UK Parkinson's disease Society Brain Bank criteria [Daniel and Lees, 1993], namely bradykinesia and at least one of the three cardinal signs (resting tremor, muscular rigidity, postural instability); a good initial response to L-dopa or dopamine agonists; unilateral onset; persistent asymmetry affecting mostly the side of onset; lack of evidence of other medical conditions associated with atypical parkinsonism (i.e. progressive supranuclear palsy or multiple-system atrophy); lack of diagnostic criteria for dementia associated with Parkinson's disease [Emre et al., 2007]; and absence of clinical depression.

The exclusion criteria for the patient group consisted of: other brain disorders apart from PD; parkinsonism due to antipsychotics or other drugs; suspected dementia with Lewy bodies (signs of cognitive impairment during the first year, transient loss of consciousness, neuroleptic sensitivity); delirium; confusion; amnestic disorder; neuropsychiatric diseases; severe vascular risk factors (heart failure, hypertension, or diabetes); vascular lesions; and past traumatic brain injury on MRI. Written informed consent was obtained from patients and controls after full explanation of the procedures. This investigation was approved by the ethics committee of Hospital Clinic, Barcelona.

Patients were clinically assessed by the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS) [Fahn and Elton, 1987] and the Hoehn and Yahr scale [1967]. They were further screened for dementia and depression using the mini-mental state examination (MMSE) [Folstein et al., 1975] and the Beck's Depression Inventory (BDI) [Beck et al., 1996], respectively. Five patients from our sample had visual hallucinations.

Demographic information including age and gender was collected from the entire sample. Furthermore, all participants underwent a neuropsychological test battery that comprised: Semantic and Phonemic Fluency tests, the Rey's Auditory Verbal Learning Test (RAVLT), the Stroop test and the forward and backward Digits subtests from WAIS-III. The procedures for neuropsychological assessment are described in Lezak et al. [2004]. PD patients were evaluated on the clinical and neuropsychological tests while on medication. Antiparkinsonian treatments were recorded and the total daily equivalent dose of levodopa was calculated for each patient. All subjects underwent neuropsychological testing in first place and MRI scanning in the same week.

Image Acquisition

Anatomical MRI scans were obtained on a 3.0T Magnetom Trio Tim Siemens (Erlangen, Germany) at the Center of Imaging Diagnosis Clinic (CDIC) of Hospital Clinic, Barcelona. MRI parameters of the three-dimensional MPRAGE Saggital ISO sequence were as follows: repetition time (TR) = 2300 ms; echo time (TE) = 2.98/3.01 ms; inversion time (TI) = 900 ms; 1 mm thickness; field of view (FOV) = 24 × 24 mm; 256 × 256 matrix. Inspection of anatomical abnormalities on MRI scans was carried out by an expert neuroradiologist (N.B.).

Brain Structural Analyses

Voxel-based morphometry

Image preprocessing was conducted using the VBM8 toolbox (available at: http://dbm.neuro.uni-jena.de/vbm) implemented in SPM8 (available at: http://www.fil.ion.ucl.ac.uk/spm/). In brief, images were classified into GM, white matter (WM) and cerebrospinal fluid (CSF) [Ashburner and Friston, 2005; Cuadra et al., 2005; Rajapaske et al., 1997; Tohka et al., 2004], the tissue classified GM maps were applied a high-dimensional DARTEL normalization [Ashburner et al., 2007] modulating for nonlinear effects only and finally smoothed using a Gaussian smoothing kernel of 12-mm full width at half-maximum. The resulting final voxel size was 1.5 mm^3.

At the second statistical level, smoothed GM images were compared between PD patients and controls using a two-sample t test, in which age and gender were included as nuisance variables. Because normalization of nonlinear effects only had been applied during VBM8 preprocessing, which corrects for differences in GM, WM, and intracranial volumes (ITV) [Buckner et al., 2004], there was no further need to control for these variables in the statistical model. Additionally, an absolute threshold mask of 0.1 was used. The final results were corrected for multiple comparisons using a family wise error (FWE) rate correction set at $P < 0.05$. The MNI coordinates of significant clusters were converted into Talairach coordinates using an automated nonlinear match method that adjusts for differences between the two atlases (available at: http://imaging.mrc-cbu.cam.ac.uk/). The Marsbar toolbox [Brett et al., 2002] was used to extract the mean GM values from significant clusters. Differences between groups in local volume reductions identified in patients compared with controls were further assessed using analyses of variance (ANOVA), with age, gender and ITV as covariates.

Description of VBM methods, statistical analyses and results were performed following the rules for reporting VBM studies by Ridgway et al. [2008].

Cortical folding

We removed 12 MRI scans (23%) from this study, seven of which belonged to patients with PD and five to healthy controls due to failure in computing a brain mask for each hemisphere (three), segmentation problems (two), errors in computation of cortical fold graphs (three), and sulcal labeling errors (four). The final MRI images from 20 patients and 20 controls were imported into the BrainVisa database (available at: http://brainvisa.info/) [Mangin

et al., 2004]. Briefly, image preprocessing included: registration to the Talairach frame; inhomogeneity bias correction [Mangin, 2000]; segmentation into GM, WM, and CSF [Mangin et al., 2004]; extraction and labeling of brain sulci [Mangin et al., 1995; Riviere et al., 2002]; and calculating global and local sulcal indices [Cachia et al., 2008; Penttila et al., 2009]. Global sulcal index was estimated for each hemisphere as the percentage ratio between total sulcal area and the outer cortex area, while local sulcal indices were calculated as the percentage ratio between the area of a labeled sulcus and the outer cortical area. For local sulcal measurements, we selected six sulci based on our study's hypothesis that PD patients would present GM reductions in temporal, limbic, paralimbic, and prefrontal areas: the inferior temporal sulcus, the collateral fissure, the occipitotemporal sulcus, the anterior cingulate sulcus, the anterior sylvian fissure, and the superior frontal sulcus (see Fig. 1). Differences in global and local sulcal indices from the selected sulci were assessed separately using multivariate ANOVA with sulcal measures as intrasubjects factors, group (PD patients, controls) as an intersubject factor and age, gender, and brain volume as covariates. The choice of including brain volume as a covariate was based on a previous report by Toro et al. [2008], in which a strong relationship was found between cortical surface area and brain volume and so we wanted to control for the confounding effects of this variable. In order to correct for multiple comparisons, a significance level of $P < 0.004$ (0.05/12 sulci) was applied to the previous analyses.

Cortical thickness

Measurements of cortical thickness were performed using the FreeSurfer software package (version 4.3.1, available at: http://surfer.nmr.harvard.edu), [Fischl and Dale, 2000; Fischl et al., 1999b]. The implemented processing stream involved: removal of nonbrain tissue; transformation to the Talairach reference space; segmentation into GM and WM [Dale et al., 1999]; correction of topological defects [Fischl et al., 2001]; intensity normalization [Dale et al., 1999]; and subvoxel representation of the GM/WM boundary and pial surfaces [Dale et al., 1999; Fischl et al., 1999a]. Cortical thickness was calculated as the shortest distance between the previous surfaces at each vertex across the cortical mantle. Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a FWHM of 15 mm and averaged across subjects. Moreover, estimated total intracranial volume (eTIV) was calculated from the Freesurfer processing stream. To assess cortical thickness differences between the two groups at each vertex of the surface we performed a general linear model controlling for the effects of age, gender, and intracranial volume. In order to correct for multiple comparisons, Monte Carlo simulations were performed to identify significant vertex-wise group cluster differences. Furthermore, in order to quantify brain alterations, regional cortical thickness values were extracted from significant clusters of the previous analysis for each subject and between group differences were assessed by means of ANOVA with age, gender and ITV as covariates.

Regional WM volumes

Using FreeSurfer (available at: http://surfer.nmr.harvard.edu), additional measurements were performed to assess the potential role of regional WM volumes underlying GM volumes, brain sulci and cortical thickness changes occurring in PD. Following the software's processing stream, after topological corrections, the cortical surface was parcellated according to procedures described by Fischl et al. [2004]. Each vertex was assigned a neuroanatomical label based on: (a) the probability of each label at each location in a surface-based atlas, based on a manually parcellated training set; (b) local curvature information; and (c) contextual information, encoding spatial neighborhood relationships between labels. Using this automated labeling system [Desikan et al., 2006; Fischl et al., 2004] the cortical surface was divided in 33 gyral-based areas in each hemisphere, which were manually inspected for accuracy. By means of a recently developed algorithm [Fjell et al., 2008; Salat et al., 2009] the WM volume in the gyri underneath each cortical label was calculated. Based on our study's hypotheses, the following WM labels were included for analysis: medial frontal, superior frontal, superior temporal, inferior temporal and insula. Differences in WM volume between patients and controls were assessed using ANOVA with volumes as intrasubjects factors, group (PD patients, controls) as an intersubject factor and age, gender, and ITV as covariates.

Statistical Analyses

To assess the relationship between whole brain indices derived from each method we performed correlation analyses using whole-brain GM volumes (VBM), global sulcal index and average cortical thickness in the following groups separately: whole sample, controls, and PD patients.

Correlation analyses were also carried out to examine the association between the previous global indices and stage of the disease, severity of motor symptoms, global cognitive performance, and age in the three groups, when appropriate. Severity of motor symptoms was indexed by the motor section (part III) of the UPDRS and the patient's disease stage was assessed by the HY rating scale. According to these scales, higher scores represent greater motor deficits and more advanced disease stage, respectively. Regarding cognitive performance, scores from all neuropsychological tests were subjected to a factor analysis to produce noncollinear estimates of global cognitive performance.

