EXPLORING THE NEUROBIOLOGICAL AND COGNITIVE CORRELATES OF NON-MOTOR SYMPTOMS IN IDIOPATHIC PARKINSON'S DISEASE

By

Hamad Alzahrani

Submitted for the degree of Doctor of Philosophy (PhD)

Department of Neuroscience

June 2013

To my parent, my wife and children (Atheer & Firas)

Acknowledgements

I would like to thank Professor Annalena Venneri for giving me the opportunity to be one of her research group and also for helping me to complete my PhD thesis. Also, I would like to thank Dr. William McGeown for teaching me how to analyse my data in the lab. Further, thanks to my second supervisor Dr. Oliver Bandmann.

Next, I would like to thank every member of our research group, especially Katija, Matteo, Sarah, Baber and Andrea for giving me support and advice during my study. Thanks also to Julia Cowx for giving me support and help.

In addition, super thanks to Dr. Mahmoud Alymani, Dr. Muhammad Alsyad and Dr. Nihal Erfan for helping and supporting me to get my scholarship to study abroad.

Finally, many thanks to my family, my friends particularly Khalaf Alsharif.

Abstract

Non-motor symptoms have a major impact on the quality of life of patients with Parkinson's Disease (PD), particularly neuropsychiatric symptoms and cognitive impairment, which have been observed even in the early stages of the disease.

The main aim of this thesis was to explore the cognitive and neural correlates of neuropsychiatric symptoms and to identify the neural damage causing cognitive impairment in PD without dementia. The neuropsychiatric inventory and a battery of neuropsychological tests were used, while voxel-based morphometry of volumetric brain scans was used to detect volumetric associations.

Depression and apathy were the most common neuropsychiatric symptoms. Multiple neuropsychiatric symptoms were associated mainly with executive dysfunction. Depression was associated with attention and short term memory impairments, whereas apathy correlated with executive dysfunction. Volume reductions in frontal and temporal lobes were detected in patients with either multiple or specific neuropsychiatric symptoms (for depression: bilateral inferior frontal gyrus, right rectal gyrus and the right parahippocampal gyrus; for apathy: inferior frontal gyrus, anterior cingulate cortex, insula and cerebellum). This study has shown that the presence of depression and apathy in PD is associated with more extensive structural impairment and suggests that their presence represents a greater risk for dementia.

In addition, this study detected brain regions that were associated with specific cognitive deficits including deficits in executive functions, abstract reasoning, memory, visual-constructional, learning and attentional abilities. In detail, deficits of executive abilities were not restricted to atrophy in fronto-striatal circuits but also implicated inferior parietal lobule, precuneus and inferior/middle/superior temporal gyrus. The identified patterns of grey matter volume loss will enable the differentiation from profiles of atrophy due to other overlapping neurodegenerative diseases.

These findings enable a more extensive understanding of the nature and neural basis of neuropsychiatric symptoms and cognitive impairment in PD and emphasise the need for earlier detection in clinical settings.

Contents

List of Abbreviations

PD= Parkinson's Disease; **PDD=** Parkinson's Disease with Dementia; **AD=** Alzheimer's Disease; **NPI=** Neuropsychiatric Inventory; **ICDs=** Impulsive Control Disorders; **DLB=** Dementia with Lewy Body; **MCI=** Mild Cognitive Impairment; **MRI=** Magnetic Resonance Imaging; **fMRI=** Functional Magnetic Resonance Imaging; **VBM=** Voxel Based Morphometry; **PET=** Positron Emission Tomography; **SPECT=** Single Photon Emission Computed Tomography; **SPM=** Statistical Parametric Mapping; **ROI=** Region of Interest; **SD=** Standard Deviation; **DAT=** Dopamine Transporter; **rCBF**= Regional Cerebral Blood Flow; **DSM-IV-TR**= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; **DSM-IV**= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; **DSM-III-R**= Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revision; **HRSD**= Hamilton Rating Scale for Depression; **AES**= Apathy Evaluation Scale; **WCST**= Wisconsin Card Sorting Test; **FAB**= Frontal Assessment Battery; **MMSE**= Mini Mental State Examination; **FOG**= Freezing of Gait; **VH**= Visual Hallucinations; **TMT**= Trail Making Test; **RAVLT**= Rey Auditory Verbal Learning Test; **WAIS**= Wechsler Adult intelligence scale; **BA**= Brodmann Area; **ALFF**= Amplitude of the Low Frequency Fluctuation; Dopamine Transporter Messenger RNA= mRNA.

1. CHAPTER ONE: PARKINSON'S DISEASE

1.1 THE HISTORY OF PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative disorder that causes motor dysfunctions (tremor, rigidity, bradykinesia and postural disturbance) (Thanvi, Munshi, Vijaykumar, & Lo., 2003). The initial symptoms reflect the deficit of a particular region of the brain called the substantia nigra, which is responsible for the synthesis and storage of the neurotransmitter dopamine. With the progression of the disease, other brain regions are also affected including the allocortex and the temporal mesocortex (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004). The substantia nigra might deteriorate for several reasons including, tumor, stroke, chemical agents or virus infection. However, the overall cause of PD is unknown (Coene, 2000; Duvoisin, 1991). In addition to motor dysfunction, PD patients commonly suffer from non-motor symptoms including mood disorder, apathy, hallucination, cognitive impairment, complex behavioural disorders, sensory dysfunction, autonomic dysfunction, and sleep disturbance (Poewe, 2008).

The most common type of parkinsonism was described by James Parkinson in 1817 (Duvoisin, 1991), in an essay he wrote about six patients who suffered from a slowly progressive physical disease. He characterized the illness as uncontrolled tremulous movement; with lessened muscular power, and a propensity for the patients to lower the trunk forward. This type of PD is sometimes also called idiopathic parkinsonism or paralysis agitans (Stern & Lees, 1982).

PD was well known for its signs and symptoms before identifying the pathological features. In the mid-19th century, Jean Marie Charcot 1887 (as cited in Duvoisin, 1991) studied patients with PD and added muscular rigidity to the known symptoms of PD and also suggested a possible form of treatment. Following this many

physicians started to study the pathological features characterised by the damage to the nervous system in PD to identify the nature of impairments causing this disease. However, they could not determine any abnormalities, and some physicians thought the impairment was located in the spinal cord, while others thought the problem was in the muscles. Tretiakoff 1919 (as cited in Duvoisin, 1991) in Paris described changes in the nerve cells in a particular brain region called the substantia nigra which is now recognised as the locus where the pathological process of PD begins.

In addition to physical dysfunction, Charcot and Vulpian 1861 (as cited in Piovezan, Teive, Piovesan, Mader, & Werneck, 2007) observed various mental changes caused by PD including loss of memory. Furthermore, in 1882, Ball (as cited in Duvoisin, 1991) described a number of patients with Parkinson's disease who also had psychiatric symptoms and in one he also observed dementia. Walshe 1955 (as cited in West, 1991) further noted that many PD patients may also have intellectual impairments. These symptoms have been confirmed by more recent research (Aarsland et al., 2009; Aarsland et al., 2007; Schneider, Althaus, Backes, & Dodel, 2008; Thanvi, et al., 2003; Weintraub, Comella, & Horn, 2008b; Wolters, 2009).

1.2 THE INCIDENCE AND PREVALENCE OF PD

PD is the second most common neurodegenerative disorder after Alzheimer's disease (AD) (Meireles & Massano, 2012). PD is more commonly found in older people and affects approximately 1% of the population over the age of 50, and up to 2.5% of the population over the age of 70 (Cummings, 1999; Marsh, 2000). There are regional variations in prevalence rates as well as in incidence rates, but overall, this disease affects approximately 120,000 people in the United Kingdom (Brain Research Trust, 2013). According to Hirtz (2007), in the United States Parkinson disease affects about 160 persons per 100,000 person-years, with approximately 59,000 new cases per year (Hirtz et al., 2007). A recent cross sectional study carried out in the United States

reported that out of 3,459,986 disabled Americans (aged 30-54), 14.354 cases were identified as having young onset PD, which means the prevalence of young onset PD is 414.9 per 100.000 disabled Americans (Willis et al. 2012). Another study reported that the prevalence rate of PD in L'Aquila district in Italy was 229.3/100,000. This rate increased with advancing age (Totaro et al., 2005). Recently, a community-based study in Egypt found that the prevalence rate of PD was 557/100,000 (Khedr et al., 2012). In Asia, the overall incidence rates of PD are between 1.5 and 17 per 100,000 person-years (Chen et al., 2001; Morioka et al., 2002; Wang, 1991). Mostly, people contract the disease at approximately 50 years of age or over, but there are cases of people being affected by the disease at a younger age (Parkinson's UK, 2013). The number of elderly people who may have the disease is expected to increase giving that the projections for the UK is aging population suggest that the number of people aged 65-74 will increase from 5.0 million in 1988 to 6.8 million in 2031, people aged 75 and over are expected to increase from 3.9 million in 1988 to 5.4 million by 2031 (West, 1991). It should be noted that PD affects men more frequently than women (Khedr, et al., 2012; Marsh, 2000; Masalha et al., 2010; Stern & Lees, 1982).

1.3 THE DIAGNOSTIC PROBLEM

Several studies have indicated clinical criteria for the diagnoses of PD. These studies emphasised that two of the following three cardinal motor features have to be observed to diagnose PD: resting tremor, rigidity and bradykinesia (Frank, Pari, & Rossiter, 2006; Jankovic, 2008; Weiner, 2008). Jankovic (2008), and Albanese (2003) outlined a further motor feature which is relevant to diagnosis which is postural instability. In addition to these symptoms there are other motor and non-motor signs including depression, anxiety, cognitive impairment, sleep disorder, sensory abnormalities, and autonomic dysfunction (Albanese, 2003; Jankovic, 2008). Ransmayr (2007) suggested different clinical criteria for the diagnosis of PD with akinesia being

an essential sign with at least one of three of the following features: tremor, rigidity and impairment of posture, gait and balance (Ransmayr, 2007).

Albanese (2003) suggested a three stage approach to the diagnosis of PD by differentiating three phases in the course of the disease. Firstly, the pre-clinical period, in which the degenerative process is incomplete, but there are no obvious signs. The second phase is the prodromal period as it is characterised by some symptoms that are not specific such as, depression, anxiety, or shoulder pain. The last phase is the symptomatic period, this means it is the phase when the first signs of PD appear (Albanese, 2003).

Recently, diagnostic criteria have been developed by the United Kingdom PD Society Brain Bank and the National institute of Neurological Disorder and Stroke (Gelb, Oliver, & Gilman, 1999; Jankovic, 2008) (see Tables 1.1 and 1.2).

Table 1.1 UK PD Society Brain Bank's clinical criteria for the diagnosis of probable PD (Gelb, et al., 1999; Jankovic, 2008)

Step 1	Bradykinesia At least one of the following criteria: Rigidity 4-6 Hz rest tremor Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
Step 2	Exclude other causes of parkinsonism
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

Table 1.2 National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for PD (Gelb, et al., 1999; Jankovic, 2008)

Group A features (characteristic of PD)	Resting tremor Bradykinesia Rigidity Asymmetric onset
Group B features (suggestive of alternative diagnoses)	Features which are unusual early in the clinical course Prominent postural instability in the first 3 years after symptom onset Freezing phenomenon in the first 3 years Hallucinations unrelated to medications in the first 3 years Dementia preceding motor symptoms or in the first year Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades Severe, symptomatic dysautonomia unrelated to medications Documentation of condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)
Criteria for definite PD	All criteria for probable Parkinson's disease are met and Histopathological confirmation of the diagnosis is obtained at autopsy
Criteria for probable PD	At least three of the four features in group A are present and None of the features in group B is present (note: symptom duration > 3 years is necessary to meet this requirement) and substantial and sustained response to levodopa or a dopamine agonist has been documented
Criteria for possible PD	At least two of the four features in group A are present; at least one of these is tremor or bradykinesia and either none of the features in group B is present or symptoms have been present <3 years and none of the features in group B is present and either substantial and sustained response to levodopa or a dopamine agonist has been documented or the patient has not had an adequate trial of levodopa or a dopamine agonist

The neuropathological criteria for diagnosing PD have been outlined in several studies. A typical neuropathology finding is loss of neurons in the substantia nigra and presence of Lewy bodies in subcortical regions (Albanese, 2003; Dickson et al., 2009; Frank, et al., 2006).

Recently, several tests have been developed to improve the diagnostic accuracy of Parkinsonism, specifically in the early stages. These tests include Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) imaging techniques (Kagi, Bhatia, & Tolosa, 2010). Dopamine Transporter (DAT) SPECT imaging is now considered as a sensitive early diagnostic test for PD. Also, the test can be used to differentiate between non-parkinsonian tremor disorders, psychogenic parkinsonism, drug-induced parkinsonism or vascular parkinsonism (Booij, Speelman, Horstink, & Wolters, 2001; Gerschlager, 2002; Poewe & Scherfler, 2003). Moreover, DAT-SPECT imaging has been used to detect disease progression because striatal tracer binding has been shown to be associated with the severity and duration of PD (Marek et al., 2001).

Furthermore, one of the most important advantages of using DAT is that dopaminergic therapy can be continued because it has no effect on DAT binding. However, dopaminergic central nervous system stimulants must be stopped before a DAT scan because these types of medication have a strong influence on the DAT scan findings (Kagi, et al., 2010).

1.4 NEUROPATHOLOGY of PD

The early symptoms of PD reflect the degeneration of the substantia nigra. Normally the nerve cells of the substantia nigra send messages through fibers which connect with other nerve cells in the deep grey matter of the cerebral hemispheres within the corpus striatum. The dopamine produced in the substantia nigra travels via connections to the corpus striatum. When the substantia nigra cells degenerate or are damaged, and cannot produce or store dopamine, the striatum will not get its supply of dopamine. The resulting symptoms from this condition are those of PD (Duvoisin, 1991). Clearly, abnormalities of the substantia nigra play an important role in causing movement disorders in PD (Coene, 2000).

According to Hatano et al (2009) neuronal loss and the presence of Lewy body are recognized in the substantia nigra pars compacta and other brain areas including the locus coeruleus, the pedunculopontine nucleus, the raphe nucleus, the dorsal motor nucleus of the vagal nerve, the olfactory bulb, and parasympathetic areas in the cerebral cortex (Hatano, Kubo, Sato, & Hattori, 2009).

The deterioration of neuromelanin containing substantia nigra pars compacta neurons leads to depigmentation of this focal region (Marsden, 1983). The consequence of striatal dopamine loss in the putamen is the appearance of two PD symptoms which are akinesia and rigidity. Approximately 80% of dopamine supply to the putamen is lost at the onset of PD symptoms and when the depletion of dopamine in the substantia nigra pars compacta reaches approximately 60% (Lee & Liu, 2008). Furthermore, there is a good correlation between the levels of substantia nigra pars compacta cell loss and the expression levels of the dopamine transporter mRNA (Uhl, Walther, Mash, Faucheux, & Javoy-Agid, 1994). However, all dopaminergic neurons are not equally affected as those in the substantia nigra (Lee & Liu, 2008).

The topography of cell loss progression in the substantia nigra in PD is different compared with normal aging. The cell loss in PD is focused in the ventrolateral and caudal areas of the substantia nigra pars compacta, whereas, in normal aging the substantia nigra pars compacta dorsomedial portion is affected (Fearnley & Lees, 1991; Hindle, 2010). Moreover, PD has a particular cell loss pattern that is not seen in other neurodegenerative diseases or in normal ageing (Hindle, 2010).

The substantia nigra in PD without dementia shows macroscopically decreased pigmentation, whereas, the striatum, cortex, ventricles, brain stem and cerebellum are unchanged compared with the pigmentation found in the brains of normal ageing individuals. In the substantia nigra, Lewy bodies appear in pigmented neurons as central cytoplasmic cleared areas (Cornford, Chang, & Miller, 1995).

The presence of Lewy bodies can be observed not only in PD but also in other diseases such as Dementia with Lewy Bodies (DLB), AD, and in healthy people of advanced age (Cookson, Hardy, & Lewis, 2008; Cornford, et al., 1995; Gibb & Lees, 1988). Although the occurrence of Lewy bodies is important as a sign of several diseases, the role of Lewy bodies is unclear in neuronal cell death (Lee & Liu, 2008).

There is a correlation between the degeneration of some of non-dopaminergic areas and PD secondary symptoms such as dementia which can be a consequence of degeneration of hippocampal structures and other cholinergic structures (Lee & Liu, 2008). Furthermore, according to Cornford et al (1995) degeneration of the basal ganglia can result in symptoms such as abnormal movement, psychiatric symptomatology and cognitive impairment (Cornford, et al., 1995).

Braak and colleagues have proposed a staging of brain pathology related to PD. The progress of PD includes six stages (table 1.3) and each stage is characterised by the presence of Lewy neurites and Lewy bodies in specific brain regions (Braak et al., 2003; Braak, et al., 2004). Table 1.3 shows the regions involved by degeneration of each of the six stages.

1.5 RISK FACTORS

The most common risk factors for developing PD are genetic factors, aging, and environmental factors. Moreover, there is an interaction between these risk factors. The changing of brain cells can be affected by aging but, neuronal death is not programmed to appear at a specific time. However, the changes due to aging interact with genes and environmental factors related to cellular and molecular brain areas to determine the age at which some cells would degenerate (Hindle, 2010).

Table 1.3 Stages in the development of PD

Stages	Affected brain regions
Stage 1	Dorsal motor nucleus of the vagal nerve and/or intermediate reticular zone.
Stage 2	Pathology of stage 1 plus damage in caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus-subcoeruleus complex.
Stage 3	Pathology of stage 2 plus pars compacta of the substantia nigra.
Stage 4	Pathology of stage 3 plus involvement of the allocortex and the temporal mesocortex.
Stage 5	Pathology of stage 4 plus damage in high order sensory association areas of the neocortex and prefrontal neocortex.
Stage 6	Pathology of stage 5 plus damage in primary sensory association areas of the neocortex and premotor areas.

1.5.1 GENETIC FACTORS

Genetic factors may play an important role in PD. The results of twin studies indicate a genetic component to the disease. However, this does not mean people carrying some genetic mutation will inevitably develop the disease, but that the possibility of such a development is slightly higher than in the rest of the population (Coene, 2000).

Although PD has been considered a non-genetic disorder for a long time, several studies have linked this disease to genetic factors (Burbulla & Kruger, 2011; Cookson & Bandmann, 2010; Poulopoulos, Levy, & Alcalay, 2012; Schiesling, Kieper, Seidel, & Kruger, 2008; van der Vegt, van Nuenen, Bloem, Klein, & Siebner, 2009). About 5% of patients who have PD clinical features have clear positive familial history. Moreover, the contribution of genetics in PD was identified by the discovery of mutations in two genes that can cause autosomal dominant (a-synuclein and LRRK2) or recessive inherited (parkin, PINK1, and DJ1) forms of the disease (Hardy, Lewis, Revesz, Lees,

& Paisan-Ruiz, 2009; Hatano, et al., 2009; Lee & Liu, 2008; Moore & Dawson, 2008; van der Vegt, et al., 2009).

1.5.1.1 GENES THAT CAUSE DOMINANT PARKINSONISM

1.5.1.1.1 Alpha- Synuclein (PARK 1 and 4)

A-Synuclein was the first gene associated with familial Parkinsonism. The α-synuclein mutation was identified in Greek/ Italian families with autosomal dominant transmission PD (Polymeropoulos et al., 1997). There are also three missense mutations associated with autosomal dominant PD which are A53T, A30P, and E46K (Burbulla & Kruger, 2011). However, these missense mutations have not been found in sporadic PD and healthy individuals (Kruger et al., 1998; Polymeropoulos, et al., 1997). Carriers of mutation of the a-synuclein gene display typical symptoms of PD e.g. rigidity, resting tremor, bradykinesia and postural instability but carriers of some mutations show a more severe phenotype with early onset and rapid disease progression (A53T) and severe dementia (A53T and E46K). In contrast, carriers of the A30P mutation display a milder phenotype (Burbulla & Kruger, 2011). Neuropathological examination of patients with α-synuclein mutations showed the presence of major Lewy bodies' pathology (Schiesling, et al., 2008; Spira, Sharpe, Halliday, Cavanagh, & Nicholson, 2001; Zarranz et al., 2004). Furthermore, α-synuclein is important in PD, because it is linked to Lewy bodies and Lewy neuritis in both familial PD patients with mutations in the α-synuclein gene and in idiopathic PD (Schiesling, et al., 2008). In fact, patients with duplication of the alpha-synuclein have autosomal dominant familial PD (Chartier-Harlin et al., 2004; Ibanez et al., 2004). Patients with multiplication of alpha-synuclein and patients with diffuse Lewy body disease have similar brain pathology. So, α-synuclein might lead to PD pathology through the over-production of wild-type proteins and the toxic-gain of functioning of mutant proteins (Hatano, et al., 2009). Compared

with duplication phenotypes, the phenotypes of multiplication cases have a tendency to have an earlier onset, more cortical involvement and a more severe form of the disease (Fuchs et al., 2007).

1.5.1.1.2 LRRK2 (PARK8)

LRRK2 mutations were initially found in large families from the Basque Country and England (Paisan-Ruiz et al., 2004). Moreover, mutations in the LRRK2 are considered the most frequent genetic cause of sporadic and familial PD (Schiesling, et al., 2008). These mutations are found to be present with no specific preference site in the gene and cause an autosomal dominant form of familial PD (Schiesling, et al., 2008). In addition, mutations in the LRRK2 are responsible for about 2% of sporadic and 10% of familial cases of PD (Berg et al., 2005; Mata, Wedemeyer, Farrer, Taylor, & Gallo, 2006). In fact, these mutations appear without a particular predilection site throughout the gene causing an autosomal dominant form of familial PD (Schiesling, et al., 2008). The most common mutation in LRRK2 G2019S was observed in 40% of familial and sporadic PD in the Arab population of North Africa (Lesage et al., 2006) and in 20% of Ashkenazi Jewish population (Ozelius et al., 2006). The G2019S mutation provides similar neurodegeneration patterns that are associated with Lewy bodies (Giasson et al., 2006; Ross & Smith, 2007; Ross et al., 2006). However, three other genes (R1441C, Y1699C, and I2020T) often lack Lewy body pathology and are accompanied with pure nigral degeneration, including neurofibrillary tangles, atypical cytosolic fibrils or motor neuron degeneration (Funayama et al., 2002; Taylor, Counsell, Harris, Gordon, & Smith, 2006; Zimprich et al., 2004).

1.5.1.2 RECESSIVE PARKINSONISM GENES

1.5.1.2.1 PARKIN (PARK2)

Parkin mutations were discovered in Japanese families and are the most common cause of autosomal recessive early-onset Parkinsonism (Mizuno et al., 2008; Schiesling, et al., 2008). Parkin mutations are responsible for approximately 50% of familial and 20% of sporadic early-onset PD patients in the European population (Lucking et al., 2000). Several studies have emphasised that the phenotypes of many patients who have parkin mutations might be clinically indistinguishable from idiopathic PD (Abbas et al., 1999; Klein et al., 2000). According to Cookson et al (2008) many mutations have been identified such as truncations, exon rearrangements and point mutations (Cookson, et al., 2008). Mutations of the Parkin gene are often considered to be the most common cause of young onset PD. Carriers of the Parkin mutation tend to be younger at disease onset, display a slower progression of the disease and often show a better response to Levodopa treatment (Khan et al., 2002; Khan et al., 2003; Lohmann et al., 2009).

1.5.1.2.2 PINK1

PINK1 mutations were initially identified in Italian and Spanish families (Valente et al., 2004). Moreover, the PINK1 mutation is the second most common autosomal recessive that has been linked to PD after the parkin gene (Hatano, et al., 2009; Valente, et al., 2004). PINK1 is associated with the PARK6 situs on chromosome 1P36 (Valente, et al., 2004). Furthermore, Klein and Schlossmacher (2007) have reported that the prevalence of PLNK1 mutations in familial or young onset PD is about 1-8%. PINK1-linked PD has a similar clinical phenotype as idiopathic PD, including a good response to levodopa, the frequent appearance of levodopa-induced dyskinesias, and the frequent appearance of dystonia. However, some patients have atypical clinical

signs associated with psychiatric disorders, dementia, and dystonia and might resemble those with parkin mutations (Klein & Schlossmacher, 2007). In fact, two studies have suggested that PINK1 might be a contributor to early-onset Parkinsonism (Klein et al., 2005; Valente, et al., 2004), but the degree of contribution of PINK1 to sporadic PD development remains unclear (Clarimon et al., 2005; Deng, Le, Zhang, Pan, & Jankovic, 2005).

Hybridization studies, in the human and the rodent brain, have indicated that PINK1 mRNA is distributed in the substantia nigra, cerebellar purkinje cells, and in the hippocampus (Blackinton et al., 2007; Taymans, Van den Haute, & Baekelandt, 2006). Moreover, Gandhi et al. (2006) found that the detection of the PINK1 protein was in a small group (5- 10%) of brainstem Lewy bodies, in cortical Lewy bodies and in glial cytoplasmic inclusion bodies. This study also reported an association between PINK1 and parkin proteins (Gandhi et al., 2006). In addition, parkin and PINK1 mutations were identified in PD cases with a younger age of onset more than in patients with the same parkin mutation alone (Funayama et al., 2008). Thus, the relationship between PINK1 and parkin suggests that both proteins may share a common pathway in PD pathogenesis (Cookson & Bandmann, 2010; Hatano, et al., 2009).

1.5.1.2.3 DJ-1 (PARK7)

The first discovered DJ-1 mutations were found in one Dutch family (Bonifati et al., 2003; van Duijn et al., 2001) with this discovery being subsequently confirmed in different families from Italy and Uruguay (van Duijn, et al., 2001). However, several studies reported that DJ-1 mutations are a rare cause of familial early-onset Parkinsonism, with a frequency of about 1-2% (Abou-Sleiman, Healy, Quinn, Lees, & Wood, 2003; Clark et al., 2004; Hering et al., 2004). In fact, atypical clinical PD symptoms can be observed in patients with homozygous mutations in the DJ-1 gene, in addition to other features such as dystonia, laterocollis, and psychiatric signs including

psychotic episodes (Hatano, et al., 2009; Yang et al., 2006). Clinically, the phenotype in patients with DJ-1 mutations is similar to the parkin or PINK1 mutant patients (Abou-Sleiman, et al., 2003; Cookson & Bandmann, 2010; Hering, et al., 2004).

The localization of DJ-1 in the human brain is mainly in astrocytes and astrocytic processes, with few or no DJ-1 immunoreactivity in neurons (Bandopadhyay et al., 2004). The high level of DJ-1 in sporadic PD patients was identified in the cerebrospinal fluid. Moreover, there was a positive correlation between DJ-1 cerebrospinal fluid levels and disease severity (Waragai et al., 2006).

Recent studies have demonstrated an association between mitochondria dysfunction and both genetic and environmental factors in PD (Burbulla & Kruger, 2011; Schapira, 2011). Mitochondrial dysfunction has been commonly associated with α-synuclein, Parkin, Pink1, DJ1 and LRRK2 (Schapira, 2011). On the other hand, environmental factors such as toxins and pesticides may increase the risk of having PD. Some of these environmental factors are supposed to interact with mitochondrial function, which may contribute to the death of dopaminergic neurons (Burbulla & Kruger, 2011).

1.5.2 AGING FACTOR

Several studies have indicated that age influences the clinical progression of PD (Halliday & McCann, 2010). The rate of motor progression is faster with advanced age and there is also a decreased responsiveness to levodopa, a more severe impairment in gait and posture, and a more severe impairment in cognition which can then result in the development of dementia in PD patients (Levy, 2007). Age was not found to be correlated with the severity of tremor, rigidity, and bradykinesia (Levy et al., 2000).

According to cross-sectional studies the rate of motor progression in PD patients with later onset is faster than those with earlier onset because the disease duration is

significantly shorter and they have a similar level of disabilities (Jankovic et al., 1990). Levodopa therapy can improve daily living activities in early onset PD more than in older onset PD (Durso, Isaac, Perry, Saint-Hilaire, & Feldman, 1993).

Cognitive impairment may be occurring in patients with PD and can be more global in older age. Patients with PD are more likely to develop dementia compared with age-matched controls. Moreover, while motor learning slows with age in PD patients, motor learning and executive function are more significantly impaired. In addition, patients with PD show significant impairments in visuo-spatial tasks compared with age-matched controls and healthy young people (Aarsland, et al., 2007).

The increased severity of cognitive impairment in PD with onset at an older age has been supported by cross-sectional neuropsychological studies (Dubois, Pillon, Sternic, Lhermitte, & Agid, 1990; Katzen, Levin, & Llabre, 1998). Furthermore, prospective cohort studies have confirmed the association of older age with the development of dementia in PD (Aarsland, Litvan, & Larsen, 2001; Hobson & Meara, 2004; Hughes et al., 2000; Marder, Tang, Cote, Stern, & Mayeux, 1995). Moreover, a longitudinal study has indicated the association of older age with a faster rate of cognitive decline in PD patients (Aarsland et al., 2004; Caparros-Lefebvre, Pecheux, Petit, Duhamel, & Petit, 1995).

Mild parkinsonian symptoms including rigidity, bradykinesia, tremor and difficulties in gait and balance have been observed during the clinical examination of older people who do not have a diagnosis of neurological diseases (Louis & Bennett, 2007). These mild parkinsonian symptoms can lead to functional difficulties such as poor performance of activities of daily living, gait and balance impairment, increased risk of dementia, Mild Cognitive Impairment (MCI) and death. Clinically, the differences between PD and mild parkinsonian symptoms include the number and

severity of parkinsonian symptoms and levodopa therapy responsiveness (Hindle, 2010).

Although the number of nigral cells declines by 4.7- 6.0% per decade from the fifth to the ninth decade of life (Gibb & Lees, 1991), this cell loss is not enough to produce parkinsonian signs (Mcgeer, Mcgeer, & Suzuki, 1977; Thiessen, Rajput, Laverty, & Desai, 1990).

1.5.3 ENVIRONMENTAL FACTORS

Several studies have reported that environmental factors are one of the most important risk factors for PD. Particularly, PD is prevalent in industrialised countries, a finding which is consistent with the involvement of industrial toxins (Tanner, 1989; Tanner et al., 1987). Environmental factors include pesticide, head trauma, diet, rural living, well water drinking, smoking, and infections. The following will explain each of these environmental risk factors in turn.

1.5.3.1 PESTICIDE EXPOSURE

Many kinds of pesticide including insecticides, herbicides, fungicides, rodenticides, and fumigants are widely used and several studies have indicated that there is a positive correlation between pesticide exposure and the risk of having PD (Bhidayasiri et al., 2011; Brown, Rumsby, Capleton, Rushton, & Levy, 2006; Van Maele-Fabry, Hoet, Vilain, & Lison, 2012; Wang et al., 2011). Humans can be exposed to pesticide directly by skin contact or indirectly by contaminated food and water or aspiration of pesticides (Lai, Marion, Teschke, & Tsui, 2002).

The duration of pesticide exposure relative to its effects was assessed in a number of studies. These studies showed a positive correlation between the duration of pesticide exposure and PD (Jimenez-Jimenez, Mateo, & Gimenez-Roldan, 1992; Morano, Jimenez-Jimenez, Molina, & Antolin, 1994; Seidler et al., 1996; Smargiassi et

al., 1998; Van Maele-Fabry, et al., 2012). In addition, Kenborg and others (2012) found that there was a dose-related link between exposure to pesticides and risk of PD (Kenborg, Lassen, Lander, & Olsen, 2012).

Ascherio et al (2006) found in a cohort study of more than 100,000 individuals that the incidence of PD is approximately 70% higher in individuals who have been exposed to pesticides than in those who have been not exposed, whereas, there was no correlation between the risk of PD and exposure to other occupational agents (Ascherio et al., 2006).

Dick and others (2007) have investigated the association between environmental factors and PD and other degenerative parkinsonian syndromes in five European countries. The sample was 959 cases of Parkinsonism (767 with PD) and 1989 controls from Scotland, Italy, Sweden, Romania, and Malta. Cases were diagnosised by using the United Kingdom PD Society Brain Bank criteria. Subjects were asked to complete an interviewer-administered questionnaire about hobby exposure to solvents, pesticides, iron, copper, and manganese as well as lifetime occupational exposure. Using regression analyses the study showed a significant association between PD/ Parkinsonism and pesticide exposure (Dick et al., 2007).

1.5.3.2 HEAD TRAUMA

Although the correlation between head trauma and Parkinsonism is unclear, some studies have reported a relationship between PD and head trauma (Lai, et al., 2002). Patrick and Levy (1922) have indicated that trauma was related to PD in approximately 15% of their patients. Moreover, Schwab and England (1968) observed that the only way for head trauma to cause Parkinsonism is when it is severe enough to cause brainstem haemorrhage (Lai, et al., 2002).

Various epidemiological studies have concentrated on life experiences and demographic factors that happened years prior to the onset of PD. Several case- control studies have positively linked head trauma to subsequent PD (Factor & Weiner, 1991; Seidler, et al., 1996; Semchuk, Love, & Lee, 1993; Taylor et al., 1999). A recent meta-analysis study reported a positive correlation between previous head injury and the risk of developing PD (Noyce et al., 2012). On the other hand, some studies did not find a significant difference between patients and controls for exposure to head trauma (Hofman, Collette, & Bartelds, 1989; McCann et al., 1998; Morano, et al., 1994; Smargiassi, et al., 1998).

1.5.3.3 DIETARY FACTORS

It has been suggested that oxidative damage may play an important role in nigral cell loss in PD (Veldman, Wijn, Knoers, Praamstra, & Horstink, 1998). Therefore, the consumption of animal fats is associated with PD which is consistent with the involvement of oxidative reactions (Logroscino et al., 1996). Although some scientists have suggested that vitamin E levels are associated with PD (de Rijk et al., 1997; Golbe, Farrell, & Davis, 1988), other studies have not found any influence of vitamin E in PD occurrence (Logroscino, et al., 1996; Morens et al., 1996; Scheider et al., 1997; Vieregge, von Maravic, & Friedrich, 1992). Similarly, Hellenbrand et al (1996) found an association between vitamin C level and the risk of developing PD (Hellenbrand et al., 1996), while other researchers found that vitamin C levels are not associated with PD (de Rijk, et al., 1997; Fernandez-Calle et al., 1993). Finally, vitamin A level has been found not to be related to the risk of developing the disease (Jimenez-Jimenez, et al., 1992).

However, according to Lai et al (2001) there is a relationship between specific diets and PD (Lai, et al., 2002). Fall et al (1999) reported a reduced risk for niacin-containing dietary items which include wine, coffee and liquor at different consumption

levels, smoked ham or meat, fried or boiled meat, egg, French loaf or white bread, and tomatoes (Fall, Fredrikson, Axelson, & Granerus, 1999). A negative correlation between both coffee and alcohol consumption and having PD has also been recently identified (Noyce, et al., 2012).

1.5.3.4 RURAL LIVING

Rajput et al (1984) observed a relationship between living in a rural environment and the risk of PD (Rajput, Offord, Beard, & Kurland, 1984). For the first time, these findings were confirmed in 1987 by Rajput et al (Rajput et al., 1987). Moreover, researchers noticed low nigral neuronal cell counts in people who live in rural areas (Thiessen, et al., 1990). Although several studies have confirmed the presence of a correlation between rural living and PD (Butterfield, Valanis, Spencer, Lindeman, & Nutt, 1993; Khedr, et al., 2012; Liou et al., 1997; Marsh, 2000; Masalha, et al., 2010; Rajput, et al., 1987; Stern & Lees, 1982; Vieregge, et al., 1992), other studies found no significant relationship (Seidler, et al., 1996; Semchuk, Love, & Lee, 1991).

1.5.3.5 WELL WATER DRINKING

Several studies have found an association between the sources of water supply and PD (Adler, 2009; Firestone et al., 2005; Jimenez-Jimenez, et al., 1992; Morano, et al., 1994; Rajput, et al., 1987; Wright & Keller-Byrne, 2005). For instance, according to Herishanu et al. (1989) the incidence of PD has been found to be approximately five times higher in each of three kibbutzims (collective rural communities) using well water than in the Negev (southern Israel) (Herishanu, Goldsmith, Abarbanel, & Weinbaum, 1989). Recently, Gatto and colleagues (2009) investigated the relationship between well-water consumption and the risk of developing PD in rural California. They found that well-water consumption increased the risk of PD (Gatto, Cockburn, Bronstein, Manthripragada, & Ritz, 2009).

On the other hand, other studies have found no correlation between PD and well water consumption (Hertzman, Wiens, Bowering, Snow, & Calne, 1990; Liou, et al., 1997; Semchuk, et al., 1991; Zayed et al., 1990).

1.5.3.6 SMOKING

Although cigarette smoking has been associated with chronic diseases such as lung and cardiovascular diseases (Ostergaard, 1977), many studies have found an association between smoking and a lower risk of PD (Hancock et al., 2007; Hertzman, et al., 1990; Kumar & Jangra, 2012; Liou, et al., 1997; Nuti, Ceravolo, Dell'Agnello, et al., 2004; Quik, 2004; Seidler, et al., 1996). Some of these studies suggested the risk of PD is twice as high in non-smokers than in smokers. However, more recently, Sipetic et al (2012) found that smoking was negatively associated with PD, regardless of the duration of smoking and the number of cigarettes smoked per day (Sipetic et al., 2012). However, other studies did not find a significant difference between PD patients and controls exposed to smoke (McCann, et al., 1998; Rajput, 1984; Wang, Fang, Cheng, Jiang, & Lin, 1993). Smokers' brains had a 40% reduction in Monoamine Oxidase B (Fowler et al., 1996). An increased concentration of dopamine in the brain is related to Monoamine Oxidase B activity reduction, because Monoamine Oxidase B breaks dopamine down (Fowler et al., 1999; Veldman, et al., 1998).

Nicotine plays an important role because it can stimulate dopamine release (Baron, 1986; Fowler, et al., 1999; Janson, Fuxe, & Goldstein, 1992), and up-regulates nicotinic receptors (Baron, 1986; Perry et al., 2007). These results were consistent with several biological hypotheses of PD. In addition, nicotine stimulates presynaptic nicotinic receptors directly (Lehouezec & Benowitz, 1991).

1.5.3.7 INFECTIONS

One of the possible environmental risk factors for PD is infections such as encephalitis lethargic during the influenza pandemic of the late 1910s. These infections led to many cases of parkinsonism (Veldman, et al., 1998). Although sporadic cases of lethargic encephalitis have been confirmed, in the majority of patients the specific virus type could not be determined (Mellon, Appleton, Gardner-Medwin, & Aynsley-Green, 1991; Picard, Hirsch, Salmon, Marescaux, & Collard, 1996).

Many reports suggest that some infectious diseases, such as HIV (Cruto, Freitas, Carvalheiras, Mendes, & Lima, 2011), Japanese B encephalitis (Butterfield, et al., 1993), influenza type A (Jang, Boltz, Webster, & Smeyne, 2009; Maurizi, 2010; Morens, et al., 1996), herpes simplex (Martyn & Osmond, 1995), and measles (Mayeux, Tang, Marder, Cote, & Stern, 1994) can be associated temporally with parkinsonism, either acutely or as a long- term complication (Veldman, et al., 1998). A study of intracerebral inoculation in mice with neurovirulent influenza type A viruses indicated that the major target for influenza type A viruses is the substantia nigra (Takahashi et al., 1995). In humans, post-encephalitic parkinsonism has been linked to influenza type A and many other viruses (Jang, et al., 2009; Maurizi, 2010). Recent studies have further supported the association between infections and PD (Arai, Furuya, Mizuno, & Mochizuki, 2006; Harris, Tsui, Marion, Shen, & Teschke, 2012; Liu, Gao, & Hong, 2003). Moreover, a case-control study in Sweden examined the relationship between infections of the central nervous system and sepsis in PD patients (Fang et al., 2012). Results showed that patients with PD were more likely to have prior hospitalizations for central nervous system infections than the controls. However, in a very recent study no association was found between previous hospitalizations for sepsis and a higher risk of PD (Fang et al., 2012).

Seroepidemiological studies could not find any evidence of the relationship between PD and infections (Elizan et al., 1979). Moreover, on histological examination, the brain of patients with PD does not show findings typical of infection and PD is not transmitted to animals by infection of affected brain region (Calne & Langston, 1983).

1.6 SIGNS AND SYMPTOMS OF PD

1.6.1 MOTOR SYMPTOMS

1.6.1.1 TREMOR

Rest tremor is considered the most common and obvious motor symptom of PD (Coene, 2000; Jankovic, 2008). Tremor occurs at a frequency of 5 to 6 beats per second; it usually begins in one hand or foot (Duvoisin, 1991). Tremor in PD can also involve the lips, chin, jaw and legs; it is less likely, however, to involve the head or voice. The tremor disappears during sleep or with action (Jankovic, 2008).

1.6.1.2 RIGIDITY

Rigidity is characterised by resistance to passive movement, it is usually observed by another person because the patient cannot feel the symptom. Patients with rigidity complain of feeling tired, experience headache which reflects the rigidity of the muscles of the head and neck, and back pain (Duvoisin, 1991). Jankovic (2008) reported that one of the most common symptoms consistent with rigidity is a painful shoulder (Jankovic, 2008). Coene (2000) indicated that rigidity is perhaps the symptom that can most severely affect everyday activities, for instance, rolling over in bed or getting out of a chair (Coene, 2000).