Additional analyses were performed to assess the correlation between regional changes detected by the three methods in each brain hemisphere, their relationship with demographic and clinical variables and the role of WM reductions in local GM, sulcal, and thickness changes in
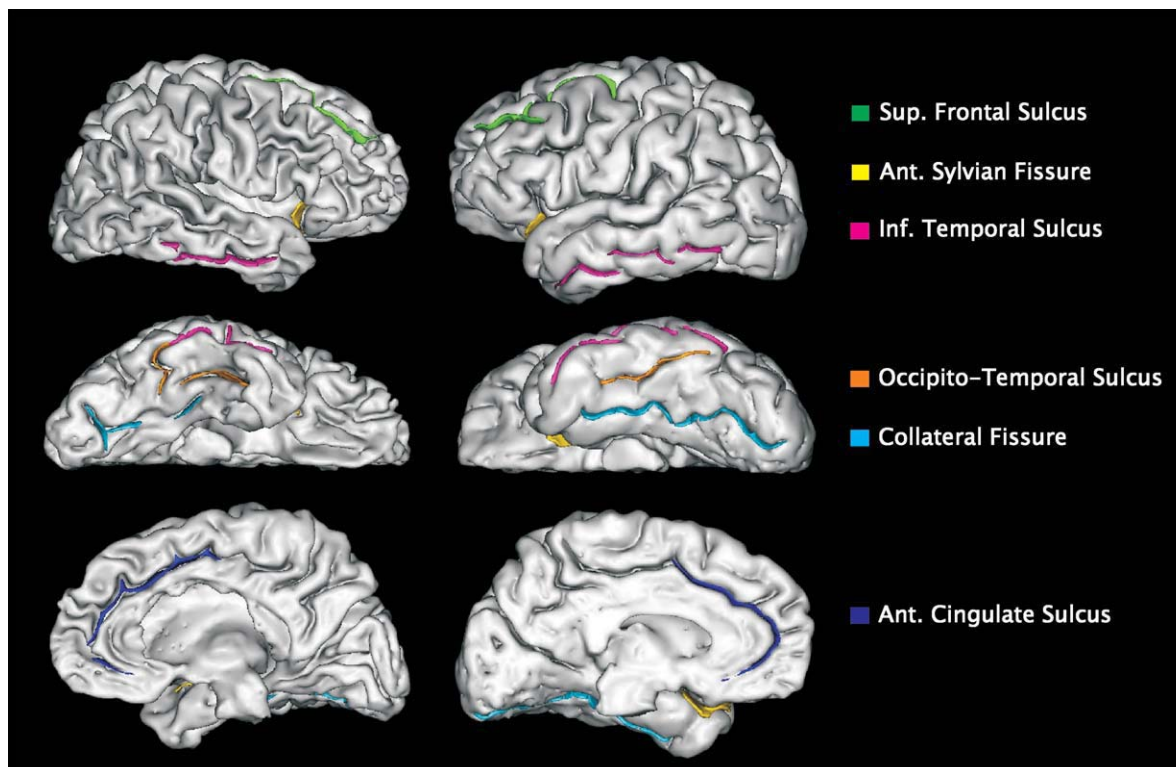
Figure 1.
Sulcal structures selected for measuring local cortical folding: the superior frontal sulcus, anterior sylvian fissure, inferior temporal sulcus, occipitotemporal sulcus, collateral fissure, and anterior cingulate sulcus. On the left: outer cortical surface of a PD patient. On the right: outer cortical surface of a control subject.
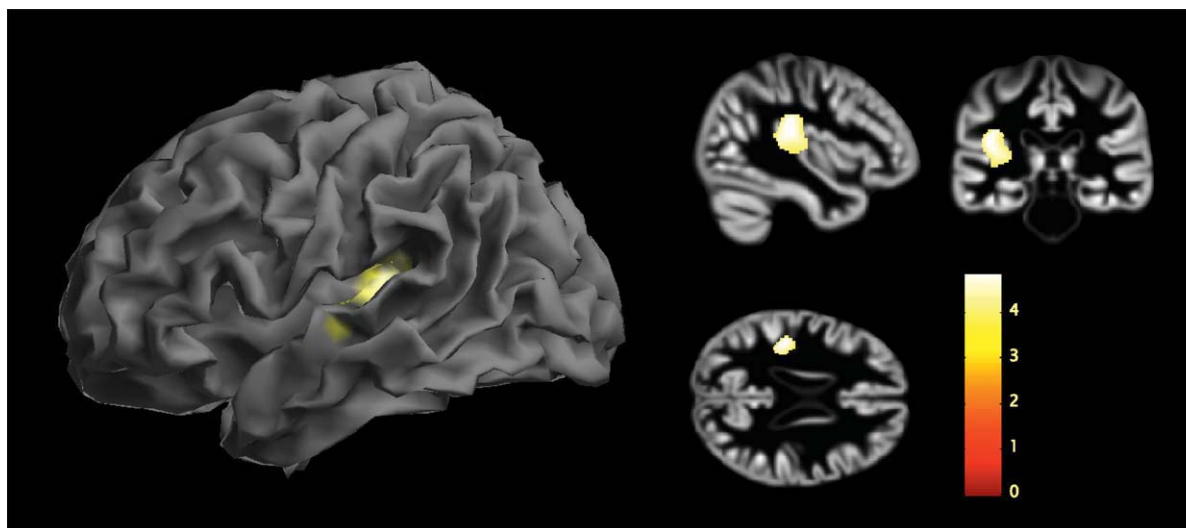
Figure 2.
Group VBM differences. Results from the analysis of VBM8 showing gray matter volume reductions in PD patients compared with healthy elderly controls are displayed in the form of statistical maps superimposed on the surface of a standardized brain and on the sample's template created during Dartel normalization with peak intensity located at the global maxima.

TABLE I. Clinical and neuropsychological data of the sample

	PD patients	Controls	x^2/t	P
Subjects	20	20	—	—
Gender (male/female)	13/7	14/6	0.11	0.739
Mean age (yr)	64 (9.53)	59.1 (10.9)	−1.52	0.136
MMSE score	28.5 (1.9)	29.8 (0.7)	2.90	0.008
HY stage	2.4 (0.9)	—	—	—
UPDRS III	24.9 (15.5)	—	—	—
Duration of disease (yr)	6.8 (5.8)	—	—	—
Dopaminergic dosis (mg)	627 (487.7)	—	—	—
Semantic fluency	15 (6.7)	20.4 (5.3)	2.80	0.008
Phonemic fluency	11.9 (6.1)	18.1 (5.8)	3.30	0.002
Rey's auditory verbal learning test				
Learning score	34.3 (11.7)	48.4 (10)	4.10	0.0002
Delayed recall score	6.7 (3.8)	10.3 (1.9)	3.73	0.001
Recognition score	17 (10.6)	25.8 (6.3)	3.18	0.003
STROOP				
Word reading	79.9 (31.7)	107.6 (17)	3.36	0.002
Colour naming	48.7 (18.1)	69 (12.4)	4.03	0.0003
Words + colours	24.8 (10.5)	41.3 (9.8)	5.04	0.00001
Interference score	−5.5 (8.5)	0.4 (7.8)	2.24	0.032
Digits				
Forward	7.5 (1.5)	8.7 (1.6)	2.40	0.022
Backward	4.2 (1.9)	6.9 (1.8)	4.53	0.00007

Values are given in means followed by (standard deviations).
MMSE score, mini-mental state examination score; HY stage, Hoehn and Yahr stage; UPDRS III, unified Parkinson's disease rating scale III (motor subscale).

controls and PD patients. Correlations in the whole sample were also carried out and have been included as Supporting Information.

For correlation analyses associated with disease stage as indexed by the HY rating scale, which is an ordinal variable, Spearman correlations were used while the rest of correlation analyses were based on Pearson coefficients. Moreover, in order to compare correlation coefficients from the previous analyses between controls and PD patients we applied Fisher's Z transformation and the difference between coefficients was computed following: $z = (Z_{r1} - Z_{r2})/\sqrt{(1/(20 - 3) + 1(20 - 3))}$.

Importantly, all the analyses performed in the PD patient's group included age and gender as nuisance variables or covariates in order to exclude their potential confounding effects from disease-related processes.

A Bonferroni-adjusted significance level of $P < 0.001$ was applied in order to correct for multiple comparisons. Statistical analyses were carried out using SPSS 16.0 (SPSS for Windows, Version 16.0.1, 2008, SPSS Inc., 1989–2007).

RESULTS

Clinical and neuropsychological data of the whole sample are presented and were analyzed as raw scores (Table I). There were no significant differences in age or gender between groups. PD patients had a lower MMSE score than controls, although none scored less than 26. Furthermore, they performed significantly worse than controls in all neuropsychological tests.

TABLE II. Significant gray matter volume reductions in PD patients compared with controls

Brain region (Brodmann area)	Cluster size (mm3)	Coordinates			PD patients, mean (SD)	Controls, mean (SD)	Main effect, F (P value)	t
		x	y	z				
L superior temporal gyrus (BA 41)	1,752	−34.7	−34.5	10	0.36 (0.04)	0.44 (0.04)	27.397 (<0.001)	4.28
		−50.5	−17.6	−1.6				4.27

The reported cluster is corrected at $P < 0.05$ FWE. The coordinates x, y, and z refer to the anatomical location, indicating standard stereotactic space as defined by Talairach and Tournoux [1988].
L, left.
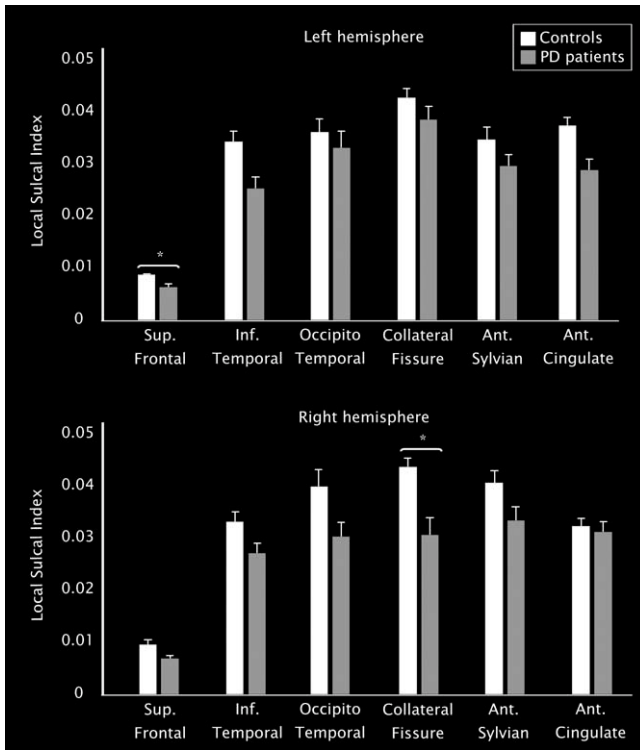
Figure 3.

Graphic presenting data distribution with average means and standard errors of local sulcal indices of PD patients and controls. (*) Indicates significant results after correction for multiple comparisons.

Regional VBM Differences

For the VBM analyses, PD patients showed significant GM volume reductions in the left superior temporal gyrus (BA 41) while controlling for age and gender effects (Fig. 2, Table II). No GM decreases were observed in controls compared with PD patients.

Regional Cortical Folding Differences

Concerning sulcal indices, ANOVA analyses showed significant local reductions in the left superior frontal sulcus (left: $F_{(1,39)} = 9.493$, $P < 0.004$) and the right collateral fissure ($F_{(1,39)} = 10.399$, $P < 0.003$) in patients compared with controls, controlling for multiple comparisons (Fig. 3, Table III). No significant differences were found for the other brain sulci or global sulcal indices.

Regional Cortical Thickness Differences

PD patients showed significant cortical thinning in the left lateral occipital cortex (maxima) that extended to inferior and superior parietal areas, with respect to controls. In addition, significant cortical thinning was also found in the right hemisphere, concretely in the inferior parietal cortex, extending into various regions of the lateral occipital, supramarginal, inferior, middle, and superior temporal cortex. Finally, cortical thinning was also observed in the right frontal cortex, comprising the pars opercularis, triangularis, precentral, and postcentral areas in PD patients

TABLE III. Results from the ANOVA analysis of global and local sulcal indices differences between PD patients and controls

	PD patients, mean (SD)	Controls, mean (SD)	Main effect, F (P value)
Left hemisphere			
Global sulcal index	1.29 (0.2)	1.39 (0.1)	1.571 (0.219)
Local sulcal indices			
Sup. frontal sulcus	0.006 (0.003)	0.009 (0.001)	9.493 (0.004)[a]
Inf. ant. temporal sulcus	0.025 (0.01)	0.034 (0.01)	6.763 (0.013)
Collateral fissure	0.033 (0.01)	0.043 (0.01)	2.187 (0.148)
Ant. cingulate sulcus	0.029 (0.01)	0.038 (0.01)	7.756 (0.008)
Ant. sylvian fissure	0.029 (0.008)	0.035 (0.008)	2.557 (0.119)
Occipitotemporal sulcus	0.033 (0.01)	0.035 (0.01)	0.116 (0.735)
Right hemisphere			
Global sulcal index	1.25 (0.2)	1.36 (0.1)	0.763 (0.389)
Local sulcal indices			
Sup. frontal sulcus	0.006 (0.002)	0.009 (0.004)	4.910 (0.033)
Inf. ant. temporal sulcus	0.027 (0.01)	0.033 (0.01)	5.147 (0.029)
Collateral fissure	0.031 (0.01)	0.044 (0.01)	10.399 (0.003)[a]
Ant. cingulate sulcus	0.031 (0.01)	0.032 (0.01)	0.021 (0.885)
Ant. sylvian fissure	0.032 (0.01)	0.04 (0.01)	3.272 (0.079)
Occipitotemporal sulcus	0.029 (0.01)	0.037 (0.01)	3.667 (0.063)

Ant., anterior; Sup., superior; Inf., inferior.
[a]Corrected for multiple comparisons.
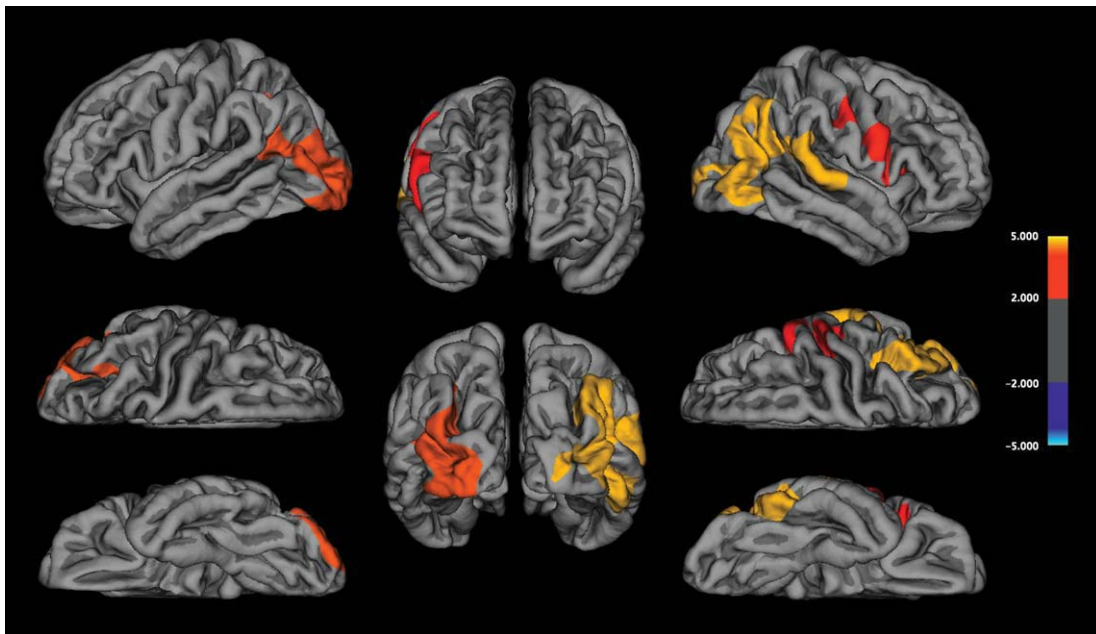
Figure 4.
Group cortical thickness differences. Results from the analysis of cortical thickness showing cortical thinning in PD patients compared with healthy elderly controls are displayed at each vertex of the surface of a standardized brain (averaged over all subjects) in terms of t statistical maps.
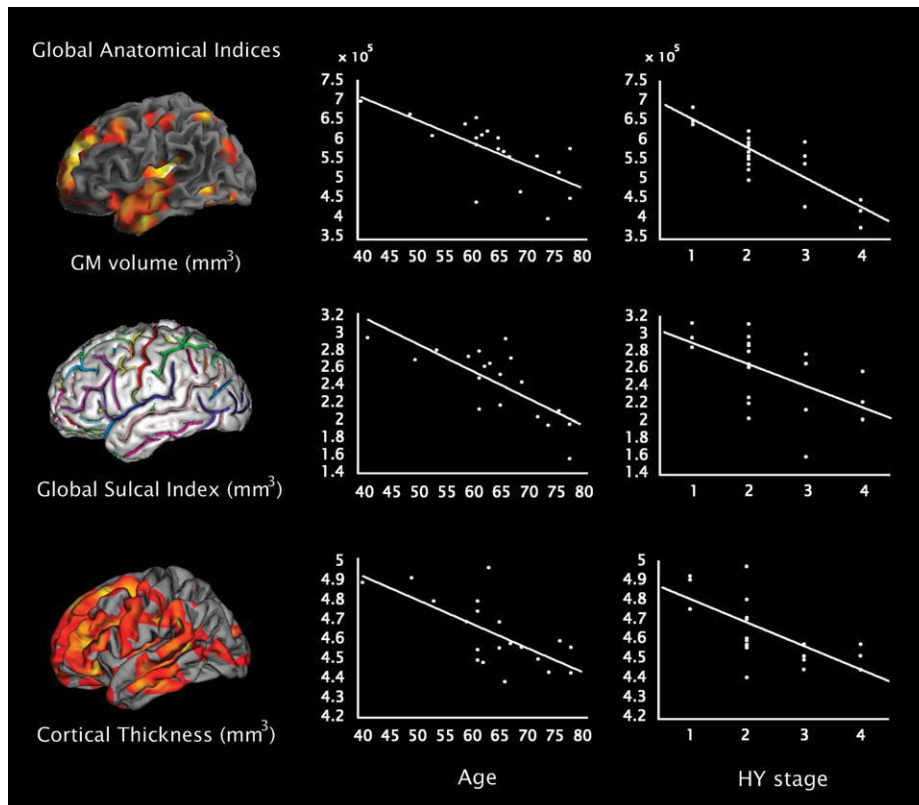
Figure 5.
Correlations between whole-brain GM volume, global sulcal index and average cortical thickness plotted versus patient's age and disease stage as indexed by the Hoehn & Yahr scale. Correlations with Hoehn & Yahr stage have not been corrected for age and gender effects only for picture purposes; the corrected values can be found in the text. All correlations were statistically significant except the one between cortical folding and Hoehn & Yahr stage.

TABLE IV. Significant clusters for the left and right hemispheres, mean cortical thickness, and *P* values from the Monte Carlo simulation resulting from the vertex-wise comparison of cortical thickness between PD patients and controls

Cortical area	Cluster size (mm^2)	Coordinates			PD patients, mean (SD)	Controls, mean (SD)	Main effect, F (P value)	CWP
		x	y	z				
Left hemisphere								
Lateral occipital	4,136.89	−24.7	−92.9	4.5	2.23 (0.13)	2.42 (0.08)	28.892 (<0.001)	0.0027
Right hemisphere								
Inferior parietal	6,513.06	45.8	−53.2	21.5	2.42 (0.14)	2.61 (0.11)	18.880 (<0.001)	0.0001
Frontal pars opercularis	2,306.74	40	17.7	7.9	2.14 (0.15)	2.29 (0.1)	9.298 (0.004)	0.0153

The reported clusters have been corrected for multiple comparisons. The coordinates x, y, and z refer to the anatomical location, indicating standard stereotactic space as defined by Talairach and Tournoux [1988].
CWP: Cluster-wise P value. P value: significant between group differences.

(Fig. 4, Table IV). No cortical thickness reductions were found in controls compared with patients.

Regional WM Volume Differences

No statistically significant differences were found between PD patients and controls in regional or global WM volumes (Supporting Information, Table I).

Correlations Between Global Cerebral Indices

Analyses performed separately in controls and PD patients did not show any significant correlations between global anatomical indices in these groups. In healthy controls, GM volumes and global sulcal index significantly correlated with age ($r = -0.714$, $P < 0.001$; $r = -0.708$, $P < 0.001$, respectively). On the other hand, in PD patients, GM volumes and cortical thickness correlated with disease stage ($r = -0.684$, $P < 0.001$; $r = -0.627$, $P < 0.001$) (Fig. 5), while controlling for age and gender effects. Moreover, correlations with age were also assessed in patients and, as opposed to controls, were found to be significant for all global indices in the following order: brain sulci ($r = -0.752$, $P < 0.001$), GM volumes ($r = -0.692$, $P < 0.001$) and cortical thickness ($r = -0.680$, $P < 0.001$) (Fig. 5). Differences in correlation coefficients between controls and PD patients were not significant for the correlation between age and GM volume ($P < 0.899$) or between age and brain sulci ($P < 0.783$). No significant correlations were found between global indices and cognitive performance or severity of motor symptoms. Correlations in the whole sample have been included as Supporting Information.

Correlations Between Regional Cerebral Indices

No significant correlations were found between local changes in GM volume, brain sulci, and thickness in PD patients or controls. Concerning the relationship between local changes and demographic/clinical variables, only the patient's age was found to correlate with reductions of the left collateral fissure ($r = -0.741$, $P < 0.001$).

We also performed additional analyses to assess the potential influence of regional WM reductions in local changes of GM volume, sulci, and mean thickness. We observed significant correlations in PD patients between the left anterior cingulate sulcus and right medial frontal ($r = 0.754$, $P < 0.001$), as well as right superior frontal WM regions ($r = 0.719$, $P < 0.001$) while controlling for age and gender effects.

No significant correlations were found between any local measures in the control's group. Correlations between regional anatomical measures in the whole sample are provided as Supporting Information.

DISCUSSION

In this study we compared voxel-based morphometry, cortical folding and cortical thickness in order to determine specific measures contributing to brain degeneration in patients with PD. Our findings suggest that these three different methods detect alterations of the GM layer in PD patients compared with healthy controls and furthermore correlate with disease stage and age, providing both complementary and related information.

To our knowledge, this is the first study to analyze patterns of regional neuroanatomical changes in PD using three widely used technical approaches. Studies using VBM have identified GM reductions in the superior temporal gyrus in nondemented PD patients [Beyer et al., 2006; Ramirez-Ruiz et al., 2007; Summerfield et al., 2005]. Our results are in accordance with these studies in that GM decreases of superior temporal areas were found as well in our sample. Moreover, compared with previous VBM studies, which have mainly used uncorrected levels of statistical significance, our study has the advantage of

including a Family Wise Error (FWE) rate correction to control for multiple comparisons, reducing the rate of false positives and thus providing true information on the comparisons that were tested.

Analyses of cortical folding showed that, in this study, PD patients presented lower sulcal indices in the left superior frontal and right collateral fissure compared with controls. To date, the only study assessing sulcal morphology in PD used a visually guided method to measure the depth of the olfactory sulcus, failing to find significant differences between patients and controls or a correlation between olfactory deficits and sulcal depth [Kim et al., 2007]. Our study has the advantage of using a method with robust computer-based identification algorithms that allows for a precise automatic labeling of brain sulci and avoiding biases introduced by visual identification methods. Moreover, it has been previously suggested that cortical complexity is more related to cortical folding and convolutions of sulcal shape than sulcal depth [Im et al., 2006, 2008b].

Concerning cortical thickness, our study showed that PD patients presented significant cortical thinning in lateral occipital and inferior parietal regions of the right hemisphere as well as left parietal, occipital, frontal, temporal and premotor areas. To our knowledge, only one study has assessed cortical thickness in PD [Lyoo et al., 2010] showing thinning of inferior parietal, latero-occipital, middle temporal, supramarginal, and frontal regions like we found in our study, but also in fusiform and lingual areas. However, the authors from the previous study considered cortical areas with an uncorrected significance level, while in our study Monte Carlo simulations were performed to control for multiple comparisons, which are far more restrictive. Hence, the differences in the results from both studies are most likely related to the applied statistical corrections.