1.6.1.3 BRADYKINESIA

Bradykinesia is described as slowness of movement, (brady means slow and kinesia means movement) (Coene, 2000). This symptom is often associated with rigidity: Bradykinesia also leads to loss of automatic movement and so movement that previously occurred unconsciously, would now have to be consciously made, for example, arm swing while walking, eye blinking, and saliva swallowing. Furthermore, bradykinesia affects fine movement, and actions requiring fine movement, such as tying shoelaces or turning a page take more time and effort (Coene, 2000; Duvoisin, 1991).

1.6.1.4 POSTURAL INSTABILITY

Postural instability usually occurs in the late stages of PD and after the onset of other clinical symptoms. Postural instability usually results in poor balance and is one of the most common causes of falls in PD patients. The risk of postural instability in PD patients increases with the presence of other parkinsonian features, such as age related sensory changes and deterioration in the ability to integrate vision (Jankovic, 2008).

1.6.2 NON-MOTOR SYMPTOMS

Non-motor features including neuropsychiatric symptoms, cognitive impairment, sensory dysfunction, autonomic dysfunction, and sleep disturbance are common in patients with PD. It is important to explore the non-motor symptoms because they can impair in daily living activities equally or more than limitations that result from motor deficits (Marsh, & Berk, 2003; Weintraub, & Stern, 2005; Weintraub, Moberg, Duda, Katz, & Sten, 2004). It is worrying to note that previous studies suggest that non-motor symptoms are commonly unrecognized by clinicians and remain untreated (Chaudhuri & Schapira, 2009).

1.6.2.1 NEUROPSYCHIATRIC SYMPTOMS

Common neuropsychiatric symptoms in PD include depression, hallucinations, anxiety and apathy (Aarsland et al., 1999). Depression is the most commonly observed neuropsychiatric symptom. Several studies have indicated that the prevalence rate of depression is approximately 40% (Aarsland, et al., 1999; Marsh, 2000; Park & Stacy, 2009). Aarsland et al (1999) investigated a range of neuropsychiatric disturbances in patients with PD and the results showed that the most common features were depression (38%), hallucinations (27%), anxiety (20%), and apathy (16.5%). The least common symptoms were euphoria (7.0%) and disinhibitions (6.5%). It was found that neuropsychiatric symptoms were more common among PD patients living in nursing homes than patients living in private houses. Although, there was no significant correlation between neuropsychiatric symptoms and the age of onset or the duration of the disease, there was a significant correlation with the stage of disease (Aarsland, et al., 1999). Neuropsychiatric symptoms will be reviewed in detail in chapter two.

1.6.2.2 COGNITIVE IMPAIRMENT

Cognitive impairment associated with PD consists of primarily a dysexecutive or subcortical syndrome, characterized by executive dysfunction, visuospatial impairment, memory deficits, and attention deficits (Marsh, 2000; Weintraub, et al., 2008b). Dementia is common in PD patients; community-based studies have shown the prevalence of dementia among PD patients to be between 28% and 44% (Hobson & Meara, 2004; Leverenz et al., 2009). Cognitive impairment will be reviewed in detail in chapter two.

1.6.2.3 SENSORY DYSFUNCTION

Sensory dysfunctions that are associated with PD include visual changes, decreased olfaction, and pain. Visual changes include changes in visual acuity, colour discrimination, contrast sensitivity, temporal sensitivity, motion perception, visual

processing speed, and peripheral visual field (Diederich, Raman, Leurgans, & Goetz, 2002; Uc et al., 2005). Loss of olfaction and discrimination is common in PD; it has been observed in up to 90% of patients and considered to be the earliest sign of PD (Braak, et al., 2003; Khan et al., 2004). Pain has been considered a common sensory dysfunction and chronic pain has been observed in approximately 40% of patients (Park & Stacy, 2009). Indeed, shoulder pain is recognised as another early or initial symptom of PD (Stamey, Davidson, & Jankovic, 2008).

1.6.2.4 AUTONOMIC DYSFUNCTION

Autonomic dysfunctions in PD include orthostatic hypotension, constipation, and excessive sweating (Stacy, 1999). Orthostatic hypotension is associated with dopaminergic medication, duration and severity of PD (Senard et al., 1997). A community based study indicated that 47% of PD patients met the diagnostic criteria for orthostatic hypotension (Allcock, Ullyart, Kenny, & Burn, 2004). Constipation is a common complaint in PD and prolonged gastrointestinal transit time has been seen in more than 80% of patients. It is likely that this is related to Lewy body pathology in the myenteric plexus and to colonic sympathetic denervation (Park & Stacy, 2009). Excessive sweating is a function of plasma levodopa fluctuations (Park & Stacy, 2009).

1.6.2.5 SLEEP DISTURBANCE

Sleep disturbance is considered the most frequent non-motor symptom of PD (Tandberg, Larsen, & Karlsen, 1998). This includes difficulties falling asleep, frequent awakenings, nocturnal cramps, rapid-eye movement, and sleep apnea (Poewe, 2008; Weintraub, et al., 2008b). Nocturnal sleep disturbance is found in 60-98% of patients with PD (Comella, 2003; Comella, Morrissey, & Leurgans, 2000). Rapid eye movement sleep behaviour disorder is characterized by the loss of normal muscle atonia during rapid eye movement sleep (Arnulf, 2006). The incidence of sleep behaviour disorder is between 15% and 60% among PD patients, and sleep behaviour disorder is considered

as a preclinical marker of parkinsonism (Arnulf, 2006). Multiple factors which may cause sleep disturbance include the motor abnormalities of Parkinsonism (such as rigidity and bradykinesia), levodopa dose, and the pathological degeneration of central sleep regulation centres in the brainstem and thalamocortical pathways (Ziemssen & Reichinann, 2007).

1.6.2.6 FREEZING OF GAIT (FOG)

FOG is one of the most disabling symptoms in PD (Okuma, 2006). It is considered a gait disorder where patients cannot initiate or continue locomotion (Fahn, 1995; Giladi, 2001; Giladi et al., 1992). In addition, FOG is usually observed in the advanced stage of the disease (Fahn, 1995; Giladi, 2001; Giladi et al., 2001). FOG occurs in various situations such as when turning, passing through a narrow space, before reaching destination, and in stressful situations (Okuma, 2006). Although the underlying pathology of FOG is unknown (Bartels et al., 2003; Moore, MacDougall, & Ondo, 2008), damage in the basal ganglia and its frontal connections can be one of the essential elements explaining the occurrence of FOG (Okuma, 2006).

The prevalence of FOG in PD has been reported as being approximately 7% in the early stages and 60% in the more advanced stages of the disease (Giladi, et al., 2001; Lamberti et al., 1997). FOG is a common cause of falls (Bloem, Hausdorff, Visser, & Giladi, 2004; Fahn, 1995; Giladi, et al., 2001), and significantly impairs quality of life (de Boer, Wijker, Speelman, & de Haes, 1996).

PD patients may experience FOG in the early stages when they are not yet receiving treatment. However, FOG in the early stages of PD is usually mild and transient. The severity of FOG in the early stages of the disease suggests an alternative diagnosis, such as pure freezing syndrome (Okuma, 2006). However, Giladi and others suggested that a longer duration of levodopa or dopamine agonist treatments are associated with FOG (Giladi, et al., 2001).

At the onset of the disease the risk factors for developing FOG are the absence of tremor and an initial gait disorder. The development of FOG in PD is highly associated with the development of balance and speech difficulties, but it is not associated with the progression of rigidity (Okuma, 2006).

FOG duration is significantly shorter in the "on" state than in the "off" state (Okuma, 2006). Schaafsma and colleagues (2003) studied 19 patients with FOG and the result showed that 95% of patients had freezing on turning in the "off" state, whereas, only 32% of patients had freezing on turning in the "on" state (Schaafsma et al., 2003).

Pathophysiology studies have suggested that FOG may be distinct from other parkinsonian symptoms. For instance, no correlation has been suggested between the frequency of occurrence of FOG and other motor symptoms of PD such as rigidity or bradykinesia, but FOG frequency has been inversely correlated with tremors (Bartels, et al., 2003; Giladi, et al., 2001).

Furthermore, Plotink and colleagues (2005) have investigated if FOG is related to asymmetric motor function. They compared PD patients who experienced FOG with PD patients who did not experience FOG. Subjects were examined in an "off" state as well as in an "on" state. The results showed that gait was more asymmetric in PD patients with FOG than in PD without FOG during "off" state and "on" state. Also, there was no correlation between asymmetry of clinical symptoms and gait asymmetry in both PD with FOG and without FOG, in "off" state and in "on" state (Plotnik, Giladi, Balash, Peretz, & Hausdorff, 2005).

Bartels and others (2003) have studied the relationships between FOG and other features of PD. Subjects were 19 PD patients with FOG and they were assessed in both "off" and "on" states. They found that the frequency of FOG was not correlated with other PD features in the "off" state, whereas, it was significantly correlated in the "on"

state, except with regards to speech and writing scores, which did not correlate with the frequency of FOG. In both "off" and "on" states levodopa significantly reduced the frequency of FOG. This reduction in FOG frequency was significantly correlated with improvement of tremor and speech, but did not correlate with an improvement in rigidity, bradykinesia, or balance (Bartels, et al., 2003).

In a different study, Giladi and others (2001) investigated the relationship between PD clinical symptoms and treatment options in patients with advanced PD and FOG. Subjects were 45 patients and the results indicated that severity of the disease at the "off" state was significantly correlated with FOG. Also, longer duration of both levodopa treatment and dopamine agonists' treatment contributed to the appearance of FOG, whereas, longer duration of amantadine treatment reduced the appearance of FOG (Giladi, et al., 2001).

Gait impairments and loss of walking automaticity are common in PD (Baltadjieva, Giladi, Gruendlinger, Peretz, & Hausdorff, 2006) along with executive function and attention impairments (Dubois & Pillon, 1997). Gait abnormalities increase when PD patients are required to respond to more than one cognitive task (a dual task). Dual tasking has been used to examine the relationship between gait and cognitive function (Della Sala, Baddeley, Papagno, & Spinnler, 1995). During a dual task condition PD patients showed shorter strides, a slower gait speed, and increased stride-to-stride variability (Galletly & Brauer, 2005; Hausdorff, Balash, & Giladi, 2003; Yogev et al., 2005). These findings were also found in other patients such as those with Alzheimers, post stroke, and in patients with head injuries (Yogev-Seligmann, Hausdorff, & Giladi, 2008).

Several studies have linked postural control and gait to cognitive function (Hausdorff, Yogev, Springer, Simon, & Giladi, 2005; Marquis et al., 2002). It has been suggested that even in healthy young subjects, these processes are not automatic; they

rely on some attentional resources (Brauer, Woollacott, & Shumway-Cook, 2002; Camicioli, Howieson, Lehman, & Kaye, 1997).

A dual task situation can also increase the occurrence of FOG (Okuma, 2006). According to Camicioli and others (1998) a dual task, particularly, a verbal fluency task increases the number of steps necessary to cover a distance of 30 feet in PD patients with FOG, but this result was not observed in PD patients without FOG. These findings suggest that patients with FOG are more likely to depend on attention that is related to frontal lobe function than patients without FOG (Camicioli, Oken, Sexton, Kaye, & Nutt, 1998).

Yogev and others (2005) investigated the relationship between cognitive function and the effects of different dual task types on gait. Thirty PD patients were matched with 28 healthy controls. The results showed that gait speed significantly decreased during dual tasking compared with usual walking in both groups. PD subjects performed worse on executive function tests compared with the control group. In addition, measures of executive function were significantly correlated with gait variability during dual tasking (Yogev, et al., 2005).

Executive function can be divided into four major components: planning, decision-making, purposive action and effective performance (Lezak, Howieson, & Lorind, 2004). When one or more of these components is impaired, it may affect the ability to walk efficiently and safely. Self-awareness of any limitation is important, particularly in the volition aspect because it might increase the risk of falling (van Iersel, Ribbers, Munneke, Borm, & Rikkert, 2007). According to Holtzer and others (2006) executive function and memory were correlated with gait speed during dual task conditions, but not with verbal IQ (Holtzer, Verghese, Xue, & Lipton, 2006).

Hausdorff and colleagues (2002) examined the effects of dual tasking on gait variability and fall risk in PD. They found that gait variability during normal walking was significantly associated with disease severity, fall risk, disease duration, cognitive function, behaviour and mood, and motor function, whereas walking while dual tasking increased gait variability. Also, during dual-task walking there was a significant association between gait variability and disease duration (Hausdorff, Balash, & Giladi, 2002).

In recent years, the relationship between gait disorder and higher- level cognitive function has received remarkable attention (Yogev-Seligmann, et al., 2008). Imaging studies have found frontal and parietal activity during locomotion (Malouin, Richards, Jackson, Dumas, & Doyon, 2003; Sheridan & Hausdorff, 2007).

1.7 TREATMENT OF PD

Although PD has been found to place a remarkable burden on patients, caregivers, and society, no cure is available (Weintraub, Comella, & Horn, 2008a). The goals of treatment are to manage the symptoms and to improve health-related quality of life (Pallone, 2007; Rezak, 2007) which can then reduce the need for hospitalization and reduce treatment costs (Weintraub, et al., 2008a).

PD can be treated by using a particular type of medication or by combining more than one type of medication. In addition, surgical treatment can be appropriate in advanced stage of the disease (Hauser, 2010; Weintraub, et al., 2008a).

According to several studies, the most effective medication for treating motor symptoms is levodopa (Hauser, 2010; Murata, 2009; Pallone, 2007; Poewe, 2009). Furthermore, Murata (2009) has indicated that levodopa should be recommended as the initial therapy for PD because it has many advantages. For example, levodopa is effective in reducing motor symptoms so to improve daily living activities (Murata,

2009). With levodopa treatment, PD patients may respond positively for up to five years; however, as PD progresses and patients continue to use levodopa, motor complications occur in some patients (Weintraub, et al., 2008a). After nine years of treatment motor complications occur in approximately 70% of PD patients (Jankovic, 2006). Moreover, levodopa treatment is associated with motor fluctuations and dyskinesias (Hauser, 2010). These motor complications lead to disease progression, which causes the non-motor features of PD such as depression, anxiety, autonomic dysfunction, cognitive impairment, and sleep disturbance to arise thus the health-related quality of life declines (Weintraub, et al., 2008a). However, the underlying mechanisms of motor complications associated with levodopa have not been discovered yet (Poewe, 2009). According to Grosset (2008) levodopa can cause pathological gambling which is a psychiatric disorder which can lead to loss of control of gambling and can affect negatively a patient's life (Grosset, 2008).

Another type of PD medication is dopamine agonists. These have been used in early PD or in combination with levodopa in the advanced stage of the disease (Weintraub, et al., 2008a). Dopamine agonists are more likely than levodopa to cause cognitive impairment, confusion, and hallucinations, particularly in older patients (Halkias, Haq, Huang, & Fernandez, 2007; Lees, 2005) thus the patient's age should be considered when making decisions about treatment and for younger patients, dopamine agonists are considered the appropriate treatment. However, some clinicians prefer to treat PD patients in the very early stages with non-dopaminergic therapy such as amantadine or monoamine oxidase type B inhibitors (Weintraub, et al., 2008a). Hauser (2010) has indicated that dyskinesia is less likely to occur with dopamine agonists. On the other hand, levodopa is associated with a high rate of motor fluctuations and dyskinesia and other symptoms for instance, nausea and vomiting (Hauser, 2010). As

initial treatment for early PD levodopa is recommended for elderly patients and dopamine agonists are recommended for younger patients (Murata, 2009).

Surgical treatment is one of the treatment options for PD patients. This type of treatment is suitable for patients in the more advanced disease stage by using a procedure of deep brain stimulation of the subthalamic nucleus. Surgery can reduce PD symptoms including tremor, bradykinesia, wearing off, and dystonia (Weintraub, et al., 2008a).

2. CHAPTER TWO: NEUROPSYCHIATRIC SYMPTOMS AND COGNITIVE IMPAIRMENT IN PD

This chapter will first review the available findings on neuropsychiatric symptoms in patients with PD, and then will review the studies of cognitive impairments in patients with PD.

2.1 NEUROSYCHIATRIC SYMPTOMS

2.1.1 PREVALENCE, CLINICAL CORRELATES AND MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS IN PD

Previous studies that have explored the neuropsychiatric symptoms in patients with PD have mainly focused on the following: depression, apathy, psychosis, hallucination, Impulse Control Disorders (ICDs) and anxiety (Gallagher & Schrag, 2012). Therefore, the following paragraphs will introduce each of these neuropsychiatric symptoms in terms of prevalence, clinical correlates and management.

According to Aarsland et al. (1999) the overall prevalence of neuropsychiatric symptoms in PD patients is 61%. The most common symptoms are depression (38%), hallucinations (27%), anxiety (20%) and apathy (16.5%). The less common symptoms are euphoria (7.0%) and disinhibitions (6.5%). A more recent study found that the prevalence of neuropsychiatric symptoms in early untreated PD patients was 56%. The most common symptoms in this study were depression (37%), apathy (27%), sleep disturbance (18%) and anxiety (17%), whereas, psychotic symptoms were found to be very rare among untreated PD patients (Aarsland, Bronnick, et al., 2009). In PD patients with dementia the prevalence of neuropsychiatric symptoms was found to be higher. In the Aarsland et al study, 50 out of 139 patients were demented (Aarsland, et al., 1999) and in a further study, Lee et al (2012) reported that 89% of PD patients with dementia

presented with at least one neuropsychiatric symptom (Lee, Tsai, Gauthier, Wang, & Fuh, 2012). Another study demonstrated an association between the total Neuropsychiatric Inventory score (NPI) (Cummings et al., 1994) and depression and anxiety (as measured by the Hospital Anxiety and Depression Scale) (Zigmond & Snaith, 1983) in non-demented PD patients. Also, the presence of neuropsychiatric symptoms was independently predicted by a longer disease duration and more severe stage of PD (Kulisevsky et al., 2008).

2.1.1.1 DEPRESSION

Several studies have indicated that the prevalence rate of depression in PD is approximately 40% (Aarsland, et al., 1999; Marsh, 2000; Park & Stacy, 2009). More specifically, a systematic review by Reijnders and colleagues (2008) showed that the prevalence of major depression in PD was 17%, of minor depression 22%, and of dysthymia 13%. Clinically, significant depressive symptoms, irrespective of those depressive disorders defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000) occurred in 35% of patients with PD (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). Recently, a cross sectional study has shown that 40.7% (5847 out of 14.354) of people with young onset PD were receiving health care for depression, which indicates a high prevalence of depression in this patient group (Willis, Schootman, Kung, & Racette, 2012). The presence of depressive symptoms in PD correlates with several factors including the advanced stages of PD, anxiety, cognitive impairment and psychosis (Rojo et al., 2003). A more recent study reported further risk factors for depression in PD. These include longer disease duration, severe motor symptoms, disease stage (according to Hoehn & Yahr, 1967 stages of PD), younger age of onset, dopaminergic medication (higher Levodopa equivalent dose), hallucinations, anxiety, cognitive impairment and sleep problems (Dissanayaka et al., 2011). Other studies have demonstrated an association

between depression and apathy (Cubo, Benito-Leon, Coronell, & Armesto, 2012; Santangelo, Vitale, Trojano, Longo, et al., 2009; Zahodne, Marsiske, Okun, & Bowers, 2012). PD patients with depression tend to experience irritability, less self-blame, guilt and sense of failure thus rarely commit suicide (Mayeux et al., 1992; Starkstein et al., 2008). In general, studies have shown that there is no relationship between family history of mood disorders and the development of depression in PD (Cummings, 1992). However, patients who experience depression before the onset of PD show more serious depressive symptoms than those who did not experience depression beforehand (Costa, Rosso, Maultasch, Nicaretta, & Vincent, 2012; Farabaugh et al., 2009). Further to this, a recently published meta-analysis study suggested that the occurrence of a mood disorder may be considered as a clinical marker for a future diagnosis of PD (Noyce, et al., 2012).

Moreover, depression in PD is often associated with increased disability, a more rapid progression of motor impairment and a decreased health-related quality of life (Barbas, 2006; Weintraub, et al., 2008b). Starkstein et al (1992) reported that PD patients with depression had deterioration in activities of daily living more than PD patients without depression (Starkstein, Mayberg, Leiguarda, Preziosi, & Robinson, 1992).

Albanese (2003) has suggested that depression may occur before the first motor symptoms of PD appear. He outlined three phases in the course of the disease. Firstly, the pre-clinical period, in which the degenerative process is incomplete, and there are no obvious signs. The second phase is the prodromal period as it is characterised by some symptoms that are not specific to PD such as, depression, anxiety, or shoulder pain. The last phase is the symptomatic period; here the first signs of PD appear (Albanese, 2003). A recent study has also proposed three possible subtypes of depression associated with PD. The first subtype is characterised by nonspecific casual comorbid depression; these

patients who would have become depressed even if they had not developed PD. Secondly, nonspecific reactive comorbid depression regards patients who would have developed depression even if they had developed another disabling medical illness but not necessarily PD. Finally, specific comorbid depression which is depression is directly linked to the pathophysiology of PD (Even & Weintraub, 2012).

The underlying mechanism of depression in PD can be explained as reflecting a combination of medical, neurochemical, and psychosocial aspects. Some studies suggest that depression is a reaction to the diagnosis of PD, while other studies propose that there is a biological risk of depression in some patients with PD (Leentjens, Van den Akker, Metsemakers, Lousberg, & Verhey, 2003; Schuurman et al., 2002). Although depressive symptoms in PD might be triggered by PD disabilities, this does not explain the high rate of depression observed in those with this disease. Indeed, the prevalence of depressive symptoms in PD patients is higher than in patients suffering from other chronic disabilities (Burn, 2002; Nuti, Ceravolo, Piccinni, et al., 2004). However, the underlying mechanism of depression in PD remains unclear (Cardoso et al., 2009; Remy, Doder, Lees, Turjanski, & Brooks, 2005).

The treatment of depression in PD includes psychosocial support, behavioural therapy, psychotherapy, drug therapy (Ziemssen & Reichinann, 2007) and deep brain stimulation (Appleby, Duggan, Regenberg, & Rabins, 2007). However, a recent report indicates that deep brain stimulation may worsen depression in some patients and preliminary findings suggest that transcranial magnetic stimulation could improve depression in some patients (Aarsland, Pahlhagen, Ballard, Ehrt, & Svenningsson, 2012).

2.1.1.2 APATHY

Apathy is the second most common neuropsychiatric symptom observed in Parkinson's disease (Aarsland, Bronnick, et al., 2009). Apathy refers to a combination of behavioural, emotional and cognitive features that lead to a reduced interest and participation in daily life activities, together with a lack of initiative and lack of concern or indifference (Dujardin et al., 2007). It is of no surprise that apathy has also been associated with a decreased quality of life and decreased activities of daily living (Benoit & Robert, 2011; Isella et al., 2002; Oguru et al., 2010; Pedersen, Larsen, Alves, & Aarsland, 2009). In addition, apathy significantly impacts the level of disability and a high level of apathy is associated with increased disability in patients with PD (Reijnders et al., 2010). Leroi and others have found a significant difference between patients with PD who have apathy and those without apathy on the Carer burden scale. Higher burden was observed in carers of PD patients with apathy and impulse control disorder compared with those without behavioural disturbances (Leroi et al., 2011). In addition, a recent study demonstrated that apathetic PD patients without dementia may also develop ICD. This study revealed a positive correlation between scores on a clinician/researcher rated apathy evaluation scale and the patient's age, age of onset, disease stage, severity of motor symptom and depression (Ahearn, McDonald, Barraclough, & Leroi, 2012).

The prevalence of apathy in PD varies from 17- 70%, depending on the assessment procedures and the characteristics of the population (Ahearn, et al., 2012; Cubo, et al., 2012; Dujardin, et al., 2007; Pluck & Brown, 2002; Starkstein et al., 2009). For example, using the Marin Apathy Evaluation Scale (Marin, Biedrzycki, & Firinciogullari, 1991), Pluck and Brown found that 37.8% of patients with PD were apathetic. Moreover, they found that apathy is more likely to be a direct symptom of PD than a psychological reaction to the disease (Pluck & Brown, 2002). Dujardin and

colleagues have extended the work of Pluck and Brown by using the Lille Apathy Rating Scale (Sockeel et al., 2006) to assess apathy in a large number of patients with PD and found that 32% of the patients in their study were apathetic (Dujardin, et al., 2007). On this note, Kirsch-Darrow and colleagues reported that apathy scores were significantly greater in PD patients than in a younger sample of individuals with dystonia (Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006). Furthermore, a more recent study has revealed that non-demented PD patients with right-side onset had significantly higher scores on the Apathy Evaluation Scale (AES) than non-demented patients with left-side onset (Bogdanova & Cronin-Golomb, 2012). In addition, recent study observed apathy in 186 (33.4%) out of 557 non-demented PD patients (Cubo, et al., 2012). This study also found that apathy was associated with older age, a lower level of education, severe motor symptoms, depression and higher comorbidity.

Apathy has also been associated with the severity of motor symptoms (Ahearn, et al., 2012; Cramer, Friedman, & Amick, 2010; Dujardin, Sockeel, Delliaux, Destee, & Defebvre, 2009; Oguru et al., 2010; Pedersen, Larsen, et al., 2009; Reijnders, et al., 2010). However, no correlation has been found between apathy scores and the duration of the disease (Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Dujardin, et al., 2009; Dujardin, et al., 2007; Pedersen et al., 2010; Reijnders, et al., 2010; Varanese, Perfetti, Ghilardi, & Di Rocco, 2011).

Currently there is no approved medication for the treatment of apathy in PD (Santangelo et al., 2012). However, there are some forms of treatment that may improve apathy in PD patients including dopamine agonists medications (Shulman, 2000) and deep brain stimulation (Appleby, et al., 2007).

2.1.1.3 PSYCHOSIS

Psychotic symptoms, specifically hallucinations and delusions, occur in up to 40% of patients with PD and are usually associated with an advanced level of PD and nursing home placement (Aarsland, Larsen, Tandberg, & Laake, 2000; Fenelon & Alves, 2010; Goetz & Stebbins, 1993; Wolters & Berendse, 2001). In addition, Visual Hallucinations (VH) in PD have been associated with longer disease duration and older age (Fenelon & Alves, 2010; Fenelon, Mahieux, Huon, & Ziegler, 2000; Gallagher & Schrag, 2012), severe motor symptoms (Bronnick, Emre, Tekin, Haugen, & Aarsland, 2011; Holroyd, Currie, & Wooten, 2001), cognitive impairment (Aarsland, et al., 1999; Bronnick, et al., 2011; Fenelon & Alves, 2010; Fenelon, et al., 2000; Grossi et al., 2005; Holroyd, et al., 2001; Ozer et al., 2007) and depression (Aarsland, et al., 1999; Holroyd, et al., 2001). According to Fenelon and Alves (2010) the lifetime prevalence of VH reaches approximately 50% (Fenelon & Alves, 2010) and several studies have indicated that VH is the most common psychotic symptom in PD patients (Aarsland, et al., 1999; Fenelon & Alves, 2010; Lee & Weintraub, 2012) with VH usually being about animals, objects, or people (Marsh, & Berk, 2003; Schneider, et al., 2008; Thanvi, Lo, & Harsh, 2005). Auditory hallucinations occur less often than VH (Schneider, et al., 2008; Weintraub, et al., 2008b). Hallucinations usually occur in patients who have received drug treatment over a long period (several months or years) (Schneider, et al., 2008; Thanvi, et al., 2005; Weintraub, et al., 2008b).

Psychosis has a major impact on quality of life and caregiver burden in PD more than for motor dysfunctions (Fenelon & Alves, 2010; Goetz & Stebbins, 1993; Schrag, Hovris, Morley, Quinn, & Jahanshahi, 2006). The prevalence of psychotic symptoms (including delirium) affects approximately 50% of all patients with PD, and usually occurs in patients who are treated with antiparkinsonian agents (Factor, Molho, Podskalny, & Brown, 1995; Lauterbach, 2005).

Furthermore, psychotic symptoms as they appear in schizophrenia (such as delusions of grandeur, being controlled by foreign forces, thought broadcasting, mind reading, and hearing voices) are almost never seen in PD patients with psychosis, unless they have comorbid psychiatric problems (Friedman, 2010).

Horlroyd and others (2001) investigated the prevalence of hallucinations and delusions in 102 patients with PD who were on antiparkinsonian treatment. They found 29.4% of patients developed hallucinations or delusions. Specifically, 26 patients (26.5%) had VH; one patient had delusions, two patients had auditory hallucinations, and one patient had gustatory hallucinations. Moreover, VH was significantly associated with worsened visual acuity, a higher depression score, a lower cognitive score, and the severity of the disease. However, there was no association between the hallucinations and the duration, levodopa treatment or other antiparkinsonian treatments (Holroyd, et al., 2001).

Aarsland and colleagues (1999) explored the prevalence and clinical correlates of psychosis in 235 patients with PD. All patients were using antiparkinsonian therapy. They found that 9.8% of patients had hallucinations with insight and 6.0% had psychosis with hallucinations or delusions. In addition, psychotic symptoms were associated with the stage of the disease, age, severity of depression, and cognitive impairment. However, there was no correlation between psychotic symptoms and the type, duration, or dose of antiparkinsonian therapy (Aarsland, et al., 1999).

Fenelon and colleagues (2000) studied the prevalence of hallucinations in 216 patients with PD. The authors found that the prevalence of hallucinations was 39.8%. Although most of the patients received a higher daily dose of levodopa, there were no significant differences between the hallucinating and non-hallucinating groups in the levodopa equivalent dose (Fenelon, et al., 2000). Recently, Lee & Weintraub (2012) investigated the prevalence of psychosis as well as the clinical and demographic

variables that may correlate with psychosis in non-demented PD patients. Psychotic symptoms occurred in 21.5% (41 out of 191) of the sample. The most common psychotic symptoms were VH (13.6%), followed by illusions of people (7.3%) and auditory hallucinations (6.3%), with the least common symptom being paranoid ideation (4.7%). Psychosis was associated with increased duration of the disease, motor score and severity of the disease. In terms of non-motor symptoms, psychosis was found to be correlated with higher depression, apathy, anxiety and daytime sleepiness (Lee & Weintraub, 2012).

Hallucinations and other psychotic symptoms in PD may be triggered by all antiparkinsonian agents. However, the most common type of antiparkinsonian agents that are associated with the occurrence of psychotic symptoms in PD is dopaminergic treatment. However, not all PD patients using dopaminergic treatment report hallucinations and there is no relationship between the simple dose-effect of dopaminergic treatment and the occurrence and severity of hallucinations (Fenelon, 2008).

Psychotic symptoms appear very rarely in early untreated patients. Aarsland and colleagues have explored the range of neuropsychiatric symptoms in early untreated PD patients and healthy control subjects. They used cluster analysis to investigate the interrelationship between the different items in the NPI. In PD patients the number of positive NPI items was higher (56%) than in the healthy control (22%). The most common symptoms were depression (37%), apathy (27%), sleep disturbance (18%) and anxiety (17%), but, psychotic symptoms were very rare among these untreated PD patients (Aarsland, Bronnick, et al., 2009).

The underlying mechanisms of psychosis in PD can be divided into two subtypes. Firstly, in patients with a disease duration of five years or less, postsynaptic dopamine receptor denervation supersensitivity in the mesolimbic/mesocortical system

may underlie the hallucinations. Secondly, in patients with a duration of more than five years, hallucinations may be mediated either by changes outside the basal ganglia or by the serotonergic system (Thanvi, et al., 2005).

The management of psychotic symptoms in PD includes modifying the use of dopaminergic drugs such as reducing the dose of dopaminergic medications or switching to other types of anti-parkinsonian treatment (Aarsland, Marsh, & Schrag, 2009) and using antipsychotic medications (Eng & Welty, 2010).

2.1.1.4 IMPULSE CONTROL DISORDERS

ICDs have been reported in PD patients (Biundo, Formento-Dojot, et al., 2011; Poletti & Bonuccelli, 2012; Voon & Fox, 2007; Weintraub et al., 2010). ICDs are defined as a group of complex behavioural disturbances that is characterised by failure to resist an impulse to perform an act that is harmful to the person or to others (Vilas, Pont-Sunyer, & Tolosa, 2012). Several types of ICDs have been identified in PD patients such as pathological gambling, compulsive buying, compulsive eating and compulsive sexual behaviour (Vilas, et al., 2012; Voon & Fox, 2007). The prevalence of ICDs in PD patients ranges from 6% in PD patients not taking dopamine agonist to 17% in those who do (Voon et al., 2006). In addition, a cross sectional study reported that the prevalence of ICDs was 13.6% (420 out of 3090) in patients with PD. Five percent experienced pathological gambling, 5.7% compulsive buying, 4.3% compulsive eating and 3.5% compulsive sexual behaviour. Moreover, ICDs were associated with younger age, being unmarried, a family history of gambling problems, current cigarette smoking, levodopa use and alcohol abuse (Weintraub, et al., 2010). Additional factors independently associated with ICDs include higher novelty seeking scores, impulse traits, impaired planning and depression (Voon & Fox, 2007). Leroi et al. have found that a higher burden was observed in carers of PD patients with ICDs than for those of patients without behavioural disorders (Leroi, et al., 2011).

Although not all PD patients taking dopaminergic drugs develop ICDs, there is strong evidence of the role of dopaminergic medications (specifically dopamine agonists) in increasing the likelihood of developing ICDs (Aarons, Peisah, & Wijeratne, 2012; Raja & Bentivoglio, 2012). It has been demonstrated that ICDs may occur due to a complex interaction between pharmacological (e.g. dopamine agonists) and non-pharmacological factors (e.g. young age of PD onset and personality traits of those described as high novelty-seeking) factors (Voon, Mehta, & Hallett, 2011).

The management of ICDs in PD is complex and so far there has been no specific therapeutic strategy strongly supported by research (Vilas, et al., 2012). However, in practice, certain strategies have been suggested and are thought to be effective in improving the management of ICDs in PD patients. These include: reducing the dosage of dopaminergic medications particularly dopamine agonists, discontinuing dopamine agonists for some patients, or switching from dopamine agonists to other medications such as L-dopa (Dodd et al., 2005; Driver-Dunckley, Samanta, & Stacy, 2003). Another study suggested non-pharmacological interventions such as deep brain stimulation (Appleby, et al., 2007).

2.1.1.5 ANXIETY

Anxiety is a common disorder in PD. A number of studies have indicated that the prevalence of anxiety among PD patients can be as high as 40% (Marsh, 2000; Marsh, & Berk, 2003; Park & Stacy, 2009; Schneider, et al., 2008). A recent study examined the prevalence of anxiety in 273 male patients with PD (aged 55 and older). Results showed that the overall prevalence of anxiety disorders was 12.8% (Qureshi, Amspoker, Calleo, Kunik, & Marsh, 2012). However, anxiety has received little attention compared with depression (Marsh, & Berk, 2003). Anxiety and depression occur in PD patients quite often (Schneider, et al., 2008) with the most common types of anxiety being generalized anxiety disorder, panic disorder, and social phobia

(Gallagher & Schrag, 2012; Marsh, 2000; Marsh, & Berk, 2003; Park & Stacy, 2009; Schneider, et al., 2008). According to Weintraub et al, (2008) some studies have indicated that generalized anxiety disorder and panic disorder in PD may occur as a reaction to the disease, on the other hand, other specialists suggest that both psychosocial and neuropathological factors may produce the disorder (Weintraub, et al., 2008b). Risk factors for anxiety in PD patients include depression and severity but not duration of PD or the young onset of this disease. It has been noted that patients with postural instability and gait problems are more likely to experience anxiety than patients with tremor-dominant symptoms (Dissanayaka et al., 2010). Recently, a study found no significant difference between non-demented PD patients with right or left side onset on the Beck Anxiety Inventory (Bogdanova & Cronin-Golomb, 2012).

The treatment of anxiety in PD may include adjustment of anti-parkinsonian medications (Aarsland, Marsh, et al., 2009) or use of anxiolytic treatments (Weintraub et al., 2005).

2.1.2 COGNITIVE CORRELATES OF NEUROPSYCHIATRIC SYMPTOMS IN PD

The following section will discuss the cognitive correlates of the most common neuropsychiatric symptoms which are depression, apathy, psychosis, impulse control disorder and anxiety.

2.1.2.1 DEPRESSION

Recent evidence has shown that depression is the most common neuropsychiatric symptom in untreated PD patients (Aarsland, Bronnick, et al., 2009). Several studies have demonstrated an association between depression and cognitive impairments in PD patients (Costa, Peppe, Carlesimo, Pasqualetti, & Caltagirone, 2006; Cubo, Bernard, Leurgans, & Raman, 2000; Fernandez et al., 2009; Kuzis, Sabe, Tiberti, Leiguarda, & Starkstein, 1997; Norman, Troster, Fields, & Brooks, 2002; Santangelo,

Vitale, Trojano, Longo, et al., 2009; Starkstein et al., 1989; Stefanova et al., 2006; Uekermann et al., 2003). In contrast, other studies did not detect a significant association between depression and cognitive function in PD (Silberman et al., 2007; Taylor, Saint-Cyr, & Lang, 1988; Taylor, Saint-Cyr, Lang, & Kenny, 1986; Troster et al., 1995; Troster, Stalp, Paolo, Fields, & Koller, 1995).

In PD, cognitive deficits may occur as a form of global cognitive decline or as an impairment of specific cognitive domains. For example, some researchers have found that higher depression scores negatively correlated with lower scores on the Mini Mental State Examination (MMSE) (Cubo, et al., 2000; Fernandez, et al., 2009) and the Dementia Rating Scale (Fernandez, et al., 2009; Norman, et al., 2002). However, these findings are not in line with other studies that found no relationship between depression and overall cognitive skills in PD (Costa, et al., 2006; Fernandez, et al., 2009; Santangelo, Vitale, Trojano, Longo, et al., 2009; Starkstein, et al., 1989).

Deficits of specific cognitive domains in depressed PD patients mainly involved the impairment of executive functions, attention and memory. In terms of executive dysfunction, Starkstein et al (1989) reported that PD patients with depression performed significantly lower than non-depressed patients on tests of executive function including the Wisconsin Card Sort Test (WCST) (categories, errors and perseverations) (Nelson, 1976), Controlled Word Association Test (Benton, 1968), Trail Making Test (TMT) (A and B) (Reitan, 1958), Design Fluency Test (Free condition) (Jones-Gotman & Milner, 1977) and the Symbol Digit Modalities (Simth, 1973). Another report studied the performance on a range of cognitive tasks in major depression and PD. This study consisted of 4 groups, PD patients with major depression, PD patients without depression, patients with major depression (without PD) and 12 healthy controls. Depressed patients with or without PD performed significantly lower on a verbal fluency test than the other groups. Whereas, depressed PD patients had significantly

lower scores on abstract reasoning task and on the set alternation task than the other three groups (Kuzis, et al., 1997). A further study found that PD patients with depression had significantly lower scores on verbal fluency and concept formation than in healthy controls. This study also reported that depressed PD patients performed significantly worse than non-depressed PD patients on working memory and concept formation tasks and on the alternate fluency task (Uekermann, et al., 2003). Other studies have also demonstrated that depressed PD patients had lower scores relative to non-depressed PD patients using a variety of executive tasks e.g. phonological verbal fluency, abstract reasoning and card sorting test (Costa, et al., 2006), letter fluency test, category fluency test and TMT (Stefanova, et al., 2006), set-shifting and response inhibition (Klepac, Hajnsek, & Trkulja, 2010), FAB and Stroop test (Santangelo, Vitale, Trojano, Longo, et al., 2009). As for deficits in other cognitive domains, earlier studies have reported an association between depression and poorer scores on tasks relating to attention (Kuzis, et al., 1997; Norman, et al., 2002), short-term memory (Uekermann, et al., 2003), and episodic and semantic memory (Butterfield, et al., 2010; Costa, et al., 2006; Fernandez, et al., 2009; Norman, et al., 2002; Stefanova, et al., 2006). In addition, another study indicated a relationship between depression and poorer performance on a range of cognitive tasks including those testing executive function, memory and visuospatial skills (Klepac, Trkulja, & Relja, 2008).

In contrast, to the above other studies were unable to detect an association between depression in PD and deficits of cognitive function. For instance, it was found that depressed PD patients did not differ from those without depression on tasks of short-term memory (Taylor, et al., 1986). Further, Troster et al (1995) reported no difference between PD patients with and without depression on any of the neuropsychological tests including the Wisconsin Card Sorting Test (Heaton, Chelune, & Talley, 1993), Controlled Oral Word Association Test (Benton, 1968), the Logical

Memory subtest of the Wechsler Scale-Revised (Wechsler, 1945), Digit Span (Wechsler, 1981), the Boston Diagnostic Aphasia Examination's Animal Naming Test (Goodglass & Kaplan, 1983) and Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983). Similar findings were reported by Troster et al. using total and subscales of the Dementia Rating Scale (Mattis, 1988) to assess cognitive abilities. These findings demonstrated no difference between patients with and without depression (Troster, Paolo, et al., 1995). Using the Stroop test (Stroop, 1935) as a measurement of frontal functions these authors were also unable to detect a significant difference between depressed and non-depressed PD patients (Silberman, et al., 2007).