When comparing regional cortical changes identified by the different methods, analyses of VBM seemed to be the most conservative, followed by cortical folding and cortical thickness. These differences between methods could be related to several issues. For instance, cortical folding and thickness are fundamentally surface-based methods measuring differences in the GM layer based on cortical surface geometry. On the contrary, VBM performs whole-brain voxel-based comparisons of the local GM between groups of subjects [Ashburner and Friston, 2000, 2001]. Previous studies combining VBM with cortical thickness show that these techniques tend to lead to different findings. For instance, in a study performed in adults with autism, Hyde et al. [2010] found cortical thickness increases in several bilateral areas of frontal, temporal, parietal and occipital lobes compared with controls. However, when VBM analyses were performed in the same data set, GM increases were only identified in the midbrain and frontal gyrus. In another study with autistic subjects, Jiao et al. [2010] constructed diagnostic models based on cortical thickness and compared them with diagnostic models rely-

ing on volumetric neurodegeneration. The authors from this study found that, similarly to our study, thickness-based diagnostic models were superior to those based on VBM, achieving the best classification performance between autistic subjects and controls. Finally, it has been reported that cortical thickness methods detect more changes in the GM layer in normal aging compared with VBM [Hutton et al., 2009]. This difference in sensitivity between these two techniques has been related to limitations of cortical GM assessment by VBM in that it merges information about morphology, size, and position [Ashburner and Friston, 2001] and the final measures include a mixture of thickness and cortical folding [Park et al., 2009; Voets et al., 2008], being therefore less specific. Moreover, VBM analyses are particularly sensitive to misregistration errors across different brains and incorrect classification of tissue classes during the segmentation process, which can be misinterpreted as cortical folding or thickness reductions, ultimately providing essentially false results [Ashburner, 2009]. By contrast, cortical thickness provides a more direct index of cortical morphology that is less susceptible to positional variance given that the extraction of the cortex follows the GM surface despite local variations in its position [Kim et al., 2005; MacDonald et al., 2001]. This method differentiates between cortices of opposing sulcal walls within the same sulcal bed, enabling more precise measurement in deep sulci [Lerch and Evans, 2005]. Moreover, one of the main advantages of cortical thickness measures is that they allow for subvoxel precision because thickness values are assigned to individual vertices instead of voxels [Fischl and Dale, 2000]. Finally, an additional issue that could be related to the differences in our results is that these different techniques require different levels of smoothing to increase the validity of the final statistical results. For instance, in VBM analyses a 12-mm smoothing kernel was selected as it has been described as the ideal compromise to improve the validity of statistical inferences, reduce interindividual variation and to obtain good spatial resolution in VBM [Salmond et al., 2002]. On the contrary, cortical folding analyses with BrainVisa do not apply smoothing during image preprocessing [Cachia et al., 2008; Kochunov et al., 2005, 2008, 2009; Liu et al., 2010; Pentilla et al., 2009]. Finally, in cortical thickness analysis, FreeSurfer calculates the level of smoothing that must be applied during the Monte Carlo simulation, which is necessary in order to correct for multiple comparisons and in the case of this study was 15 mm.

What are our results reflecting with respect to PD? Our study's hypotheses were based on the well-established staging of brain pathology by Braak et al. [2000, 2003, 2004], according to which PD patients become symptomatic in the last disease stages 4, 5, and 6. Briefly, in stage 4, neural damage occurs in temporal and paralimbic cortices while in stage 5 the lesions extend to the superior temporal gyrus, parietal cortex, and prefrontal areas. Finally, in stage 6, cortical pathology spreads into first order

association areas, premotor fields and even, occasionally, to primary sensory and motor regions. Patients that participated in this study were all in the symptomatic stages of PD, however, our main question regarded in which of the previously described stages they could be placed. On one hand, VBM results showed GM reductions in superior temporal areas, which is fairly consistent with pathological changes occurring in stage 5. Analyses of cortical folding revealed sulcal decreases in medial inferior temporal and frontal regions, which are usually affected during stages 4 and 5. Finally, cortical thickness analyses showed thinning of regions consistent with stages 4 and 5 and furthermore, first order areas and premotor fields, which are only compromised in the last stage of brain pathology of the disease. Overall, these findings seem to suggest that cortical thickness might be more sensitive to pathological damage occurring in PD compared with cortical folding and finally VBM. This result is interesting and shows agreement with previous reports of cortical thickness in AD in that cortical thinning mirrors pathological changes identified with histology [Lerch et al., 2005; Singh et al., 2006; Seo et al., 2007]. For instance, in a study by Lerch et al. [2005], AD patients presented greater thinning in the medial temporal lobes as well as the posterior cingulate region, parietal and orbitofrontal cortex, showing agreement with progression of senile plaques and neurofibrillary tangles according to Braak's staging for AD [Braak et al., 1991, 1996]. Cortical thickness is related to neuronal structural complexity features such as neuronal size, presynaptic terminals, and complexity of dendritic arborizations. In postmortem studies, frontal and temporal neocortical regions show evidence of cortical thinning with increasing age in the absence of neuronal number or density loss [Freeman et al., 2008]. Hence, changes in cortical thickness could be occurring much before than neuronal death takes place, indicating preclinical stages of a disease as suggested by Fennema-Notestine et al. [2009]. In line with this, and similarly to our study, the only previous study assessing cortical thickness in PD [Lyoo et al., 2010] also showed cortical thinning consistent with later stages of brain pathology in these patients, suggesting that cortical thickness changes could occur early in the clinical course of PD. However, future longitudinal studies with wider sample sizes of patients as well as pathological postmortem confirmation would be required to assess the relationship between cortical thickness and Braak's staging.

Although no significant relationships were found between global cerebral indices, both GM volumes and cortical thickness correlated with disease stage in PD patients, indicating they are sensitive to disease progression. Moreover, all global anatomical measures were significantly related to age and specifically local reductions of the left collateral fissure correlated with age in the patient's group. It is well known that age is a strong predictive factor for development of dementia [Hobson and Meara, 2004] and is associated with greater neurodegenerative and pathological changes in PD [Bouchard et al.,

2007; Emre et al., 2003]. Thus, our findings seem to confirm the importance of this variable in PD-related progression.

Interestingly, even though no significant WM decreases were found in PD patients with respect to controls, WM volume was generally reduced in most regions in patients and in particular, medial and superior frontal WM showed to be significantly related to one particular brain sulcus, the left anterior cingulate. Recent studies have shown that widening of cortical sulci has been primarily associated with decreased gyral WM volume in MCI, AD [Im et al., 2008a] and normal aging [Kochunov et al., 2009]. According to the well known tension-based theory of morphogenesis [Hilgetag and Barbas, 2006; Van Essen, 1997], cortical folding processes and development of brain sulci are the result of mechanical tension produced by WM fibers that pull anatomical regions that are strongly connected towards one another. In our study, we did not find a significant relationship between WM volumes with any other anatomical measures but brain sulci, suggesting that, in agreement with the tension-based theory, regional WM volume reductions could be playing a role in the genesis of cortical folding alterations in PD, similarly to previous reports in other diseases [Im et al., 2008a]. However, future studies including more sensitive measures of WM such as WM connectivity with FA would be required to understand better the relationship between folding indices and gyral WM volumes in PD.

Overall, our results suggest that surface-based methods of cortical folding and especially of cortical thickness are sensitive to PD-related neural degeneration. According to Panizzon et al. [2009], in genetic studies, using GM volume as an endophenotype for a disorder may actually confound the underlying architecture of brain structure given that it conflates the contributions of thickness and surface area and therefore may not capture the basic structural elements of the cortex. Our results seem to confirm these findings and strongly encourage the use of folding and thickness analyses in future studies assessing cortical atrophy in PD.

One of the limitations of this study was the small sample size, which reduced the statistical power of our findings. This factor also limits the interpretation of our results in the wider context of the neuropathology of Parkinson's disease, since we did not include newly diagnosed patients or advanced patients with Parkinson's disease and dementia (PDD). Moreover, although cortical thickness, folding and VBM detected changes in the cortical GM layer of PD patients with respect to controls, one would need pathological postmortem confirmation of our findings to know the true GM changes occurring in PD. Therefore, future studies assessing wider samples of PD patients in the different stages of the disease and involving postmortem pathological confirmation, would be essential to further assess the progression of the anatomical reductions and relationship between the methods used in this study with pathological changes.

CONCLUSIONS

We found that, compared with healthy controls, PD patients presented significant reductions of GM volume, sulcal indices and cortical thickness that correlated with the disease stage and age. However, surface-based methods of cortical folding and especially cortical thickness seemed to be more sensitive to GM changes occurring in PD compared with VBM, indicating that these methods provide relevant information on cortical degeneration in PD.

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SUPPLEMENTAL RESULTS

Supplementary Table 1: Results from the ANOVA analysis of white matter volume differences between PD patients and controls

	PD patients Mean (SD)	Controls Mean (SD)	Main effect F (p value)
Left hemisphere			
Global WM	232365.8 $\pm$ 28293.7	247344.1 $\pm$ 27111.4	1.398 (0.245)
Medial Frontal	24845.2 $\pm$ 3275.9	26322 $\pm$ 2617.8	1.106 (0.3)
Superior Frontal	17303.3 $\pm$ 2526.8	18649.9 $\pm$ 2057.4	1.551 (0.221)
Superior Temporal	7325.7 $\pm$ 992.4	7992.3 $\pm$ 981.6	3.487 (0.07)
Inferior Temporal	20087.7 $\pm$ 2918.3	22168.7 $\pm$ 2760	3.241 (0.08)
Anterior Insula	8529.8 $\pm$ 763.8	8876.9 $\pm$ 691.3	2.162 (0.15)
Right hemisphere			
Global WM	234354.8 $\pm$ 26514.4	245477.3 $\pm$ 27401.6	0.374 (0.545)
Medial Frontal	23330.2 $\pm$ 3768.7	25488.5 $\pm$ 2257.6	3.066 (0.089)
Superior Frontal	16172.7 $\pm$ 3241.7	17884.3 $\pm$ 1684.5	2.284 (0.140)
Superior Temporal	6564.7 $\pm$ 1175.8	6522.7 $\pm$ 1640.5	0.072 (0.789)
Inferior Temporal	20090.9 $\pm$ 3000.8	21519.4 $\pm$ 3042.9	0.535 (0.469)
Anterior Insula	8145.6 $\pm$ 874.4	8694.6 $\pm$ 1111.8	2.212 (0.146)

Correlations between Global Cerebral Indices in the Whole Sample

When considering the whole group of participants, GM volumes correlated with global sulcal index (r = 0.723, p < 0.001) and average cortical thickness (r = 0.611, p < 0.001). All global indices correlated with age (GM volumes: r = - 0.689, p < 0.001; sulci: r = - 0.704, p < 0.001; thickness: r = - 0.557, p < 0.001), whereas global cognitive performance obtained from the factor analysis only correlated with GM volumes (r = 0.614, p < 0.001) and global sulci (r = 0.575, p < 0.001).

Correlations between Regional Cerebral Indices in the Whole Sample

In the whole sample, left temporal GM volumes significantly correlated with the left inferior temporal sulcus (r = 0.638, p < 0.001) as well as with cortical thickness in inferior parietal (r = 0.708, p < 0.001) and lateral occipital regions (r = 0.587, p < 0.001).

Concerning correlations with demographic variables, age was found to significantly correlate with the collateral fissure (r = - 0.609, p < 0.001) in the whole sample.

Finally, WM volumes in the left/right medial and superior frontal regions significantly correlated with the left anterior cingulate sulcus (r = 0.580, p < 0.001; r = 0.630, p < 0.001; r = 0.599, p < 0.001; r = 0.626, p < 0.001, respectively). We also observed that left inferior temporal WM volumes correlated with the right temporal sulcus (r = 0.532, p < 0.001), whereas right superior temporal WM volumes correlated with the left temporal sulcus (r = 0.508, p < 0.001). The left occipito-temporal sulcus showed to be significantly correlated with inferior WM temporal volume (0.499, p < 0.001) and finally right insular WM volumes correlated with the left anterior cingulate (r = 0.537, p < 0.001). No correlations were found between regional cortical thickness and local WM volumetric measures.

Chapter 5.
General Discussion & Conclusions

1. Discussion

This thesis comprises three different studies that were designed to increase the understanding of the underlying neuroanatomical and neurofunctional correlates of verbal fluency impairment in PD as well as the characteristics of cortical degeneration occurring in this disorder compared to normal aging. In order to achieve these goals, different neuroimaging modalities such as structural and functional MRI were used, in addition to noninvasive brain stimulation, a promising tool that allows exploring brain networks and induces plastic changes in brain activity and behavior (Fregni and Pascual-Leone, 2007). The results that were found shaded light into previously unstudied issues related to PD, increasing the knowledge on some of the cerebral pathological changes that affect patients with this disorder.

It is well established that, even without concomitant dementia, PD can have a deleterious effect on certain cognitive processes (Kehagia et al., 2010). In line with this, the abilities that have been found to be most susceptible to this disease are those that require manipulation of information, planning and strategy formation, which are usually referred to as executive functions (Henry and Crawford, 2004). Impairment of executive functions may be observed very early in the course of the disease (McKinlay et al., 2010) and has been suggested to be caused by dysfunction in prefrontal areas that are connected with the basal ganglia through cortical-subcortical circuits (Cummings et al., 1993).

Deficits in semantic and phonemic verbal fluency have been consistently found in patients with PD and are thought to reflect executive dysfunction (Henry and Crawford, 2004). However, despite of being one of the main features of cognitive decline in this disease, the structural cerebral correlates of these deficits have not been previously explored.

It is well known from studies in patients with focal brain lesions that there is some discrepancy regarding the underlying pathological substrates of semantic and phonemic impairment. On one hand, some studies have found that phonemic fluency is significantly compromised in patients with frontal lesions, while semantic fluency is impaired only in patients with temporal lesions (Baldo et al., 2006). On the other hand, other studies have shown that there is no such dissociation and that both fluencies are similarly impaired in patients with frontal lobe damage (Baldo et al., 2001). The first study of this thesis was aimed at investigating the GM correlates of

semantic and phonemic fluency performance in nondemented patients with PD by using VBM methods. Interestingly, in this study we found that semantic scores significantly correlated with a number of brain areas such as the inferior and middle frontal gyri, inferior and middle temporal gyri, parahippocampus, caudate and the cerebellum. The association that was found between frontal and temporal areas with semantic performance suggests that this cognitive function imposes demands not only upon executive processes, which rely on frontal lobe areas, but also on semantic memory, which relies on temporal regions (Henry and Crawford, 2004), in PD patients. By contrast to semantic fluency, no correlations were found between GM density and scores on the phonemic task. The absence of a significant correlation for phonemic performance was associated with the functional rather than structural nature of some executive deficits occurring in PD, being caused by imbalanced neural levels of dopamine in cortico-striatal circuitries (Owen et al., 1997).

However, presently we dispose of additional information regarding the sample assessed in this first study. As mentioned in the published manuscript, this sample consisted of patients that were at moderate and advanced stages of PD as indexed by the Hoehn & Yahr rating scale and that had significant motor impairment measured by the UPDRS. Importantly, fourteen of the patients of that sample had persistent visual hallucinations, which are a well-known risk factor for development of dementia in this disorder (Fenelon et al., 2000). In a posterior longitudinal study (Ibarretxe-Bilbao et al., 2010), twelve of these hallucinating patients were re-assessed and it was found that 75% of them developed dementia at follow-up, which was two years after baseline evaluation. In addition, VBM analyses showed these patients presented significant reductions of GM in widespread limbic, paralimbic and posterior neocortical regions at follow-up and, importantly, one of the greatest cognitive declines was observed precisely on semantic fluency, by contrast to phonemic fluency. In line with this, in a previous study assessing the neuropsychological correlates of hallucinations in PD it was shown that the progression in severity of hallucinations was related to tasks measuring posterior cortical deficits superimposed on a progressive impairment in tasks measuring frontostriatal cognitive functions (Llebaria et al., 2010).

Overall, these findings suggest that the correlations that were found between GM and semantic fluency and the lack of them in the case of phonemic fluency could be related with a stronger

association between semantic fluency and dementia as well as greater posterior GM cortical reductions. This assumption is in agreement with the findings of Williams-Gray et al. (2007; 2009) who found that semantic, by contrast to phonemic fluency, was a significant predictor of dementia in a large sample of PD patients, after correcting for age confounds. According to the authors, the dissociation that was observed between semantic and phonemic fluency in terms of predicting dementia indicates that it is the semantic temporal component of the fluency task that is predictive of cognitive decline rather than the frontally-based strategic retrieval common to both fluency tasks. These findings are consistent with the correlations we found between semantic performance and temporal regions in PD patients in this thesis's first study.

Regarding the neurochemical basis of cognitive deficits in PD, Williams-Gray et al. (2009) also showed that those deficits based on frontal areas are affected by a genetically determined variation in catechol-O-methyltransferase (COMT) activity, an effect that is probably mediated by modulation of cortical dopamine levels. By contrast, impairment on tasks with a more temporal and parietal basis, which evolve into later occurring dementia, were not influenced by COMT genotype, but by the microtubule-associated protein tau (MAPT) H1/H1 genotype, which predisposes to a higher burden of tau aggregates in the neocortex. Hence, the cognitive syndromes 'frontal executive' and 'posterior cortical' seem to be dissociable in terms of their genetic basis and relationship to dementia. Cognitive deficits that are associated with posterior cortical areas, might be associated with later occurring dementia in PD (Pagonabarraga et al., 2008) and these posterior alterations might have a non-dopaminergic aetiology (Williams-Gray et al., 2009).

Based on the results of the first study, a second study was designed in order to further explore the dissociation between semantic and phonemic fluency. In this second work, a new sample of nondemented patients was recruited, which differed from the sample of the first study in that they were younger, were at earlier disease stages and were less impaired on motor functions as indexed by the UPDRS. The aim of this study was to assess the effects of tDCS applied to the left dorsolateral prefrontal cortex and the left temporo-parietal cortex on four functional networks on fMRI: general verbal fluency, semantic fluency, phonemic fluency and in the deactivation task-related network that presented high spatial correspondence with the DMN. Overall, the results of this study showed that prefrontal stimulation induced greater functional connectivity

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changes in the four studied networks compared to temporo-parietal tDCS. Concretely, tDCS to the left prefrontal cortex increased functional coupling between frontal, parietal areas and the fusiform gyrus for both fluency networks; between frontal and parietal areas in the phonemic compared to the semantic network; and between temporal and other posterior cortical areas in the semantic compared to the phonemic network. These areas have been previously found to be involved in several processes relevant for verbal fluency such as word production (Costafreda et al., 2006), switching between retrieval strategies (Gurd et al., 2002), word recognition (McCandliss et al., 2003) and semantic memory (Henry and Crawford, 2004). Finally, prefrontal stimulation also increased connectivity between the areas that usually show themselves in deactivation in the DMN such as the medial frontal, posterior cingulate and bilateral parietal areas in the deactivation task-related pattern network. The increment of deactivation of the DMN is important as it has been found to correlate with better subsequent cognitive performance (Sala-Llonch et al., 2011) and there is increasing evidence showing that PD is associated with reduced deactivations of the DMN compared to healthy elders (van Eimeren et al., 2009; Delaveau et al., 2010; Ibarretxe-Bilbao et al., 2011). Hence, the results that were found suggest that prefrontal stimulation might have contributed to normalize brain functioning and possibly improve subsequent verbal fluency performance in PD patients.

By contrast to prefrontal tDCS, temporo-parietal stimulation did not significantly increase or decrease functional connectivity in any networks compared to prefrontal tDCS. These results suggest that, at least at initial stages of PD, the prefrontal cortex is likely to be more important for both phonemic and semantic fluencies than posterior cortical areas located on the temporal and parietal cortices. In addition, these results could be attributed to the influence tDCS might have exerted on frontal dopamine levels. As previously mentioned, it is well known that dopamine depletion frontal-subcortical dysfunction is one of the earliest changes occurring in PD (Kehagia et al., 2010) and patients from this thesis's second study were at initial stages of PD. The prefrontal cortex plays an important role in regulating the release of dopamine in subcortical structures and studies using noninvasive brain stimulation such as TMS, have shown that by stimulating the prefrontal cortex, increases in endogenous dopamine release occurs in the caudate levels in healthy subjects (Strafella et al., 2001). This could be the reason why prefrontal tDCS increased functional connectivity in fluency networks more than temporo-parietal stimulation.

Although semantic networks were related to functional connectivity increases in temporal areas compared to phonemic fluency networks, in this study temporo-parietal tDCS did not show any effect on semantic networks compared to prefrontal stimulation. These results are in agreement with a previous study by Foltynie et al. (2004), in which a large cohort of patients at early stages of PD was divided into four groups based on performance on the Tower of London test and a pattern recognition task: cognitively intact patients, patients with frontostriatal cognitive deficits (impairment on the Tower of London), with temporal lobe cognitive deficits (impairment on the pattern recognition task) and with both frontostriatal and temporal lobe deficits (impairment on both tasks). The results from this study showed that while patients with frontostriatal deficits and patients with both frontostriatal and temporal lobe deficits presented a significant impairment in semantic fluency, those patients with only temporal lobe deficits did not perform worse on semantic fluency compared to cognitively intact patients. These findings, together with the results from the second study of this thesis, suggest that although semantic fluency is associated with temporal lobe functioning, temporal regions by themselves are not sufficient to cause impairment in semantic fluency at early disease stages of PD.

In addition to modulating brain functional networks, in this study prefrontal tDCS also increased performance on the phonemic fluency task compared to temporo-parietal stimulation. Moreover, this behavioral effect on the phonemic task showed a strong positive association with functional connectivity increases in the phonemic network after prefrontal stimulation, suggesting there might be a causal relationship between these two events. These results shed light onto the underlying mechanisms of tDCS in PD by which increases in functional connectivity in frontal-parietal networks could lead to a significant behavioral phonemic improvement in these patients. Although performance in semantic fluency did not show a significant improvement after prefrontal stimulation, patients did produce more words after frontal tDCS compared to temporo-parietal tDCS. This suggests that there was not enough statistical power to achieve significance due to variability in the fluency scores or the small sample size in the present study. In addition, it also suggests that semantic fluency, compared to phonemic fluency, relies on a more widespread neural network.