Despite the amount of research which has examined the association between depression and cognitive functions in PD, various shortcomings in these studies limit the validity of their conclusions. These limiting factors include the exclusion of other neuropsychiatric symptoms, the small numbers of participant in some studies and the use of screening instruments that measure limited cognitive functions.

2.1.2.2 APATHY

In the literature, it has been demonstrated that apathy is associated with cognitive dysfunction (Aarsland, et al., 1999; Butterfield, et al., 2010; Drijgers, Dujardin, Reijnders, Defebvre, & Leentjens, 2010; Dujardin, et al., 2009; Isella, et al., 2002; Levy, 1998; Moretti et al., 2012; Pedersen, Alves, Aarsland, & Larsen, 2009; Pluck & Brown, 2002; Reijnders, et al., 2010; Starkstein et al., 1992; Varanese, et al., 2011; Zgaljardic et al., 2007), depression (Dujardin, et al., 2009; Dujardin, et al., 2007; Isella, et al., 2002; Levy, 1998; Oguru et al., 2010; Pedersen, Larsen, et al., 2009; Reijnders, et al., 2010; Starkstein, Mayberg, Preziosi, et al., 1992; Zgaljardic, et al., 2007) and anxiety (Bogdanova & Cronin-Golomb, 2012).

Although apathy and depression can co-exist in PD, several studies have found that apathy may occur in the absence of depression (Aarsland, et al., 1999; Aarsland,

Marsh, et al., 2009; Cubo, et al., 2012; Isella, et al., 2002; Kirsch-Darrow, et al., 2006; Levy, 1998; Pedersen, Larsen, et al., 2009; Starkstein, Mayberg, Preziosi, et al., 1992; Zgaljardic, et al., 2007).

Apathy in PD patients has been found to be associated with executive dysfunction (Aarsland, et al., 1999; Bogdanova & Cronin-Golomb, 2012; Butterfield, et al., 2010; Dujardin, et al., 2009; Isella, et al., 2002; Pluck & Brown, 2002; Varanese, et al., 2011; Zgaljardic, et al., 2007). For instance, Aarsland et al. (1999) examined cognitive functions in PD patients with and without dementia (Hoehn and Yahr stage from mild to severe) and apathy was found to be significantly associated with dementia and the number of errors on the Stroop test (Aarsland, et al., 1999). Another study assessed the cognitive functions of 30 PD patients (13 of them with apathy as assessed by Marin's Apathy Scale) (Marin, et al., 1991). This study included patients with dementia and six of the overall sample of patients were treated with antidepressants. Apathy was significantly associated with executive dysfunctions (Evaluated by the Executive Interview developed by (Royall, Mahurin, & Gray, 1992), category fluency and letter fluency (Isella, et al., 2002). A further study demonstrated that non-demented PD patients with apathy performed significantly worse than PD patients without apathy on tasks of verbal fluency (both letter and category fluency), working memory, and verbal abstraction (Zgaljardic, et al., 2007). Dujardin and colleagues evaluated cognitive functions in non-demented PD patients (20 with apathy and 20 without apathy). They concluded that after an 18 month follow-up, apathetic PD patients had more cognitive deficits, mainly executive dysfunction and were more likely to meet the criteria for dementia compared with non-apathetic PD patients (Dujardin, et al., 2009). In addition, another study reported a negative correlation between apathy and both executive functions and memory scores in non-demented PD patients (Butterfield, et al., 2010). A further study indicated that apathetic PD patients without dementia had significantly

lower scores than those without apathy on immediate free recall, short delay free recall, long delay free recall, long delayed cued recall, delayed recognition (Delis, Kramer, & Kaplan, 2002), WCST (Heaton, et al., 1993) and digit span backward (Varanese, et al., 2011).

A recently published study examined two groups of PD patients with akinetic-rigid type (n= 56) and tremor-dominant type (n= 47) in terms of the prevalence, clinical and cognitive correlates of apathy. Patients with akinetic-rigid type showed a greater insight into their situation, as measured by the Clinical Insight Rating Scale (Ott et al., 1996), and their caregiver's burden (as assessed by the Relative Stress Scale) (Greene, Smith, Gardiner, & Timbury, 1982) was more severe compared with the other group of patients. Patients with tremor-dominant type had more depressive symptoms, as tested by the Cornell Scale for Depression in Dementia (Alexopoulos, Abrams, Young, & Shamoian, 1988). However, patients with akinetic-rigid type manifested more apathy (measured by both clinician/researcher rated apathy evaluation scale and the self-report rated apathy evaluation scale) (Marin, et al., 1991) than the other group of patients. As for cognitive functions, akinetic patients performed significantly worse on tasks of frontal lobe function e.g. the FAB (Dubois, Slachevsky, Litvan, & Pillon, 2000), phonemic fluency (Thurstone & Thurstone, 1962) and interference error on the Stroop test (Stroop, 1935) compared with PD patients with tremor-dominant type (Moretti, et al., 2012).

Another study was recently carried out to explore the cognitive profile of two forms of neurodegenerative diseases (PDD and AD). This study consisted of 61 non-depressed patients (29 PDD and 32 AD), 29 patients with apathy (14 PDD and 15 AD) and 32 patients without apathy (15 PDD and 17 AD). This study used clinical judgment to determine the presence of an apathy syndrome, and cognitive tasks tapping memory, visuospatial and executive functions. The results showed that apathetic PD patients with

dementia performed significantly poorer than non-apathetic PD patients with dementia on tasks of executive function and that AD patients with apathy had significantly lower scores than AD patients without apathy on these tasks. Finally, apathetic AD patients had a significantly poorer performance than apathetic PD patients with dementia on a memory task (Grossi et al., 2012). However, Robert et al (2012) studied 45 non-demented PD patients and found that apathy did not correlate with executive functions. In this study the assessments of executive functions included WCST (Heaton, et al., 1993), TMT (B-A) (Reitan, 1958), verbal fluency (Thurstone & Thurstone, 1962) and the Stroop Test (Stroop, 1935).

Other studies have reported an association between apathy and global cognitive impairment in PD patients (Levy, 1998; Reijnders, et al., 2010) and other neurological diseases e.g. Alzheimer Disease, Frontotemporal Dementia and Progressive Supra-nuclear Palsy (Levy, 1998).

In the literature, the exploration of apathy and cognitive abilities in PD patients did not take the stage of PD into account. In other words, previous studies have not explored the association between apathy and cognitive skills in the early stages of PD. Further, earlier studies have used a limited number of participants or used general cognitive measurements which do not assess a broader range of cognitive domains.

2.1.2.3 PSYCHOSIS

The most common psychotic symptom in PD is visual hallucination (Grossi, et al., 2005). Several studies have observed cognitive decline in patients with PD who have VH (Bronnick, et al., 2011; Grossi, et al., 2005; Morgante et al., 2012; Ozer, et al., 2007; Ramirez-Ruiz, Junque, Marti, Valldeoriola, & Tolosa, 2007). For example, a study explored the cognitive features of non-demented PD patients with hallucinations (n=14) compared with non-demented PD patients without hallucinations (n=34). In this study VH occurred in 9/14 patients (three patients had both visual and auditory

hallucinations and two had pure auditory hallucinations). Patients with hallucinations performed significantly lower than patients without hallucinations on the tasks that explored executive functioning such as phonemic and category fluency tasks and verbal learning (immediate recall) (Grossi, et al., 2005). Another study examined the presence of cognitive impairment in 63 non-demented PD patients (33 patients with VH and 30 patients without VH). Patients with VH had significantly lower scores relative to patients without VH on the short test of mental status (Kokmen, Smith, Petersen, Tangalos, & Ivnik, 1991), Stroop test (both time and error) (Stroop, 1935), category fluency task (Thurstone & Thurstone, 1962), Wechsler memory scale (both immediate and delayed recall) (Wechsler, 1945) and clock drawing test (Brodaty & Moore, 1997). However, there were no significant differences between the two subgroups of PD in the Benton's face recognition test (Benton & Van Allen, 1968), Wisconsin Card Sorting Test (Heaton, et al., 1993) and Judgement of Line Orientation test (Benton, Hamsher, Varney, & Spreen, 1983). These results suggest that PD patients with VH might have deterioration in frontal and memory functions (Ozer, et al., 2007). Moreover, a further study reported that PD patients with VH (n=20) had cognitive impairment in the visual memory task and visuoreceptive-visuospatial functions compared with PD patients without VH (n=20) (Ramirez-Ruiz, et al., 2007).

A recent study investigated cognitive decline in non-demented PD patients with and without psychosis. After a two year follow up, patients with psychosis (n=37) had significantly lower scores than patients without psychosis (n=443) on the MMSE (Folstein, Folstein, & McHugh, 1975). However, there were no significant differences between the two subgroups of PD patients in the Frontal Assessment Battery and tasks of attention/memory (Morgante, et al., 2012). This study did not find any significant differences between patients with and without psychosis in the cognitive domains, which could be explained by recruiting patients in the very early stages of PD. A

recently published study examined cognitive decline in non-demented PD patients with VH (n=46) and without (n=64). Results revealed that patients with VH performed significantly lower than patients without this symptom on tasks of executive function (FAB and Stroop) and on the delayed recall part of the visual memory test (Rey complex figure delayed recall) (Shin et al., 2012).

2.1.2.4 IMPULSE CONTROLS DISORDERS

Few studies have examined cognitive functioning in PD patients with ICDs. The cognitive domain that appears to be mostly impaired in PD patients with ICDs is executive functioning (Biundo, Formento-Dojot, et al., 2011; Santangelo, Vitale, Trojano, Verde, et al., 2009; Vitale et al., 2011). Biundo and others (2011) examined the differences in cognitive functions between PD patients with and without ICDs (33 patients had ICDs and 24 without ICDs) using a comprehensive neuropsychological battery. Results showed that there were no significant differences between the two subgroups of patients on tests of global cognitive abilities, verbal and non-verbal memory, abstract reasoning, visuo-spatial memory and attention. In addition, in terms of executive functions, this study did not find any differences between the two subgroups of patients in the Frontal Assessment Battery (Dubois, et al., 2000), Stroop tests (Stroop, 1935) and TMT (part A) (Reitan, 1958). However, significant differences were detected in TMT (part B) and (part B minus A) (Biundo, Formento-Dojot, et al., 2011). Furthermore, other studies have reported memory impairment in PD patients with ICDs, particularly, in spatial working memory tasks assessed by the Cambridge Automated Neuropsychological Test Battery (Voon et al., 2010), short-term memory and working memory as measured by digit span forward and backward (Djamshidian et al., 2010).

2.1.2.5 ANXIETY

Only two studies have investigated the relationship between anxiety and cognitive functions in PD patients (Bogdanova & Cronin-Golomb, 2012; Foster et al.,

2010). The first study reported that left-lateralized PD patients with anxiety performed significantly worse than right-lateralized PD patients with anxiety on working memory tasks, i.e. the digit span subtest of the Wechsler memory scale (Foster, et al., 2010). The second study reported that in PD patients with right-side onset, anxiety scores were significantly correlated with verbal tasks e.g. verbal fluency test, Boston naming test and California verbal learning test (Bogdanova & Cronin-Golomb, 2012).

2.1.3 NEUROANATOMICAL CORRELATES OF NEUROPSYCHIATRIC SYMPTOMS IN PD

Prior reports mainly examined specific neuropsychiatric features such as depression, apathy, psychosis, ICDs, and anxiety. Therefore, this section will review the imaging studies that have explored the neuroanatomical correlates of neuropsychiatric symptoms.

2.1.3.1 DEPRESSION

Previous imaging studies have attempted to explore the neural bases of depression in patients with only major depressive disorder and PD patients with and without depression using different imaging techniques. For instance, patients with only major depressive disorder showed an increased metabolism and rCBF in the left mediodorsal thalamus (Carlson, Thase, Bogers, Kupfer, & Drevets, 2005). In PD patients, a PET study reported that depressed patients, when compared with non-depressed patients, had lower [11C] RTI-23 binding in the locus coeruleus bilaterally and in the limbic system including mediodorsal thalamus bilaterally, the right amygdala and the left ventral striatum (Remy, et al., 2005). Moreover, an fMRI study detected reduced activation in the left mediodorsal nucleus of the thalamus and in medial prefrontal cortex in depressed PD patients (Cardoso, et al., 2009). A recently published PET study reported that in patients with PD, depression scores (as assessed by Beck

Depression Inventory) correlated with increased brain metabolism in the bilateral amygdala (Huang et al., 2013).

Other studies have emphasised the important role of the dorsomedial prefrontal cortex in patients with depressive disorder and PD patients with depression. A number of PET studies have demonstrated a decreased rCBF and metabolism in the dorsomedial prefrontal cortex in patients with only a depressive disorder (Biver et al., 1994; Drevets, 1999). Another PET study found that PD patients with depression had a decreased cerebral blood flow in the medial frontal cortex and in the anterior cingulate cortex when compared with PD patients without depression and controls (Ring et al., 1994). More recently a meta-analysis study revealed that patients with major depressive disorder had grey matter reduction in the anterior cingulate cortex and in the dorsolateral and dorsomedial prefrontal cortex compared with healthy controls (Bora, Fornito, Pantelis, & Yucel, 2012).

A VBM study reported that depressed PD patients had lower grey matter density in the left inferior orbito-frontal gyrus, bilateral rectal gyrus and the right superior temporal pole compared with non-depressed PD patients (Feldmann et al., 2008). Correlational analysis showed that high depression scores were associated with less grey matter volume in the right rectal gyrus and bilateral middle/inferior orbito-frontal regions. Another VBM study revealed that PD patients with depression had significantly lower grey matter volume values in the right posterior cingulate cortex, the right inferior temporal gyrus and right hippocampus compared with healthy controls. However, there was no correlation between the scores of the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) and grey matter loss (Kostic et al., 2010).

Prior investigations have demonstrated the role of the cingulate cortex, particularly the anterior cingulate cortex, in depression disorder. For instance, metabolism and cerebral blood flow studies have shown a decrease in the subgenual

anterior cingulate cortex in unipolar and bipolar depression compared with controls (Drevets et al., 1997; Kegeles et al., 2003). This finding is in line with a recent meta-analysis study that reported grey matter loss in the anterior cingulate cortex in patients with major depressive disorder (Bora, et al., 2012). However, in PD patients only, one PET study found that depressed patients had a reduction in rCBF of the anterior cingulate cortex when compared with non-depressed patients and healthy controls (Ring, et al., 1994).

A limited number of studies have investigated white matter volume in PD patients with depression. Kostic et al. (2010) found that PD patients with depression had white matter loss in the right anterior cingulate bundle, inferior orbitofrontal regions and in the left inferior parietal lobe compared with healthy controls. While the results of group comparisons between all patients with PD versus healthy controls showed no significant difference. Furthermore, the outcome of correlation analyses revealed that high HRSD scores correlated with white matter loss in the right inferior orbitofrontal region (Kostic, et al., 2010). Additionally, using other imaging techniques such as diffusion tensor imaging indicated reductions in fractional anisotropy values in the white matter of the frontal lobe bilaterally, possibly representing dysfunction in bilateral anterior cingulate bundles, in depressed PD patients when compared with non-depressed PD patients (Matsui et al., 2007). Using the same imaging technique Li and others (2010) reported a reduction in the mediodorsal nucleus of the thalamus bilaterally in depressed PD patients (Li et al., 2010). More recently an imaging study examined white matter hyperintesities changes in non-demented PD patients with and without depression (disease onset for all patients was above the age of 60) and healthy controls. This study detected no significant difference between healthy controls and all PD patients (with and without depression); even though depressed patients had more

common frontal white matter hyperintesities, the difference in scores did not reach a significance level (Petrovic et al., 2012).

In summary, two VBM studies have explored the neural correlates of depression in PD patients (Feldmann, et al., 2008; Kostic, et al., 2010) but, these studies have various limitations. For instance, in the Feldmann et al. study, PD patients were in the moderate stage of the disease (Hoehn- Yahr, 1967). The exploration of depression in patients with early stage of PD may allow for effective diagnosis and intervention. In addition, the earlier studies did not covariate for total intracranial volume, which might have contributed to the results of grey matter reduction. Furthermore, the authors used the Montgomery-Asberg Depression Rating Scale to assess depression and relied on reports of previous episodes of other neuropsychiatric symptoms in order to exclude patients who had these symptoms. Finally, the Kostic et al. study included PD patients in the mild to moderate stages, smaller sample size and included 8 patients who were treated with antidepressants.

2.1.3.2 APATHY

Despite the fact that apathy is probably the most frequently observed neuropsychiatric symptom in PD patients, the neural bases of apathy in PD patients remain unclear. Few studies have investigated the underlying mechanism of apathy in PD using a variety of imaging techniques. A PET study of 20 non-demented PD patients (mild to moderate stage) revealed that apathy (as assessed by the Apathy Evaluation Scale) (Marin, et al., 1991) was negatively correlated with [^{11}C] RTI-32 binding (dopamine and noradrenaline) in the bilateral ventral striatum (Remy, et al., 2005). Another PET study investigated apathy in 12 non-demented PD patients (moderate stage) after deep brain stimulation of the subthalamic nucleus using the Apathy Evaluation Scale (Marin, et al., 1991). In this study, positive correlations were identified between apathy scores and glucose metabolism in the right middle frontal gyrus (BA

10) and right inferior frontal gyrus (BA 46); whereas, apathy scores were negatively correlated with glucose metabolism in the bilateral posterior cingulate gyrus (BA 31) and left middle frontal lobe (BA 9) (Le Jeune et al., 2009). A VBM study explored the neuroanatomical correlates of apathy in non-demented PD patients (mild to moderate stage). Higher apathy scores (as measured by the NPI) (Cummings, et al., 1994) were negatively correlated with lower grey matter density in the left precentral gyrus (BA 6), the bilateral inferior parietal gyrus (BA 40), the bilateral inferior frontal gyrus (BA 44, 47), the bilateral insula and the right posterior cingulate gyrus (BA 31) (Reijnders, et al., 2010). An fMRI study investigated the specific characteristics of apathy, depression, and motor progression in the resting state in 22 non-demented PD patients (stage of PD was not specified) using the Amplitude of the Low Frequency Fluctuation (ALFF) (a full brain measure that allows researchers to look at resting state signal across the whole brain in their sample on a voxel by voxel basis). Higher apathy scores were associated with increased normalized ALFF signal in the right middle orbital frontal gyrus and in the subgenual cingulate bilaterally. Conversely, higher apathy scores were correlated with decreased activity in the left supplementary motor region, the left inferior parietal lobule and the left fusiform gyrus. Severity of depression was correlated with increased normalized ALFF signal in the right subgenual cingulate, the bilateral cuneus, the right lateral geniculate and the right mesial frontal gyrus (Skidmore et al., 2011).

A recent PET study explored the neural bases of apathy in 45 non-demented PD patients without depression. Apathy was assessed by AES (Marin, et al., 1991), other measures were also used e.g. Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979) and Mattis Dementia Rating Scale (Mattis, 1988). However, the stage of PD the patients were at was not mentioned in this study. Results showed that AES scores correlated positively with cerebral metabolism in the right inferior frontal gyrus, right middle frontal gyrus, right cuneus and right insula. Negative

correlations were identified between the AES scores and cerebral metabolism in the bilateral cerebellum, particularly the inferior semilunar lobule (Robert, et al., 2012). A more recent PET study in PD patients showed that apathy scores (as measured by the Apathy Evaluation Scale) (Marin, et al., 1991) correlated with increased metabolism in the anterior cingulate and orbitofrontal lobe bilaterally (Huang, et al., 2013). However, a different study did not identify any specific measure of frontotemporal atrophy correlating with the presence or severity of apathy (Isella, et al., 2002).

To my knowledge, none of the earlier studies has investigated the white matter changes in patients with PD who have apathy. However, in other neurological disorders such as Alzheimer's disease this point has been studied with one study reporting that apathetic AD patients had a significantly greater amount of frontal white matter hyperintensities than non-apathetic AD patients (Starkstein, et al., 2009).

It can be noticed from the above review that the association between apathy and white matter volume in PD has not yet been explored. In addition, only one VBM study has investigated grey matter volume in PD but this study had various limitations such as the inclusion of patients with only mild apathy scores and the use of only a correlational analysis design. Indeed, there is evidence that apathy is associated with atrophy of the frontal and cingulate cortex in PD (Le Jeune, et al., 2009; Reijnders, et al., 2010).

2.1.3.3 PSYCHOSIS

Most of the earlier imaging studies that attempted to explore psychosis in patients with PD focused on the study of visual hallucination. For instance, a PET study investigated the presence of cerebral glucose metabolism in non-demented PD patients with and without VH (n=11 and n=8 respectively) who were in an advanced stage of the disease by using [18F] fluorodeoxyglucose PET. The results revealed that patients with VH had hypermetabolism in the left superior frontal gyrus when compared with those without VH (Nagano-Saito et al., 2004). Furthermore, a SPECT study explored the

neural substrate of VH in 24 PD patients with nonpsychotic VH and 41 PD patients without VH. Patients with VH showed a lower Regional Cerebral Blood Flow (rCBF) in the right fusiform gyrus and higher rCBF in the right superior and middle temporal gyri than PD patients without VH (Oishi et al., 2005). In addition, other fMRI studies reported the dysfunction of frontal activation in PD patients with VH. For instance, Ramirez-Ruiz and colleagues (2008) studied the pattern of brain activation in PD patients with VH using the fMRI one-back face detection task (complex visual stimuli). The sample was of 20 non-demented PD patients in the advanced stages of PD (10 patients with VH and 10 patients without VH) and 10 healthy controls. Brain activation was measured during the presentation of face stimuli (activation condition) and of colored mosaics (control condition) (Haxby et al., 2001). PD patients with VH showed significant reductions in the activation of several right prefrontal areas including the inferior (Brodmann Area (BA), 10, 47), superior (BA 6/8), middle frontal (BA 8) and anterior cingulate gyrus (BA 31/32) when compared with non-hallucinating PD patients. During the control condition, PD patients with VH showed hyper-activation in the right inferior frontal gyrus when compared with non-hallucinating PD patients (Ramirez-Ruiz et al., 2008).

A Voxel Based Morphometry (VBM) study investigated the reductions of hippocampal volume in 44 PD patients with dementia (PDD), 9 non-demented patients with VH, and 19 PD patients without dementia and without VH and 56 healthy controls. PDD patients and PD patients with VH had significant grey matter loss in the hippocampus compared with healthy controls. PDD patients had grey matter loss in the entire hippocampus whereas in PD patients with VH grey matter reduction was only detected in the anterior regions of the hippocampus. The comparison of grey matter loss in patients and controls showed that 78% of PDD patients, 31% PD patients with VH and 26% PD patients without VH had hippocampal grey matter loss (Ibarretxe-Bilbao et

al., 2008). Another VBM study reported that in non-demented PD patients (n=40) higher hallucinations scores (assessed by the NPI) (Cummings, et al., 1994) were associated with lower grey matter volume values in several brain regions including the bilateral frontal areas, right occipital and temporal visual association cortex, left inferior temporal lobule and the left parahippocampal gyrus (Bruen et al., 2011). In addition, a recent VBM study examined the neural correlates of VH in non-demented PD patients with and without VH (n=46 and n=64 respectively) (Shin, et al., 2012). Visual hallucinations were assessed by the NPI (Cummings, et al., 1994). Patients with VH had significantly lower grey matter volume in the right orbitofrontal gyrus, left temporal and thalamic areas compared with PD patients without VH (Shin, et al., 2012). In a psychiatric population, particularly patients with hallucinations (without PD), a VBM study revealed a negative correlation between hallucination scores (assessed by the Brief Psychiatric Rating Scale) and reduction of grey matter volume in the left superior temporal gyrus, left thalamus and bilateral cerebellum. While a group comparison analysis showed significant grey matter volume loss in the left superior temporal gyrus, the left middle frontal gyrus and the right cuneus compared with healthy controls (Neckelmann et al., 2006).

2.1.3.4 IMPULSE CONTROL DISORDERS

Frontal lobe atrophy has been reported in PD patients with ICDs. A VBM study examined brain volume changes in non-demented PD patients with and without ICDs (n=33 with ICDs and n=24 without) and 22 healthy controls. The Minnesota Impulsive Disorders Interview was used to assess ICDs. When compared with healthy controls, PD patients (with and without ICDs), had a significantly lower grey matter volume in the bilateral middle frontal gyrus and right superior frontal gyrus (Biundo, Formento-Dojot, et al., 2011). The association between neuropsychiatric features and frontal lobe atrophy has also been identified in patients with other neurodegenerative diseases. For

instance, one VBM study explored the relationship between grey matter volume and neuropsychiatric symptoms in patients with mild AD (n= 19). Correlation analysis revealed a significant negative association between grey matter volume and the total NPI score in the bilateral middle frontal gyrus, right orbitofrontal gyrus and left inferior temporal gyrus (Vasconcelos et al., 2011).

2.1.3.5 ANXIETY

To my knowledge only one recent imaging study attempted to examine the association between anxiety and brain metabolism changes in patients with PD. Huang et al. (2013) studied the correlation between anxiety scores (as assessed by the Beck Anxiety Inventory) (Beck & Steer, 1990) and brain metabolism in 26 non-demented patients with PD. This study used an ROI technique to explore PD-related regions e.g. the lentiform nucleus, motor cortex, cingulate cortex, occipital lobe, frontal cortex, cerebellum, limbic system and temporoparietal association cortex. The anxiety scores correlated with decreased metabolism in the caudate nucleus bilaterally (Huang, et al., 2013).

2.2 COGNITIVE IMPAIRMENT IN PD

Cognitive impairments have been observed even in the early stages of PD. These cognitive deficits include executive function, memory, visuospatial skills and attention ability (Aarsland, Marsh, et al., 2009; Foltynie, et al., 2004; Muslimovic, Post, Speelman, & Schmand, 2005; Wu et al., 2012). It has been demonstrated that the underlying mechanisms of cognitive dysfunction in PD patients without dementia reflect the atrophy of fronto-striatal circuits (which link the frontal lobe to the basal ganglia), particularly in executive dysfunctions (Lewis, Dove, Robbins, Barker, & Owen, 2003; Monchi et al., 2004; Owen, 2004; Zgaljardic et al., 2006). In addition, memory impairments are thought to be secondary to retrieval deficit. They have also

been associated with the dysfunction of fronto-striatal circuits (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991). Using different imaging techniques, few studies have investigated the neural correlates of cognitive impairments in PD. The following text will introduce the main findings of prior studies that have explored cognitive impairments including general cognitive abilities, executive function, memory, verbal fluency, visuospatial and visuoperceptual functions and facial emotion recognition.

Using a Region of Interest (ROI) technique, Camicioli et al. (2003) found a significant correlation between MMSE scores and the left, but not right hippocampal volume in PD patients (Camicioli et al., 2003). In addition, a VBM study explored the cognitive decline and grey matter reduction in PD patients (not treated with anti-parkinsonian drugs) using total z scores of multiple neuropsychological tests e.g. executive function, attention, learning and memory, and visuospatial/visuopreceptual function (Dalrymple-Alford et al., 2011). This study revealed a significant correlation between total cognitive z scores and grey matter density in the bilateral posterior cingulate, precuneus cortex, superior parietal lobule, lateral occipital cortex, superior middle and inferior frontal gyri, precentral gyri, insula cortex, superior and middle temporal gyri, hippocampi, medial thalamic region and left amygdala (Melzer et al., 2012). However, another MRI study did not detect a correlation between grey matter volume and global cognitive abilities as assessed by the MMSE (Folstein, et al., 1975) in non-demented PD patients (Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009).

In PD, the association between executive dysfunction and grey matter volume has been reported by a small number of VBM studies. For instance, the combined score of executive function tests (Stroop test, TMT (Part B) and the Digit Ordering Test) was found to be significantly associated with grey matter volume values in the bilateral middle temporal gyrus, the bilateral caudate, the left cerebellum, and the left precuneus

(Camicioli et al., 2009). Using an ROI technique, another study examined the neural correlates of decision-making ability in non-demented PD patients. A significant correlation was found between the total scores on the Iowa Gambling Task (Bechara, Damasio, Damasio, & Lee, 1999) and the left orbitofrontal cortex but not the amygdala (Ibarretxe-Bilbao et al., 2009).

Memory dysfunctions have also been observed in non-demented PD patients. It has been demonstrated that memory deficits are linked to atrophy of the medial temporal lobe (Ibarretxe-Bilbao, Junque, Marti, & Tolosa, 2011). An MRI study reported that left hippocampal volume loss was negatively correlated with verbal memory scores in PD patients with and without dementia (Camicioli, et al., 2003). This latter finding was in line with that of another study which included only non-demented PD patients (Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004). Additionally, this study found that patients had atrophy in the bilateral prefrontal and hippocampal areas when compared with healthy controls (Bruck, et al., 2004). Although another report indicated bilateral hippocampal atrophy in both groups of PD patients (with and without dementia) when compared with healthy controls, no correlation was found between medial temporal lobe atrophy and cognitive decline (as measured by Cambridge Cognitive Examination) (Roth et al., 1986) in both groups of patients (Tam, Burton, McKeith, Burn, & O'Brien, 2005). However, using Rey's Auditory verbal Learning Test (delay recall) (Rey, 1964), a VBM study revealed a significant correlation between scores on the memory task and grey matter density in the bilateral head of the hippocampus in patients with PD (Ibarretxe-Bilbao, et al., 2008). Another VBM study showed a significant association between long delay free recall scores on the California Verbal Learning Test (Delis, et al., 2002) and grey matter volume values in the left middle temporal and left fusiform gyrus, the left uncus, the right temporal lobe (Sub-gyral) and the left putamen in non-demented patients with PD (Camicioli, et al., 2009).

The above reports have demonstrated the important role of temporal lobe abnormalities, predominantly in the hippocampus, in memory decline in patients with PD.

Another cognitive domain that has been found to be impaired even in the early stages of PD is verbal fluency (Henry & Crawford, 2004a; Obeso, Casabona, Bringas, Alvarez, & Jahanshahi, 2012). In PD, both phonemic and semantic deficits are said to be related to the dysfunctions of the frontal lobe (Ibarretxe-Bilbao, et al., 2011). A VBM study explored the neural correlates of verbal fluency (Thurstone & Thurstone, 1962) in non-demented PD patients (Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009). A positive correlation was found between grey matter density and semantic fluency scores in the right inferior frontal gyrus, left rectal gyrus, bilateral inferior temporal gyrus, left middle temporal gyrus, left superior temporal gyrus, right caudate head, right caudate body, left anterior nucleus of the thalamus, bilateral parahippocampus and bilateral cerebellum. However, there no correlation was found between grey matter density and phonemic fluency scores (Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009). In other neurodegenerative diseases such as AD, positive correlations were found between both phonemic and semantic fluency and grey matter density (Venneri et al., 2008). Phonemic fluency scores were associated with grey matter loss in the bilateral medial frontal gyrus, the left middle and superior frontal gyrus, the right inferior frontal gyrus, the bilateral cingulate gyrus, the left insula, the left middle temporal gyrus, the right superior temporal gyrus, the left lingual gyrus, the right supramargingal gyrus, the right preceuneus and the right cerebellum. Whereas, semantic fluency scores correlated with grey matter density in the left medial frontal gyrus, the middle and superior temporal gyrus, the right fusiform gyrus, the bilateral anterior cingulate gyrus, the right insula, the left middle occipital gyrus, the bilateral cuneus, the left lingual gyrus and the cerebellum bilaterally (Venneri, et al., 2008). In healthy individuals, fMRI studies have reported brain activations during a

semantic fluency task in the inferior frontal gyrus bilaterally, the left medial temporal lobe, the left superior parietal lobule, and the left posterior parahippocampal gyrus (Pihlajamaki et al., 2000), whereas, during the phonemic fluency task, brain activities were observed in the left middle frontal gyrus, left inferior frontal gyrus, bilateral anterior cingulate gyrus and left medial prefrontal cortex (Abrahams et al., 2003).

In non-demented PD patients, a VBM study has reported an association between visuoperceptual functions (measured by Benton's Facial Recognition Test) (Benton & Van Allen, 1968) and grey matter reduction in the left fusiform gyrus, left inferior frontal gyrus, right parahippocampal gyrus, left middle occipital gyrus, right posterior cingulate and left cerebellum. In addition, the Visual Form Discrimination Test scores (Benton, Hamsher, Varney, & Spreen, 1994) (according to the authors, this test evaluates both visuoperceptual and visuospatial functions) correlated with grey matter reduction in the bilateral superior parietal lobule, left inferior frontal gyrus, left middle frontal gyrus and right superior occipital gyrus (Pereira, Junque, Marti, Ramirez-Ruiz, Bargallo, et al., 2009). Using an ROI technique, a study revealed a correlation between the total score on the Ekman 60 Faces Test (Ekman & Friesen, 1976 as cited in Ibarretxe-Bilbao, et al., 2009) (which assessed recognition of facial emotion expressions) and the orbitofrontal cortex but not with amygdala in early PD patients (Ibarretxe-Bilbao, et al., 2009).

In contrast to the studies above, a VBM study of early PD patients found no association between grey matter density and scores of the verbal memory, attention-executive and visuospatial functions (Dalaker et al., 2009). Various reasons can be given to explain the difference in findings between this latter study and prior studies. For instance, the Dalaker et al (2009) study included patients with shorter duration of disease (mean 30.8 months), who were not taking any anti-parkinsonian medications, and included younger subjects (mean 64.4 Standard Deviation (SD) 9.6).

Other previous studies also have limitations. For instance, some included patients with VH (Ibarretxe-Bilbao, et al., 2008; Pereira, Junque, Marti, Ramirez-Ruiz, Bargallo, et al., 2009; Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009) while other reports did not indicate whether neuropsychiatric symptoms were among the exclusion criteria and it has been demonstrated that neuropsychiatric symptoms affect cognitive abilities (Costa, et al., 2006; Drijgers, et al., 2010; Dujardin, et al., 2009; Fernandez, et al., 2009; Isella, et al., 2002; Morgante, et al., 2012; Oguru et al., 2010; Santangelo, Vitale, Trojano, Longo, et al., 2009). Furthermore, some studies included patients with dementia (Costa, et al., 2006; Drijgers, et al., 2010; Dujardin, et al., 2009; Fernandez, et al., 2009; Isella, et al., 2002; Morgante, et al., 2012; Oguru et al., 2010; Santangelo, Vitale, Trojano, Longo, et al., 2009) and some previous research explored limited cognitive domains within the same cohort.

3. CHAPTER THREE: AIMS AND OBJECTIVES

The existing literature has provided evidence of the crucial effect of non-motor symptoms in patients with PD. Non-motor symptoms, particularly neuropsychiatric symptoms and cognitive impairment, negatively affect quality of life of PD patients who developed these symptoms. The neuropsychiatric symptoms and cognitive impairment also cause impairments in daily living activities equal to or more than the limitations that result from motor deficits, and may lead patients to live in nursing homes. Some studies have demonstrated that neuropsychiatric symptoms and cognitive impairment also occur even in the early stages of the disease. Prior research has suggested that these symptoms frequently go unrecognised by clinicians and remain untreated. In addition, the prevalence of neuropsychiatric symptoms and cognitive impairment tends to be very high in PD patients; this certainly requires further investigation.

Although from a review of the literature it appears that some investigations have examined the association between cognitive abilities and specific neuropsychiatric symptoms in PD patients, none have investigated the cognitive profile of specific neuropsychiatric symptoms in these patients although prior research has provided evidence of the occurrence of neuropsychiatric symptoms as independent isolated symptoms or as multiple symptoms in PD patients. In addition, there are some methodological issues that have been raised following studies that examined specific neuropsychiatric symptoms. For instance, when examining cognitive decline within a group of patients with a particular neuropsychiatric symptom, it is very important to exclude other neuropsychiatric symptoms. The use of this method will allow us to gain a better understanding of the possible biological mechanisms when breaking down the result for each specific symptom. However, most previous work did not take this issue into account. Another point is that certain studies assess only global cognitive abilities

or limited cognitive domains. Similar methodological issues have been found in some published studies that have attempted to explore the brain regions that may correlate with specific neuropsychiatric symptoms. Therefore, the aim of chapter four of this project is to explore the cognitive and neuroanatomical correlates of neuropsychiatric symptoms in general and then to explore the most common neuropsychiatric symptoms in particular. The current study will use a large sample of non-demented PD patients whose overall cognitive profile is still broadly intact. The Neuropsychiatric Inventory (Cummings, et al., 1994) will be used to assess neuropsychiatric symptoms and an extensive battery of neuropsychological tests to measure multiple cognitive abilities. The neuroanatomical correlates will be detected using volumetric structural brain data acquired with MRI and data will be analysed using a voxel based approach with the Statistical Parametric Mapping software (SPM8).

The last experiment in this project will focus on the neural correlates of cognitive impairment in non-demented PD patients. It has been suggested that cognitive decline in non-demented PD patients is triggered by the reduction of dopamine input to fronto-striatal circuits (which link the frontal lobe to the basal ganglia). Few imaging studies have explored the underlying mechanisms of cognitive impairments in PD and there are some limitations observed in the previous work, for example the inclusion of PD patients with neuropsychiatric symptoms or dementia. In fact, these symptoms may contribute to cognitive decline in those patients. Excluding these symptoms can give a clearer picture of early cognitive dysfunctions in PD patients. Finally, prior work has only examined limited cognitive domains, thus, the current study will focus on exploring the correlation between grey matter volume and cognitive performance and competency within a sample of non-demented PD patients without any neuropsychiatric symptoms using an extensive battery of neuropsychological tests to evaluate multiple cognitive domains.

The research objectives of this project are as follows:

1- To explore the cognitive and neuroanatomical correlates of neuropsychiatric symptoms in general in PD. Based on the earlier studies that investigated the cognitive and neural correlates of specific neuropsychiatric symptoms in PD (chapter 2, sections 2.1.2 and 2.1.3), we expect patients with neuropsychiatric symptoms to have more cognitive impairments than patients without any neuropsychiatric symptoms particularly in executive functioning. In addition, patients with neuropsychiatric symptoms may also show lower grey and white matter volume, especially in the frontal lobe compared with patients without any symptoms or healthy controls. This point will be studied in detail in chapter 4, experiments 1 and 2.

2- To explore the cognitive and neuroanatomical correlates of depression in PD. From the previous review (chapter 2, sections 2.1.2.1 and 2.1.3.1) we hypothesised that patients with depression may show more cognitive decline than patients without any neuropsychiatric symptoms. The prediction for the present study is to find grey and white matter loss in the frontal lobe areas in patients with depression when compared with patients without any neuropsychiatric symptoms or with healthy controls. This point will be studied in detail in chapter 4, experiments 3 and 4.

3- To explore the cognitive and neuroanatomical correlates of apathy in PD. Apathy has been associated with cognitive decline, particularly in executive functions and with atrophy of the frontal and cingulate cortex in patients with PD. Therefore, we expect to find a similar pattern of cognitive impairments and grey and white matter loss in similar anatomical structures in patients with apathy. This point will be studied in detail in chapter 4, experiments 5 and 6.

4- To explore the cognitive and neuroanatomical correlates of both depression and apathy in PD. Prior studies of both depression and apathy in patients with PD have reported an association between these symptoms and cognitive decline. Based on that our hypothesis is that PD patients who developed both depression and apathy may show lower cognitive performance when compared with patients who have not developed any neuropsychiatric symptoms. In addition, in psychiatric population, there is evidence of the association between both depression and apathy and atrophy of the frontal lobe. Thus, it can be predicted that patients with PD who have both depression and apathy may display grey and white matter reduction in the frontal lobe regions. This point will be studied in detail in chapter 4, experiments 7 and 8.

5- To explore the correlation between grey matter volume and cognitive impairments in PD. Cognitive impairments in patients with PD have been linked to the reduction of dopamine input to fronto-striatal circuits. However, it can be predicted that the decline of particular cognitive domains would correlate with different anatomical structures. This point will be studied in detail in chapter 5, experiment 9.