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Finally, the third study of this thesis had a different aim compared to the other two studies. This study was focused on assessing the contribution by three widely used neuroimaging techniques to characterize cortical degeneration occurring in nondemented stages of PD compared to normal aging. Neuroimaging measures hold promise as potential providers of biomarkers that can aid in the early and more accurate clinical diagnosis, monitor disease progression and effectiveness of therapeutic trials (Dubois et al., 2007; Frank et al., 2003; Galasko, 2005). In addition, these measures may facilitate the discrimination of PD from other types of neurodegenerative disorders and similarly to what has been found for AD, provide greater statistical power in clinical trials, allowing for smaller sample sizes (Thal et al., 2006).

VBM has largely contributed to the current success of neuroimaging techniques. By comparing the local amount of GM across populations after 3-dimensional spatial alignment, it provides information on cortical and subcortical GM reductions occurring in a group of patients with a specific disease compared to healthy matched individuals (Ashburner, 2009). Indeed, the majority of studies evaluating GM changes on MRI in patients with PD have used VBM to perform the imaging analyses, reporting whole-brain GM loss mainly in frontal and temporal areas in nondemented stages of PD (Burton et al., 2004; Nagano-Saito et al., 2005; Summerfield et al., 2005; Beyer et al., 2007; Biundo et al., 2011), which further extend to neocortical areas with disease progression and development of dementia (Burton et al., 2004; Summerfield et al., 2005; Melzer et al., 2011; Song et al., 2011).

However, one of the main issues related to VBM is the lack of specificity of this technique given that the resulting measures of GM volume or density are a mixture of cortical thickness and cortical folding, which makes difficult the interpretation of the results (Mechelli et al., 2005).

Hence, in light of these limitations, the third study of this thesis was designed in order to compare GM changes in PD patients with healthy elders as the result of alterations in GM volume assessed by VBM, cortical thickness assessed by FreeSurfer and cortical folding using BrainVisa. The former methods have been extensively used to assess pathological changes in neurodegenerative disorders (Im et al., 2008; Du et al., 2007; Dickerson et al., 2008) as well as changes occurring in healthy aging (Kochunov et al., 2005; 2008; Fjell et al., 2009), being properly validated. There were several goals to this study, the most important of which

consisted of evaluating to what extent these methods provide convergent or divergent information on cortical changes in PD. In addition, another goal was to evaluate the relationship between GM volume, thickness and folding and relevant demographic and clinical variables such as age, HY stage, severity of motor symptoms as indexed by the UPDRS and cognitive impairment as a compound index of performance on the Rey's Auditory Verbal Learning, Stroop, forward and backward Digits from WAIS, verbal fluency and the MMSE tests. Finally, the association between global and regional anatomical measures provided by each method was also assessed both in patients and controls as well as the whole sample.

The main finding of this study was that the different neuroimaging techniques that were used to assess different characteristics of the GM layer showed different results in terms of the location and extent of changes detected in patients compared to controls. In particular, while VBM showed GM reductions in the left superior temporal gyrus, cortical folding revealed significant decreases in the right collateral fissure and left superior frontal sulcus and finally cortical thickness detected widespread thinning in bilateral occipital and parietal areas as well as in right frontal and temporal regions. Whereas the results provided by VBM and cortical thickness analyses showed agreement with previous studies in PD using these concrete techniques (Summerfield et al., 2005; Beyer et al., 2007; Lyoo et al., 2010), the present study, being the first in comparing them in the same sample of patients with PD show that they provide very different results, with VBM being the most conservative. In addition, cortical folding of the particular sulci that were tested in this study cannot be compared with previous studies as the only works assessing brain sulci in PD only measured the olfactory sulcus as they were focused on brain abnormalities underlying olfactory dysfunction (Kim et al., 2007; Wang et al., 2011).

Overall the findings that were found suggest that surface-based measures of cortical folding and cortical thickness detect more changes in the GM layer compared to VBM methods. This finding together with the fact that these measures provide a direct index of morphological changes occurring in the brain rather than a mixture of different morphological properties as in VBM, strongly encourage their use in future studies assessing cortical atrophy in PD. Previous studies assessing both cortical thickness and GM volume with VBM have shown that thickness measures are more sensitive to subtle cortical changes in the human brain, identifying more widespread changes in healthy aging (Hutton et al., 2009) and patients with autism (Hyde et al., 2010),

compared to VBM. Importantly, in one study calculating specific statistical measures of sensitivity, specificity, accuracy and receiver operating characteristic curves (ROC) (Jiao et al., 2010) it was shown that diagnostic models based on cortical thickness outperformed those based on GM volumes providing the best classification performance between children with autism and controls.

These differences between methods have been related with the fact that while VBM measures combine information on size, morphology and position, cortical thickness is less susceptible to positional variance given that the extraction of the cortex follows the GM surface despite local variations in its position (Kim et al., 2005; MacDonald et al., 2001). In addition, cortical thickness enables more precise measurement in deep sulci (Lerch and Evans, 2005) and allows for subvoxel precision because thickness values are assigned to individual vertices instead of voxels (Fischl and Dale, 2000). Finally, VBM methods have been associated with a number of limitations and potential confounds such as sensitivity to misregistration problems, difficulties in spatial normalization and segmentation of atypical brains and the relatively imprecise image registration. In addition, since VBM relies on parametric procedures, the results that is provides would only be valid if the residuals, after fitting the model, are normally distributed, raising the possibility that non-normality in the error terms can make statistical inferences invalid in some studies (Mechelli et al., 2005; Ashburner, 2009).

Concerning the relationship between global brain measures derived from VBM, thickness and folding, although no correlations were found in controls or PD patients, when the whole sample was considered, GM volumes showed to correlate with both global sulcal index and average cortical thickness (supplementary material), suggesting that VBM measures could indeed be combining folding and thickness information of the brain (Ashburner, 2009) and that there was a lack of statistical power when the groups were analysed separately likely due to small group sizes. Similarly, several significant correlations emerged between regional anatomical measures when the whole sample was analysed.

In PD patients specifically, a relationship was found between disease stage and global GM volume and thickness as well as an association between the patient's age and all global cerebral measures, especially of cortical folding or brain sulci, indicating that these brain measures tap

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specific disease-related and age-related processes in PD. In addition, in controls both GM volume and folding significantly correlated with age.

Hence, to conclude, although all the neuroimaging methods provided relevant information on cortical atrophy in patients with PD, surface-based methods of cortical folding and thickness seemed to be more sensitive in detecting GM changes compared to voxel-based methods. The findings from this study seem to agree with the study by Panizzon et al. (2009), according to which using GM volume as an endophenotype for a disorder may actually confound the underlying architecture of brain structure given that it conflates the contributions of thickness and surface area and therefore may not capture the basic structural elements of the cortex.

2. Conclusions

The main conclusions that can be derived from the studies of this thesis are the following:

- In moderate and advanced stages of PD, semantic fluency impairment is associated with GM loss in frontal as well as temporal cortical regions, suggesting that both executive functions and semantic memory could be underlying semantic fluency deficits in these patients.

- At early stages of PD, tDCS to the left prefrontal dorsolateral cortex increases functional connectivity in both semantic and phonemic fluency networks compared to temporo-parietal stimulation, suggesting that the frontal cortex is likely to be crucial for both types of fluencies in these stages.

- Increases of functional connectivity in phonemic fluency networks significantly correlated with behavioral improvement on the phonemic fluency task, indicating a causal relationship between these two events and that tDCS can improve cognitive functions in PD by increasing functional connectivity.

- In addition, prefrontal tDCS also increased deactivation between areas of the default-mode network compared to temporo-parietal tDCS, suggesting that frontal stimulation contributes to normalizing brain activity in PD as this disorder has been previously associated with decreased pathological deactivation of the DMN.

- Amongst the most widely used neuroimaging analysis techniques to assess cortical changes in GM, cortical thickness seems to be the most sensitive, followed by cortical folding and finally voxel-based morphometry.

- Cortical thickness and GM volume were significantly correlated with the stage of the disease, while all measures especially of cortical folding were strongly correlated to the age of PD patients. In healthy controls, significant correlations were found between age

and GM volume and cortical folding. These results suggest that these anatomical measures are differentially sensitive to disease severity and aging effects.

Resumen de la tesis

1. Introducción

Actualmente, la enfermedad de Parkinson (EP) es el segundo trastorno neurodegenerativo más frecuente después de la enfermedad de Alzheimer. Afecta a 100.000 personas en España y más de 4 millones en todo el mundo. Los efectos devastadores de esta enfermedad se demuestran por el hecho de que los pacientes con EP presentan un riesgo de mortalidad de dos a cinco veces mayor en comparación con el envejecimiento sano (Louis et al., 1997). Además, los estudios recientes sugieren que la carga social y económica de la EP en la sociedad aumentará en las próximas décadas junto al envejecimiento de la población en todo el mundo (Lau y Breteler, 2006). De hecho, se espera que en el año 2040 la EP y otras enfermedades neurodegenerativas superen la frecuencia de cáncer entre las personas mayores (Lilienfeld y Perl, 1993).

Al ser un trastorno del movimiento, el síntoma principal de la EP es el deterioro de las funciones motoras. Sin embargo, la disfunción cognitiva actualmente se reconoce como una característica más de la EP (Emre et al., 2007), que está presente desde las fases iniciales de la enfermedad y que afecta a la mayoría de los pacientes a medida que la enfermedad va avanzando. El deterioro cognitivo en la EP incluye déficits ejecutivos, visuoespaciales y de memoria que juegan un papel relevante en la calidad de vida en estos pacientes (para revisión ver Kehagia et al. 2010) y están asociados a un mayor riesgo de desarrollar demencia (Aarsland et al., 2001).

Entre los déficits cognitivos más comunes en la EP se encuentra el deterioro de la fluidez semántica y fonémica que normalmente se atribuye al deterioro de las funciones ejecutivas (Henry and Crawford, 2004). La fluidez verbal es una prueba neuropsicológica clásica que mide la cantidad de palabras generadas en respuesta a una letra o una categoría en un tiempo limitado. Las pruebas de fluidez verbal proporcionan un instrumento para evaluar cómo los individuos organizan su conocimiento. Para tener éxito en estas pruebas, hay que tener una buena capacidad para organizar la producción en términos de grupos de palabras relacionadas de manera significativa, así como buena memoria a corto plazo para acordarse de las palabras que ya se han dicho (Estes, 1974). Las pruebas de fluidez fonémica implican la generación de palabras de acuerdo con una letra inicial (por ejemplo, la letra p) mientras que las pruebas de fluidez semántica consisten en producir palabras que pertenecen a una categoría tal como nombres de animales (Lezak et al., 2004).

Aunque todavía no se han establecido biomarcadores definitivos para la EP (Maetzler et al., 2009), los métodos de neuroimagen ofrecen la posibilidad de trazar los sustratos neurobiológicos del deterioro motor y cognitivo en estos pacientes. Entre las técnicas de neuroimagen disponibles, la resonancia magnética estructural y funcional (RM, RMf) produce imágenes del cerebro que proporcionan valores cuantitativos de la atrofia cerebral y disfunción cerebral, respectivamente. Estas técnicas son importantes porque proporcionan información sobre los procesos de neurodegeneración que se producen en la EP en comparación con el envejecimiento sano, así como los procesos patológicos que subyacen el deterioro cognitivo en estos pacientes. Además de la neuroimagen, otro método que permite el estudio de las redes cerebrales y su alteración en la EP es la estimulación cerebral no invasiva, que, además de modular la conectividad funcional, potencialmente podría ser usada como una herramienta para la rehabilitación cognitiva y motora en estos pacientes (Fregni y Pascual-Leone et al., 2007).

2. Objetivos

Esta tesis tiene dos objetivos principales. En primer lugar, este trabajo representa un intento de caracterizar los correlatos cerebrales estructurales y funcionales de la fluidez semántica y fonémica en pacientes con EP mediante el uso de técnicas de resonancia magnética cerebral y de estimulación no invasiva como la estimulación transcraneal por corriente directa (ETCD). En segundo lugar, dado que hasta hoy no se ha realizado una comparación de la capacidad de las diferentes técnicas de análisis de RM para caracterizar la degeneración cortical en la EP, se evaluaron los cambios específicos en diferentes características de la sustancia gris (SG) para determinar si la atrofia cerebral que ocurre en la EP se puede atribuir a cambios en el volumen de SG, del pliegue cortical o de grosor cortical.

Para llevar a cabo estos objetivos se diseñaron tres estudios:

- El estudio de los correlatos cerebrales estructurales de la fluencia verbal en la enfermedad de Parkinson (Estudio 1).
- El estudio de la modulación inducida por la estimulación transcraneal por corriente directa (ETCD) en las redes de fluidez verbal en la enfermedad de Parkinson (Estudio 2).

- Evaluación de la degeneración cortical en pacientes con la enfermedad de Parkinson mediante la morfometría basada en voxeles, pliegue cortical, y grosor cortical (Estudio 3).

3. Métodos/Resultados

Estudio 1. En este estudio se aplicó la técnica de morfometría basada en vóxeles para investigar los sustratos neuroanatómicos del deterioro en la fluidez semántica y fonémica. Se llevaron a cabo correlaciones entre la densidad de la sustancia gris y el rendimiento tanto en la fluidez semántica como en la fluidez fonémica en 32 pacientes con enfermedad de Parkinson sin demencia. Los resultados mostraron que la sustancia gris en áreas temporales, frontales y del cerebelo correlacionó con las puntuaciones en la fluidez semántica. Por el contrario, no se encontraron correlaciones entre la sustancia gris y la fluidez fonémica ni para las funciones cognitivas generales.

Estudio 2. En el segundo estudio, dieciséis pacientes con EP fueron aleatorizados para recibir ETCD en la corteza prefrontal dorsolateral izquierda (CPFDL) y en la corteza temporo-parietal izquierda (CTP) de forma contrabalanceada. Inmediatamente después de la estimulación, los pacientes realizaron un paradigma de fluidez verbal dentro del escáner de RMf. Los cambios inducidos por la ETCD en los patrones de activación y desactivación relacionados con la tarea de fluidez verbal fueron estudiados mediante el análisis de componentes independientes. Los resultados mostraron que la ETCD sobre la CPFDL comparada con la estimulación sobre la CTP aumentó la conectividad funcional en las redes de la fluidez verbal y en las redes de desactivación relacionadas con la tarea. Además, la ETCD sobre la CPFDL aumentó el rendimiento en la tarea de fluidez fonémica, tras ajustar por el rendimiento base.

Estudio 3. En este estudio se evaluó la degeneración cortical en 20 pacientes con enfermedad de Parkinson sin demencia (EP) y 20 controles sanos, utilizando tres métodos neuroanatómicos cuantitativos: voxel-based morphometry (VBM), plegamiento cortical, y grosor cortical. Se evaluó la relación entre las medidas globales y regionales de volumen de SG, índices de surcos, y espesor cortical derivados de los métodos anteriores, así como su asociación con el rendimiento cognitivo, edad, la gravedad de los síntomas motores y el estadio de la enfermedad. Los análisis de VBM mostraron reducciones del volumen de SG en la circunvolución temporal izquierda en

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los pacientes en comparación con los controles. Las medidas de pliegue cortical revelaron una disminución significativa en los surcos frontal izquierdo y colateral derecho en los pacientes. Finalmente, el análisis de grosor cortical mostró un adelgazamiento cortical extenso que implicaba en el hemisferio derecho las regiones occipital lateral y parietal lateral y en el hemisferio izquierdo, además de la implicación del cortex posterior, se observó adelgazamiento en áreas frontales motoras y premotoras. El estudio de correlaciones puso en evidencia que en los pacientes, todas las medidas anatómicas globales correlacionaron con la edad, mientras que el volumen de SG y el grosor cortical, pero no las de pliegue cortical, correlacionaron significativamente con el estadio de la enfermedad. En los controles, se encontró una asociación significativa entre el volumen global de SG y el pliegue cortical global con la edad. En resumen, el grosor cortical es la medida que más diferencia pacientes con EP y controles y que además indica evolución de la enfermedad.

4. Discusión

Esta tesis está formada por tres estudios que se han diseñado para incrementar el conocimiento sobre los correlatos neuroanatómicos y neurofuncionales subyacentes al deterioro de la fluidez verbal en la EP, así como las características de la degeneración cortical que se producen en este trastorno en comparación con el envejecimiento sano.

El primer estudio de esta tesis tenía como objetivo investigar los correlatos de SG de la fluidez semántica y fonémica en pacientes con EP sin demencia mediante el uso de la morfometría basada en vóxeles (VBM, del inglés voxel-based morhometry). En este estudio se encontró que las puntuaciones de fluidez semántica correlacionaron significativamente con una serie de áreas cerebrales tales como las circunvoluciones frontales inferior y media, los giros temporales inferior y medio, el parahipocampo, el caudado y el cerebelo. La asociación que se encontró entre las áreas frontales y temporales con el rendimiento en la tarea semántica sugiere que esta función cognitiva se basa no sólo en procesos ejecutivos, que dependen de las áreas del lóbulo frontal, sino también en la memoria semántica, que está relacionada con regiones temporales (Henry y Crawford, 2004), en pacientes con EP. En contraste con la fluidez semántica, no se encontraron correlaciones entre la densidad de SG y las puntuaciones en la tarea fonémica. La ausencia de una correlación significativa para el rendimiento de la fluidez fonémica se asoció

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con la naturaleza funcional, más que estructural de algunos déficits ejecutivos que se producen en la EP. Probablemente los déficits de fluidez fonémica junto con otros déficits ejecutivos como la memoria de trabajo siendo son causados por el desequilibrio en los niveles de dopamina en los circuitos fronto-estriatales (Owen et al., 1997). Sin embargo, actualmente disponemos de información adicional con respecto a la muestra evaluada en este primer estudio. Como se mencionó en el articulo, esta muestra estaba formada por pacientes que se encontraban en fases moderadas y avanzadas de la EP tal como indicaba la escala de Hoehn y Yahr y la UPDRS. Además, catorce de los pacientes de esta muestra padecía de alucinaciones visuales persistentes, que son uno de los factores de riesgo más importantes para el desarrollo de demencia en la EP (Fénelon et al., 2000). En un estudio longitudinal posterior (Ibarretxe-Bilbao et al., 2010), se volvió a evaluar doce de estos pacientes con alucinaciones y se encontró que el 75% de ellos desarrollaron demencia durante el seguimiento, que fue dos años después de la evaluación basal. Además, los análisis de VBM mostraron que estos pacientes presentaron una reducción significativa de la SG en amplias regiones límbicas, paralímbicas y neocorticales posteriores en el seguimiento y uno de los mayores deterioros cognitivos se observó precisamente en la fluidez semántica y no en la fluidez fonémica. En general, estos hallazgos sugieren que las correlaciones que se encontraron entre la SG y la fluidez semántica y la falta de ellas en el caso de la fluidez fonémica en el primer estudio de esta tesis podrían estar relacionados con la presencia de una asociación más fuerte entre la fluidez semántica y el desarrollo futuro de demencia, así como una mayor reducción de la SG cortical, lo cuál estaría de acuerdo con estudios que muestran que la fluidez semántica es un predictor de demencia y esta asociada a disfunciones de las áreas frontales y temporales (Williams-Gray et al., 2007; 2009).

Basándonos en los resultados del primer estudio, se diseñó un segundo estudio con el objetivo de explorar más a fondo la disociación entre la fluidez semántica y fonémica, mediante diseños experimentales. En este segundo trabajo, se reclutó una nueva muestra de pacientes sin demencia, que difería de la muestra del primer estudio en que eran más jóvenes, estaban en etapas tempranas de la enfermedad y estaban menos afectados según la UPDRS en las funciones motoras. El objetivo de este estudio fue evaluar los efectos de la ETCD aplicadas a la corteza prefrontal dorsolateral izquierda y a la corteza temporo-parietal izquierda en cuatro redes neuronales mediante RMf. Las redes implicadas en la fluidez verbal general, la fluidez semántica, la fluidez fonémica y en la desactivación de las redes relacionadas con la tarea con

una elevada correspondencia espacial con la default-mode network (DMN). En general, los resultados de este estudio demostraron que la estimulación prefrontal induce mayores cambios en la conectividad funcional en las cuatro redes neuronales estudiadas, en comparación con la ETCD en la corteza temporo-parietal. Estos cambios se observaron en áreas previamente relacionadas con varios procesos relevantes para la fluidez verbal, como la producción de palabras (Costafreda et al., 2006), el cambio entre estrategias (Gurd et al., 2002), reconocimiento de palabras (McCandliss et al. 2003) y la memoria semántica (Henry y Crawford, 2004). Por último, la estimulación prefrontal también incrementó la conectividad entre las áreas que generalmente se muestran desactivadas en la DMN. El incremento de la desactivación de la DMN está en consonancia con otros estudios en los que se ha encontrado que correlaciona con un mejor rendimiento en tareas cognitivas (Sala-Llonch et al., 2011) y otros estudios previos que muestran que la EP está asociada con una reducción de estas desactivaciones en comparación con las personas sanas (van Eimeren et al, 2009). Delaveau et al, 2010; Ibarretxe-Bilbao et al, 2011). Por lo tanto, los resultados hallados sugieren que la estimulación prefrontal podrá haber contribuido a la normalización del funcionamiento cerebral y posiblemente a una mejora en el rendimiento posterior en fluidez verbal en pacientes con EP. Al contrario de la ETCD prefrontal, la estimulación temporo-parietal no aumentó ni disminuyó significativamente la conectividad funcional en ninguna red neuronal en comparación con la estimulación prefrontal. Estos resultados sugieren que, al menos en las etapas iniciales de la EP, es probable que la corteza prefrontal sea más importante para el control y modulación de la fluidez verbal fonémica y semántica que las áreas corticales posteriores situadas en las cortezas temporal y parietal. Finalmente, también se observó que la estimulación prefrontal mejoró el rendimiento de los pacientes en la tarea de fluidez fonémica, lo cuál correlacionó con el aumento de conectividad funcional de la red neuronal de la fluidez fonémica tras la estimulación prefrontal. Este resultado parece estar indicando una relación causal entre estos dos eventos.