4. CHAPTER FOUR: NEUROPSYCHIATRIC SYMPTOMS IN PD

4.1 EXPERIMENT 1 – COGNITIVE CORRELATES OF NEUROPSYCHIATRIC SYMPTOMS IN PD

4.1.1 INTRODUCTION

A small number of studies have investigated the cognitive abilities of patients with PD who develop multiple neuropsychiatric symptoms. One study examined executive functions and neuropsychiatric features in 20 non-demented patients with PD (mild to severe stages) and 20 healthy controls. This study used Trail Making Test (TMT) (part B) (Reitan, 1958) to measure set-shifting, Stroop Test (inhibition subtest) (Stroop, 1935), the MMSE (Folstein, et al., 1975), the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) and the Scales for Outcome in PD-psychiatric Complications (Goetz et al., 2008); this questionnaire includes also a subsection to assess the presence of visual misperception and hallucinations. When compared with healthy controls, patients with PD with neuropsychiatric symptoms (visual hallucinations, depression and anxiety) had significantly lower scores in the MMSE and the Stroop Test but not in the TMT. In addition, patients who had only hallucinations (n= 10) performed significantly lower in both TMT and Stroop Test but not on the MMSE compared with patients without hallucinations (Lewis, Shine, Duffy, Halliday, & Naismith, 2012). Another study found correlations between the total NPI scores and executive dysfunction (as measured by verbal fluency (Thurstone & Thurstone, 1962)) in non-demented patients with PD (Kulisevsky, et al., 2008). A further study recently examined the relationship between neuropsychiatric symptoms and cognitive performance in untreated patients with PD without dementia (n= 30) (Poletti et al., 2012). The assessments of neuropsychiatric symptoms included the Geriatric

Depression Scale Short Form, the Toronto Alexithymia Scale, the Barratt Impulsiveness Scale, the Maudsley Obsessive-Compulsive Questionnaire, and the Hamilton Rating Scale for Anxiety. This particular study also included neuropsychological assessments measures testing executive functions (Frontal Assessment Battery (FAB) and verbal fluency), verbal memory (Rey Auditory Verbal Learning Test-RAVLT), visuospatial processing (Benton's Judgment of Line Orientation Test, Raven Coloured Progressive Matrices), naming (Boston Naming Test) and constructional praxis (Rey-Osterrieth Complex Figure Copy Test). The results showed that ten patients had depression, 6 patients had alexithymia, 6 patients were anxious, and 3 patients had impulsive symptoms. In addition, 8 patients displayed impaired performance on at least one cognitive test. The Geriatric Depression Scale scores were associated with both immediate and delayed recall scores in the RAVLT. Also, Alexithymia scores correlated with the RAVLT immediate recall scores. While, obsessive compulsive symptoms were associated with FAB and semantic verbal fluency scores (Poletti, et al., 2012).

As we noted in chapter two (section 2.1.2), most of the previous studies have looked at cognitive function in patients with PD with specific neuropsychiatric symptoms without controlling for the presence of other concurrent symptoms and only two studies have attempted to explore the cognitive profile of patients with multiple neuropsychiatric symptoms (Lewis, et al., 2012; Poletti, et al., 2012). These studies examined cognitive performance in only small samples of patients and they studied limited neuropsychiatric symptoms. Thus, the present work aimed to explore the cognitive profile of non-demented PD patients with neuropsychiatric symptoms (patients presenting with one or several symptoms) using extensive neuropsychological testing. Based on previous evidence, it can be predicted that patients with

neuropsychiatric symptoms might have more cognitive impairments than patients without any neuropsychiatric symptoms, particularly in executive functioning.

4.1.2 METHOD

4.1.2.1 SAMPLE

Sixty five patients with idiopathic PD (31 males and 34 females) participated in this study. The patients were a retrospective sample recruited from a neurology Parkinson outpatient clinic. The patients were diagnosed based on the UK PD Brain Bank Criteria (Hughes, Daniel, Kilford, & Lees, 1992). There were forty one (63.1%) patients with the tremoric form of PD, 24 (36.9%) patients with rigidity, 44 (67.7%) patients with bradykinesia and 14 (21.5%) patients with balance instability. All patients had extensive neuropsychological screening, neuropsychiatric assessment using the NPI (Cummings, et al., 1994), structural MRI scanning and neurological examination. All patients were in the mild to mild-moderate disease stage, according to the Hoehn and Yahr staging (Hoehn & Yahr, 1967). None of the patients had a history of psychiatric disorders and the neuropsychiatric symptoms started after the onset of PD. All patients were treated with a combination of levodopa and variable doses of dopamine agonists but none were treated with antidepressants. The mean age of all PD patients was 65.28 years (SD= 9.30, range 44-80), their mean education was 11.08 years (SD= 4.35, range 4-18), their mean disease duration was 8.35 years (SD= 5.27) and their mean MMSE score was 27.95 (SD= 1.8, range 24- 30). The patient sample was divided into two subgroups according to the presence or absence of neuropsychiatric symptoms measured by the NPI (Cummings, et al., 1994). Patients were considered as having neuropsychiatric symptoms if they obtained a score of 1 or higher in one or more of the 14 symptom fields in the NPI (see below the assessment of neuropsychiatric symptoms). Patients who scored zero on all symptom fields were considered to be without neuropsychiatric symptoms. Forty three (66.2 %) patients had one or more

neuropsychiatric symptoms and 22 (33.8 %) had no neuropsychiatric symptoms (Figure 4.1).

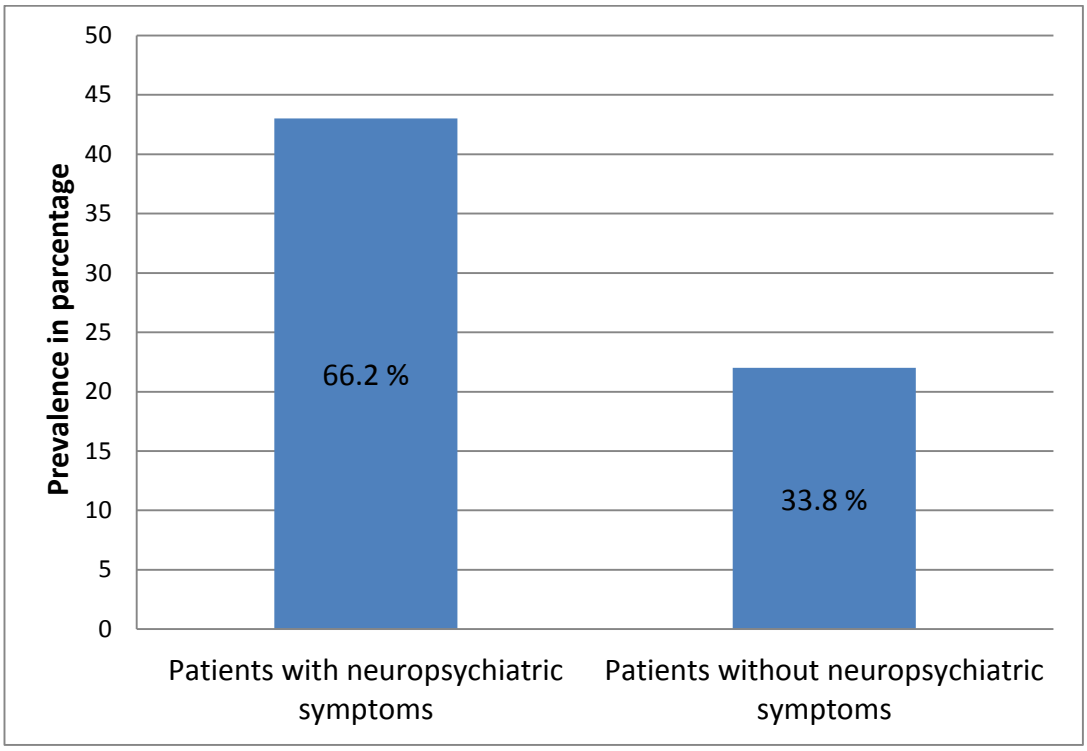

Fig 4.1 Percentage of PD with and without neuropsychiatric symptoms

The mean age of the PD subgroup with neuropsychiatric symptoms was 64.4 years (SD= 9.56, range, 44-80), their mean education was 11.12 years (SD= 4.33, range 4-18), their mean disease duration was 8.6 years (SD= 5.50) and their mean MMSE score was 27.8 (SD= 1.82 range, 24- 30). The mean age of the PD subgroup without any neuropsychiatric symptoms was 67.1 years (SD= 8.7, range 48-80), their mean education was 11.00 years (SD= 4.5 range, 5-18), their mean disease duration was 7.86 years (SD= 4.87) and their mean MMSE score was 28.32 (SD= 1.34, range 24- 30).

4.1.2.2 ASSESSMENTS OF NEUROPSYCHIATRIC SYMPTOMS

The Neuropsychiatric Inventory is designed to assess 10 behavioural disturbances, namely, delusion, hallucinations, dysphoria, anxiety, euphoria, agitation/aggression, apathy, irritability/lability, disinhibition, and aberrant motor behaviour (Cummings, et al., 1994). In addition, Cummings, 1997 added two scales to

assess night behaviour disturbance and appetite/eating disorders (Cummings, 1997). The maximum score that can be obtained in each behavioural domain is 12 which represents severe behaviour disturbance. Additional symptom fields which were also assessed were obsessive compulsive disorders and phobia.

In the present study, neuropsychiatric symptoms were assessed using both the NPI (Cummings, et al., 1994) and the DSM-IV-TR (American Psychiatric Association, 2000). Each patient and their caregiver had had an interview with an experienced psychologist who also completed the NPI.

4.1.2.3 NEUROPSYCHOLOGICAL ASSESSMENTS

All PD patients completed a comprehensive neuropsychological battery of tests. This included:

4.1.2.3.1 MINI MENTAL STATE EXAMINATION (MMSE)

The MMSE is a screening instrument that assesses overall cognitive functioning. It tests for concentration, orientation, attention, memory and language. This examination takes five to ten minutes to administer and a total score of 30 can be achieved (Folstein, et al., 1975).

4.1.2.3.2 RAVEN'S PROGRESSIVE MATRICES (PM38)

A shortened version of PM38 was used. The test includes 4 sets (A, B, C, and D) of twelve black and white patterns which consist of visual pattern matching and similarity problems. This test is easy to administer. Only correct responses given within 30 minutes are considered in the scoring (Caffarra, Vezzadini, Zonato, Copelli, & Venneri, 2003). The participant has to conceptualize spatial and design relationships increasing in difficulty from very simple to very complex and abstract (Lezak, Howieson, Bigler, & Tranel, 2012; Lezak, et al., 2004). The score ranges from 0 to 48.

4.1.2.3.3 STROOP TEST

This test examines focussed attention abilities. A shortened version specifically designed to test elderly patients was used (Venneri et al., 1993). It contains 30 colour names (red, green and blue) in one sheet. In the first part of this test the subject is asked to read the colour word name printed in black. In the second part the subject is required to name the colour of 30 dots. In the third part, the participant is asked to name the colour in which each colour word is printed. There is no congruency between the colour word and the colour of the ink a word is written in. The examiner has to record the time for each part of the test and the number of errors. This test is scored by subtracting the average time of part one and two from the time of the third part. The same procedures apply for obtaining an error score (Caffarra, et al., 2002; Lezak, et al., 2012; Lezak, et al., 2004; Stroop, 1935).

4.1.2.3.4 TRAIL MAKING TEST (TMT)

The purpose of this test is to assess scanning and visuomotor tracking, divided attention, and cognitive flexibility. The TMT includes two parts, A and B. In part A the participant must draw straight lines to connect numbers in sequence on one sheet. Then in part B, the subject has to connect items in sequence alternating between numbers and letters. The participant is asked to connect numbers and letters as fast as he/she can without lifting the pencil from the sheet (Giovagnoli et al., 1996; Lezak, et al., 2004). Reitan (1958) introduced a scoring method which is the one commonly used today. This method requires the examiner to point out any errors that occur during the test, so that the participant can complete the test without errors. Completion time for each trial is recorded (Reitan, 1958).

4.1.2.3.5 CATEGORY AND LETTER FLUENCY

In these tests the participant is asked to produce as many words as possible from each of two semantic categories (animals and fruits) or in the letter fluency task to say as many words as possible that begin with the letter P, L, F. Sixty seconds for each trial are given (Lezak, et al., 2004).

4.1.2.3.6 SIMILARITIES TEST

This test is part of the Wechsler Adult intelligence scale (WAIS) and assesses verbal concept formation. The subject must explain how the words in a pair are similar. The word pairs range from simple (for example, orange-banana) to difficult (Wechsler, 1997a). There are two levels for passing items, if an abstract generalization is given, 2 points are given to that item and if a specific concrete likeness is given on a response only 1 point is given to that item.

4.1.2.3.7 REY COMPLEX FIGURE TEST

The Rey Complex Figure Test was designed to investigate both perceptual organization and visual memory abilities. There are 18 elements and 36 points to be achieved on this test. The participant is asked to copy the complex figure onto a sheet of paper. After a 10 minute delay the participant is asked to reproduce the figure from memory. Two separate scores are given: one for the object copy and one for the delayed copy from memory (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002a; Lezak, et al., 2012; Lezak, et al., 2004).

4.1.2.3.8 DIGIT SPAN

The Digit Span Test is a part of the WAIS. This test requires recall of digits forward and recall of digits backward. Both tests contain seven pairs of random number sequences, the examiner reads out the number sequences aloud at the rate of one digit per second (Lezak, et al., 2012; Lezak, et al., 2004; Wechsler, 1997a). Essentially, both

tests involve auditory attention and short-term retention capacity. However, digit span backward requires more mental effort than digit forward because a participant has to store a number of digits and manipulate them around at the same time. This mental process suggests an involvement of working memory in the digit backward task (Lezak, et al., 2012), therefore also assessing executive skills.

4.1.2.3.9 FRONTAL ASSESSMENT BATTERY (FAB)

This test usually takes 10 minutes to be completed. It examines the following six abilities: conceptualization (similarities), generation (letter fluency), motor sequencing (Luria's, palm–edge–fist), sensitivity to interference (conflict task), inhibitory control (go/no-go task) and environmental autonomy (imitation or utilization behaviour test). The total score is 18, with higher scores indicating better performance (Appollonio et al., 2005; Dubois, et al., 2000; Lezak, et al., 2012; Lezak, et al., 2004).

4.1.2.3.10 CORSI BLOCK-TAPPING TEST (VISUAL-SPATIAL SPAN)

The Corsi Block-tapping Test assesses visual-spatial short term memory. It consists of nine block cubes fastened to a black board in a random order. The examiner taps the blocks in a prearranged sequence, then the participant must reproduce the same tapping pattern (Lezak, et al., 2012; Lezak, et al., 2004; Spinnler, 1987).

4.1.2.3.11 REY AUDITORY VERBAL LEARNING TEST (RAVLT)

The Rey Auditory Verbal Learning Test (Rey, 1964) measures verbal memory and learning abilities. This test consists of 15 words and has two parts. The first part assesses immediate recall skills. In this part a list of 15 words is repeated five times, then for each trial the participant has to tell the examiner all words he or she can remember. The score of this part ranges from 0 to 75 depending on the total number of recalled words. The second part evaluates the ability of delayed recall after 15 minutes.

The examiner asks the participant to repeat any words he or she can remember from the word list (Lezak, et al., 2012; Lezak, et al., 2004).

4.1.2.4 STATISTICAL ANALYSES

An independent T-test and a series of independent T-tests were carried out to compare the demographic data and neuropsychological test scores of the two subgroups (patients with PD with and without neuropsychiatric symptoms). To account for multiple comparisons, this study used a significance level of 0.004 for overall comparisons among groups, except for the group comparison of demographical data, for which the significance level was 0.01.

Further statistical analyses were also carried out to examine the relationship between the MMSE scores and other variables e.g. total NPI scores, number of symptoms and individual symptom scores.

Multiple regression analyses were also carried out to see which of the demographic data (age, education and disease duration) and MMSE can explain the variation in the total NPI score and the variation in each neuropsychological test.

4.1.3 RESULTS

4.1.3.1 FREQUENCY OF NEUROPSYCHIATRIC SYMPTOMS IN THE GROUP OF PATIENTS WITH PD

The present study showed that 43 patients with PD had neuropsychiatric symptoms whereas 22 patients had no neuropsychiatric symptoms (see figure 4.1). Further analyses were carried out to determine the frequencies of neuropsychiatric symptoms in this patient sample. The most common neuropsychiatric symptoms were depression (27 patients), apathy (25 patients), hallucinations (21 patients) and anxiety (20 patients). The results also showed that there were 19 patients with sleeping problems, 18 patients with irritability, 17 patients with agitation/aggression, 15 patients

with eating disorder, 12 patients with obsessive compulsive disorder, 11 with motor behaviour problems, 8 patients with disinhibition, 6 patients with elation/euphoria, 5 patients with delusions and 3 patients with phobia (see figure 4.2).

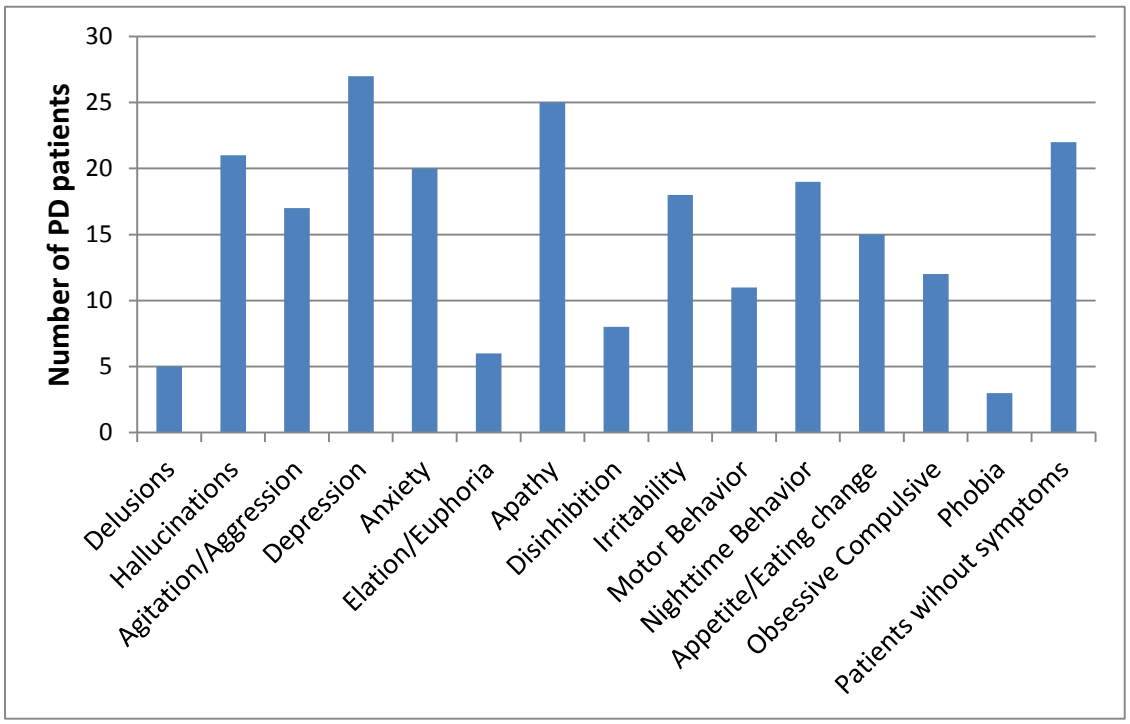

Fig. 4.2 the frequencies of neuropsychiatric symptoms in the PD sample

It should be noted that some patients had more than one symptom which means for instance that some of the 27 patients, who had depression, may also have other neuropsychiatric symptoms. To clarify this point, the chart below illustrates the number of patients with neuropsychiatric symptoms (see figure 4.3).

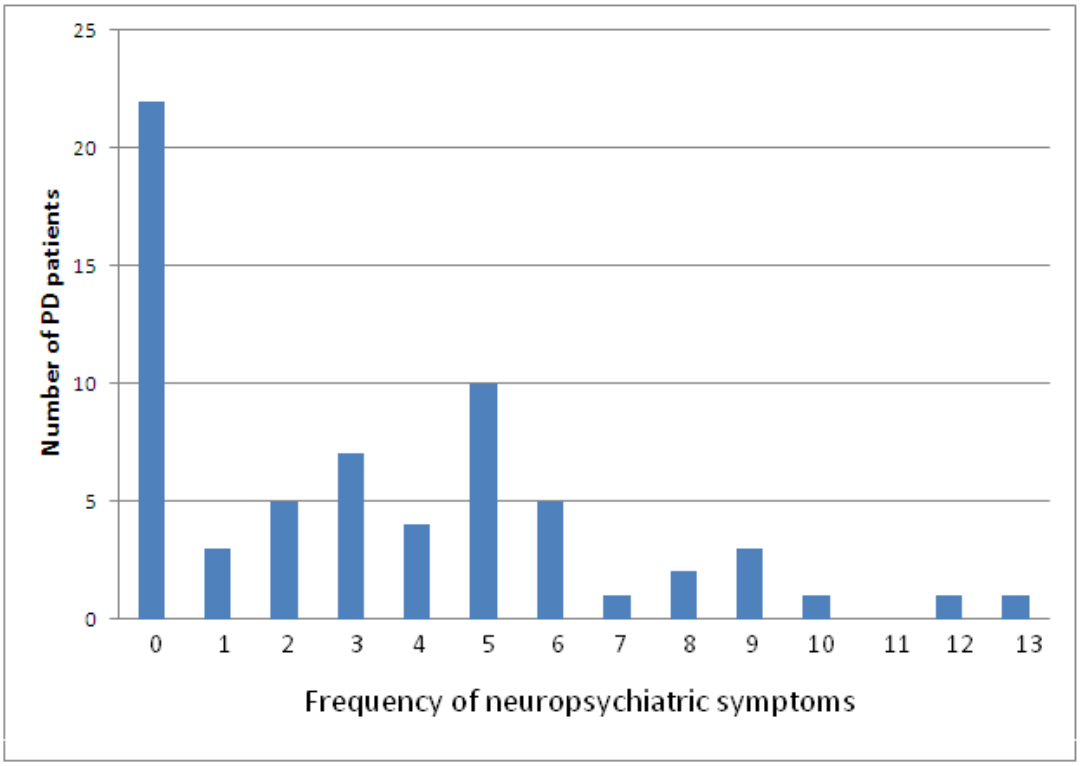

Fig 4.3 Frequency of combinations of neuropsychiatric symptoms in the group of patients with PD

Figure 4.3 shows that 3 patients had one neuropsychiatric symptoms, 5 patients had 2 symptoms, 7 patients had 3 symptoms, 4 patients had 4 symptoms, 10 patients had 5 symptoms, 5 patients had 6 symptoms, one patient had 7 symptoms, 2 patients had 8 symptoms, 3 patients had 9 symptoms, one patient had 10 symptoms, one patient had 12 symptoms and another patient had 13 neuropsychiatric symptoms.

4.1.3.2 DEMOGRAPHICAL AND MENTAL STATE SCREENING DATA ANALYSES

An independent T-test was carried out to compare the demographic variables of the PD subgroups with and without neuropsychiatric symptoms. There was no significant difference between the two subgroups of patients in age $t(63) = 1.13$, $p > .01$, education $t(63) = -.10$, $p > .01$, or duration of disease $t(63) = -.53$, $p > .01$. In addition, there was no significant difference in the mean MMSE scores of the two subgroups $t(63) = .23$, $p > .01$ (Table 4.1).

Table 4.1 Mean (SD) Age, Education, Duration of disease and MMSE of PD patients with and without neuropsychiatric symptoms (NPSS)

	PD with NPSS (N = 43)	**PD without NPSS (N = 22)**	***P***
Age	64.4 (9.6)	67.1 (8.7)	.264
Education	11.12 (4.3)	11.00 (4.5)	.920
Duration of disease	8.60 (5.50)	7.9 (4.87)	.596
MMSE	27.77 (1.82)	28.32 (1.59)	.234

4.1.3.3 COGNITIVE PROFILE OF PD PATIENTS WITH AND WITHOUT NEUROPSYCHIATRIC SYMPTOMS

Independent T-tests were carried out to compare the scores obtained by patients with PD with and without neuropsychiatric symptoms on each test in the neuropsychological battery. The subgroup with neuropsychiatric symptoms had lower scores than the subgroup without neuropsychiatric symptoms in all neuropsychological tests. After correcting for multiple comparisons, significant differences between the two subgroups of patients were found in the Similarities Test $t(59)= 3.48$, $p < .004$, Digit Span (backward) $t(53)= 4.75$, $p < .004$ and Frontal Assessment Battery $t(61)= 3.25$, $p < .004$. In addition, scores on other neuropsychological tests approached significance level, e.g. Stroop Test (error) $t(50)= -2.01$, $p = 0.049$, Rey Complex Figure (copy) $t(59)= 2.33$, $p = 0.023$, Rey Complex Figure (delayed) $t(56)= 2.07$, $p = 0.042$, Digit Span (forward) $t(45)= 0.86$, $p = 0.006$ and Rey 15-word Memory Test $t(62)= 2.86$, $p = 0.006$. However, there were no significant differences between the two PD subgroups in any of the other neuropsychological tests, e.g. Raven's Progressive Matrices $t(57)= 1.13$, $p > .004$, Stroop Test (time) $t(53)= -.428$, $p > .004$, TMT $t(39)= -.40$, $p > .004$, Letter Fluency Test $t(62)= 1.54$, $p > .004$, Category Fluency Test $t(62)= .58$, $p > .004$ and the Visual-spatial span $t(45)= -.31$, $p > .004$ (see table 4.2).

Table 4.2 Mean (SD), and *P* value of scores on the neuropsychological tests achieved by PD with and without neuropsychiatric symptoms (NPSS)

	PD with NPSS (N = 43)	**PD without NPSS (N = 22)**	***p***
Raven's Progressive Matrices	26.53 (8.52)	29.4 (10.58)	.263
Stroop test			
Time interference effect	37.10 (36.23)	33.32 (17.89)	.671
Error interference effect	3.48 (5.07)	1.13 (1.55)	.049
Trail Making Test	70 (41.58)	64.37 (58.74)	.688
Letter Fluency Test	31.02 (11.21)	36.05 (14.33)	.128
Category Fluency Test	33.76 (10.03)	35.41 (11.98)	.562
Similarities Test	**14.38 (4.77)**	**18.32 (3.07)**	**0.001***
Rey Complex Figure			
Direct copy	27.19 (6.56)	31.02 (5.08)	0.023
Delayed copy	11.28 (5.59)	14.65 (6.19)	0.042
Digit Span			
Forward	5.63 (1.86)	7.67 (2.99)	0.006
Backward	**3.18 (1.33)**	**4.68 (.78)**	**0.000***
Frontal Assessment Battery	**9.74 (7.25)**	**14.29 (3.85)**	**0.002***
Visual-spatial span	4.36 (1.43)	4.21 (1.76)	.762
Rey 15-word Memory Test	5.62 (4.23)	8.55 (3.14)	0.006

*Significant difference between PD with and without neuropsychiatric symptoms $P < 0.004$ (corrected for multiple comparison)

4.1.3.4 CORRELATION ANALYSES

Correlation analyses were carried out with MMSE scores and other variables including total NPI scores, number of symptoms and individual symptom scores. First, there was a significant negative relationship between total NPI scores and MMSE scores (r= -.278, $P = 0.025$). Higher total NPI scores were associated with lower performance on the MMSE. Second, there was a negative correlation between MMSE scores and number of neuropsychiatric symptoms (r= -.285, $p = 0.021$). Third, there was a negative correlation between disinhibition scores (r=-.386, $P = 0.001$) and MMSE scores but not with other symptoms. Delusions scores were positively associated with hallucinations scores (r=.787, $P = 0.000$), disinhibition scores (r=.359, $P = 0.003$), aberrant motor behaviour scores (r=.452, $P = 0.000$) and appetite/eating change scores (r=.462, $P = 0.000$). Hallucinations scores were positively correlated with depression scores (r=.386, $P = 0.002$), apathy scores (r=.370, $P = 0.002$), disinhibition scores (r=.362 $P = 0.003$) and with appetite/eating change scores (r=.395 $P = 0.001$). A significant positive relationship was found between agitation scores and disinhibition

scores (r=.375, *P* = 0.002), irritability scores (r=.604, *P* = 0.000), aberrant motor behaviour scores (r=.434 *P* = 0.000), night time behaviour scores (r=.359, *P* = 0.003), appetite/eating change scores (r=.373, *P* = 0.002) and obsessive compulsive behaviour scores (r=.621, *P* = 0.000). Depression scores were positively correlated with anxiety scores (r=.785, *P* = 0.000), apathy scores (r=.624, *P* = 0.000) and with appetite/eating change scores (r=.473, *P* = 0.000). In addition, anxiety scores were positively associated with apathy scores (r=.485, *P* = 0.000) and with appetite/eating change scores (r=.445, *P* = 0.000). Euphoria scores were significantly correlated with only disinhibition scores (r=.501, *P* = 0.000). Moreover, there was a positive relationship between apathy scores and appetite/eating change scores (r=.493, *P* = 0.000). Disinhibition scores were positively associated with irritability scores (r=.426, *P* = 0.000) and night time behaviour scores (r=.435, *P* = 0.000). Irritability scores were associated with night time behaviour scores (r=.445, *P* = 0.000) and obsessive compulsive behaviour scores (r=.474, *P* = 0.000). Aberrant motor behaviour scores were positively associated with appetite/eating change scores (r=.361, *P* = 0.003), obsessive compulsive behaviour scores (r=.451, *P* = 0.000) and phobia (r=.465, *P* = 0.000). Night time behaviour scores positively correlated with appetite/eating change scores (r=.359, *P* = 0.003) (see table 4.3). Moreover, there was no correlation between disease duration and total NPI scores or with disease duration and specific symptoms.

Table 4.3 Correlations between MMSE scores and neuropsychiatric symptoms scores

	MMSE	Delusions	Hallucinations	Agitation	Depression	Anxiety	Euphoria	Apathy	Disinhibition	Irritability	Aberrant Motor Behaviour	Nighttime Behaviour	Appetite/ Eating Change	Obsessives Compulsive	Phobia
MMSE	_	-.066	-.291	-.057	-.171	-.270	-.146	-.135	-.386*	-.206	.023	-.198	-.010	.007	.148
Delusions	-.066	_	-.787*	-.326	-.279	.151	.194	.306	.359*	.290	.452*	.254	.462*	.063	.028
Hallucinations	-.291	.787*	_	.216	.386*	.342	.223	.370*	.362*	.284	.289	.233	.395*	-.062	-.002
Agitation	-.057	.326	.216	_	.194	.281	.122	.185	.375*	.604*	.434*	.359*	.373*	.621*	-.046
Depression	-.171	.279	.386*	.194	_	.785*	.107	.624*	.226	.225	.114	.291	.473*	.023	-.055
Anxiety	-.270	.151	.342	.281	.785*	_	-.067	.485*	.155	.238	.191	.332	.445*	.079	-.073
Euphoria	-.146	.194	.223	.122	.107	-.067	_	-.013	.501*	.285	.198	.200	.016	.166	.232
Apathy	-.135	.306	.370*	.185	.624*	.485*	-.013	_	.126	.213	.155	.047	.493*	-.062	-.056
Disinhibition	-386*	.359*	.362*	.375*	.226	.155	.501*	.126	_	.426*	.218	.435*	.211	.243	.033
Irritability	-.206	.290	.284	.604*	.225	.238	.285	.213	.426*	_	.327	.445*	.252	.474*	-.085
Aberrant Motor Behaviour	.023	.452*	.289	.434*	.114	.191	.198	.155	.218	.327	_	.335	.361*	.451*	.456*
Nighttime Behaviour	-.198	.254	.233	.359*	.291	.332	.200	.047	.435*	.445*	.335	_	.359*	.351	.129
Appetite/ Eating Change	-.010	.462*	.395*	.373*	.473*	.445*	.016	.493*	.211	.252	.361*	.359*	_	.158	.054
Obsessives Compulsive	.007	.063	-.062	.621*	.023	.079	.166	-.062	.243	.474*	.451*	.351	.209	_	.777
Phobia	.148	.028	-.002	-.046	-.055	-.073	.232	-.056	.033	-.085	.465*	.129	.054	-.036	_

*Value is significant at P < 0.003 (two-tailed).

4.1.3.5 MULTIPLE REGRESSION ANALYSES

A regression analysis was carried out for the total NPI as a dependent variable and the predictors were MMSE, education, age and duration of disease. The four predictors produced a significant model F (4, 59) = 2.65, *P*= 0.04, which accounted for 15.2 % of the variance in the total NPI. Of the four predictors, MMSE β= -0.35, t(59)= -2.695, *P*= 0.009 was significant.

A regression analysis was also carried out for each neuropsychological test as a dependent variable and the predictors were MMSE, education, age and duration of disease for all regression analyses. The four predictors produced a significant model F (4, 54) = 5.735, *P*= 0.001, which accounted for 29.8 % of the variance in the Raven's Progressive Matrices. Of the four predictors, age β= -0.247, t(54)= -2.118, *P* = 0.04 and duration of disease β= -.294, t(54)= -2.449, *P*= 0.02 were significant. In this model MMSE approached significance level β= .249, t(54)= 1.971, *P*= 0.054. In addition, the predictors produced a significant model F (4, 50) = 3.545, *P*= 0.01, which accounted for 21 % of the variance in the Stroop (time). Of the four predictors, MMSE was significant β= -0.434, t(50)= -3.178, *P* = 0.003. A regression analysis also with the same predictors produced a significant model F (4, 59) = 4.161, *P*= 0.005, which accounted for 22 % of the variance in the Letter Fluency Test. Of the four predictors, MMSE was significant β= 0.367, t(59)= 2.962, *P* = 0.004. The predictors also produced a significant model F (4, 59) = 8.330, *P*= 0.000, which accounted for 36.1 % of the variance in the Category Fluency Test. Of the four predictors, MMSE β= 0.415, t(59)= 3.700, *P* = 0.000 and age β= -0.397, t(59)= -3.772, *P* = 0.000 were significant. Also, the four predictors produced a significant model F (4, 56) = 7.334, *P*= 0.000, which accounted for 34.4 % of the variance in the Similarities Test. Of the four predictors, MMSE β= 0.443, t(56)= 3.779, *P* = 0.000 and education β= 0.284, t(56)= 2.537, *P* = 0.014 were significant. However,

the regression analyses with the same predictors failed to produce a significant model for the other neuropsychological tests (see table 4.4).

Table 4.4 regression analyses for variables predicting the total NPI and neuropsychological tests

	Predictors											
	MMSE[a]			**Age[b]**			**Education[c]**			**Duration of disease[d]**		
Independent variables	**R^2**	**F**	***p***	**R^2**	**F**	***p***	**R^2**	**F**	**p**	**R^2**	**F**	***p***
Total NPI	**.074**	**4.95**	**0.03**	**.102**	**3.48**	**0.04**	**.150**	**3.53**	**0.02**	**.152**	**2.65**	**0.04**
Raven's Progressive Matrices	**.163**	**11.07**	**0.002**	**.218**	**7.82**	**0.001**	**.220**	**5.18**	**0.003**	**.298**	**5.74**	**0.001**
Stroop test (Time)	**.210**	**14.06**	**0.000**	**.210**	**6.93**	**0.002**	**.220**	**4.81**	**0.005**	**.221**	**3.55**	**0.013**
Stroop test (Error)	.043	2.23	0.14	.043	1.10	0.34	.043	0.73	0.54	.046	0.57	0.69
Trail Making Test	.097	4.17	0.048	.167	3.81	0.03	.169	2.52	0.07	.172	1.87	0.14
Letter Fluency Test	**.169**	**12.62**	**0.001**	**.205**	**7.85**	**0.001**	**.220**	**5.63**	**0.002**	**.220**	**4.16**	**0.005**
Category Fluency Test	**.206**	**16.07**	**0.000**	**.359**	**17.11**	**0.000**	**.359**	**11.22**	**0.000**	**.361**	**8.33**	**0.000**
Similarities Test	**.267**	**21.498**	**0.000**	**.267**	**10.57**	**0.000**	**.343**	**9.898**	**0.000**	**.344**	**7.33**	**0.000**
Rey Complex Figure (Copy)	.056	3.48	0.07	.088	2.80	0.07	.127	2.78	0.049	.159	2.65	0.043
Rey Complex Figure (Delayed)	.092	5.69	0.02	.125	3.92	0.03	.125	2.57	0.06	.133	2.03	0.10
Digit Span Forward	.014	0.66	0.42	.019	0.42	0.66	.026	0.38	0.768	.062	0.69	0.60
Digit Span Backward	.015	0.81	0.37	.024	0.65	0.53	.030	0.52	0.67	.030	0.39	0.82
Frontal Assessment Battery	.001	0.032	0.86	.001	0.02	0.98	.005	0.095	0.96	.005	0.07	0.99
Visual-spatial span	.001	0.03	0.86	.004	0.095	0.91	.019	0.27	0.85	.021	0.23	0.92
Rey 15-word Memory Test	.055	3.624	0.06	.072	2.37	0.10	.082	1.79	0.16	.082	1.32	0.27

a. Predictors: (Constant), MMSE

b. Predictors: (Constant), MMSE, Age

c. Predictors: (Constant), MMSE, Age, Education

d. Predictors: (Constant), MMSE, Age, Education, duration of disease

4.1.4 DISCUSSION

The present study showed that the prevalence of neuropsychiatric symptoms in PD patients was 66.2%, which is similar to previously reported data that found the prevalence of neuropsychiatric symptoms in patients with PD to be 61% (Aarsland, et al., 1999) and 64.8% (Leroi, Pantula, McDonald, & Harbishettar, 2012). The high prevalence of neuropsychiatric symptoms found in the current study suggests that these symptoms should be considered when a diagnosis of PD is given. However, another study reported a lower prevalence of neuropsychiatric symptoms (56%) in early untreated PD patients (Aarsland, Bronnick, et al., 2009). Although the latter study controlled for the potential effect of dopaminergic drugs on the genesis of neuropsychiatric symptoms, some patients were treated by antidepressants and anxiolytics medications which might have reduced the presence of depression and anxiety. The current study indicated that the most common neuropsychiatric symptoms were depression and apathy as supported by other research, (Aarsland, Bronnick, et al., 2009; Aarsland, et al., 2007). Furthermore, the correlational analyses also showed that depression was strongly associated with apathy and anxiety, implying that in the early stages of PD, mood alteration and apathy are the predominating symptoms rather than psychotic symptoms. Previous studies also reported an association between depression and apathy (Cubo, et al., 2012; Santangelo, Vitale, Trojano, Longo, et al., 2009; Zahodne, et al., 2012) and between depression and anxiety (Dissanayaka, et al., 2011).

From the regression analyses, MMSE was the only significant predictor of the total NPI scores with higher MMSE scores associated with fewer symptoms. Age, education and duration of disease failed to predict scores on the NPI. This finding lends support to Aarsland et al (1999) which reported a significant association between the severity of neuropsychiatric symptoms and MMSE but not with age or duration of disease in PD. However, Kulisevsky et al (2008) found that in PD the presence of

neuropsychiatric symptoms was predicted by longer disease duration but not by level of education, which is partially in line with the findings of the present study, as education was not a predictor of neuropsychiatric symptoms in PD. This difference between findings might be a result of the inclusion of patients in the mild-severe stages in the Kulisevsky et al. study which may explain why disease duration was a predictor of neuropsychiatric symptoms in PD.

The MMSE was the most significant predictor of performance on some neuropsychological tests, mainly those tasks assessing frontal functioning. Age, education and disease duration did not explain a significant amount of variation amongst the other neuropsychological tests.

The difference in cognitive abilities found between the two subgroups of patients, suggests that the presence of neuropsychiatric symptoms can affect cognitive skills in patients at the prodromal stages of PD. Particularly, significant differences were detected on tests that mainly assess executive functioning (inhibitory control and working memory), which fits the profile for patients with frontal lobe dysfunction, implying an association with neuropsychiatric symptoms in PD. Moreover, the association between neuropsychiatric symptoms and executive dysfunction has been reported in non-demented PD patients, (Kulisevsky, et al., 2008; Lewis, et al., 2012), again, adding to the conclusion that neuropsychiatric symptoms in PD may be associated with frontal lobe dysfunction.

In general, there are three core types of executive functions which are inhibitory control, working memory and cognitive flexibility (Miyake et al. 2000). Thus perhaps, the inability to perform well on the tasks that assess executive functions in PD route from a poor working memory and a lack of control over the stimuli presented to them in the context of prefrontal cortex damage. Furthermore, the atrophy observed within the frontal circuits clearly contributes to the manifestation of neuropsychiatric symptoms in

PD, leading to poor self-control and a weak attention span (including both behavioural and cognitive abnormalities). The current findings also showed that there were scores on other neuropsychological tests which approached significance level when the two subgroups of patients were compared. These tests include the Stroop Test (error), the Rey Complex Figure (both copy and delayed), the Digit Span (forward) and the Rey 15-word Memory Test. However, the two latter tests were the ones which were clearly approaching significance level ($P < 0.006$) which may suggest a possible impairment of attention and memory abilities in PD patients with multiple neuropsychiatric symptoms. The high prevalence of patients with the tremoric form of PD in the present sample could explain the limited cognitive impairments we found in the present study.

On another note, there have been similar patterns of association observed in neurodegeneration related to AD type pathology in experiments in which patients with Mild Cognitive Impairment (MCI) with neuropsychiatric symptoms have also been studied with comprehensive battery of neuropsychological tests. For instance, Rosenberg and colleagues (2011) found that the presence of executive dysfunction in MCI was associated with greater severity of neuropsychiatric symptoms as assessed by the NPI, specifically depression, anxiety, agitation, apathy, disinhibition, irritability, and sleep disturbance (Rosenberg et al. 2011). This finding is also supported by another study by Ellison et al (2008) who reported that the most frequent symptoms were depression/dysphoria, apathy, anxiety, irritability/lability and nighttime abnormal behavior in MCI. Another study (Edwrad et al. 2009) showed that MCI patients with a high number of neuropsychiatric symptoms (four or more) are more likely than patients with fewer symptoms (up to three) to have the amnestic form of MCI, which most likely reflects the presence of AD neurodegeneration leading to AD dementia. Amnestic MCI patients with more neuropsychiatric symptoms had a greater risk of developing dementia than those with fewer symptoms (Edward et al. 2009).