Por último, el tercer estudio de esta tesis tenía un objetivo diferente en comparación con los otros dos estudios. Este estudio se centró en la evaluación de la contribución de tres técnicas de neuroimagen para estudiar la degeneración cortical que ocurre en la EP sin demencia en comparación con controles sanos. Las medidas de neuroimagen resultan prometedoras, ya que han demostrado ser potentes biomarcadores en la enfermedad de Alzheimer y lo podrían ser también para la EP. Pueden contribuir a un diagnóstico clínico precoz y más preciso, evaluar la

progresión de la enfermedad y la eficacia de los ensayos clínicos (Dubois et al, 2007; Frank et al, 2003; Galasko, 2005).

La VBM ha contribuido en gran medida al éxito actual de las técnicas de neuroimagen. De hecho, la mayoría de los estudios que han evaluado los cambios de SG en RM en pacientes con EP han utilizado VBM para realizar los análisis de imagen, mostrando pérdida de SG sobre todo en áreas frontales y temporales en etapas iniciales y moderadas de la EP (Burton et al, 2004.; Nagano-Saito et al, 2005; Summerfield et al, 2005; Beyer et al, 2007; Biundo et al, 2011), que se van extendiendo hacia áreas neocorticales con la progresión de la enfermedad y desarrollo de demencia (Burton et al,.. 2004; Summerfield et al, 2005; Melzer et al, 2011; Song et al, 2011).

Sin embargo, uno de los principales problemas relacionados con la VBM es la falta de especificidad de esta técnica ya que al ser una medida de volumen mezcla información sobre el grosor cortical y el plegamiento cortical, lo cuál dificulta la interpretación de los resultados (Mechelli et al., 2005).

En el tercer estudio de la tesis, pues, se compararon los cambios de SG mediante el volumen de SG de la VBM, el grosor cortical medido con el FreeSurfer y el pliegue cortical usando el BrainVisa. Estos métodos han sido ampliamente utilizados para evaluar los cambios patológicos en enfermedades neurodegenerativas (Im et al, 2008; Du et al, 2007; Dickerson et al, 2008) así como los cambios que ocurren en el envejecimiento sano (Kochunov et al, 2005, 2008; Fjell et al, 2009), aunque en general se usan de forma aislada. En este estudio se observó que mientras que la VBM mostró reducciones de SG en la circunvolución temporal superior izquierda, las medidas de pliegue cortical revelaron una disminución significativa en la fisura colateral derecha y el surco frontal superior izquierdo y el método de grosor cortical detectó un adelgazamiento extenso en las áreas occipitales y parietales bilaterales, así como en las regiones frontales y temporales derechas. En general, estos resultados sugieren que las medidas basadas en la superficie cortical como de pliegue y grosor detectan más cambios en la SG respecto a la VBM. Estas diferencias entre los métodos se han relacionado con el hecho de que, mientras que las medidas de VBM combinan información sobre el tamaño, la morfología y la posición, las medidas de grosor y plegamiento cortical son menos susceptibles a la variación de posición, dado que la extracción de la corteza sigue la superficie de GM a pesar de las variaciones locales en su posición (Kim et al, 2005; MacDonald et al, 2001). Además, el grosor cortical permite una medición más precisa en los surcos profundos (Lerch y Evans, 2005) y una precisión a nivel de

subvoxel porque los valores de espesor se asignan a los vértices individuales en lugar de vóxeles (Fischl y Dale, 2000). Por último, la VBM tiene una serie de limitaciones tales como la sensibilidad a problemas de registro, dificultades en la normalización espacial y segmentación de cerebros atípicos y el registro relativamente impreciso de las imágenes. Además, dado que la VBM se basa en procedimientos paramétricos, los resultados que proporciona sólo son válidos si los residuos, después de ajustar el modelo, se distribuyen normalmente, aumentando la posibilidad de que la falta de normalidad en los términos de error pueda dar lugar a inferencias estadísticas inválidas en algunos estudios (Mechelli et al, 2005; Ashburner, 2009).

En cuanto a la relación entre las medidas cerebrales globales derivados de la VBM, el grosor y pliegue cortical, el volumen de SG mostró una correlación con el índice global de los surcos y el grosor cortical medio, lo cuál sugiere que, efectivamente, las medidas de VBM son una mezcla de información de pliegue y grosor tal como había destacado Ashburner (2009). En concreto en los pacientes con EP, se encontró una relación entre el estadio de la enfermedad y el volumen global de SG y el espesor cortical, así como una asociación entre la edad de los pacientes y todas las medidas globales cerebrales, especialmente las de pliegue cortical, lo cuál indica que estas medidas son sensibles a los cambios neurodegenerativos relacionados con el avance de la enfermedad y con la edad en la EP.

5. Conclusiones

Las principales conclusiones de esta tesis son las siguientes:

• En las fases moderadas y avanzadas de la EP, el deterioro en la fluidez semántica está asociado con la pérdida de SG en áreas frontales y temporales. No se ha hallado un correlato para la fluidez fonémica.

• En las etapas iniciales de la EP, la ETCD en la corteza prefrontal dorsolateral izquierda en comparación con la estimulación temporo-parietal aumenta la conectividad funcional en las redes neuronales de fluidez semántica y fonémica, lo cuál sugiere que la corteza prefrontal es más importante para monitorizar ambas fluencias en estas etapas.

• El aumento de conectividad funcional en las redes de fluidez fonémica correlacionó con la mejora en el rendimiento en esta tarea, lo cuál sugiere una relación causal entre estos dos

eventos y que, el mecanismo explicativo de que la ETCD puede mejorar la fluidez fonémica en la EP, es el aumento de la conectividad funcional.

• La estimulación prefrontal también aumentó la desactivación entre las áreas de la DMN comparada con la ETCD temporo-parietal, lo cuál sugiere que la estimulación prefrontal contribuye a la normalización de la actividad cerebral en la EP ya que este trastorno se ha asociado a una reducción patológica de la desactivación de la DMN.

• Entre las técnicas más utilizadas de neuroimagen para evaluar los cambios en la SG, las medidas de grosor cortical parece ser las más sensibles a la atrofia cortical que ocurre durante el curso de la EP, seguida por las medidas de pliegue cortical y finalmente la VBM.

• La edad de los pacientes está relacionada con todas las medidas evaluadas, mientras que el estadio motor de la enfermedad correlaciona con el grosor cortical y volumen de SG, lo cuál indica que estas medidas de RM anatómicas son sensibles a los procesos neurodegenerativos directamente relacionados con la enfermedad.

Estudio 1. Correlatos cerebrales estructurales de la fluencia verbal en la enfermedad de Parkinson

Resumen

Las pruebas de fluidez verbal son de las más utilizadas para evaluar la disfunción cognitiva presente en la enfermedad de Parkinson. Los déficits en estas pruebas se observan incluso en etapas iniciales de este trastorno. En este estudio se aplicó voxel-based morphometry para investigar los sustratos neuroanatómicos del deterioro en la fluidez semántica y fonémica. Se realizaron correlaciones entre la densidad de sustancia gris y el rendimiento tanto en fluidez semántica como en la fluidez fonémica en 32 pacientes con enfermedad de Parkinson sin demencia. Los resultados mostraron que la sustancia gris en áreas temporales, frontales y del cerebelo correlacionó con las puntuaciones en la fluidez semántica. Por el contrario, no se encontraron correlaciones entre la sustancia gris y la fluidez fonémica o para las funciones cognitivas generales. Estos resultados sugieren que el deterioro de la fluidez semántica está relacionado con cambios estructurales en la sustancia gris en regiones que participan en las redes del lenguaje y que no puede tomarse como una medida específica de función ejecutiva o frontal.

Estudio 2. La modulación en las redes de fluidez verbal inducida por estimulación transcraneal por corriente directa (ETCD) en la enfermedad de Parkinson.

Resumen

Antecedentes. La fluidez verbal se basa en la actividad coordinada entre áreas frontales y temporales izquierdas. Los pacientes con enfermedad de Parkinson (EP) presentan déficits de fluidez fonémica y semántica. Estudios recientes sugieren que la estimulación transcraneal por corriente directa (ETCD) mejora los patrones adaptativos de la actividad cerebral entre áreas que están conectadas funcionalmente.

Objetivos. El objetivo de este estudio fue evaluar las diferencias en los efectos inducidos por la ETCD aplicada a áreas frontales y temporo-parietales en las redes funcionales de fluidez fonémica y semántica en pacientes con EP.

<u>Métodos</u>. Dieciséis pacientes fueron aleatorizados para recibir ETCD en la corteza prefrontal dorsolateral izquierda (CPFDL) y en la corteza temporo-parietal izquierda (CTP) de forma contrabalanceada. Inmediatamente después de la estimulación, los pacientes realizaron un paradigma de la fluidez verbal dentro del escáner de resonancia magnética funcional. Los cambios inducidos por la ETCD en los patrones de activación y desactivación relacionados con la tarea de fluidez verbal fueron estudiados mediante el análisis de componentes independientes.

<u>Resultados</u>. La ETCD sobre la CPFDL aumentó la conectividad funcional en las redes de la fluidez verbal y en las redes de desactivación relacionadas con la tarea comparado con la ETCD en la CTP. Además, la ETCD sobre la CPFDL aumentó el rendimiento en la tarea de fluidez fonémica, después de ajustar por el rendimiento base en fluidez fonémica antes de recibir estimulación.

<u>Conclusiones</u>. Estos resultados proporcionan evidencia de que la ETCD en regiones específicas del cerebro induce cambios en las redes funcionales de gran escala que subyacen a los efectos de comportamiento y sugieren que la ETCD podría ser útil para mejorar la fluidez fonémica en la EP.

Estudio 3. Evaluación de la degeneración cortical en pacientes con la enfermedad de Parkinson mediante voxel-based morphometry, plegamiento cortical, y grosor cortical

Resumen

Los métodos de neuroimajen no invasivos como la IRM proporcionan información útil sobre la involución cerebral y procesos degenerativos. En este estudio, se evaluó la degeneración cortical en 20 pacientes con enfermedad de Parkinson sin demencia (EP) y 20 controles sanos, utilizando tres métodos neuroanatómicos cuantitativos: voxel-based morphometry (VBM), plegamiento cortical (BrainVisa), y grosor cortical (FreeSurfer). Se examinó la relación entre los volúmenes de sustancia gris (SG) global y regional, índices de surcos, y las medidas de espesor cortical derivadas de los métodos anteriores, así como su asociación con el rendimiento cognitivo, edad, la gravedad de los síntomas motores, y el estadio motor de la enfermedad. Los análisis de VBM mostraron reducciones del volumen de SG en la circunvolución temporal izquierda en los pacientes en comparación con los controles. Las medidas de pliegue cortical revelaron una disminución significativa en los surcos frontal izquierdo y colateral derecho en los pacientes.

Finalmente, el análisis de grosor cortical mostró un adelgazamiento cortical extenso en las regiones occipital lateral y parietal lateral derechas y en áreas temporales, frontales y premotoras izquierdas. Además, se encontró que, en los pacientes, todas las medidas anatómicas globales correlacionaron con la edad, mientras que el volumen de SG y el grosor cortical correlacionaron significativamente con el estadio de la enfermedad. En los controles, se encontró una asociación significativa entre el volumen global de SG y el plegamiento cortical global con la edad. En general, estos resultados sugieren que los tres métodos diferentes utilizados en este estudio proporcionan información complementaria y relacionada sobre los cambios neurodegenerativos que ocurren en la EP, sin embargo, las medidas basadas en la superficie de la corteza de plegamiento cortical y especialmente de espesor cortical parecen ser más sensibles que la VBM en identificar los cambios regionales en la SG asociados a la EP.

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