A systematic review study of MCI patients indicated that the prevalence of neuropsychiatric symptoms ranged from 35% to 75% with the most common being depression, apathy, anxiety and irritability (Apostolova and Cummings, 2007; Edward et al. 2009; Feldman et al. 2004). These studies also reported that MCI patients with behavioral disturbances are more likely to develop AD than patients without these features. Furthermore, Trivedi et al. (2013) reported that neuropsychiatric symptoms (as measured by the NPI) were significantly more in severity and frequency in patients with MCI than in healthy participants, and demented patients had significantly more neuropsychiatric problems than MCI and healthy groups. Other studies have shown that there was a negative association between frequency of neuropsychiatric symptoms and MMSE scores in patients with MCI (Edward et al. 2009; Feldman et al. 2004).

In view of the findings of the present study and the MCI studies, it can be said that the development of neuropsychiatric symptoms goes in parallel with cognitive decline and should be thoroughly assessed in patients with cognitive impairment. These findings also raise the question of whether treatment of neuropsychiatric symptoms in PD or MCI might prevent or delay progression to dementia. Further investigation is required to address this point.

In the literature, little is known about the global cognitive abilities of PD patients with multiple neuropsychiatric symptoms. However, the current findings of the correlation analyses suggest a probable association between overall cognitive impairments and neuropsychiatric symptoms (both in severity and number). Thus, the presence of neuropsychiatric symptoms may represent a higher risk of developing global cognitive impairments in this patient's group. This result is supported by previous research which reported a significant difference between PD patients with neuropsychiatric symptoms and healthy controls on the MMSE (Lewis, et al., 2012).

The following study will explore the neuroanatomical correlates of presence/absence of neuropsychiatric symptoms in PD and compare the patients with a group of healthy controls to investigate which brain areas may underlie the occurrence of neuropsychiatric symptoms.

4.2 EXPERIMENT 2 – NEUROANATOMICAL CORRELATES OF NEUROPSYCHIATRIC SYMPTOMS IN PD

4.2.1 INTRODUCTION

The underlying mechanisms of specific neuropsychiatric symptoms in patients with PD has been the object of investigation of a few studies and to my knowledge only one imaging study has attempted to explore the neural correlates of a range of neuropsychiatric symptoms in this patient population. Particularly, an imaging study investigated anterior and posterior cingulate integrity in 20 non-demented patients with neuropsychiatric symptoms (visual hallucinations, depression and anxiety) and 20 healthy controls (Lewis, et al., 2012). This study used the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) and the Scales for Outcome in PD-psychiatric Complications (Goetz, et al., 2008). Patients with neuropsychiatric features had a lower metabolism than healthy controls in the anterior cingulate cortex. However, no significant difference was detected between both two groups in the posterior cingulate cortex.

In patients with PD showing visual hallucinations, several imaging studies have demonstrated an association between frontal lobe atrophy and VH (Nagano-Saito, et al., 2004; Ramirez-Ruiz, et al., 2008; Shin, et al., 2012). VH have also been linked to other brain regions including anterior cingulate gyrus (Ramirez-Ruiz, et al., 2008), temporal lobe (Bruen, et al., 2011; Oishi, et al., 2005; Shin, et al., 2012), parahippocampal gyrus (Bruen, et al., 2011; Ibarretxe-Bilbao, et al., 2008), thalamus (Shin, et al., 2012) and occipital cortex (Bruen, et al., 2011). Patients with hallucinations (without PD) showed grey matter volume loss in the left superior temporal gyrus, left middle frontal gyrus and the right cuneus. Whereas, correlation analysis showed a negative association between grey matter loss and hallucinations scores in the left superior temporal gyrus,

left thalamus and bilateral cerebellum (Neckelmann, et al., 2006). In patients with PD and Impulse Control Disorder (ICD), a recent study has reported that ICD was associated with grey matter loss in the frontal cortex (Biundo, et al., 2011). In AD, the total NPI scores were negatively correlated with grey matter volume in the frontal and temporal cortex (Vasconcelos, et al., 2011).

From the above literature review, it appears that only one study has tried to explore the neural correlates of neuropsychiatric symptoms in patients with PD in a comprehensive manner (Lewis, et al., 2012). However, some limitations were evident in this study including a small sample size, the examination of patients with only three neuropsychiatric symptoms, and a sole focus on the cingulate cortex. Therefore, the present study aimed to explore whether there were specific structural abnormalities underling neuropsychiatric symptoms in a large sample of non-demented patients with PD. Based on prior studies of specific neuropsychiatric symptoms in patients with PD, AD or psychiatric disorders, and based on the findings from experiment 1 in which impairments in frontal lobe functions were identified by neuropsychological assessment, it can be predicted that patients with PD having multiple neuropsychiatric symptoms may have grey and white matter volume reduction in the frontal cortex when compared with patients without any symptoms or healthy controls.

4.2.2 METHOD

4.2.2.1 SAMPLE

The patients with Parkinson's disease who took part in the imaging study were a subgroup of those who took part in the behavioural study (see section 4.1.2.1). This study included a smaller sample size because not all patients had been eligible for an MRI scan. Fifty one patients with idiopathic PD (27 male and 24 female) took part in this study. The mean age of all patients was 65.33 years (SD= 8.55, range 46-83), their

mean education was 11.25 years (SD= 4.60 range 4-18), their mean disease duration was 8.1 years (SD= 4.74) and their mean MMSE score was 27.96 (SD= 1.77 range 24-30). The patients were divided into two subgroups according to their NPI score, 29 patients had one or more neuropsychiatric symptoms and 22 patients had no neuropsychiatric symptoms. Patients were considered without neuropsychiatric symptoms if they scored zero on all symptom fields. The mean age of the patients with neuropsychiatric symptoms was 65.28 years (SD= 10.47, range 46-83), their mean education was 11.3 years (SD= 4.6 range 4-18), their mean disease duration was 8.2 years (SD= 5.01) and their mean MMSE score was 27.6 (SD= 1.95 range 24- 30). The mean age of the patients without any neuropsychiatric symptoms was 66.1 years (SD= 8.5, range 48-80), their mean education was 11.2 years (SD= 4.7 range 5-18), their mean disease duration was 7.9 years (SD= 4.5) and their mean MMSE score was 28.5 (SD= 1.34 range 26- 30). The imaging study also included twenty four matched controls (6 male and 18 female) for comparison. The mean age of this healthy control sample was 61.7 years (SD= 9.5, range 50- 81), their mean education was 12.2 (SD= 5.5 range 5-24) and all achieved a MMSE score of 30/30. None of the controls had a history of neurological or psychiatric diseases.

4.2.2.2 STRUCTURAL MRI SCANNING: ACQUISITION AND ANALYSIS

Three dimensional T1- weighted MRI images were acquired on a 1.5 T Philips Achieva Scanner. Voxel dimensions were 1.04 x 1.04 x 0.6 mm. Field of view was 230 mm with a matrix size of 240 x 240 x 280. A number of pre-processing steps were followed to isolate the grey and white matter from the 3D T1-weighted structural scans before performing the statistical analysis using SPM8 imaging analysis software (Wellcome Centre for Neuroimaging, London, UK).

To correct for global differences in brain shape, structural images were warped to standard stereotactic space and segmented to extract grey matter, white matter, and

cerebrospinal fluid using the default segmentation procedure available in SPM8. The grey and white matter segments were then modulated to correct for changes in volume induced by non-linear normalization and smoothed using a Gaussian filter set at 8 mm to reduce possible error from between subject variability in local anatomy and render the data more normally distributed. These smoothed grey and white matter segments were entered into a voxel-based independent T test analysis for group comparisons to investigate the differences in grey and white matter volumes between the sample groups (all PD patients' versus healthy control, PD patients with neuropsychiatric symptoms versus healthy control, PD without any neuropsychiatric symptoms versus healthy control, and PD with neuropsychiatric symptoms versus PD without any neuropsychiatric symptoms). Age, number of years of education, gender, and Total Intracranial Volume were also included in the model as covariates. The x, y, z coordinates of significant areas obtained from the analyses were first converted into Talairach coordinates using the mni2tal Matlab routine and then identified using the Talairach Daemon Client (http://www.talairach.org/). Unless otherwise stated, a cluster corrected height threshold of $p < 0.001$ was used in all analyses. An extent threshold was also applied to the different analyses.

A T2–weighted axial scan and a coronal Fluid Attenuated Inversion Recovery (FLAIR) scan were acquired after the 3-dimensional scan acquisition to better highlight any vascular load and ensure that all participants included in the 3-dimensional structural imaging study had no significant vascular burden.

This study also used univariate analyses of variance to compare the three groups (PD with neuropsychiatric symptoms, PD without any neuropsychiatric symptoms and controls) in the demographical data and global cognitive screening as assessed by the MMSE.

4.2.3 RESULTS

4.2.3.1 DEMOGRAPHICAL AND MENTAL STATE SCREENING DATA ANALYSES

Univariate analyses of variance were carried out to compare the three groups (PD with neuropsychiatric symptoms, PD without any neuropsychiatric symptoms and controls) in age, education, MMSE and disease duration for patients groups. The controls and PD subgroups showed no significant difference in age [F (2, 72) = .76, P > .01] or education [F (2, 72) = .306, P > .01], but there was a significant difference in MMSE [F (2, 72) = 19.69, p = .000]. Post hoc (Bonferroni) comparisons showed that there was no significant difference between PD with and without neuropsychiatric symptoms in MMSE but there was a significant difference between controls and each of the two groups of patients. Also, PD patients with and without neuropsychiatric symptoms did not differ for duration of disease [F (1, 49) = .038, P > .01] (Table 4.5).

Table 4.5 Mean (SD) Age, Education, Duration of disease and MMSE scores of PD patients with neuropsychiatric symptoms (NPSS), PD patients without any neuropsychiatric symptoms, and controls

	PD with NPSS (N = 29)	**PD without NPSS (N = 22)**	**Controls (N = 24)**	***P***
Age	65.3 (10.5)	66.14 (8.5)	62.79 (9.77)	.472
Education	11.3 (4.61)	11.23 (4.71)	12.21 (5.49)	.738
Duration of disease	8.17 (5.01)	7.91 (4.5)	__	.847
MMSE	27.55 (7.96)	28.50 (1.34)	30.00 (.000)	.000*

*Significant difference between controls and the two groups of patients (Using Bonferroni Post-hoc test)

4.2.3.2 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF GREY MATTER

All patients with PD versus controls: when compared with healthy controls, all patients had significantly less grey matter volume in several brain areas including, the bilateral inferior frontal gyrus, right middle frontal gyrus, right postcentral gyrus, right inferior parietal lobule, bilateral superior parietal lobule, left subcallosal gyrus, bilateral angular gyrus, bilateral precuneus, bilateral parahippocampal gyrus, bilateral cerebellum

(anterior lobe, culmen), right cerebellum (posterior lobe, declive) and right inferior temporal gyrus (Table 4.6 and Figure 4.4).

Table 4.6 Areas of significant grey matter volume value differences between all patients with PD and controls

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Inferior frontal gyrus	L	9	1602	0.000	5.81	-51	7	24
	L	10			5.46	-38	47	3
	L	10			5.06	-46	43	-4
Middle frontal gyrus	R	10	1318	0.000	5.60	36	51	5
Inferior frontal gyrus	R	46			5.37	44	39	13
	R	45			4.98	50	37	4
Postcentral gyrus	R	5	284	0.000	5.52	32	-42	57
Inferior parietal lobule	R	40			4.72	42	-35	42
Superior parietal lobule	R	7			4.65	22	-51	60
Middle frontal gyrus	R	6	305	0.000	5.21	38	8	51
	R	8			4.80	42	12	44
	R	6			4.52	44	-1	48
Subcallosal gyrus	L	34	132	0.004	4.99	-14	1	-12
Inferior parietal lobule	R	40	234	0.001	4.92	46	-55	34
Angular gyrus	R	39			4.20	48	-66	31
Precuneus	R	39			4.08	40	-66	36
Parahippocampal gyrus	R	19	776	0.000	4.80	22	-53	-6
Cerebellum (Anterior lobe)	R				4.72	24	-26	-21
Inferior temporal gyrus	R	37			4.63	48	-24	-18
Angular gyrus	L	39	125	0.001	4.65	-42	-60	38
Superior parietal lobule	L	7			4.48	-30	-60	42
Precuneus	L	39			4.11	-42	-70	37
Cerebellum (Posterior lobe)	L		846	0.000	4.48	-32	-61	-12
Parahippocampal gyrus	L	19			4.37	-18	-49	-6
Cerebellum (Anterior lobe)	L				4.32	-24	-51	-14

R = Right L = Left BA = Brodmann Area

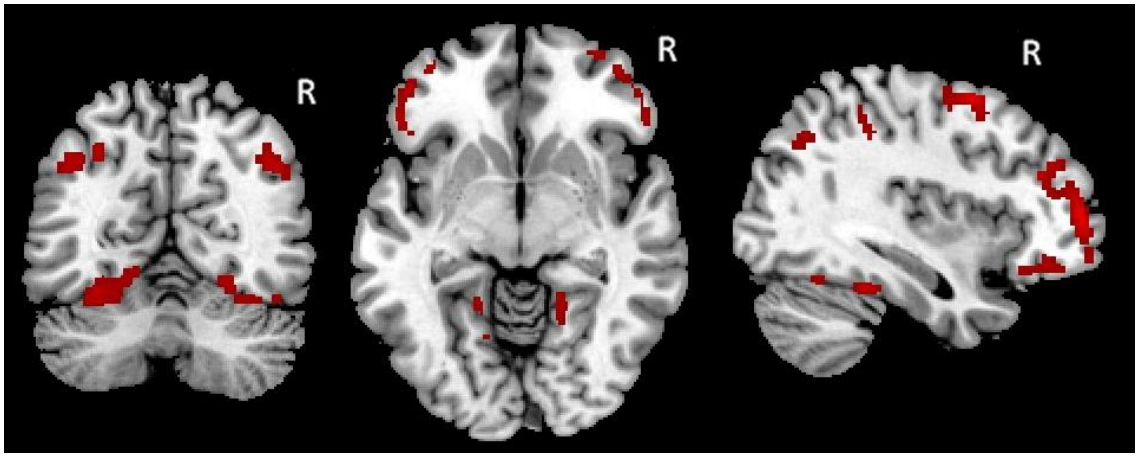

Fig 4.4 Areas of significantly less grey matter volume values in all patients with PD when compared with healthy controls

Patients with PD with neuropsychiatric symptoms versus controls: Patients with neuropsychiatric symptoms had significantly less grey matter volume in the bilateral inferior frontal gyrus, bilateral middle frontal gyrus, left precentral gyrus, right fusiform gyrus, bilateral parahippocampal gyrus, right middle temporal gyrus, bilateral angular gyrus, right inferior parietal lobule, right postcentral gyrus, left cerebellum (anterior lobe, culmen), left cerebellum (posterior lobe, tuber and declive), left superior occipital gyrus and right anterior cingulate when compared with healthy controls (Table 4.7 Figure 4.5).

Table 4.7 Areas of significant grey matter volume value differences between patients with PD with neuropsychiatric symptoms and controls

Brain areas	**R/L**	**BA**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
						X	**Y**	**Z**
Inferior frontal gyrus	R	45	1118	0.000	5.68	50	37	6
Middle frontal gyrus	R	10			5.39	38	51	7
Inferior frontal gyrus	R	45			5.12	53	31	2
Precentral gyrus	L	9	1607	0.000	5.17	-42	16	40
Middle frontal gyrus	L	9			5.05	-44	30	26
Inferior frontal gyrus	L	9			5.05	-50	7	25
Fusiform gyrus	R	20	708	0.000	5.04	40	-40	-18
Parahippocampal gyrus	R	19			4.60	24	-55	-6
	R	35			4.52	26	-26	-21
Middle temporal gyrus	R	19	340	0.000	4.96	55	-63	18
Angular gyrus	R	39			4.44	50	-68	31
	R	39			4.34	44	-58	38
Parahippocampal gyrus	L	34	117	0.005	4.92	-16	1	-12
Inferior frontal gyrus	R	9	282	0.000	4.91	50	7	24
Middle frontal gyrus	R	8			4.51	42	12	44
	R	6			4.32	40	6	51
Inferior parietal lobule	R	40	275	0.000	4.90	44	-37	44
Postcentral gyrus	R	5			4.48	32	-40	57
Inferior parietal lobule	R	40			4.21	51	-29	46
Cerebellum (Posterior lobe)	L		985	0.000	4.87	-44	-52	-23
Cerebellum (Anterior lobe)	L				4.74	-34	-40	-23
Cerebellum (Posterior lobe)	L				4.50	-30	-61	-9
Precuneus	L	19	118	0.004	4.77	-42	-72	35
Superior occipital gyrus	L	19			3.90	-38	-80	32
Angular gyrus	L	39			3.86	-42	-60	36
Anterior cingulate	R	32	197	0.010	4.57	4	43	2
	R	32			4.01	8	39	11
	R	24			3.82	2	32	17

R = Right L = Left BA = Brodmann Area

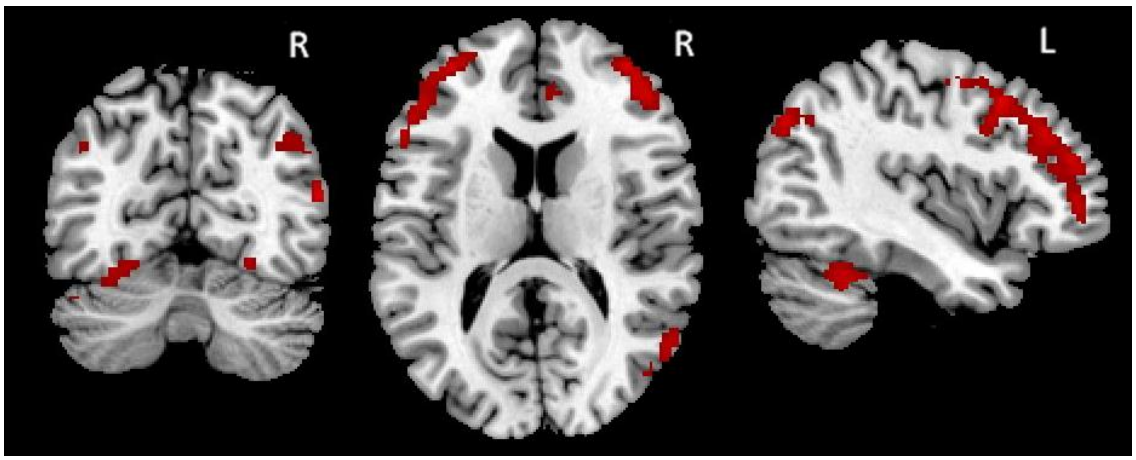

Fig 4.5 Areas of significantly less grey matter volume values in patients with PD with neuropsychiatric symptoms when compared with healthy controls

Patients with PD without any neuropsychiatric symptoms versus controls: Patients without any neuropsychiatric symptoms had less grey matter volume in the left inferior frontal gyrus, bilateral middle frontal gyrus and the right postcentral gyrus when compared with healthy controls (Table 4.8 and Figure 4.6).

Table 4.8 Areas of significant grey matter volume value differences between patients with PD without any neuropsychiatric symptoms and controls

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Inferior frontal gyrus	L	9	68	0.001	5.26	-51	5	26
Middle frontal gyrus	L	10	104	0.000	4.97	-36	49	1
Postcentral gyrus	R	5	50	0.016	4.95	32	-44	59
Middle frontal gyrus	R	10	64	0.003	4.89	38	50	-1
Inferior frontal gyrus	L	44	70	0.000	4.77	-50	16	14

R = Right L = Left BA = Brodmann Area

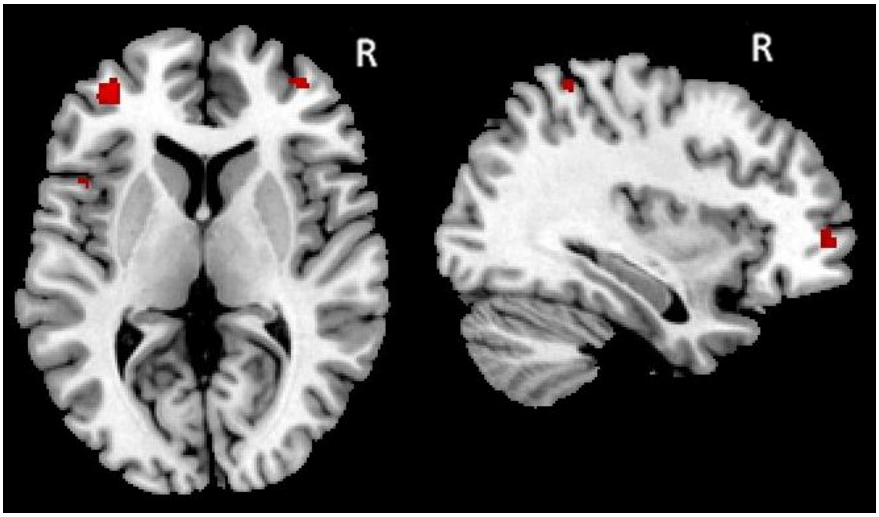

Fig 4.6 Areas of significantly less grey matter volume values in the left inferior frontal gyrus, bilateral middle frontal gyrus and the right postcentral gyrus in patients with PD without any neuropsychiatric symptoms when compared with healthy controls

Patients with PD with neuropsychiatric symptoms versus PD patients without neuropsychiatric symptoms: there was no significant difference between patients with and without neuropsychiatric symptoms at the corrected cluster level. However, at the uncorrected cluster level, significant grey matter volume differences between the two subgroups were detected. Patients with neuropsychiatric symptoms had smaller grey matter volume in several brain areas including the left parahippocampal gyrus, left cerebellum (anterior lobe, culmen), bilateral cerebellum (posterior lobe, declive), left inferior frontal gyrus, left superior frontal gyrus, left middle frontal gyrus, left insula and left superior temporal gyrus. The significance level for this comparison was 0.01 (Table 4.9 and Figure 4.7).

Table 4.9 Areas of significant grey matter volume value differences between PD subgroups with and without neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (uncorrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Parahippocampal gyrus	L	19	325	0.021	4.02	-38	-47	-6
Cerebellum (Anterior lobe)	L				3.41	-36	-36	-22
Cerebellum (Posterior lobe)	L				2.59	-40	-57	-17
	R		423	0.010	3.97	40	-78	-15
	R				3.74	48	-71	-30
	R				3.21	36	-63	-12
Inferior frontal gyrus	L	10	332	0.020	3.31	-42	39	11
Superior frontal gyrus	L	10			2.96	-26	48	18
Middle frontal gyrus	L	10			2.83	-36	46	22
Insula	L		338	0.019	3.24	-42	-19	1
Superior temporal gyrus	L	41			3.08	-44	-28	16
	L	21			2.92	-51	-21	-1

R = Right L = Left BA = Brodmann Area

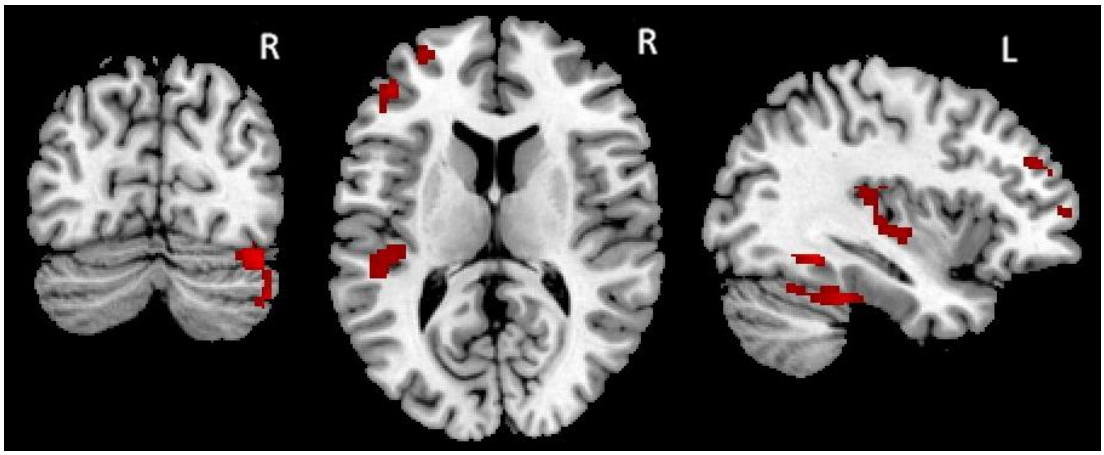

Fig 4.7 Areas of significantly less grey matter volume values in PD patients with neuropsychiatric symptoms when compared with PD patients without any neuropsychiatric symptoms

4.2.3.3 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF WHITE MATTER

All patients with PD versus controls: when compared with controls, all patients had significantly less white matter volume in the left precentral gyrus, left postcentral gyrus, bilateral anterior cingulate, bilateral middle frontal gyrus, right insula, right parahippocampal gyrus and left frontal lobe (Table 4.10 and Figure 4.8).

Table 4.10 Areas of significant white matter volume value differences between all patients with PD and controls.

Brain areas	R/L	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
					X	Y	Z
Precentral gyrus	L	555	0.000	5.01	-32	-13	45
	L			4.49	-32	-8	34
Postcentral gyrus	L			4.48	-32	-23	42
Anterior cingulate	R	1163	0.000	4.88	20	45	7
Middle frontal gyrus	R			4.85	28	4	35
Sub-lobar (Insula)	R			4.72	30	26	13
Parahippocampal gyrus	R	108	0.007	4.79	38	-45	2
Frontal lobe (Sub-Gyral)	L	273	0.001	4.46	-26	34	11
Middle frontal gyrus	L			4.44	-26	23	25
Anterior cingulate	L			4.20	-20	43	3

R = Right L = Left

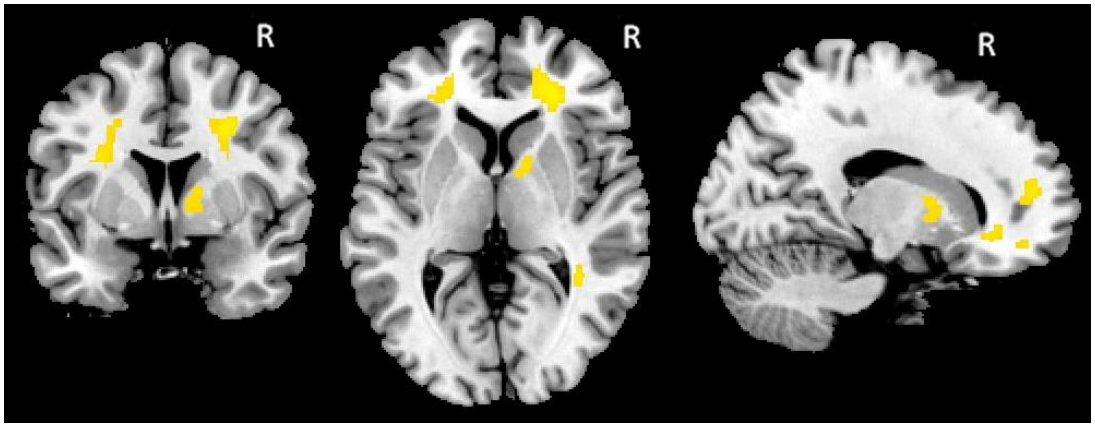

Fig 4.8 Areas of significantly less white matter volume values in all patients with PD when compared with healthy controls

Patients with PD with neuropsychiatric symptoms versus controls: there was a significant difference between patients with neuropsychiatric symptoms and healthy controls in white matter volume values. Patients with neuropsychiatric symptoms had less white matter volume in the right parahippocampal gyrus, bilateral middle frontal

gyrus, bilateral insula, bilateral anterior cingulate, left precentral gyrus, left inferior frontal gyrus and left caudate compared with healthy controls (Table 4.11 and Figure 4.9).

Table 4.11 Areas of significant white matter volume value differences between patients with PD with neuropsychiatric symptoms and controls.

Brain areas	R/L	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
					X	Y	Z
Parahippocampal gyrus	R	194	0.001	5.19	38	-45	2
Middle frontal gyrus	R	1058	0.000	5.12	28	4	37
Sub-lobar (Insula)	R			4.86	32	26	15
Anterior cingulate	R			4.65	20	43	5
Precentral gyrus	L	508	0.000	4.87	-36	-6	32
	L			4.58	-30	-15	45
	L			4.48	-32	1	24
Inferior frontal gyrus	L	139	0.001	4.49	-34	35	-3
Anterior cingulate	L			4.06	-26	34	11
	L			3.99	-20	43	3
Caudate	L	67	0.028	4.34	-36	-43	2
Middle frontal gyrus	L	68	0.004	4.31	-26	23	25
	L			3.93	-20	28	24
Sub-lobar (Insula)	L			3.90	-38	18	14

R = Right L = Left

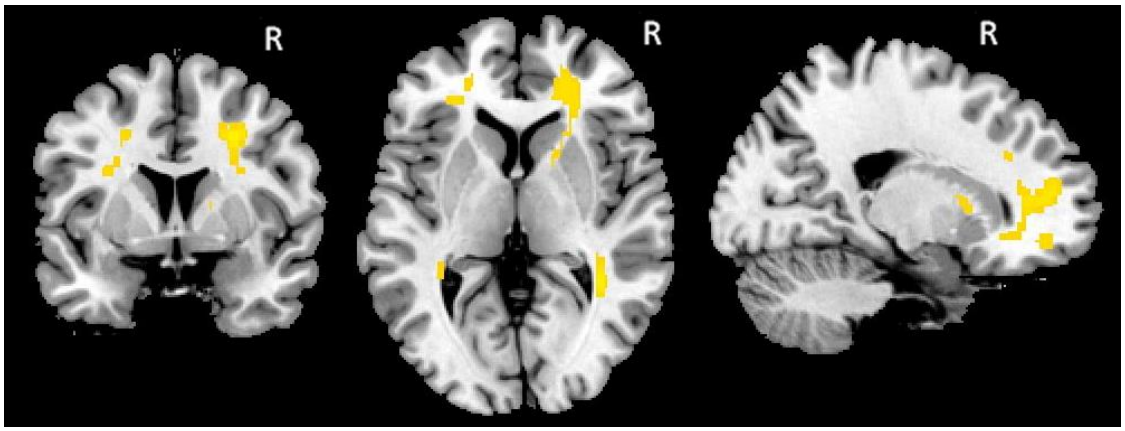

Fig 4.9 Areas of significantly less white matter volume values in patients with PD with neuropsychiatric symptoms when compared with healthy controls

Patients with PD without any neuropsychiatric symptoms versus controls: Patients without any neuropsychiatric symptoms had significantly less white matter volume values in the right medial frontal gyrus and left precentral gyrus (Table 4.12 and Figure 4.10).

Table 4.12 Areas of significant white matter volume value differences between patients with PD without any neuropsychiatric symptoms and controls.

Brain areas	R/L	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
					X	Y	Z
Medial frontal gyrus	R	36	0.020	4.25	20	47	9
Precentral gyrus	L	40	0.009	4.17	-36	-17	41

R = Right L = Left

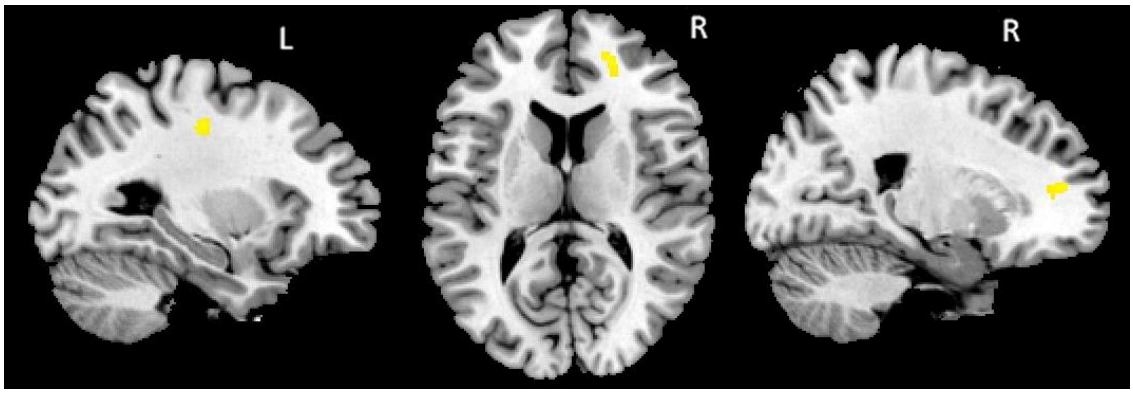

Fig 4.10 Areas of significantly less white matter volume values in patients with PD without any neuropsychiatric symptoms when compared with healthy controls

Patients with PD with neuropsychiatric symptoms versus patients with PD without any neuropsychiatric symptoms: There was no significant difference in the white matter volume values between patients with and without neuropsychiatric symptoms.

4.2.4 DISCUSSION

In this experiment, we identified some structural brain regions that might underlie the occurrence of neuropsychiatric symptoms in patients who have PD. In patients with neuropsychiatric symptoms, the largest cluster size of grey and white matter loss was found mainly in the frontal lobe areas. There was also a large cluster of reduction in white matter volume in the region of the insula. An fMRI study reported that the orbital frontoinsular regions are connected with other brain areas including subcortical structures (Seeley et al., 2007). The basal ganglia as part of subcortical structures when dysfunctional is important to the manifestation of neuropsychiatric

symptoms in patients with PD (Ring & Serra-Mestres, 2002). In particular, dysfunction of the dopaminergic system is crucial because it plays an integrative and regulatory role in the development and interpretation of emotions, motor and reward processes (Aarsland, Marsh, et al., 2009; Ring & Serra-Mestres, 2002). These data suggest that this regulation of the brain network including the frontal lobe, insula and the basal ganglia might be an important consideration in the manifestation of neuropsychiatric symptoms in PD.

The present study also found significant grey and white matter loss in the anterior cingulate gyrus in patients with neuropsychiatric symptoms. This result is in line with an earlier study that reported metabolic alteration in the anterior cingulate in PD patients who developed neuropsychiatric symptoms (Lewis, et al., 2012). A study of the resting state networks demonstrated that there are interconnections between the anterior cingulate and insular regions bilaterally in the white matter tracts (van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009). Another report indicated that the insular cortex is linked to other brain areas i.e. prefrontal cortex, orbitofrontal cortex, visual association cortex and anterior cingulate cortex (Nagai, Kishi, & Kato, 2007). This report also suggested that the insular cortex is involved in the regulation of mood disorder, obsessive compulsive disorder, panic disorder and schizophrenia (Nagai, et al., 2007). The findings in the current study suggest that dysfunction within a network of structures including the anterior cingulate gyrus and the insula might be the genesis of neuropsychiatric symptoms in PD.

The present study did not find differences between patients with neuropsychiatric symptoms and controls in the basal ganglia except for the caudate area in the white matter. This might be due to the early phase of the disease. Another explanation might be related to the use of a whole brain analysis approach rather than a

region of interest analysis approach for group comparison. If this latter approach had been used some differences might have emerged. Additionally, brain vulnerability in the caudate region might have more substantial influence on the manifestation of neuropsychiatric symptoms; this speculation is supported by a VBM study that found an association between atrophy in the caudate nucleus and neuropsychiatric symptoms in mild AD (Bruen et al. 2008). It is also possible that in the early stages of PD there might be only a functional deficit in the basal ganglia regions related to dysfunction of some neurochemical circuits which have not yet reached a sufficient threshold to have caused detectable significant structural changes. For instance, dysfunction of a combination of dopaminergic, serotoninergic and noradrenergic pathways in the limbic system has been detected in patients with PD with depression (Remy, et al., 2005).

4.2.5 GENERAL DISCUSSION

This study is the first to have explored both the behavioural and the anatomical correlates of neuropsychiatric symptoms in the same cohort of patients with PD. The presence of neuropsychiatric symptoms was associated with decreased cognitive functioning and was also linked to atrophy in specific brain regions. For instance, we found that patients with neuropsychiatric symptoms showed executive dysfunction with accompanying atrophy of the inferior frontal gyrus and anterior cingulate cortex. In normal participants, deficits of the executive function have been associated with grey matter loss in the inferior frontal gyrus and anterior cingulate cortex (Takeuchi et al., 2012). Likewise, in this study, patients with neuropsychiatric symptoms who performed lower on the Rey 15-word Memory Test showed reduced grey matter in the middle temporal gyrus. Impaired performance on this test has been shown to be associated with temporal lobe atrophy (Lezak, et al., 2012). These data therefore suggest that patients with PD who have neuropsychiatric symptoms exhibit lower cognitive performance and show damage to the corresponding neuroanatomical regions.

The following experiments will try to clarify more closely which deficits underlie the most common neuropsychiatric symptoms in PD, depression and apathy. This will include both cognitive and anatomical investigation.

4.3 EXPERIMENT 3 – COGNITIVE CORRELATES OF DEPRESSION IN PD

4.3.1 INTRODUCTION

Depression is the most common neuropsychiatric disorder in PD (Aarsland, Bronnick, et al., 2009) and has been associated with cognitive impairments in this patient sample (Santangelo, Vitale, Trojano, Longo, et al., 2009). Several studies have shown that patients with PD with depression score significantly lower on the neuropsychological tests than those who are not depressed or healthy controls (Costa, et al., 2006; Cubo, et al., 2000; Fernandez, et al., 2009; Kuzis, et al., 1997; Norman, et al., 2002; Santangelo, Vitale, Trojano, Longo, et al., 2009; Starkstein, et al., 1989; Stefanova, et al., 2006; Uekermann, et al., 2003). However, in other studies cognitive performance did not differ significantly between patients with and without depression (Silberman, et al., 2007; Taylor, et al., 1988; Taylor, et al., 1986; Troster, Paolo, et al., 1995; Troster, Stalp, et al., 1995).

Some studies have reported an association between depression in PD and global cognitive decline (Cubo, et al., 2000; Fernandez, et al., 2009; Norman, et al., 2002). For instance, some research has shown a negative correlation between Depression scores and global cognitive functioning as assessed by the MMSE (Cubo, et al., 2000; Fernandez, et al., 2009) or by the Dementia Rating Scale (Fernandez, et al., 2009; Norman, et al., 2002). In contrast, other studies have found no association between depression and global cognitive impairment (Costa, et al., 2006; Santangelo, Vitale, Trojano, Longo, et al., 2009; Starkstein, et al., 1989).

Further studies have found that depression is associated with impairments in specific cognitive domains. Starkstein and others (1989) studied the relationships between depression and cognitive impairment in 78 patients with PD (15 with major depression, 19 with minor depression and 44 without depression). Depression was

assessed by the Hamilton Rating Scale for Depression (Hamilton, 1960) and with the DSM-III criteria (American Psychiatric association, 1980). Patients with major depression had significantly lower scores than non-depressed patients on tests of executive function such as on the Wisconsin Card Sort Test (categories, errors and perseverations) (Heaton, et al., 1993), Controlled Word Association Test (Benton, 1968), Trail Making Test (A and B) (Reitan, 1958), Design Fluency Test (free condition) (Jones-Gotman & Milner, 1977) and Symbol Digit Association Test (Simth, 1973). However, there was no significant difference between patients with minor depression and non-depressed patients (Starkstein, et al., 1989). Another study investigated cognitive functions in major depression and PD using 4 groups of participants (19 patients with major depression, 31 patients without depression, 27 patients with major depression (without PD) and 12 healthy controls). Patients with major depression (with or without PD) had significantly lower scores on a verbal fluency test and a verbal auditory attention test compared with both patients with PD without depression and healthy controls. Whereas, patients with PD with depression had significantly lower scores on an abstract reasoning task and on a set alternation task when compared with the other three groups (Kuzis, et al., 1997).

Uekermann and others (2003) studied cognitive dysfunction and depression in PD. This study used the Bond-Lader Visual Analogue Scale (Bond & Lader, 1974) to assess present mood state, a scale which comprises 16 pairs of adjectives describing present-state arousal and affects such as happy- sad. Compared to healthy controls, patients with PD with depression had significantly lower scores on verbal fluency, short-term memory and concept formation. In addition, patients with depression performed significantly worse than patients with PD without depression on tasks of working memory, and concept formation and on the alternate fluency task (Uekermann, et al., 2003).

Another study explored the pattern of cognitive impairment in 16 depressed patients with PD and 54 non-depressed patients with PD Using DSM-IV (American Psychiatric Association, 2000) and HRDS (Hamilton, 1960) to assess depression. This study used the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) to assess global cognitive functioning (verbal and performance), the Rey Auditory Verbal Learning Test (Rey, 1964) to assess verbal memory, Letter Fluency Test, Category Fluency Test (Thurstone & Thurstone, 1962), TMT (Reitan, 1958), Boston Naming Test (Kaplan, et al., 1983), the Hooper Visual Organization Test (Lezak, et al., 2004), a Spatial Recognition Memory Tasks and the Paired Associates Learning Task (Wechsler, 1945). Compared to non-depressed patients with PD, patients with depression had significantly lower scores on the performance tests in the Wechsler Adult Intelligence Scale-Revised, as well as on the neuropsychological tests assessing executive functions, working memory and language (Stefanova, et al., 2006).

Costa and colleagues (2006) investigated the relationship between depression (major and minor) and neuropsychological impairments in patients with PD. Three groups of patients with PD participated in the study (18 with major depression, 21 with minor depression and 32 without depression). Depression was assessed by a structured interview based on the DSM-IV criteria (American Psychiatric Association, 2000) and depression severity was measured by the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Neuropsychological assessment included tests assessing verbal and visual episodic memory, working memory, executive functions, abstract reasoning and visual-spatial and language abilities. Patients with PD with major depression performed worse than those without depression on two long-term verbal episodic memory tests, an abstract reasoning task and on three tests of executive functioning. However, patients with PD with minor depression showed no significant

differences in performance when compared with either patients with PD with or without major depression (Costa, et al., 2006).

The involvement of executive dysfunctions in patients with PD with depression has also been supported by a recent study which investigated the relationship between depression (assessed by DSM-IV and Hamilton Rating Scale for Depression) and cognitive dysfunctions in non-demented patients with PD. Patients with depression performed significantly worse than those without depression on tests of executive functioning including the Frontal Assessment Battery and Stroop Test (colour naming and interference) (Santangelo, Vitale, Trojano, Longo, et al., 2009). However, other studies have reported a correlation between depression and memory scores but not with executive functions scores (Butterfield, et al., 2010). A recent cross-sectional study explored the global and specific cognitive impairments in 82 patients with PD with depressive symptoms (Fernandez, et al., 2009). This study assessed cognitive functions using the Digit Span Test (attention and short term memory) (Wechsler, 1981), the Boston Naming Test (naming) (Kaplan, et al., 1983), the Hopkins Verbal Learning Test (verbal memory and language) (Benedict, Schretlen, Groninger, & Brandt, 1998), the Trail Making part B and Animal Fluency Tests (assessing processing speed and executive functions respectively) and the Judgment of Line Orientation (Benton, et al., 1983) and Face Recognition Tests (visual-spatial processing) (Benton & Van Allen, 1968). This study found that BDI (Beck, et al., 1961) scores correlated with MMSE (Folstein, et al., 1975) scores, Dementia Rating Scale (Mattis, 1988) total scores, and with scores on the Boston Naming Test (Kaplan, et al., 1983) and on the Hopkins Verbal Learning Test delayed recall. Similarly, when comparing the cognitive performance of patients with PD who scored less than 14 on the BDI versus those who scored more than 14, a significant difference was found between the two groups on the Boston Naming Test. This study suggests that depressive symptoms correlated with

global cognitive impairments as well as specific cognitive domains which were naming, verbal memory, and language (Fernandez, et al., 2009). Depression in PD has also been associated with memory and attention deficits (Norman, et al., 2002).

In contrast to the studies outlined above, some research has found no differences between patients with PD with and without depression in both global cognitive functioning and specific cognitive tests. Troster et al (1995) found that patients with PD with and without depression performed worse than healthy controls on the immediate and delayed verbal recall tasks, semantic fluency, and problem solving tasks. However, there was no significant difference between patients with PD with depression and those without depression on any of the neuropsychological tests including on the WCST (Heaton, et al., 1993), Controlled Oral Word Association Test (Benton, 1968), Logical Memory subtest of the Wechsler Scale-Revised (Wechsler, 1945), Digit Span (Wechsler, 1981), the Boston Diagnostic Aphasia Examination's Animal Naming Test (Goodglass & Kaplan, 1983) and Boston Naming Test (Kaplan, et al., 1983). Another study investigated the cognitive performance of 45 patients with PD with depression, 45 patients with PD without depression and 45 healthy controls using the Dementia Rating Scale (Mattis, 1988) to assess cognitive abilities and the Beck Depression Inventory (Beck, et al., 1961) to measure depression. Both PD patients with and without depression had significantly lower scores on the Dementia Rating Scale total scores, conceptualization and initiation compared with healthy controls. In addition, patients with depression had significantly lower scores on construction and memory subtests when compared with healthy controls, but no differences were found between patients with PD with or without depression (Troster, Paolo, et al., 1995).

Taylor and colleagues (1986) investigated Short-term memory in 15 depressed patients with PD and 15 non-depressed patients with PD using several tests such as the

Digit Span (Part of Wechsler Adult Intelligence Scale-Revised) (Wechsler, 1981), Logical Memory (Wechsler, 1945), the Visual Reproduction and the Paired Associates Learning Test (Wechsler, 1945). However, the performance of the two groups of patients did not differ on any of the short-term memory tests (Taylor, et al., 1986). More recently, Silberman and others (2007) explored frontal functions in patients with PD with and without depression. There were 18 patients with depression and 28 without depression. Depression was identified using the DSM-IV criteria (American Psychiatric Association, 2000) and frontal functions evaluated using the Stroop Test (Stroop, 1935). Patients with depression showed no significant difference on this frontal task when compared with those without depression (Silberman, et al., 2007).

The previous studies raise some issues that need to be considered. For instance, none of the previous studies indicated whether patients with PD with depression also had other associated neuropsychiatric symptoms such as apathy, hallucinations or anxiety. Indeed, several studies have found that in PD, apathy is often associated with depression (Drijgers, et al., 2010; Dujardin, et al., 2007; Isella, et al., 2002; Levy, 1998; Oguru, et al., 2010; Pedersen, Larsen, et al., 2009; Reijnders, et al., 2010; Starkstein, Mayberg, Preziosi, et al., 1992; Zgaljardic, et al., 2007) as well as hallucinations and anxiety (Aarsland, et al., 2007; Aarsland, Marsh, et al., 2009; Marsh, & Berk, 2003; Schneider, et al., 2008; Thanvi, et al., 2003; Weintraub, et al., 2008b). Therefore, the presence of other neuropsychiatric symptoms might have had an impact on the previous findings. Furthermore, some of the previous studies used a small number of participants and some used screening instruments to assess general cognitive abilities which are insufficiently sensitive to identify subtle deficits in specific areas of cognition.

The aim of the present study was to explore the cognitive profile of patients with PD with and without depression using a large sample of non-demented patients and an

extensive battery of neuropsychological tests. The hypothesis was that patients with PD with depression would have greater cognitive impairments than patients without any neuropsychiatric symptoms.

4.3.2 METHOD

4.3.2.1 SAMPLE

Fifty Patients with idiopathic PD (27 male and 23 female) participated in this study. The patients were retrospectively recruited from those who had attended a Parkinson's disease outpatient clinic and had received a diagnosis based on the UK PD Brain Bank Criteria (Hughes, et al., 1992). All patients had had extensive neuropsychological screening, neuropsychiatric assessment using the NPI, structural MRI scanning and neurological examination. All patients were in the mild to mild-moderate disease stage, according to the Hoehn and Yahr staging (Hoehn & Yahr, 1967). None of the patients had a history of psychiatric disorders and the neuropsychiatric symptoms had started after the onset of PD. All patients were treated with a combination of levodopa and variable doses of dopamine agonists but none were treated with antidepressants. The mean age of all patients was 65.3 years (SD= 9.6, range 46-83), their mean education was 11.3 years (SD= 4.6 range 4-18), their mean disease duration was 8.16 years (SD= 4.74) and their mean MMSE score was 27.9 (SD= 1.8 range 24- 30).The patient sample was divided into two subgroups according to their NPI score for depression, 27 (54%) patients with PD with depression and 23 (46%) with no neuropsychiatric symptoms (see figure 4.11).

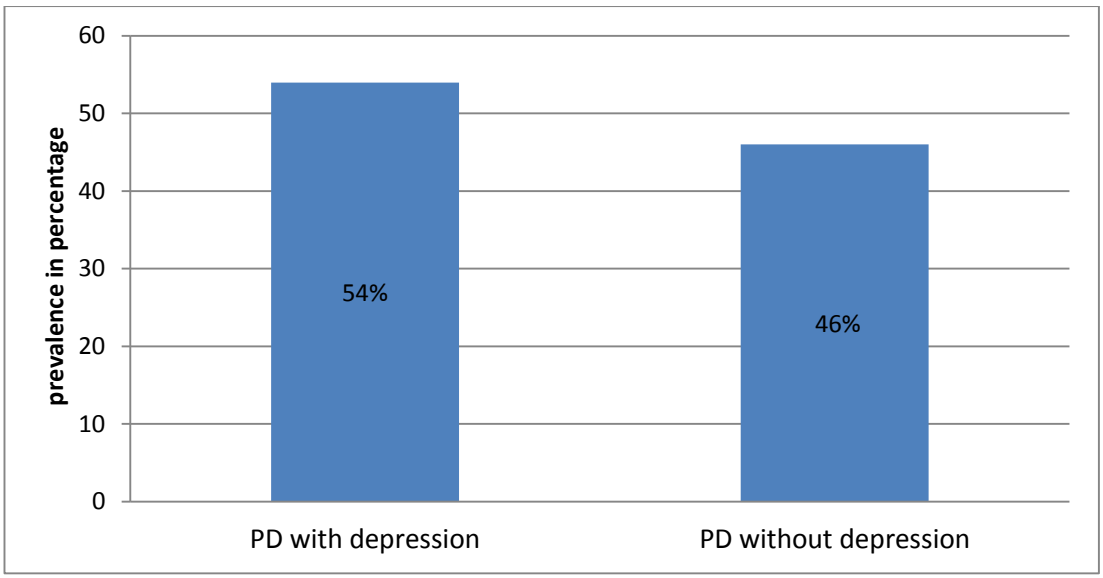

Fig 4.11 Percentage of PD with depression and PD without depression

The mean age of the patients with depression was 64.6 years (SD= 11.2, range 46-83), their mean education was 11.8 years (SD= 4.8 range 4-18), their mean disease duration was 8.1 years (SD= 4.9) and their mean MMSE score was 27.6 (SD= 2.1 range 24- 30). The mean age of the patients with PD without any neuropsychiatric symptoms was 66.0 years (SD= 7.6, range 47-79), their mean education was 10.7 years (SD= 4.4 range 5-18), their mean disease duration was 8.2 years (SD= 4.7) and their mean MMSE score was 28.4 (SD= 1.3 range 26- 30).

4.3.2.2 ASSESSMENTS OF DEPRESSION

Depression had been assessed using the NPI (Cummings, et al., 1994), the Beck Depression Inventory (Beck, et al., 1961), and using the Diagnostic and Statistical Manual of Mental Disorders criteria (American Psychiatric Association, 2000). Each patient and their caregiver had had an interview with an experienced psychologist who also completed the NPI. The NPI assesses the presence or absence, severity and frequency of 14 symptom fields. The depression scores from the NPI were then entered in the statistical analyses.

4.3.2.3 NEUROPSYCHOLOGICAL ASSESSMENTS

This study used the same neuropsychological assessments that were described in detail in the previous study (chapter 4, section 4.1.2.3, pages 79-83).

4.3.2.4 STATISTICAL ANALYSES

A series of independent T-tests were carried out to compare the two groups' (patients with PD with depression and without neuropsychiatric symptoms) demographic data and scores on the neuropsychological tests. Further statistical analyses were also carried out to examine the relationship between depression scores and neuropsychological test scores using Pearson's correlation test.

To correct for multiple comparisons, this study used a significance level of $p < 0.004$ for both overall comparisons among groups and for paired correlations, with the exception of the comparison of group demographical data, for which the significance level was $p < 0.01$.

4.3.3 RESULTS

4.3.3.1 DEMOGRAPHICAL AND MENTAL STATE SCREENING DATA ANALYSES

Firstly, an independent T-test was carried out to compare the PD subgroup with depression with those with no neuropsychiatric symptoms. There was no significant difference between the two subgroups of patients in age $t(48) = -1.9$, $p > .01$, education $t(48) = 1.2$, $p > .01$, or duration of disease $t(48) = -0.7$, $p > .01$. Neither was any significant difference found in the mean MMSE scores of the two subgroups $t(48) = 1.8$, $p > .01$ (Table 4.13).

Table 4.13 Mean (SD) Age, Education, Duration of disease and MMSE of patients with PD with depression and those without any neuropsychiatric symptoms (NPSS)

	PD with depression (N = 27)	**PD without NPSS (N = 23)**	***P***
Age	64.6 (11.2)	66.0 (7.6)	.621
Education	11.9 (4.8)	10.65 (4.44)	.351
Duration of disease	8.11 (4.86)	8.22 (4.69)	.892
MMSE	27.56 (2.0)	28.39 (1.34)	.098

4.3.3.2 COGNITIVE PROFILE OF PATIENTS WITH PD WITH AND WITHOUT DEPRESSION

A series of independent T-tests were also carried out to compare the performance of patients with PD with and without depression on the neuropsychological tests in the battery. Patients with depression had lower scores than those without any neuropsychiatric symptoms on most of the neuropsychological tests. However, the only test on which the difference in scores approached a significance level was the Frontal Assessment Battery t(22) = 3.030, p = .006. There were no significant differences between the two patients subgroups in any of the other neuropsychological tests, i.e. Raven's Progressive Matrices t(44) = -2.90, p > .004, Stroop Test (time) t(44) = -.635, p > .004, Stroop Test (error) t(45)= -.753, p > .004, TMT (part B minus part A) t(30) = .181, p > .004, Letter Fluency Test t(47) = 1.348, p > .004, Category Fluency Test t(47) = 1.73, p > .004, Similarities Test t(46) = -369, p > .004, Rey Complex Figure (copy) t(46) = 1.435, p > .004, Rey Complex Figure (delayed) t(44) = .428, p > .004, Digit Span (forward) t(26) = .743, p > .004, Digit Span (backward) t(26) = 1.135, p > .004, Visual-spatial span t(23) = .000, p > .004 and Rey 15-word Memory Test t(29) = 1.924, p > .004 (see Table 4.14).

Table 4.14 Mean (SD), and *P* value of scores on neuropsychological tests achieved by PD with depression and PD without any neuropsychiatric symptoms (NPSS)

	PD with depression (N = 27)	**PD without NPSS (N = 23)**	***p***
Raven's Progressive Matrices	27.91 (10.3)	27.09 (8.97)	.773
Stroop test			
Time interference effect	41.31 (42.39)	35.16 (17.06)	.529
Error interference effect	2.88 (4.23)	1.96 (4.13)	.455
Trail Making Test	62.20 (36.91)	65.29 (56.30)	.858
Letter Fluency Test	30.46 (12.21)	34.87 (10.46)	.184
Category Fluency Test	31.85 (12.27)	37.30 (9.41)	.090
Similarities Test	16.28 (5.54)	15.74 (4.51)	.714
Rey Complex Figure			
Direct copy	27.38 (6.22)	29.93 (6.01)	.158
Delayed copy	11.85 (6.17)	12.61 (5.84)	.671
Digit Span			
Forward	6.05 (1.18)	6.56 (.882)	.267
Backward	3.95 (1.08)	4.22 (1.09)	.536
Frontal Assessment Battery	**13.57 (2.69)**	**16.40 (1.43)**	**.006**
Visual-spatial span	4.40 (1.06)	4.40 (.97)	1.000
Rey 15-word Memory test (delayed)	6.62 (3.074	9.14 (2.81)	.019

Correlation analyses were carried out with depression scores and neuropsychological tests scores. There was a significant relationship between depression scores and Digit Span scores (forward) (r= -.53, *P* =0.004). Higher depression scores were associated with lower performance on this test. However, depression scores were not significantly correlated with Raven's Progressive Matrices scores (r= -.06, *P* = .691), Stroop scores (Time) (r= .100, *P* = .509), Stroop scores (Error) (r= .284, *P* = .053), TMT scores (r= .040, *P* = .828), Letter Fluency scores (r= -.28, *P* = 0.05), Category Fluency scores (r= -.246, *P* = 0.09), Similarities Test scores (r= -.160, *P* = .277), Rey Complex Figure (copy) scores (r= -.36, *P* = 0.012), Rey Complex Figure (delayed recall) scores (r= -.200, *P* = .183), Digit Span scores (backward) (r= -.41, *P* = 0.03), Frontal Assessment Battery scores (r= -.343, *P* = .101), Visual-spatial span scores (r= .052, *P* = .807), Rey 15-word Memory Test scores (r= -.339, *P* = .062) and MMSE scores (r= -.29, *P* = 0.04) (see table 4.15).

Table 4.15 Correlations between depression scores and neuropsychological tests scores

	Depression	Raven's Progressive Matrices	Stroop tests (Time)	Stroop tests (Error)	Trail making test	Letter fluency	Category fluency	Similarities test	Rey complex figure (Copy)	Rey complex figure (Delayed)	Digit span (Forward)	Digit span (Backward)	Frontal assessment battery	Visual-spatial span	Rey 15-word Memory Test	MMSE
Depression	_	-.060	.100	.284	.040	-.282	-.246	-.160	-.361	-.200	-.525*	-.405	-.343	.052	-.339	-.286
Raven's Progressive Matrices	-.060	_	-.379	-.302	-.597*	.329	.556*	.453*	.433*	.328	.490	.519	.297	.241	.412*	.524*
Stroop tests (Time)	.100	-.379	_	.060	.580*	-.353	-.392	-.527*	-.059	-.108	-.187	-.331	-.430	-.158	-.285	-.540*
Stroop tests (Error)	.284	-.302	.060	_	.062	-.331	-.238	-.357	-.365	-.259	-.459	-.248	-.576*	-.448	-.338	-.344
Trail making test	.040	-.597*	.580*	.062	_	-.290	-.467	-.220	-.221	-.197	-.289	-.410	-.049	-.236	-.352	-.442
Letter fluency	-.282	.329	-.353	-.331	-.290	_	.643*	.457*	.224	.372	.280	.429	.621*	.307	.499	.441*
Category fluency	-.246	.556*	-.392	-.238	-.467	.643*	_	.433*	.279	.348	.387	.555*	.399	.393	.487	.514*
Similarities test	-.160	.453*	-.527*	-.357	-.220	.457*	.433*	_	.143	.148	.511	.626*	.359	.404	.453	.463*
Rey complex figure (Copy)	-.361	.433	-.059	-.365	-.221	.224	.279	.143	_	.625*	.408	.298	.125	.140	.226	.182
Rey complex figure (Delayed)	-.200	.328	-.108	-.259	-.197	.372	.348	.148	.625*	_	.066	.156	.221	.435	.085	.175
Digit span (Forward)	-.525*	.490	-.187	-.459	-.289	.280	.387	.511	.408	.066	_	.653*	.654*	.144	.574*	.456
Digit span (Backward)	-.405	.519	-.331	-.248	-.410	.429	.555*	.626*	.298	.156	.653*	_	.556	.024	.563	.468
Frontal assessment battery	-.343	.297	-.430	-.576*	-.049	.621*	.399	.359	.125	.221	.654*	.556	_	.289	.673*	.687*
Visual-spatial span	.052	.241	-.158	-.448	-.236	.307	.393	.404	.140	.435	.144	.024	.289	_	.521	.135
Rey 15-word Memory Test	-.339	.412	-.285	-.338	-.352	.499	.487	.453	.226	.085	.574*	.563	.673*	.521	_	.552*
MMSE	-.286	.524*	-.540*	-.344	-.442	.441*	.514*	.463*	.182	.175	.456	.468	.687*	.135	.552*	_

*Value is significant at P < 0.004 (two-tailed).

4.3.4 DISCUSSION

The prevalence of depressive symptoms in this study (54%) is higher than the estimated rate of 40% reported in various published studies (Aarsland, et al., 1999; Marsh, 2000; Park & Stacy, 2009). However, Schwarz and others (2011) have reported that the prevalence of depressive symptoms in patients with PD vary between 3% and 80% (Schwarz et al., 2011). This difference in the prevalence of depression in PD may be explained by different diagnostic criteria being used across studies to assess depressive symptoms as well as differences in the demographical characteristics of the samples such as the severity of PD (Schwarz, et al., 2011). The high prevalence of depressive symptoms found in our sample, suggests that the examining of PD patients for these symptoms should have priority in clinical settings.

In the present study, depression was not associated with global cognitive functioning as assessed by the MMSE. A lack of association between depression and MMSE scores has been reported previously (Cubo, et al., 2000; Fernandez, et al., 2009). Therefore, our results suggest that depressive symptoms probably have no influence on global cognitive abilities, particularly in early non-demented patients with PD.

While some studies have reported a lack of any noticeable difference between patients with PD with and without depression on neuropsychological testing (Silberman, et al., 2007; Taylor, et al., 1988; Taylor, et al., 1986; Troster, Paolo, et al., 1995; Troster, Stalp, et al., 1995), a significant negative correlation between depression and Digit Span Forward scores, a test of attention and short term memory (Lezak, et al., 2004) was found in the present study. This result is in line with previous studies that found a significant association between depression and

attention (Kuzis, et al., 1997; Norman, et al., 2002) and short term memory (Uekermann, et al., 2003) in patients with PD. Other studies have also reported a significant difference between PD patients with and without depression on performance of cognitive tests with lower scores being observed in depressed subgroups (Costa, et al., 2006; Cubo, et al., 2000; Fernandez, et al., 2009; Kuzis, et al., 1997; Santangelo, Vitale, Trojano, Longo, et al., 2009; Starkstein, et al., 1989; Stefanova, et al., 2006; Uekermann, et al., 2003). One reason why the present study found no significant difference between the two subgroups of patients with PD in cognitive functioning might be the exclusion of patients who also had other neuropsychiatric symptoms. For instance, apathy has been associated with depression in similar patients (Drijgers, et al., 2010; Dujardin, et al., 2009; Dujardin, et al., 2007; Isella, et al., 2002), so the presence of other neuropsychiatric symptoms in earlier studies might have had an impact on their findings. Another reason might be that the current subgroups of patients were milder in severity than in previous samples. It should be noted that, there was no attempt to classify depression into minor and major types in our study and some prior reports have shown that cognitive changes are present in patients with PD with major depression but not in patients with minor depressive symptoms (Kuzis, et al., 1997; Starkstein, Mayberg, Leiguarda, et al., 1992).

The present findings of the correlation analyses suggest that attention and short term memory skills are possibly the first cognitive domains to be influenced by depressive symptoms in the early stages of PD.

4.4 EXPERIMENT 4 – NEUROANATOMICAL CORRELATES OF DEPRESSION IN PD

4.4.1 INTRODUCTION

Several studies have investigated the underlying mechanisms of depression in patients with severe symptoms with and without PD by using different techniques. Carlson and others (2005) explored the neural correlates in patients with major depressive disorder without PD and found increased metabolism and rCBF in the left mediodorsal thalamus (Carlson, et al., 2005). This result was consistent with a post-mortem study that found an increased number of neurons in the mediodorsal nucleus of the thalamus in patients with major depressive disorder (Young, Holcomb, Yazdani, Hicks, & German, 2004a).

A previous study has shown a decrease in dopamine and noradrenaline innervations in the limbic system in patients with PD (Remy, et al., 2005). Using PET, Remy and others (2005) compared two groups of patients with PD (8 with depression and 12 without depression). They found that patients with depression had lower [11C] RTI-23 binding in the locus coeruleus bilaterally and in all regions in the limbic system including the mediodorsal nucleus of the thalamus bilaterally, the right amygdala and the left ventral striatum when compared with patients without depression (Remy, et al., 2005).

Another study investigated the underlying mechanism of depression in PD by using an event-related functional MRI paradigm based on a series of Ekman's faces portraying different intensities of sadness. In addition, this study used the Hamilton Rating Scale for Depression (Hamilton, 1960) to assess this symptom. First, the fMRI data showed decreased activation in the left mediodorsal nucleus of the

thalamus and in medial prefrontal cortex in depressed patients with PD. Second, based on the results of previous studies researchers carried out a region of interest analyses to compare structural volume in the thalamus in patients with and without the symptom. They found increased grey matter volume in the mediodorsal thalamic nuclei bilaterally. This study indicated an involvement of limbic structures such as the thalamus in depression in patients with PD (Cardoso, et al., 2009).

Dysfunction in the dorsomedial prefrontal cortex also seems to play an important role in major depressive disorder both in patients with and without PD. Several PET studies have shown decreased rCBF and metabolism in the dorsomedial prefrontal cortex in subjects with primary depressive disorder (Biver, et al., 1994; Drevets, 1999). In addition, a recent meta-analysis of VBM studies examined grey matter changes in major depressive disorder. This research analysed a total of 23 studies which evaluated grey matter volumes in 986 patients with major depressive disorder as compared with 937 healthy controls. The results revealed that grey matter volumes were significantly reduced in the anterior cingulate cortex and dorsolateral and dorsomedial prefrontal cortex (Bora, et al., 2012). The involvement of dysfunction in the dorsomedial prefrontal cortex has been reported in depressed patients with PD. Using PET, Ring and colleagues (1994) investigated the biological correlates of depression in PD. These researchers studied 10 patients with major depression, 10 patients without depression and 10 healthy controls and found a bilateral decrease in cerebral blood flow in anteromedial regions of the medial frontal cortex and in the anterior cingulate cortex (BA, 9 and 32) in patients with depression compared with those without depression and controls. The results of this study were compared with previous findings from 10 patients with primary depression. The findings of both studies overlapped which indicates that patients

with PD with depression and patients with primary depression show similar brain dysfunctions (Ring, et al., 1994).

Other studies using VBM have shown a reduction in middle frontal cortex and other brain regions. Feldmann and others (2008) investigated grey matter reductions in 23 patients with PD with depression, 27 without depression and 16 healthy controls using VBM. First, the results of the group comparisons showed no significant difference in grey matter density between controls and all patients with PD (with and without depression). However, there was a significant decrease in grey matter density in the left inferior orbito-frontal gyrus, bilateral rectal gyrus and the right superior temporal pole in depressed patients compared with non-depressed patients. Second, the results of a regression analysis showed that high depression scores were associated with less grey matter volume in the right rectal gyrus, right parahippocampal and bilateral middle/inferior orbito-frontal regions in depressed patients with PD (Feldmann, et al., 2008). A further study compared grey matter and white matter in 24 non-depressed patients with PD, 16 depressed patients with PD and 26 healthy controls using VBM (Kostic, et al., 2010). Group comparisons showed that both groups of patients with PD had grey matter loss in the right anterior cingulate cortex and insula, and in the left middle frontal and angular gyri when compared with controls. Patients with depression had significantly less grey matter volume in the right posterior cingulate cortex, the right inferior temporal gyrus and right hippocampus when compared with controls. There was no correlation between the scores on the HRSD and grey matter loss (Kostic, et al., 2010). Another VBM study showed less grey matter volumes in the right inferior frontal gyrus in patients with major depressive disorders when compared with healthy controls (van Tol et al., 2010).

Another brain area which seems to be crucial in depression disorder is the subgenual anterior cingulate cortex. Metabolism and cerebral blood flow studies have shown a decrease in the subgenual anterior cingulate cortex in unipolar and bipolar depression when compared with healthy controls (Drevets, et al., 1997; Kegeles, et al., 2003).

A small number of studies have investigated white matter reduction in patients with PD with depression. To my knowledge only one VBM study has looked at white matter volume changes within this patient population. Kostic and others (2010) found that patients with PD with depression had white matter loss in the right anterior cingulate bundle, right inferior orbitofrontal regions and in the left inferior parietal lobe when compared with healthy controls. However, there were no differences in white matter loss between subgroups of patients with PD with and without depression when compared with healthy controls. Moreover, correlation analyses showed that high HRSD scores correlated with white matter loss in the right inferior orbitofrontal region (Kostic, et al., 2010). A further study using diffusion tensor imaging found reductions in fractional anisotropy values in the white matter of the frontal lobe bilaterally, possibly representing dysfunction in bilateral anterior cingulate bundles, in depressed patients with PD when compared with non-depressed patients (Matsui, et al., 2007). A volumetric reduction in the mediodorsal nuclei of the thalamus has been also found in depressed patients with PD using diffusion tensor MRI (Li, et al., 2010). Li and others (2010) studied possible white matter microstructural changes in the thalamus which could be related to depression in patients with PD. They found decreased white matter fractional anisotropy values in the bilateral mediodorsal thalamic regions in PD with depression compared with non-depressed patients (Li, et al., 2010). A recent imaging study investigated white

matter hyperintesities changes in 34 non-demented patients with PD with depression, 25 without depression, and 30 healthy controls. The disease onset for all patients was above the age of 60. Results showed no differences between controls and all patients with PD (with and without depression); although depressed patients had more commonly frontal whiter matter hyperintesities, the score difference did not rich significance level (Petrovic, et al., 2012).

The present study was designed to explore the underlying neuroanatomical substrate of depression in a large sample of patients with PD whose overall cognitive profile was still broadly intact. The NPI was used to assess depression and SPM8 software was used for group comparison analysis (all PD patients' versus healthy control, PD with depression versus healthy control, PD without any neuropsychiatric symptoms versus healthy control, and PD with depression versus PD without any neuropsychiatric symptoms) and correlation analysis of 3-dimensional structural MRI scans of the brains of PD patients and healthy controls. This study was designed to explore grey and white matter deficits which may underlie the occurrence of depression in PD and to test for any associated subtle cognitive alteration that might emerge from the patients' cognitive profile.

From previous studies, it can be predicted that patients with depression may show grey matter loss in the frontal lobe when compared with patients without depression or healthy controls. In addition, patients with depression may have white matter loss in the frontal lobe when compared with patients without any neuropsychiatric symptoms or healthy controls.

4.4.2 METHOD

4.4.2.1 SAMPLE

The imaging study used the same sample of patients as the behavioural study (see section 4.3.2.1). In addition to this, the imaging study also included twenty four matched controls (6 male and 18 female) for comparison. The mean age of this healthy control sample was 61.7 years (SD= 9.5, range 50- 81), their mean education was 12.2 (SD= 5.5 range 5- 24) and all achieved a MMSE score of 30/30. None of the controls had a history of neurological or psychiatric diseases.

4.4.2.2 STRUCTURAL MRI SCANNING: ACQUISITION AND ANALYSIS

The acquisition and analysis of structural MRI scans have already been described in the imaging study of neuropsychiatric symptoms (chapter 4, section 4.2.2.2, pages 99-100). In addition, a multiple regression analysis was carried out in this study to investigate linear correlations between grey matter concentration and the severity of depression in patients with PD. The x, y, z coordinates of significant areas obtained from the analyses were first converted into Talairach coordinates using the mni2tal Matlab routine and then identified using the Talairach Daemon Client (http://www.talairach.org/). Unless otherwise stated a cluster corrected height threshold of $p < 0.001$ was used in all analysis.

4.4.3 RESULTS

4.4.3.1 DEMOGRAPHICAL AND MENTAL STATE SCREENING DATA ANALYSES

Univariate analyses of variance were carried out to compare the three groups (PD with depression, PD without any neuropsychiatric symptoms and healthy controls) in age, education, MMSE and disease duration for patients groups. The controls and PD subgroups were not significantly different in age [$F(2, 71) = 1.25$, *P*

> .01] or education [F (2, 71) = .655, *P* > .01], but there was a significant difference in MMSE [F (2,71) = 18.82, *p* = .000]. Post hoc (Bonferroni) comparisons showed that there was no significant difference between PD with depression and PD without any neuropsychiatric symptoms in MMSE but there was a significant difference between the controls and each of the two groups of patients. Additionally, patients with depression and patients without any neuropsychiatric symptoms did not differ for duration of disease [F (1, 48) = .006, *P* > .01] (Table 4.16).

Table 4.16 Mean (SD) Age, Education, Duration of disease and MMSE of PD patients with depression, PD patients without any neuropsychiatric symptoms (NPSS), and controls

	PD with depression (N = 27)	**PD without NPSS (N = 23)**	**Controls (N = 24)**	***P***
Age	64.6 (11.2)	66.0 (7.6)	62.79 (9.77)	.271
Education	11.9 (4.8)	10.65 (4.44)	12.21 (5.49)	.539
Duration of disease	8.11 (4.86)	8.22 (4.69)	__	.892
MMSE	27.56 (2.0)	28.39 (1.34)	30.00 (.000)	.000*

*Significant difference between controls and the two groups of patients (Using Bonferroni Post-hoc test)

4.4.3.2 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF GREY MATTER

All patients with PD versus controls: significant grey matter volume differences from controls were detected in the PD patients. Less grey matter volume values in patients group were found in the right parietal lobe (supramarginal gyrus, inferior parietal lobule), right superior temporal gyrus, right cerebellum, and occipital lobe (lingual gyrus) when compared with healthy controls (Table 4.17 and Figure 4.12).

Table 4.17 Areas of significant grey matter volume value differences between patients with PD and controls

Brain areas	**R/L**	**BA**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
						X	**Y**	**Z**
Supramarginal Gyrus	R	40	337	0.004	4.55	38	-37	33
Inferior Parietal Lobule	R	40			4.01	48	-42	44
Superior Temporal Gyrus	R	39			3.71	46	-53	32
Cerebellum (declive)	R		316	0.036	4.15	4	-77	-21
Lingual Gyrus	L	18			3.93	-10	-88	-16

R = Right L = Left BA = Brodmann Area

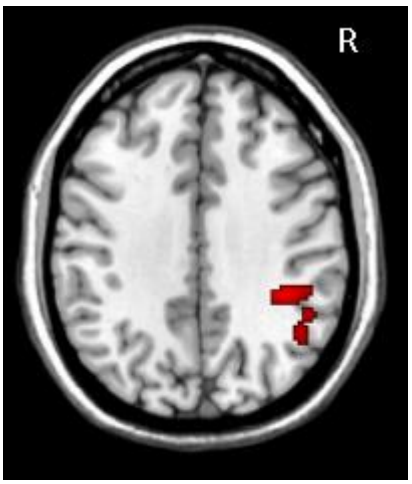

Fig 4.12 Areas of significantly less grey matter volume values in right parietal cortex in all patients with PD when compared with healthy controls

Patients with PD with depression versus controls: significantly less grey matter volume in patients with depression when compared with healthy controls was found in the left precentral gyrus, the parietal lobe including left postcentral gyrus and right inferior parietal lobule, and the right superior temporal gyrus (Table 4.18 and Figure 4.13).

Table 4.18 Areas of significant grey matter volume value differences between patients with PD with depression and controls

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Postcentral Gyrus	L	2	591	0.022	4.18	-51	-24	34
	L	3			3.16	-42	-21	47
Precentral Gyrus	L	6			2.97	-42	-7	46
Superior Temporal Gyrus	R	39	956	0.019	3.66	46	-53	30
Inferior Parietal Lobule	R	40			3.50	48	-42	44
	R	40			3.40	42	-35	42

R = Right L = Left BA = Brodmann Area

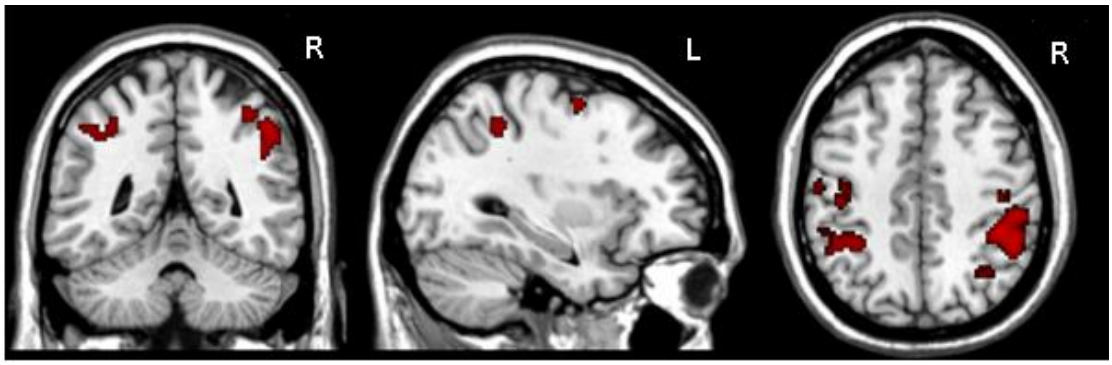

Fig 4.13 Areas of significantly less grey matter volume values in patients with PD with depression when compared with healthy controls

Patients with PD without any neuropsychiatric symptoms *versus controls*: there was no significant difference between patients without neuropsychiatric symptoms and healthy controls at the corrected cluster level. However, at the uncorrected cluster level this patients group without any neuropsychiatric symptoms had significantly less volume values in several brain regions. Significant clusters were found in the precentral gyrus bilaterally, the left medial frontal gyrus, the right inferior parietal lobule, and the right supramarginal gyrus (Table 4.19 and Figure 4.14).

Table 4.19 Areas of significant grey matter volume value differences between patients with PD without any neuropsychiatric symptoms and controls

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (uncorrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Precentral Gyrus	R	6	445	0.032	3.75	44	-3	48
	R	4			2.81	46	-15	47
	R	4			2.77	38	-15	58
	L	6	353	0.017	3.46	-36	-7	57
Medial Frontal Gyrus	L	6			3.41	-12	3	61
	L	6			3.34	-14	-5	57
Inferior Parietal Lobule	R	40	240	0.047	3.43	40	-37	39
	R	40			3.37	48	-44	43
Supramarginal Gyrus	R	40			3.00	46	-41	33

R = Right L = Left BA = Brodmann Area

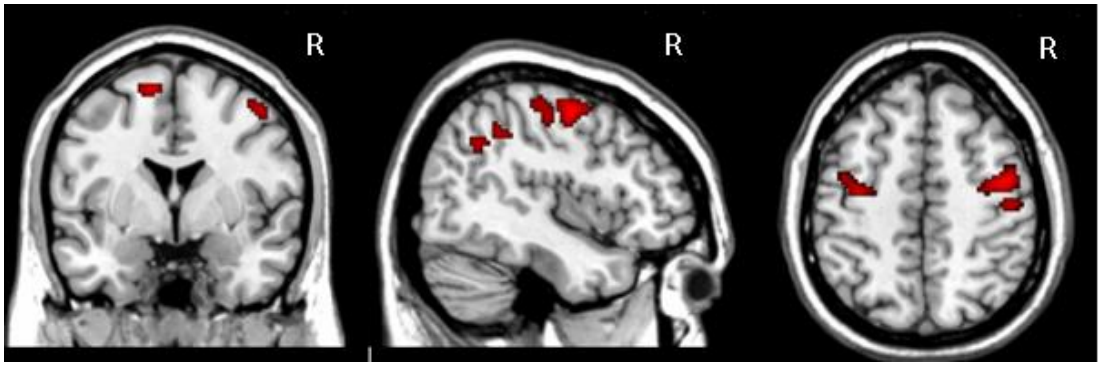

Fig 4.14 Areas of significantly less grey matter volume values in patients with PD without any neuropsychiatric symptoms when compared with healthy controls

Patients with PD with depression versus patients with PD without any neuropsychiatric symptoms: significantly less grey matter volume in patients with depression when compared with patients with no neuropsychiatric symptoms was found in the right occipital lobe (cuneus), the left inferior occipital gyrus, the left parahippocampal gyrus, the left insula, the right inferior temporal gyrus, the left middle temporal gyrus, the left fusiform gyrus, and the left superior temporal gyrus (Table 4.20 and Figure 4.15).

Table 4.20 Areas of significant grey matter volume value differences between patients with PD with depression and patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Cuneus	R	18	3946	0.000	3.87	4	-93	6
Inferior Occipital Gyrus	L	18			3.81	-32	-92	-6
Inferior Temporal Gyrus	R	37			3.70	55	-59	-5
Middle Temporal Gyrus	L	21	3411	0.000	3.85	-53	-33	-1
Fusiform Gyrus	L	36			3.78	-46	-40	-22
Parahippocampal Gyrus	L	36			3.63	-36	-34	-20
Insula	L		1116	0.040	3.77	-46	-34	20
	L				3.42	-42	16	-1
Superior Temporal Gyrus	L	42			3.44	-55	-19	12

R = Right L = Left BA = Brodmann Area

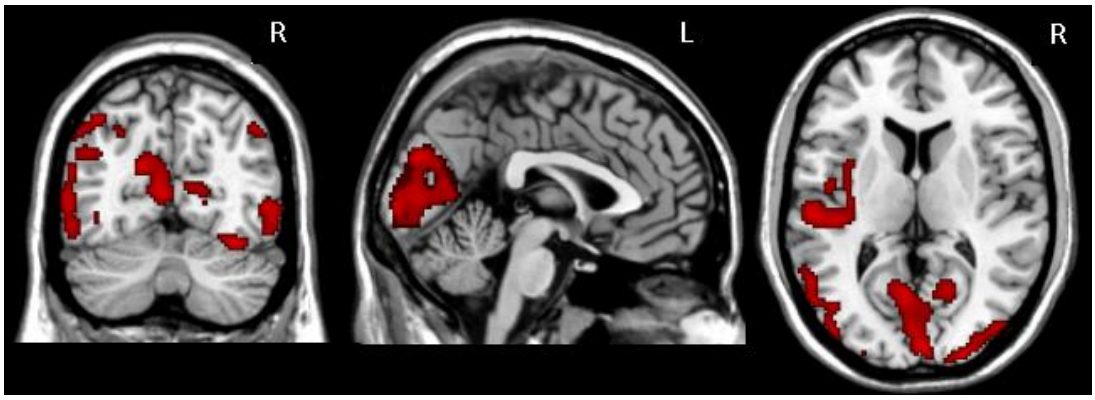

Fig 4.15 Areas of significantly less grey matter volume values in patients with PD with depression when compared with patients with PD without any neuropsychiatric symptoms

4.4.3.3 VOXEL-BASED CORRELATION ANALYSES OF GREY MATTER

A multiple regression analysis was used to identify brain regions that correlated with depression scores. There was a negative correlation between the severity of depression and grey matter volume values in several brain regions including the bilateral orbitofrontal gyrus (BA, 47 and 11), the right rectal gyrus, the bilateral insula, the right parahippocampal gyrus, the bilateral superior temporal gyrus, the right inferior temporal gyrus, the left middle temporal gyrus, the right middle occipital gyrus, and the left cerebellum (Table 4.21, Figure 4.16 and 4.17).

Table 4.21 Areas of negative correlation between grey matter volume values and depression scores in patients with PD

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Inferior Frontal Gyrus	L	47	1145	0.000	- 0.82	4.48	-40	23	-3
Orbitofrontal Gyrus	L	11			-0.81	4.41	-35	37	-8
Superior Temporal Gyrus	L	41			- 0.81	4.37	-44	-28	16
Insula	L				- 0.793	4.20	-40	12	-2
Parahippocampal Gyrus	R	34	393	0.004	- 0.81	4.47	24	3	-14
Insula	R				- 0.767	3.91	42	8	-1
Superior Temporal Gyrus	R	22			- 0.76	3.80	51	8	-4
Inferior Temporal Gyrus	R	20	764	0.000	- 0.813	4.45	61	-49	-13
Superior Temporal Gyrus	R	39			- 0.794	4.22	53	-57	19
Middle Occipital Gyrus	R	19			- 0.794	4.22	51	-74	2
Cerebellum (Culmen)	L		345	0.002	- 0.81	4.41	-38	-53	-19
	L				- 0.78	4.04	-36	-42	-18
	L				- 0.754	3.78	-44	-42	-20
Middle Temporal Gyrus	L	21	345	0.003	- 0.803	4.33	-55	-33	-1
	L	37			- 0.79	4.16	-55	-66	7
	L	37			- 0.78	4.00	-57	-62	-1
Rectal Gyrus	R	11	394	0.021	- 0.781	4.07	4	30	-23
Inferior Frontal Gyrus	R	11			- 0.77	3.90	18	38	-22

R = Right L = Left BA = Brodmann Area

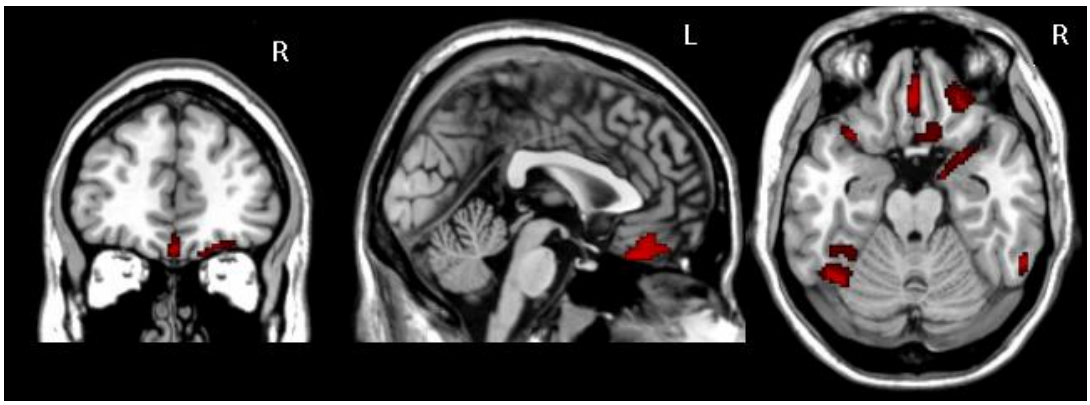

Fig 4.16 Areas of significant correlation between grey matter volume values in bilateral orbitofrontal cortex and depression scores in patients with PD

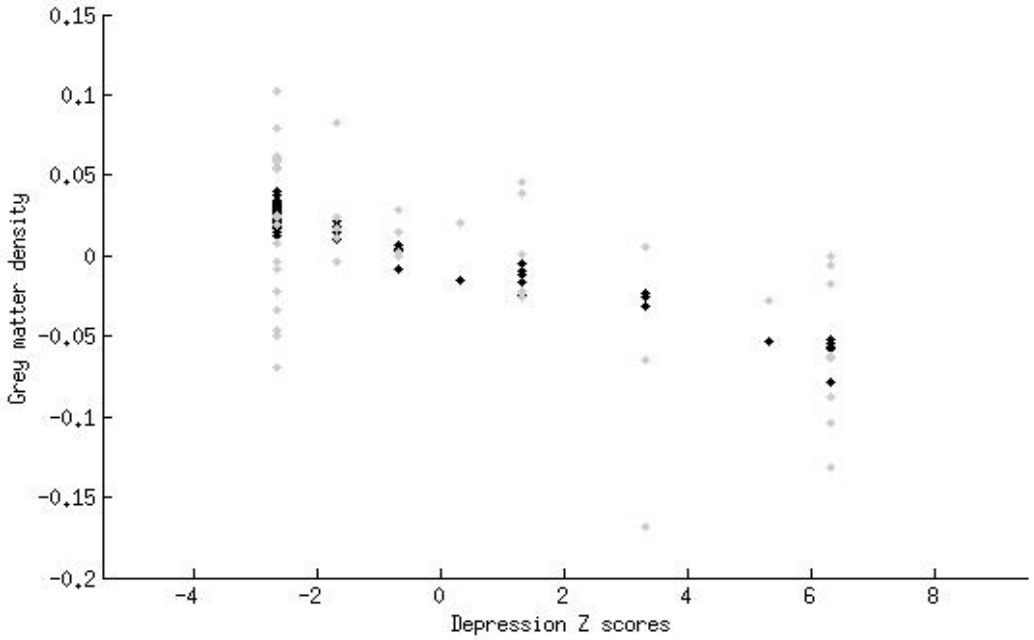

Fig 4.17 Scatterplot showing the negative correlation between grey matter density values and depression scores (expressed as z scores) in the most significant cluster (left inferior frontal gyrus)

4.4.3.4 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF WHITE MATTER

For all VBM group comparisons of white matter, significant differences were detected at the $P < 0.01$ significance levels.

All patients with PD versus controls: There was no significant white matter volume difference between all patients with PD and healthy controls at the corrected cluster level. However, at the uncorrected cluster level, patients had significantly less white matter volume values in the right inferior frontal gyrus, right precentral gyrus, left parietal lobe (precuneus), left posterior cingulate, left parahippocampal gyrus and temporal lobe when compared with healthy controls (Table 4.22 and Figure 4.18).

Table 4.22 Areas of significant white matter volume value differences between patients with PD and controls

Brain areas	R/L	Cluster Size	Cluster-level *P*-value (uncorrected)	Z value at Local Maximum	Talairach coordinates		
					X	Y	Z
Inferior Frontal Gyrus	R	206	0.027	4.35	53	3	24
Precentral Gyrus	R			2.91	59	-1	17
Parietal Lobe (precuneus)	L	246	0.005	4.00	-8	-57	30
Posterior Cingulate	L			3.41	-8	-53	23
Sub-lobar (Extra-Nuclear)	R			2.90	6	-36	17
Parahippocampal Gyrus	L	354	0.007	3.96	-40	-32	-14
Temporal Lobe (Sub-Gyral)	L			3.51	-42	-10	-11

R = Right L = Left

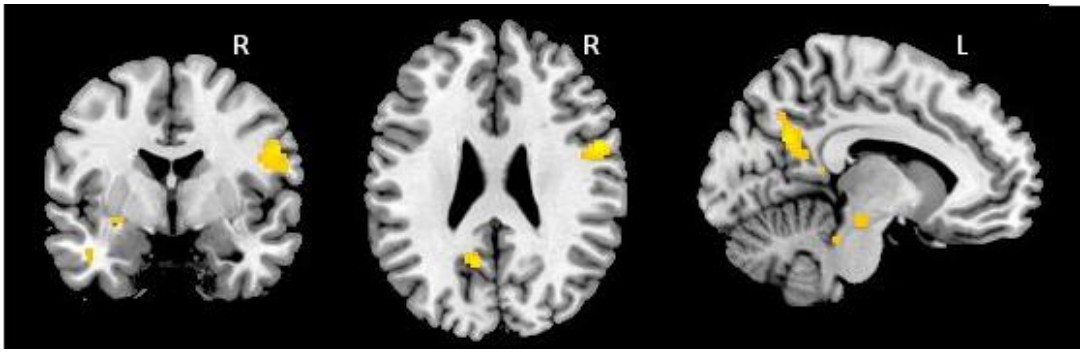

Fig 4.18 Areas of significantly less white matter volume values in right frontal lobe, left parietal lobe, left temporal lobe and left limbic lobe in all patients with PD when compared with healthy controls

Patients with PD with depression versus controls: significantly less white matter volume was found in the right inferior frontal gyrus when patients with depression were compared with healthy controls (Table 4.23 and Figure 4.19).

Table 4.23 Areas of significant white matter volume value differences between patients with PD with depression and controls

Brain areas	R/L	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
					X	Y	Z
Inferior Frontal Gyrus	R	152	0.024	4.08	53	3	24

R = Right L = Left

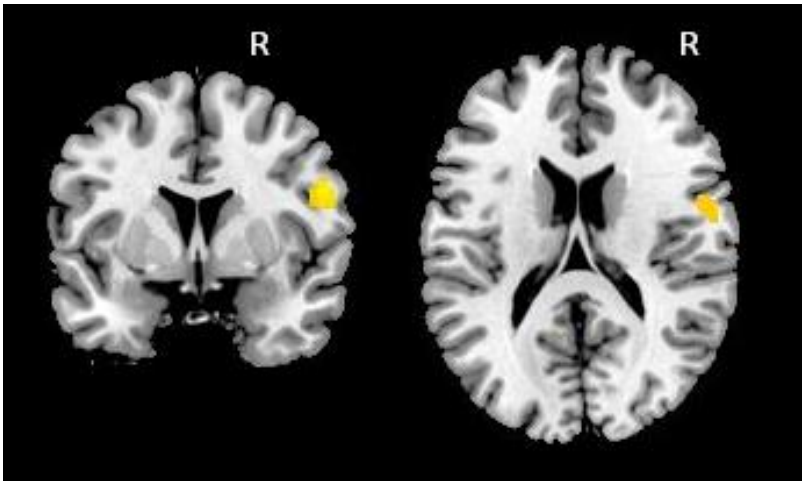

Fig 4.19 Area of significantly less white matter volume values in patients with PD with depression when compared with healthy controls

Patients with PD without any neuropsychiatric symptoms versus controls: when compared to healthy controls, patients with no neuropsychiatric symptoms had significantly less volume values in the left fusiform, left temporal lobe, bilateral posterior cingulate and the left precuneus (Table 4.24 and Figure 4.20).

Table 4.24 Areas of significant white matter volume value differences between patients with PD without any neuropsychiatric symptoms and controls

Brain areas	**R/L**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
					X	**Y**	**Z**
Fusiform	L	426	0.016	4.20	-42	-30	-14
Temporal lobe (sub-gyral)	L			3.97	-44	-13	-21
	L			3.10	-40	-8	-11
Posterior cingulate	L	796	0.001	3.89	-8	-53	23
	R			3.46	24	-52	14
	R			3.39	8	-50	19
Precuneus	L			2.95	-8	-60	40

R = Right L = Left

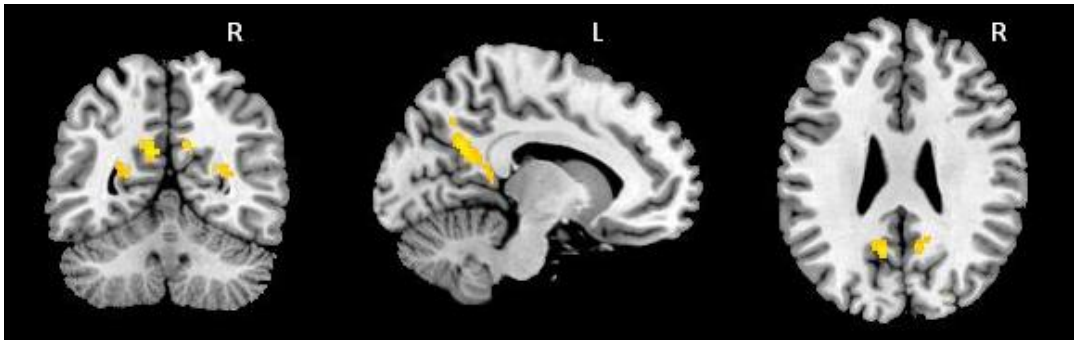

Fig 4.20 Areas of significantly less grey matter volume values in patients with PD without any neuropsychiatric symptoms when compared with healthy controls

Patients with PD with depression versus patients with PD without any neuropsychiatric symptoms: There was no significant difference between patients with depression and patients without any neuropsychiatric symptoms in the white matter volume values.

4.4.4 DISCUSSION

The findings from grey matter analyses indicated that there were volumetric reductions in some brain areas that are associated with the presence of depressive symptoms in patients with PD. These areas included structures in the frontal, temporal and parietal lobes, the insula and the parahippocampal gyrus. Particularly, the association we found in the left orbito-frontal gyrus, rectal gyrus, right superior temporal gyrus and right parahippocampal gyrus has been reported in patients with PD with depression by a published VBM study (Feldmann, et al., 2008). Dysfunctions of the orbito-frontal areas and the rectal gyrus have also been reported in patients with depressive disorders (Ballmaier et al., 2004; Bremner et al., 2002; Taylor et al., 2003; van Tol, et al., 2010). Other imaging studies reported atrophy of the frontal lobe in depressed patients with PD (Cardoso, et al., 2009; Ring, et al., 1994). Patients with depression in our study also showed white matter loss in the right inferior frontal gyrus. This result is supported by a previous VBM study that

found a reduction of the white matter in the same brain area in depressed patients with PD (Kostic, et al., 2010). Moreover, white matter reduction in the frontal lobe has been associated with major depressive disorder (without PD) (Colloby et al., 2011; Ma et al., 2007). From the above findings, it seems that the development of depressive symptoms in PD may be related to volumetric reductions in cortical and sub-cortical areas, particularly in the frontal lobe.

4.4.5 GENERAL DISCUSSION

This study is the first to have investigated both the behavioural and the anatomical correlates of depression in the same cohort of patients with PD. The behavioural findings showed that although patients with depression performed lower than patients without depression on almost all neuropsychological tests, there were no major statistically significant differences between the two subgroups of patients. However, the imaging results revealed that depression was strongly associated with atrophy of some brain regions, mainly in the frontal lobe. These findings suggest that depressive symptoms in early PD might reveal a greater or earlier impact of the disease on brain structure while functional abilities being sustained through other mechanisms of brain or cognitive reserve.

This study did not identify significant differences in grey and white matter volume in the frontal regions in patients with depression when compared with patients without any neuropsychiatric symptoms. These results are parallel to those of the neuropsychological study, although a trend was detected in the neuropsychological study, in particular the Frontal Assessment Battery on which a non-significant difference between the two groups of patients was found. This may be related to the grey matter atrophy in the left precentral gyrus in depressed patients when compared with healthy controls. Volumetric reduction in the left precentral

gyrus has been previously associated with major depressive disorder (Frodl et al., 2009).

In our sample, severity of depression was associated with deficits of attention. Several studies have reported that deficits of attention are common in patients with major depressive disorder (Paelecke-Habermann, Pohl, & Leplow, 2005; Paradiso, Lamberty, Garvey, & Robinson, 1997; Tham et al., 1997; Weiland-Fiedler et al., 2004).

Some of the brain regions we identified involve areas which have been seen to play role in major depressive disorder such as the frontal cortex, cingulate gyrus and the limbic systems. It is important to mention that the regions that are associated with emotion control and regulation such as areas of the limbic system are also highly associated with depression as this involves an inability to regulate such emotions effectively (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Goldin, McRae, Ramel, & Gross, 2008). These findings suggest that fronto-subcortical networks, including the prefrontal cortex, the cingulate cortex, and the hippocampus may also have an impact on the presence of depression in early PD. However, the present study also found an involvement of other brain areas such as the superior temporal gyrus and the insula, which have been linked with depression in patients with PD (Feldmann, et al., 2008; Kostic, et al., 2010). Therefore, our findings suggest that the underlying mechanism of depression in PD may involve other brain areas that were not seen in patients with only major depressive disorder.

Prior studies have also suggested that the pathophysiology of depression in PD may be explained by the abnormalities of some neurochemical circuits (Cummings & Masterman, 1999; Halliday et al., 1990; Remy, et al., 2005). For instance, it has been suggested that dopamine deficiency which is the main feature of

PD is followed by degeneration of other neurotransmitter systems such as noradrenergic and serotoninergic brainstem nuclei (Halliday, et al., 1990). Dysfunction of a combination of dopaminergic, serotoninergic and noradrenergic pathways in the limbic system has been observed in depressed PD patients (Remy, et al., 2005).

The investigation of patients in only the mild stages of the disease might be seen as a limitation of this study in terms of the full development of depression symptomatology. Indeed, previous studies have indicated that depressive symptoms increase in frequency with disease severity (Rojo, et al., 2003). However, studying early patients may allow the identification of selective brain abnormalities which may explain the appearance of the symptom selectively; in more advanced stages of the disease neurodegeneration might be more widespread as a consequence of disease progression thus there might be additional symptoms and abnormalities that compromise the selectivity of the findings.

4.5 EXPERIMENT 5 – COGNITIVE CORRELATES OF APATHY IN PD

4.5.1 INTRODUCTION

Several studies have indicated that apathy is correlated with cognitive impairments (Aarsland, et al., 1999; Drijgers, et al., 2010; Dujardin, et al., 2009; Isella, et al., 2002; Levy, 1998; Moretti, et al., 2012; Pedersen, Alves, et al., 2009; Pluck & Brown, 2002; Reijnders, et al., 2010; Starkstein, Mayberg, Preziosi, et al., 1992; Zgaljardic, et al., 2007), depression (Drijgers, et al., 2010; Dujardin, et al., 2009; Isella, et al., 2002; Levy, 1998; Oguru, et al., 2010; Pedersen, Alves, et al., 2009; Reijnders, et al., 2010; Starkstein, Mayberg, Preziosi, et al., 1992; Zgaljardic, et al., 2007), and anxiety (Bogdanova & Cronin-Golomb, 2012).

Many studies have investigated cognitive performance in patients with PD with apathy using a variety of neuropsychological tests. These studies compared the cognitive performance of apathetic patients with PD with that of healthy controls, of patients with other neurological conditions or of patients with PD without apathy. The findings of these studies will now be summarised.

Apathy has been associated with deficits in verbal memory and speed of processing; Starkstein and colleagues (1992) investigated the cognitive correlates of apathy in 50 non-demented patients with PD. 21 patients showed apathy, 6 patients showed apathy without depression, 15 patients had both apathy and depression, and 16 patients had no apathy or depression. Marin's Apathy Scale (Marin, et al., 1991) was used to assess apathy and MMSE (Folstein, et al., 1975), WCST (Nelson, 1976), Controlled Word Association Test (Benton, 1968), TMT (Reitan, 1958) and Digit Span (forward and backward) (Wechsler, 1981) to assess cognitive performance. Patients with apathy showed greater deficits in verbal memory and timed task TMT

(part B) when compared with patients with PD without apathy. However, there was no significant difference between apathetic patients and non-apathetic patients in MMSE scores, digit span (forward and backward) and TMT (part A) (Starkstein, Mayberg, Preziosi, et al., 1992).

Levy and others (1998) found that apathy correlated with cognitive impairment (assessed by MMSE) in four neurological conditions (PD, Alzheimer's Disease, Frontotemporal Dementia and Progressive Supra-nuclear Palsy) (Levy, et al., 1998). This study used the NPI (Cummings, et al., 1994) to measure apathy.

Reijnders and others (2010) found that apathy in PD correlated with the total score on the Cambridge Cognitive Examination (Roth, et al., 1986) and MMSE (Folstein, et al., 1975) when they used the Lille Apathy Rating Scale (Sockeel, et al., 2006) and the Apathy Evaluation Scale (ASE) (Marin, et al., 1991) as measurements of apathy. However scores on the Cambridge Examination of Cognition in the Elderly and MMSE did not correlate with the apathy subscale of the NPI (Reijnders, et al., 2010).

Several studies have indicated an association between apathy and executive functions. Aarsland and others (1999) examined the cognitive performance of 139 patients with PD using the MMSE (Folstein, et al., 1975), the Dementia Rating Scale (Mattis, 1988) and the Stroop Test (Stroop, 1935). Apathy was assessed by the apathy subscale of the NPI (Cummings, et al., 1994). Sixteen and half percent of the sample with PD had apathy, 4.3% had apathy without depression, and 12.2% had both apathy and depression. In this study, apathy was significantly correlated with dementia and the number of errors on the Stroop test (a test of executive functions) (Aarsland, et al., 1999). Also, Isella and colleagues (2002) assessed the cognitive functions of 30 patients with PD (13 of them with apathy as assessed by Marin's

Apathy Scale) (Marin, et al., 1991). Apathy was significantly correlated with deficits in executive functions (assessed by the Executive Interview) (Royall, et al., 1992), category fluency, letter fluency and levodopa daily dosage. However, apathy was not correlated with the Mattis Dementia Rating Scale scores, free recall of a short story, score on the Rey figure (copy and recall) tasks and Corsi's spatial memory span (Isella, et al., 2002).

Pluck and Brown (2002) investigated the relation between apathy and cognitive deficits and aspects of personality in 45 non-demented patients with PD (26 patients with low apathy and 11 with high levels of apathy) and 17 similarly disabled patients with osteoarthritis using the MMSE (Folstein, et al., 1975), the Cambridge Cognitive Examination (Roth, et al., 1986), WCST (Heaton, et al., 1993), Stroop Test (Stroop, 1935), category fluency part of the Cambridge Cognitive Examination, Controlled Word Association Test (Benton, 1968) and the tridimensional personality questionnaire (Cloninger, Svrakic, & Przybeck, 1993). Apathy was assessed using the AES (Marin, et al., 1991). Patients with PD had significant higher scores than patients with osteoarthritis. There were no differences in personality traits between the two groups of patients or between patients with PD with low or high levels of apathy. Compared with patients with osteoarthritis, patients with PD showed more impairments in the Category Fluency Task and in the Stroop Test (reading and colour naming but not in the interference condition). However, patients with PD with higher apathy levels had more cognitive impairments than patients with PD with lower apathy levels in the Cambridge Cognitive Examination total score, the Cambridge Cognitive Examination sub scales (Language, memory, praxis and calculation), Category Fluency, WCST (categories

and total errors) and Stroop. There was no difference between PD with low or high apathy levels in MMSE score (Pluck & Brown, 2002).

Zgaljardic and others (2007) assessed the cognitive abilities in 32 non-demented patients with PD and 29 healthy controls. They used the Frontal Systems Behavioural Scale (Grace & Malloy, 2001 as cited in Zgaljardic, et al., 2007) to assess apathy. Compared with healthy controls, patients with PD had significantly lower scores on the cognitive component of the assessment (for instance, Stroop test, letter fluency, category fluency, digit span and executive dysfunction). Patients with apathy also performed significantly worse than those without apathy on the letter fluency test, category fluency test and the conceptualization subtest from the Mattis Dementia Rating Scale (Zgaljardic, et al., 2007).

Dujardin and colleagues (2009) examined cognitive functions in 40 non-demented patients with PD (20 with apathy and 20 without apathy) twice, at study entry and after an 18 month follow-up period, using the LARS (Sockeel, et al., 2006) to measure apathy. At study entry, patients with apathy performed worse than non-apathetic patients on the Mattis Dementia Rating Scale (Mattis, 1988), the 16-item recall test, total free recall, test of executive functions (Stroop Test and Symbol Digit Association Test) and the Animal Category Fluency Test. After the 18 month follow-up, apathetic patients had more cognitive decline than non-apathetic patients, and also met criteria for dementia, suggesting that apathy may be a negative prognostic indicator in PD (Dujardin, et al., 2009). Also, Butterfield and others found a negative correlation between apathy and both executive functions and memory scores (Butterfield, et al., 2010).

A recent study investigated cognitive abilities in patients with PD (23 with apathy and 25 without apathy) using the AES (Marin, et al., 1991) and digit span

(Wechsler, 1981), the Delis-Kaplan Executive Function Test (Delis & Kaplan, 2001), the California Verbal Learning Test (Delis, et al., 2002) (immediate free recall, short delay free recall, long delay free, long delayed cued, delayed recognition and learning) and the WCST (Heaton, et al., 1993). There was a significant difference between patients with and without apathy on immediate free recall, short delay free recall, long delay free, long delayed cued, delayed recognition, digit span backward, and WCST (total correct, non-perseverative errors and categories completed (Varanese, et al., 2011). A further study reported that in patients with PD with left-side onset, apathy scores significantly correlated with scores on non-verbal tasks e.g. Trial Making Test (part B), Wechsler Memory Test and Visual Symbol Search Test (Bogdanova & Cronin-Golomb, 2012). Another recent study indicated that apathetic patients with PD with akinetic-rigid type performed significantly worse on tasks assessing functions associated with the frontal lobe e.g. the FAB (Dubois, et al., 2000), phonemic fluency (Thurstone & Thurstone, 1962) and interference error on the Stroop test (Stroop, 1935) when compared with patients with PD with tremor-dominant type (Moretti, et al., 2012). The association between apathy and executive dysfunction has also been observed in patients with PD with dementia and in patients with AD (Grossi, et al., 2012). A contrasting study however did not find any correlation between apathy and scores on tests of executive functions (Robert, et al., 2012).

Based on Hoehn and Yahr staging (1967), none of the previous studies explored the cognitive abilities of those patients with apathy at an early stage of PD. While some of the previous studies have not indicated the stage of severity of PD (Isella, et al., 2002; Levy L., 1998; Starkstein, Mayberg, Preziosi, et al., 1992), other studies only investigated patients in the moderate stage (Dujardin, et al., 2009; Pluck

& Brown, 2002; Reijnders, et al., 2010; Zgaljardic, et al., 2007). In addition, these studies used a limited number of participants and some only used screening instruments that assessed general cognitive abilities but did not evaluate a broader range of cognitive areas.

The aim of the present study was therefore, to outline the cognitive profile of patients with PD with and without apathy from a large sample of non-demented patients at an early stage of disease using an extensive battery of neuropsychological tests. It can be predicted that patients with apathy might have more cognitive impairments (particularly in executive functions) than patients without neuropsychiatric symptoms.

4.5.2 METHOD

4.5.2.1 SAMPLE

Sixty five Patients with idiopathic PD (31 male and 34 female) participated in this study. The patients were retrospectively recruited among those who had had extensive assessment by a PD outpatient clinic. The patients were diagnosed based on the UK PD Brain Bank Criteria (Hughes, et al., 1992). All patients had extensive neuropsychological screening, neuropsychiatric assessment using the NPI, structural MRI scanning and neurological examination. All patients were in the mild to mild-moderate disease stage, according to the Hoehn and Yahr staging (Hoehn & Yahr, 1967). None of the patients had a history of psychiatric disorders and the neuropsychiatric symptoms started after the onset of PD. All patients were treated with a combination of levodopa and variable doses of dopamine agonists but none were treated with antidepressants. The mean age of the sample was 65.28 years (SD= 9.30, range 44-80), their mean education was 11.08 years (SD= 4.35 range 4-18),

their mean disease duration was 8.35 years (SD= 5.27) and their mean MMSE score was 27.95 (SD= 1.8 range 24- 30). The sample of patients with PD was divided into two subgroups according to their NPI score for apathy, 25 (38%) patients with apathy and 40 (62%) patients without neuropsychiatric symptoms (see figure 4.21).

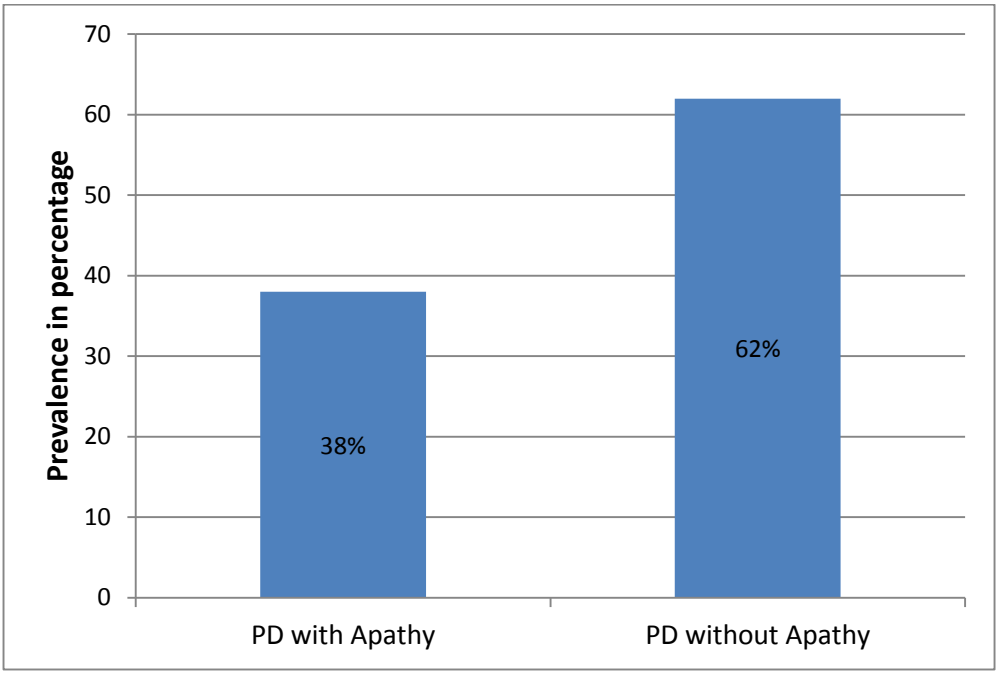

Fig 4.21 Percentage of PD with apathy and PD without apathy

In the sample with PD, the mean age of the subgroup with apathy was 68.20 years (SD= 8.35, range 49-80), their mean education was 10.28 years (SD= 4.27 range 5-18), their mean disease duration was 8.92 years (SD= 6.2) and their mean MMSE score was 27.5 (SD= 1.9 range 24- 30). The mean age of the subgroup without neuropsychiatric symptoms was 63.83 years (SD= 9.45, range 47-79), their mean education was 11.58 years (SD= 4.4 range 4-18), their mean disease duration was 8.0 years (SD= 4.64) and their mean MMSE score was 28.3 (SD= 1.6 range 24-30).

4.5.2.2 ASSESSMENTS OF APATHY

Apathy was assessed using the NPI (Cummings, et al., 1994), and DSM-IV-TR (American Psychiatric Association, 2000). Each patient and their caregiver had had an interview with an experienced psychologist who also completed the NPI. The NPI assesses the presence or absence, severity and frequency of 14 symptom fields. Apathy scores from the NPI were then entered in the statistical analyses.

4.5.2.3 NEUROPSYCHOLOGICAL ASSESSMENTS

This study used the same neuropsychological assessments that were described in detail in the previous study (chapter 4, section 4.1.2.3, pages 79-83).

4.5.2.4 STATISTICAL ANALYSES

An independent T-test and a series of independent T-tests were carried out to compare the demographic data and neuropsychological test scores of the two subgroups (PD with and without neuropsychiatric symptoms). Further statistical analyses were also carried out to examine the relationship between apathy scores and neuropsychological test scores using Pearson's correlation test. To account for multiple comparisons, this study used a significance level of 0.004 for both overall comparisons among groups and for paired correlations, except for the group comparison of demographical data, for which the significance level was 0.01.

4.5.3 RESULTS

4.5.3.1 DEMOGRAPHICAL AND MENTAL STATE SCREENING DATA ANALYSES

An independent T-test was carried out to compare the patients' subgroups with apathy and without neuropsychiatric symptoms. There was no significant difference between the two subgroups of patients in age $t(63) = -1.897$, $p > .01$, education $t(63) = 1.172$, $p > .01$, or duration of disease $t(63) = -0.682$, $p > .01$.

Neither was any significant difference was found in the mean MMSE scores of the two subgroups t(63) = 1.750, $p > .01$ (Table 4.25).

Table 4.25 Mean (SD) Age, Education, Duration of disease and MMSE of patients with PD with apathy and patients with PD without neuropsychiatric symptoms (NPSS)

	PD with apathy (N = 25)	**PD without NPSS (N = 40)**	***P***
Age	68.20 (8.35)	63.83 (9.45)	.062
Education	10.28 (4.27)	11.58 (4.37)	.246
Duration of disease	8.92 (6.21)	8.00 (4.64)	.498
MMSE	27.48 (1.92)	28.25 (1.59)	.085

4.5.3.2 COGNITIVE PROFILE OF PATIENTS WITH PD WITH AND WITHOUT APATHY

A series of independent T-tests were also carried out to compare the performance of patients with PD with and without neuropsychiatric symptoms on the neuropsychological tests in the battery. The subgroup with apathy had lower scores than the subgroup without apathy on the Stroop Test (error) t(63) = -3.16, $p < .004$ and the Letter Fluency Test t(63) = 3.17, $p < .004$. There were no significant differences between the two subgroups in any of the other neuropsychological tests, i.e. Raven's Progressive Matrices t(63) = 2.91, $p > .004$, Stroop Test (time) t(54) = 0.43, $p > .004$, TMT t(63) = 1.54, $p > .004$, Category Fluency Test t(63) = 2.64, $p > .004$, Similarities Test t(63) = 1.26, $p > .004$ Rey Complex Figure (copy) t(63) = 2.92, $p > .004$, Rey Complex Figure (delayed) t(57) = 1.75, $p > .004$, Digit Span (forward) t(38) = 0.80, $p > .004$, Digit Span (backward) t(38) = 1.01, $p > .004$, Frontal Assessment Battery t(37) = 2.63, $p > .004$, Visual-spatial span t(37) = 1.02, $p > .004$ and Rey 15-word Memory Test t(43) = 2.47, $p > .004$ (see table 4.26).

Additional correlation analyses were carried out with apathy scores as the dependant variable and neuropsychological test scores as the independent variable in

turn. There was a significant relationship between apathy scores and Letter Fluency scores (r= -.38, *P* = 0.002). Higher apathy scores were associated with a lower performance on the Letter Fluency Test. However, apathy scores were not significantly correlated with scores on Raven's Progressive Matrices (r= -.22, *P* = .08), TMT (r= -.13, *P* = .29), Category Fluency (r= -.32, *P* = 0.009), Similarities Test (r= -.12, *P* = .34), Rey Complex Figure (copy) (r= -.26, *P* = 0.04), Rey Complex Figure (delayed) (r= -.23, *P* = .08), Stroop Test (time) (r= .036, *P* = .79), Stroop Test (error) (r= .27, *P* = .03), Frontal Assessment Battery (r= -.34, *P* = .04), Digit Span (forward) (r= -.23, *P* = .15), Digit Span (backward) (r= -.199, *P* = .22), Visual-spatial span (r= -.18, P = .26), Rey 15-word Memory Test (r= -.304, *P* = .04) and MMSE (r=-.28, *P* = .02) (see table 4.27).

Table 4.26 Mean (SD), and *P* value of scores on neuropsychological tests achieved by PD with apathy and PD without neuropsychiatric symptoms (NPSS).

	PD with apathy (N = 25)	**PD without NPSS (N = 40)**	***p***
Raven's Progressive Matrices	20.44 (13.57)	28.7 (9.35)	.005
Stroop test			
Time interference effect	33.43 (18.82)	37.16 (35.49)	.671
Error interference effect	**3.88 (5.68)**	**.93 (1.37)**	**.002***
Trail Making Test	31.28 (46.67)	51.08 (52.68)	.129
Letter Fluency Test	**26.32 (8.88)**	**36.15 (13.78)**	**.002***
Category Fluency Test	29.36 (11.03)	36.73 (10.87)	.010
Similarities Test	13.84 (6.27)	15.80 (5.99)	.212
Rey Complex Figure			
Direct copy	23.50 (9.79)	29.56 (6.92)	.005
Delayed copy	10.78 (5.40)	13.49 (6.06)	.086
Digit Span			
Forward	5.86 (1.29)	6.15 (1.01)	.426
Backward	3.79 (.69)	4.12 (1.11)	.320
Frontal Assessment Battery	13.77 (2.56)	15.69 (1.93)	.012
Visual-spatial span	4.36 (1.08)	4.72 (1.06)	.316
Rey 15-word Memory Test	6.33 (2.98)	9.02 (2.03)	.029

*Significant difference between PD with apathy and PD without neuropsychiatric symptoms *P* < 0.004 (corrected for multiple comparison)

Table 4.27 Correlations between apathy scores and neuropsychological tests scores

	apathy	Raven's Progressive Matrices	Trail making test	Letter fluency	Category fluency	Similarities test	Rey complex figure (Copy)	Rey complex figure (Delayed)	Stroop tests (Time)	Stroop tests (Error)	Frontal assessment battery	Digit span (Forward)	Digit span (Backward)	Visual-spatial span	Rey 15-word Memory Test	MMSE
apathy	_	-.219	-.134	-.383*	-.322	-.121	-.261	-.227	.036	.272	-.336	-.233	-.199	-.184	-.304	-.280
Raven's Progressive Matrices	-.219	_	.111	.401*	.544*	.579*	.465*	.308	-.349	-.090	.531*	.284	.315	.243	.574*	.538*
Trail making test	-.134	.111	_	.020	-.057	.150	.210	.126	.114	-.195	.420	-.115	-.042	-.106	.109	.171
Letter fluency	-.383*	.401*	.020	_	.686*	.526*	.221	.412*	-.331	-.169	.567*	.371	.445	.355	.542*	.461*
Category fluency	-.322	.544*	-.057	.686*	_	.436*	.318	.366	-.359	-.170	.629*	.419	.533*	.386	.714*	.534*
Similarities test	-.121	.579*	.150	.526*	.436*	_	.358	.199	-.602*	-.110	.485*	.448	.488*	.283	.491*	.423*
Rey complex figure (Copy)	-.261	.465*	.210	.221	.318	.358	_	.607*	-.039	-.130	.426	.236	.178	.258	.485*	.208
Rey complex figure (Delayed)	-.227	.308	.126	.412*	.366	.199	.607*	_	-.089	-.141	.398	.174	.220	.190	.388	.236
Stroop tests (Time)	.036	-.349	.114	-.331	-.359	-.602*	-.039	-.089	_	.043	-.448	-.147	-.287	-.227	-.384	-.440*
Stroop tests (Error)	.272	-.090	-.195	-.169	-.170	-.110	-.130	-.141	.043	_	-.282	-.275	-.163	-.192	-.132	-.222
Frontal assessment battery	-.336	.531*	.420	.567*	.629*	.485*	.426	.398	-.448	-.282	_	.462	.418	.343	.678*	.680*
Digit span (Forward)	-.233	.284	-.115	.371	.419	.448	.236	.174	-.147	-.275	.462	_	.609*	.227	.419*	.482*
Digit span (Backward)	-.199	.315	-.042	.445	.533*	.488*	.178	.220	-.287	-.163	.418	.609*	_	.049	.480*	.482*
Visual-spatial span	-.184	.243	-.106	.355	.386	.283	.258	.190	-.227	-.192	.343	.227	.049	_	.438	.159
Rey 15-word Memory Test	-.304	.574*	.109	.542*	.714*	.491*	.485*	.388	-.384	-.132	.678*	.419	.480*	.438	_	.611*
MMSE	-.280	.538*	.171	.461*	.534*	.423*	.208	.236	-.440*	-.222	.680*	.482*	.482*	.159	.611*	_

*Value is significant at $P < 0.004$ (two-tailed).

4.5.4 DISCUSSION

The prevalence of apathy in this study (38%) is similar to that reported in previous published reports (Cubo, et al., 2012; Pedersen, Larsen, et al., 2009; Pluck & Brown, 2002; Starkstein, Mayberg, Preziosi, et al., 1992; Zgaljardic, et al., 2007). Apathy was not associated with duration of disease in the current study, which is in line with what has been reported previously (Butterfield, et al., 2010; Dujardin, et al., 2009; Dujardin, et al., 2007; Pedersen, et al., 2010; Reijnders, et al., 2010; Varanese, et al., 2011). Apathy was not associated with global cognitive functioning as assessed by MMSE (Folstein, et al., 1975). The finding of a dissociation between apathy and MMSE scores in this study is also in line with previous reports (Reijnders, et al., 2010; Starkstein, Mayberg, Leiguarda, et al., 1992; Varanese, et al., 2011); Pedersen et al (2009) found, however, that apathy was associated with MMSE scores, which may be explained by the inclusion of demented patients in their study. Dujardin et al (2009) reported that apathetic patients with PD with dementia had more cognitive impairments than non-apathetic patients with PD. It may will be that the symptoms of apathy in the early stages of PD may not affect global cognitive abilities.

Although patients with apathy performed lower than those without neuropsychiatric symptoms on all neuropsychological tests, significant differences were detected in those tasks assessing executive functions. Correlation analyses confirmed that high apathy scores correlated significantly with poorer performance on tests of executive function. Executive dysfunction might reflect the difficulty in response inhibition, in thinking flexibly and switching response sets in the present

sample, suggesting that executive function tasks should be made a priority when evaluating patients with apathy at the early stages of PD.

The impairment of executive functions in patients with PD with apathy detected with the Stroop test has been found in previous studies (Aarsland, et al., 1999; Dujardin, et al., 2009; Moretti, et al., 2012). Functional imaging studies have indicated the important role of the anterior cingulate cortex, which is activated during the Stroop test (Ravnkilde, Videbech, Rosenberg, Gjedde, & Gade, 2002). The evidence from this fMRI study might provide an explanation for the differences between the two subgroups on the Stroop task in the current study. Given this behavioural finding it would be useful to carry out an anatomical study to better explain these differences. Additionally, the current study found a significant association between apathy and letter fluency scores which is in line with previous findings (Isella, et al., 2002; Moretti, et al., 2012; Zgaljardic, et al., 2007). Moreover, a similar pattern of executive dysfunction has been reported in apathetic patients with PD with dementia and apathetic patients with AD (Grossi, et al., 2012). Taken together, the findings of the current study highlight the presence of a strong association between apathy and the presence of executive deficits. Impairments of executive functions may reflect deficits in the frontal lobe, and indeed previous anatomical studies have reported an association between apathy and deficits in structures or in the functioning of the frontal lobe (Le Jeune, et al., 2009; Reijnders, et al., 2010; Skidmore, et al., 2011).

Most of the previous studies that assessed cognitive functions in patients with PD with apathy reported more cognitive impairments than found by the present study (Butterfield, et al., 2010; Dujardin, et al., 2009; Pluck & Brown, 2002;

Varanese, et al., 2011). One reason for this difference could be because the previous studies did not correct for either multiple comparisons or paired correlations. Furthermore, Pluck and Brown (2002) used an inappropriate level of significance ($P < 0.10$), a choice that is neither justified nor accurate in view of conventional standard statistical practice.

4.6 EXPERIMENT 6 – NEUROANATOMICAL CORRELATES OF APATHY IN PD

4.6.1 INTRODUCTION

Although apathy is one of the most common neuropsychiatric features of PD, only limited imaging studies have investigated this symptom in this disease. Apathy has been associated with deficits of the prefrontal-basal ganglia system (Levy & Dubois, 2006). A PET study showed that apathy was inversely correlated with [^{11}C] RTI-32 binding (dopamine and noradrenaline) in the bilateral ventral striatum (Remy, et al., 2005). Another PET study was carried out by Le Jeune and others (2009) to investigate apathy in 12 patients with PD after deep brain stimulation of the subthalamic nucleus using the Apathy Evaluation Scale (Marin, et al., 1991). They found that high apathy scores were positively correlated with glucose metabolism in the right frontal middle gyrus (BA 10) and right inferior frontal gyrus (BA 46). Negative correlations were also identified between apathy and glucose metabolism in the bilateral posterior cingulate gyrus (BA 31) and left middle frontal lobe (Le Jeune, et al., 2009). Recently, Reijders and colleagues (2010) studied the neuroanatomical correlates of apathy in patients with PD. A VBM technique was used to detect a possible correlation between grey matter density values and severity of apathy. The results showed that apathy was not correlated with the severity of motor symptoms, disease duration or proportion of patients taking levodopa or a dopamine agonist. In addition, high apathy scores were negatively correlated with less grey matter density in the left precentral gyrus (BA 6), the bilateral inferior parietal gyrus (BA 40), the bilateral inferior frontal gyrus (BA 44, 47), the bilateral insula and the right posterior cingulate gyrus (BA 31) (Reijnders, et al., 2010).

Another fMRI study (Skidmore, et al., 2011) investigated the specific characteristics of apathy, depression, and motor progression in the resting state in 22 non-demented patients with PD using the Amplitude of the Low Frequency Fluctuation technique. The authors examined how apathy and depression were related to disease severity. Correlational analyses showed that higher apathy scores were associated with increased normalized ALFF signal in the right middle orbital frontal gyrus and in the subgenual cingulate bilaterally. However, higher apathy scores were correlated with decreased activity in the left supplementary motor region, the left inferior parietal lobule and the left fusiform gyrus. In contrast, the severity of depression was correlated with increased normalized ALFF signal in the right subgenual cingulate, the bilateral cuneus, the right lateral geniculate and the right mesial frontal gyrus (Skidmore, et al., 2011).

Recent a PET study examined the possible association between apathy and brain metabolism in 45 patients with PD without dementia or depression (Robert, et al., 2012). This study used the AES (Marin, et al., 1991) to assess apathy, Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979) and Mattis Dementia Rating Scale (Mattis, 1988). However, the stage of severity of PD was not reported in this study. The results revealed positive correlations between AES scores and cerebral metabolism in the right inferior frontal gyrus, right middle frontal gyrus, right cuneus and right insula. Negative correlations were identified between AES scores and cerebral metabolism in the bilateral cerebellum particularly the inferior semilunar lobule (Robert, et al., 2012). Isella and others (2002) studied the morphometric correlates of apathy in 30 patients with PD and 25 healthy controls using Marin's Apathy Scale (Marin, et al., 1991) and did not find any specific

measure of frontotemporal atrophy correlating with the presence or severity of apathy (Isella, et al., 2002).

To my knowledge, there is no study which has investigated white matter volume in patients with PD with apathy. However, in other neurological disorders, for instance AD, few studies have reported that apathy is associated with white matter abnormalities dysfunctions in frontal and cingulate regions. A structral MRI study has found that patients with AD with apathy showed a significantly greater amount of frontal white matter hyperintensities than patients without apathy (Starkstein, et al., 2009). In addition, another study (Migneco et al., 2001) compared cerebral blood flow in elderly demented and non-demented patients with and without apathy using SPECT. Brain perfusion was measured by 99mTc-labeled bicisate. Patients with apathy showed significantly decreased 99mTc-labeled bicisate in the anterior cingulate when compared with patients without apathy (Migneco, et al., 2001). The cingulate area was also identified when comparing patients with AD with apathy with patients with AD without apathy (Benoit et al., 2002).

The present study was designed to explore the neuroanatomical abnormality associated with apathy in a large sample of patients with PD whose overall cognitive profile was still broadly intact. In addition, according to the Hoehn and Yahr stages (1967), all patients had mild PD. The NPI was used to assess apathy and SPM8 software was used for group comparison analysis (all patients with PD versus healthy control, PD with apathy versus healthy control, PD without apathy versus healthy control, and PD with apathy versus PD with no neuropsychiatric symptoms) and correlation analysis of 3-dimensional structural MRI scans of the brains of

patients with PD. This study was designed to explore grey and white matter deficits which may underline the occurrence of apathy in PD.

From previous studies of apathy in PD or other neurological disorders, it can be predicted that patients with apathy may show grey matter loss in the frontal lobe and anterior cingulate cortex when compared with patients without apathy or healthy controls. In addition, patients with apathy may have white matter loss in the frontal and cingulate regions when compared with patients without neuropsychiatric symptoms or healthy controls.

4.6.2 METHOD

4.6.2.1 SAMPLE

Forty patients with idiopathic PD (20 male and 20 female) participated in this study. This was a subset of that who took part in the previous behavioural study of apathy. The mean age of all patients was 67.73 years (SD= 8.06, range 48-80), their mean education was 11.1 years (SD= 4.56 range 5-18), their mean disease duration was 8.98 years (SD= 5.27) and their mean MMSE score was 27.9 (SD= 1.7 range 24- 30). The patient sample was divided into two subgroups according to their NPI score for apathy, 18 patients with apathy and 22 patients without any neuropsychiatric symptoms. The mean age of the patients with apathy was 68.72 years (SD= 8.44, range 49-80), their mean education was 10.9 years (SD= 4.5 range 5-18), their mean disease duration was 10.3 years (SD= 5.98) and their mean MMSE score was 27.2 (SD= 1.8 range 24- 30). The mean age of patients without neuropsychiatric symptoms was 66.1 years (SD= 8.5, range 48-80), their mean education was 11.2 years (SD= 4.7 range 5-18), their mean disease duration was 7.9 years (SD= 4.5) and their mean MMSE score was 28.2 (SD= 1.3 range 26- 30). In

addition, this imaging study used the same healthy control sample that has been already described in the imaging study of depression (see section, 4.4.2.1, page 131).

4.6.2.2 STRUCTURAL MRI SCANNING: ACQUISITION AND ANALYSIS

The acquisition and analysis of structural MRI scanning have already been described in the imaging study of neuropsychiatric symptoms (chapter 4, section 4.2.2.2, pages 99-100). In addition, a multiple regression analysis was also carried out in this study to investigate linear correlations between grey matter concentration and severity of apathy in PD. The x, y, z coordinates of significant areas obtained from the analyses were first converted into Talairach coordinates using the mni2tal Matlab routine and then identified using the Talairach Daemon Client (http://www.talairach.org/). Unless otherwise stated a cluster corrected height threshold of $p < 0.001$ was used in all analyses.

4.6.3 RESULTS

4.6.3.1 DEMOGRAPHICAL AND MENTAL STATE SCREENING DATA ANALYSES

Univariate analyses of variance were carried out to compare the three groups (PD with apathy, PD without neuropsychiatric symptoms and controls) in age, education, MMSE and disease duration for patients groups. The controls and patients subgroups showed no significant difference in age [$F(2, 63) = 2.31$, $P > .01$] or education [$F(2, 63) = .39$, $P > .01$], but there was a significant difference in MMSE [$F(2, 63) = 25.965$, $p = .000$]. Post hoc (Bonferroni) comparisons showed that there was no significant difference between the patient subgroup with apathy and those without neuropsychiatric symptoms in MMSE but there was a significant difference between controls and each of the two subgroups of patients. Also, patients with

apathy and patients without neuropsychiatric symptoms did not differ for duration of disease [F (1, 39) = 2.1, *P* > .01] (Table 4.28).

Table 4.28 Mean (SD) Age, Education, Duration of disease and MMSE of patients with PD with apathy, patients with PD without neuropsychiatric symptoms (NPSS), and controls

	PD with apathy (N = 18)	**PD without NPSS (N = 22)**	**Controls (N = 24)**	***P***
Age	68.7 (8.4)	66.1 (8.5)	62.79 (9.77)	.108
Education	10.9 (4.5)	11.2 (4.7)	12.21 (5.49)	.678
Duration of disease	10.3 (5.978)	7.9 (4.5)	__	.162
MMSE	27.22 (1.8)	28.2 (1.4)	30.00 (.000)	.000*

*Significant difference between controls and the two groups of patients (Using Bonferroni Post-hoc test)

4.6.3.2 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF GREY MATTER

All patients with PD versus controls: when compared with healthy controls, patients had significantly less grey matter volume in several brain areas, including, the bilateral inferior frontal gyrus, bilateral middle frontal gyrus, right postcentral gyrus, bilateral superior parietal lobule, left subcallosal gyrus, bilateral inferior parietal lobule, bilateral parahippocampal gyrus, bilateral cerebellum (posterior lobe, declive), right cerebellum (anterior lobe, culmen), right lingual gyrus, left sub-gyral, and the right superior frontal gyrus (Table 4.29 and Figure 4.22).

Table 4.29 Areas of significant grey matter volume value differences between all patients with PD and controls

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Inferior frontal gyrus	L	9	1242	0.000	6.24	-51	5	26
Middle frontal gyrus	L	46			5.03	-42	26	23
	L	46			5.03	-38	45	5
	R	8	1496	0.000	5.37	44	16	42
Inferior frontal gyrus	R	46			5.31	44	39	11
Middle frontal gyrus	R	10			5.25	36	51	3
Postcentral gyrus	R	5	173	0.000	5.32	32	-44	57
Superior parietal lobule	R	7			4.61	20	-53	58
Subcallosal gyrus	L	34	124	0.004	4.93	-14	3	-12
Inferior parietal lobule	R	40	102	0.002	4.63	42	-35	42
Parahippocampal gyrus	R	34	69	0.013	4.60	20	1	-10
Cerebellum (Posterior Lobe)	R		100	0.015	4.55	8	-79	-20
Parahippocampal gyrus	R	19	275	0.001	4.51	22	-53	-7
Cerebellum (Anterior lobe)	R				4.44	22	-26	-21
Lingual gyrus	R	19			4.14	16	-47	-3
Inferior frontal gyrus	R	9	86	0.003	4.50	53	5	22
Superior parietal lobule	L	7	92	0.002	4.47	-28	-50	58
Inferior parietal lobule	L	40			3.92	-26	-38	53
Superior parietal lobule	L	7	71	0.005	4.34	-30	-60	44
Inferior frontal gyrus	L	40			4.19	-38	-58	40
Cerebellum (Posterior lobe)	L		481	0.001	4.33	-32	-65	-12
Parahippocampal gyrus	L	19			4.29	-18	-49	-6
Cerebellum (Posterior lobe)	L				4.06	-22	-53	-12
Superior frontal gyrus	R	11	117	0.010	4.28	24	46	-17
Middle frontal gyrus	R	11			4.09	34	34	-12
Superior frontal gyrus	R	11			3.81	32	54	-14

R = Right L = Left BA = Brodmann Area

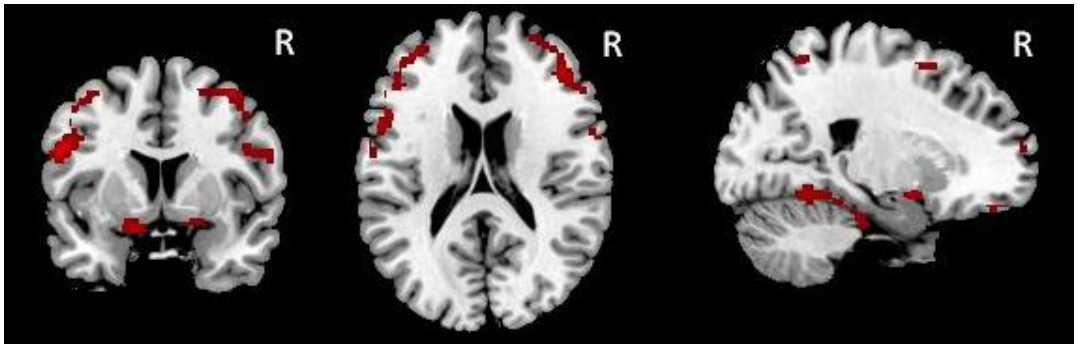

Fig 4.22 Areas of significantly less grey matter volume values in all patients with PD when compared with healthy controls

Patients with PD with apathy versus controls: patients with apathy had significantly less grey matter volume in the bilateral inferior frontal gyrus, bilateral middle frontal gyrus, right inferior parietal lobule, left parahippocampal gyrus, left

cerebellum (anterior lobe, culmen), left cerebellum (posterior lobe, tuber), left fusiform gyrus and the left cingulate gyrus when compared with healthy controls (Table 4.30 Figure 4.23)

Table 4.30 Areas of significant grey matter volume value differences between patients with PD with apathy and controls

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Inferior frontal gyrus	R	45	834	0.000	5.35	50	37	7
Middle frontal gyrus	R	10			4.77	40	51	7
	R	9			4.74	44	34	26
Inferior parietal lobule	R	40	100	0.001	5.09	44	-39	44
Middle frontal gyrus	L	9	719	0.000	4.81	-44	31	28
	L	10			4.68	-42	43	14
Inferior frontal gyrus	L	9			4.66	-51	7	25
Parahippocampal gyrus	L	34	67	0.021	4.59	-16	1	-12
Cerebellum (Anterior lobe)	L		295	0.001	4.37	-34	-40	-23
(Posterior lobe)	L				4.14	-44	-52	-23
Fusiform gyrus	L	19			4.08	-24	-61	-7
Cingulate gyrus	L	24	69	0.032	4.03	-2	-2	42

R = Right L = Left BA = Brodmann Area

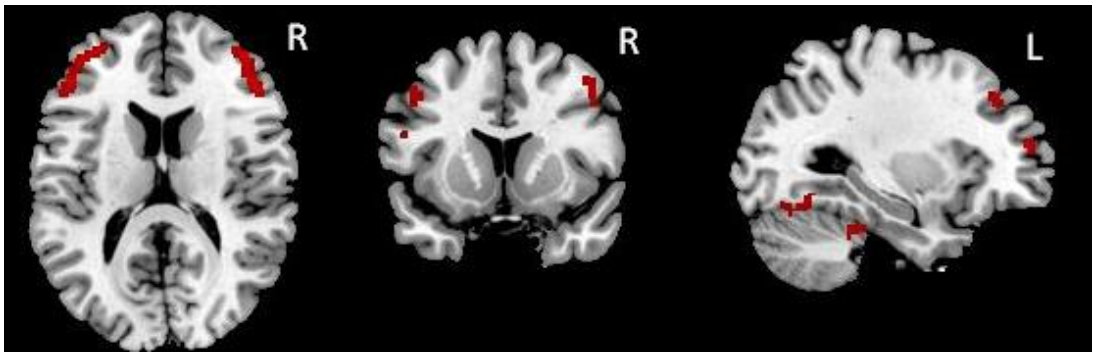

Fig 4.23 Areas of significantly less grey matter volume values in patients with PD with apathy when compared with healthy controls

Patients with PD without neuropsychiatric symptoms versus controls: No significant difference was found at the corrected cluster level. However, at an uncorrected cluster level, patients without neuropsychiatric symptoms had less grey matter volume in the left inferior frontal gyrus and the left middle frontal gyrus when compared with healthy controls (Table 4.31 Figure 4.24).

Table 4.31 Areas of significant grey matter volume value differences between patients with PD without neuropsychiatric symptoms and healthy controls.

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (uncorrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Inferior frontal gyrus	L	9	56	0.001	5.28	-51	5	26
Middle frontal gyrus	L	10	71	0.002	4.63	-36	45	5

R = Right L = Left BA = Brodmann Area

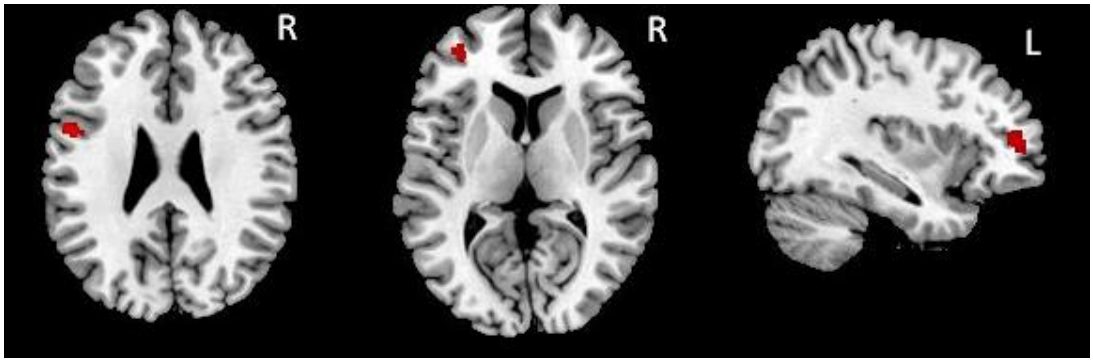

Fig 4.24 Areas of significantly less grey matter volume values in left inferior frontal gyrus and middle frontal gyrus in patients with PD without neuropsychiatric symptoms when compared with healthy controls

Patients with PD with apathy versus patients with PD without neuropsychiatric symptoms: there was no significant difference between patients with apathy and patients without neuropsychiatric symptoms at the corrected cluster level. However, at the uncorrected cluster level ($p < 0.01$) significant grey matter volume differences between the subgroups were detected in several brain areas including the left inferior frontal gyrus, left middle frontal gyrus, left precentral gyrus, left cingulate gyrus, right anterior cingulate, left temporal gyrus and the left insula in which patients with apathy had significantly less grey matter volume (Table 4.32 Figure 4.25).

Table 4.32 Areas of significant grey matter volume value differences between patients with PD with apathy and patients with PD without neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (uncorrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
Inferior frontal gyrus	L	46	670	0.002	3.67	-44	39	9
Middle frontal gyrus	L	46			3.44	-48	34	15
Precentral gyrus	L	6			3.42	-44	21	34
Cingulate gyrus	L	32	471	0.007	3.64	0	34	26
Anterior cingulate	R	32			3.37	4	41	13
	R	32			2.79	2	44	-6
Superior temporal gyrus	L	41	407	0.011	3.42	-48	-32	13
Sub-lobar (Insula)	L				3.26	-40	-12	-1
	L				2.86	-42	-19	3

R = Right L = Left BA = Brodmann Area

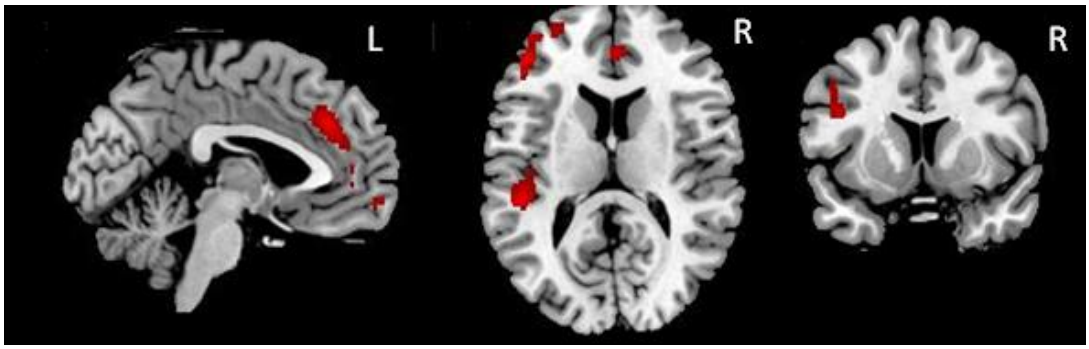

Fig 4.25 Areas of significantly less grey matter volume values in patients with PD with apathy when compared with patients with PD without neuropsychiatric symptoms

4.6.3.3 VOXEL-BASED CORRELATION ANALYSES OF GREY MATTER

A multiple regression analysis was used to identify the brain regions that correlated with apathy. A significant level of $p < 0.01$ was chosen. There was a negative correlation between the severity of apathy and grey matter volume values in several brain regions including the left superior temporal gyrus, left transverse temporal gyrus, left insula, left inferior frontal gyrus, left middle frontal gyrus, left medial frontal gyrus and right anterior cingulate (Table 4.33, Figure 4.26 and 4.27).

Table 4.33 Areas of negative correlation between grey matter volume values and apathy scores in patients with PD

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Superior temporal gyrus	L	41	424	0.020	- 0.75	3.63	-44	-28	14
Transverse temporal gyrus	L	41			- 0.65	2.86	-57	-19	12
Sub-lobar (Insula)	L				- 0.64	2.84	-42	-19	6
Inferior frontal gyrus	L	47	104	0.027	- 0.71	3.31	-42	19	-3
Middle frontal gyrus	L	9	53	0.034	- 0.70	3.28	-46	19	29
Medial frontal gyrus	L	32	71	0.032	- 0.69	3.20	0	6	46
	L	9	159	0.035	- 0.64	2.80	-2	51	20
Anterior cingulate	R	32	103	0.043	- 0.59	2.55	2	43	13

R = Right L = Left BA = Brodmann Area

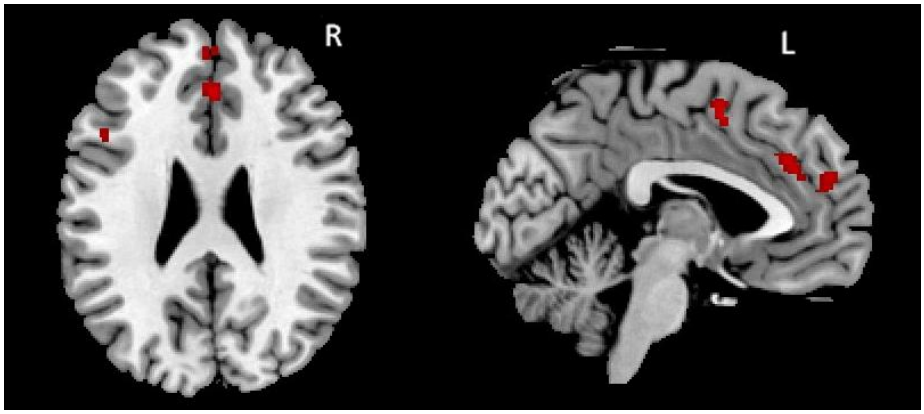

Fig 4.26 Areas of significant correlation between grey matter volume values in the left frontal cortex and apathy scores in patients with PD

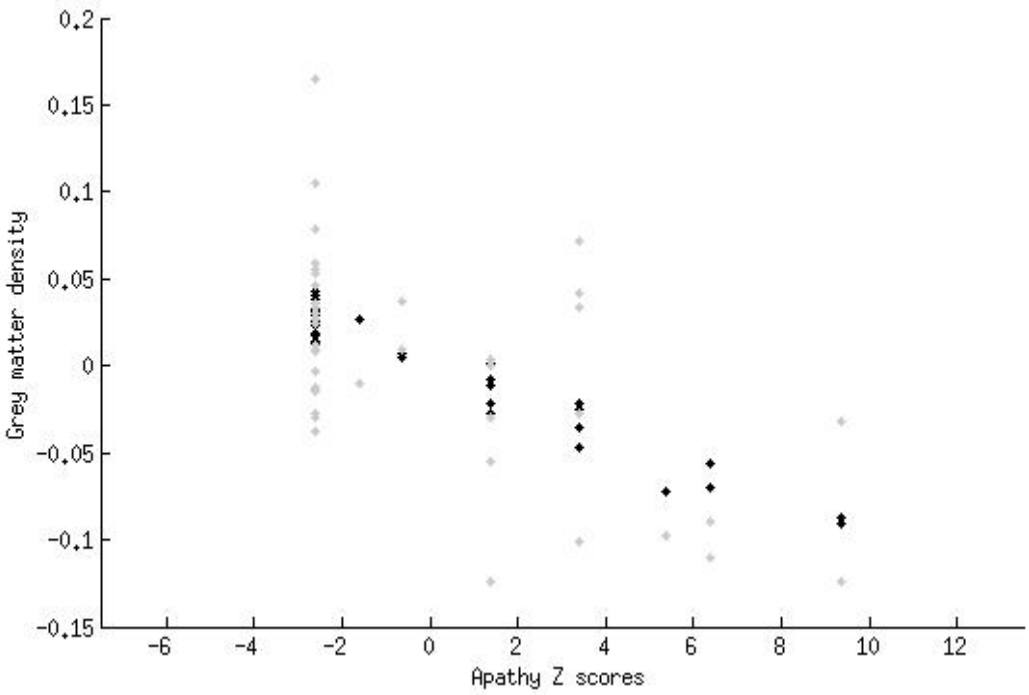

Fig 4.27 Scatterplot showing the negative correlation between grey matter density values and apathy scores (expressed as z scores) in the most significant cluster (left superior temporal gyrus)

4.6.3.4 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF WHITE MATTER

For all VBM group comparisons of white matter, significant differences were detected at the $p < 0.001$ significance level.

All patients with PD versus controls: when compared with controls, all patients had significantly less white matter volume in the left precentral gyrus, bilateral middle frontal gyrus, right anterior cingulate and right insula (Table 4.34 Figure 4.28).

Table 4.34 Areas of significant white matter volume value differences between all patients with PD and controls.

Brain areas	**R/L**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
					X	**Y**	**Z**
Precentral gyrus	L	2513	0.000	4.92	-30	-15	41
Middle frontal gyrus	L			4.41	-26	23	23
Precentral gyrus	L			4.34	-30	1	24
Anterior cingulate	R	2926	0.000	4.72	22	41	7
Middle frontal gyrus	R			4.69	28	4	35
Sub-lobar (Insula)	R			4.63	28	28	12

R = Right L = Left

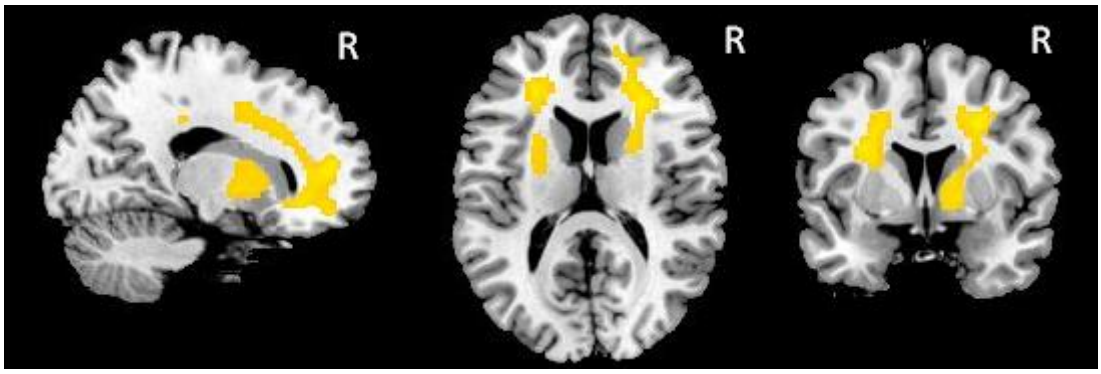

Fig 4.28 Areas of significantly less white matter volume values in all patients with PD when compared with healthy controls

Patients with PD with apathy versus controls: Patients with apathy had less white matter volume in the bilateral middle frontal gyrus, right insula, bilateral anterior cingulate gyrus, and left precentral gyrus when compared with controls (Table 4.35 Figure 4.29).

Table 4.35 Areas of significant white matter volume value differences between patients with PD with apathy and controls.

Brain areas	**R/L**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
					X	**Y**	**Z**
Middle frontal gyrus	R	2655	0.000	5.28	28	4	37
Sub-lobar (Insula)	R			4.55	28	26	12
Anterior cingulate gyrus	R			4.44	20	41	5
	L	2669	0.000	4.95	-14	17	30
Precentral gyrus	L			4.51	-32	1	22
Middle frontal gyrus	L			4.48	-26	23	23

R = Right L = Left

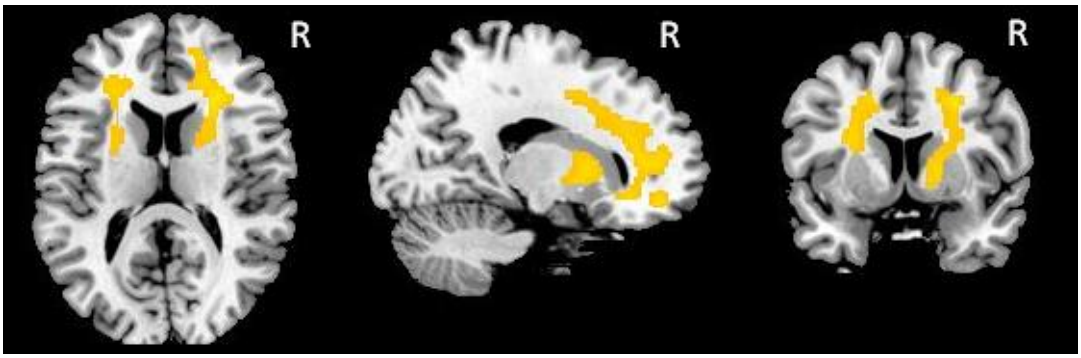

Fig 4.29 Areas of significantly less white matter volume values in patients with PD when compared with healthy controls

Patients with PD without neuropsychiatric symptoms versus controls: There was no significant difference between patients without neuropsychiatric symptoms and healthy controls at the corrected cluster level. However, at the uncorrected cluster level, patients without neuropsychiatric symptoms had significantly less white matter volume values in the right medial frontal gyrus, left precentral gyrus, left middle frontal gyrus and left anterior cingulate (Table 4.36 and Figure 4.30).

Table 4.36 Areas of significant white matter volume value differences between patients with PD without neuropsychiatric symptoms and controls.

Brain areas	**R/L**	**Cluster Size**	**Cluster-level *P*-value (uncorrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
					X	**Y**	**Z**
Medial frontal gyrus	R	396	0.000	4.34	20	47	9
Frontal lobe (sub-gyral)	R			3.37	26	28	12
	R			3.32	18	33	-7
Precentral gyrus	L	143	0.017	4.19	-32	-15	43
Middle frontal gyrus	L	110	0.032	3.54	-28	21	28
Frontal lobe (sub-gyral)	L			3.34	-26	34	11
Anterior cingulate	L			3.25	-20	43	3

R = Right L = Left

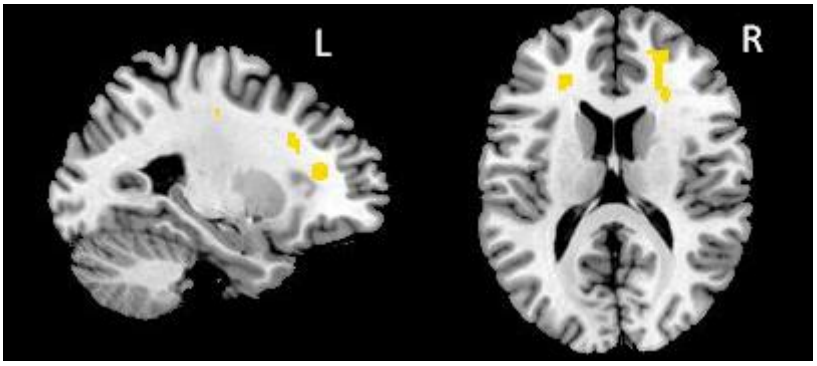

Fig 4.30 Areas of significantly less white matter volume values in patients with PD without neuropsychiatric symptoms when compared with healthy controls

Patients with PD with apathy versus patients with PD without neuropsychiatric symptoms: There was no significant difference between patients with apathy and patients without neuropsychiatric symptoms in white matter volume values.

4.6.4 DISCUSSION

The present findings identified some brain regions that may play an important role in the presence of apathy in early PD. In patients with apathy, a larger cluster of grey and white matter loss was found in frontal lobe areas, anterior cingulate cortex and the insula, which is in line with previous findings (Reijnders, et al., 2010). These results were confirmed by the findings of grey matter correlation analyses. Consistent with the present findings, earlier studies in AD patients with apathy reported a white matter reduction in the frontal lobe (Starkstein, et al., 2009) and in the anterior cingulate cortex (Migneco, et al., 2001). Functionally, the insular regions are connected with the anterior cingulate cortex and the frontal lobe, particularly, the inferior frontal gyrus (van den Heuvel, et al., 2009), all areas that are functionally connected in healthy participants and are parallel to the anatomical areas observed in the present study. Therefore, dysfunction in this brain network may contribute to the presence of apathy in PD as there seems to be both functional and structural grounds for this explanation. It has been suggested that the insula plays a role in subjective emotional experience; atrophy in this area may reflect loss of emotional responsiveness or spontaneous emotion, which is considered as one of the most prominent features of apathy (Davidson & Irwin, 1999). In older people with only apathy (without PD), higher apathy scores were associated with grey matter reduction in the right anterior cingulate gyrus (Lavretsky, Ballmaier, Pham, Toga, & Kumar, 2007). This brain area has a major functional impact in terms of the initiation and motivational drivers for goal directed behaviours and activities, and atrophy to this region, therefore, may lead to behavioural and cognitive changes with a consequent loss of goal directed actions (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001).

Levy and Dubois (2006) suggested that apathy may occur as a consequence of disturbance in the prefrontal-basal ganglia system and distinguish three subtypes of processing disturbance which are emotional-affective, cognitive, and auto-activation. Specifically, the auto-activation deficit has been associated with frontal white matter lesions (Levy & Dubois, 2006). In addition, the involvement of the cingulate gyrus and premotor cortex, as found in the present study, lend support to the hypothesis that deficits of auto-activation processing could be responsible for apathy in PD.

4.6.5 GENERAL DISCUSSION

The behavioural results (experiment 5) lend support to the present imaging findings of greater grey and white matter atrophy particularly in the frontal lobe and the anterior cingulate cortex in patients with apathy. For instance, the significant difference between patients with and without apathy on the Stroop Test can be explained by structural atrophy in the anterior cingulate cortex, since this brain area is found to be activated during the Stroop Test (Ravnkilde, et al., 2002). Moreover, the impairment of executive function found in the present study may reflect neuroanatomical atrophy in the frontal lobe regions. Therefore, these findings suggest that patients with PD who have apathy may have executive dysfunction as they show damage to the corresponding structural regions.

Grey matter loss in the inferior parietal gyrus was also observed in apathetic patients with PD (Reijnders, et al., 2010). This structural loss has also been linked to executive dysfunction in PD (Matsui et al., 2006). It has been suggested that the parietal lobe plays a crucial role in incorporating information from different senses and processes (Reijnders, et al., 2010). Kjaer et al (2002) hypothesised that the

inferior parietal gyrus, the precuneus and the anterior cingulate gyrus constitute a functional network of reflective self-awareness. These findings therefore imply that executive dysfunction in patients with PD with apathy may reflect damage not only in the frontal lobe but also in the parietal lobe with the consequent disruption of associated functions and cognitive processing.

Interestingly, the present study also identified grey matter loss in the left cerebellum. This result supports a recent PET study which demonstrated negative correlations between apathy and cerebral metabolism in the bilateral cerebellum in patients with PD (Robert, et al., 2012). There is some evidence indicating the role of the cerebellum in cognition and emotion with some clinical case reports having demonstrated that cerebellar lesions are responsible for a range of behavioural abnormalities (such as apathy), emotional dysregulation and executive dysfunction (Schmahmann, Weilburg, & Sherman, 2007), all relevant for apathy. These observations are supported by the existence of structural connections between the cerebellum and the prefrontal cortex via the thalamus (Middleton & Strick, 1994). The current findings seem to support this view, suggesting that an overall disruption of a cerebellum/frontal network of structures may be a relevant prerequisite for the presence of apathy and executive dysfunction in PD.

4.7 EXPERIMENT 7 – COGNITIVE CORRELATES OF DEPRESSION AND APATHY IN PD

4.7.1 INTRODUCTION

Although depression and apathy may occur independently in PD, several studies have reported that they may be present at the same time (Aarsland, et al., 1999; Cubo, et al., 2012; Dujardin, et al., 2007; Kirsch-Darrow, et al., 2006; Oguru, et al., 2010; Pedersen, Larsen, et al., 2009; Santangelo, Vitale, Trojano, Longo, et al., 2009; Starkstein, Mayberg, Preziosi, et al., 1992). However, most of the previous studies reported only on the prevalence of both depression and apathy in patients with PD (which ranged from 11% to 43%) (Dujardin, et al., 2007; Kirsch-Darrow, et al., 2006; Levy, 1998; Oguru, et al., 2010; Pedersen, Larsen, et al., 2009; Starkstein, Mayberg, Preziosi, et al., 1992; Ziropadja, Stefanova, Petrovic, Stojkovic, & Kostic, 2012). Another study found that depression and apathy together occurred in 36.9% of patients with PD (133 out of 360) and that both symptoms were associated with age, duration of disease and severity of motor symptoms (Ziropadja, et al., 2012). Similar findings were reported in a large study in which the two symptoms occurred together in 38.6% (215 out of 557) of non-demented patients with PD. Both neuropsychiatric symptoms were associated with severe motor symptoms and increased comorbidity (Cubo, et al., 2012), with another study reporting that in PD, depression and apathy were associated with poor quality of life (Oguru, et al., 2010).

Depression in elderly people has been associated with both apathy and cognitive deficits (Feil, Razani, Boone, & Lesser, 2003). Feil and colleagues (2003) investigated apathy and cognitive abilities in 89 non-demented elderly individuals with depression using MMSE (Folstein, et al., 1975), DSM-III-R (American

Psychiatric association, 1980), HRSD (Hamilton, 1960), 4-item apathy subscale of the HRSD (Hamilton, 1960), and a range of neuropsychological tests assessing executive abilities, information processing speed, language skills, verbal and non-verbal memory, attention and constructional skills. It was found that both depression and apathy were significantly correlated with performance on the Stroop test (part A and B) (Feil, et al., 2003). However, Marin and colleagues (2003) investigated apathy and executive function in elderly people with depression using the MMSE (Folstein, et al., 1975), the Dementia Rating Scale (Mattis, 1988), the HRSD (Hamilton, 1960), the 4-item apathy subscale of the HRSD (Hamilton, 1960), the Executive Interview and the Controlled Oral Word Association Test (Benton, 1968) and found that all participants (there were 52 participants (mean MMSE score = 27.1 range from 18 to 30)) performed within the normal range on cognitive tasks. In addition, depression and apathy measures were not correlated with performance on any of the cognitive measures (Marin, Butters, Mulsant, Pollock, & Reynolds, 2003).

To my knowledge only two studies have investigated the cognitive abilities of patients with PD who manifest both depression and apathy (Santangelo, Vitale, Trojano, Longo, et al., 2009; Starkstein, Mayberg, Preziosi, et al., 1992). Starkstein and others (1992) studied the clinical and cognitive correlates of apathy and the dissociation between apathy and depression in 50 non-demented patients (15 of which had both depression and apathy) using the DSM-III (American Psychiatric association, 1980), HRSD (Hamilton, 1960), Marin's Apathy Scale (Marin, et al., 1991), and a range of neuropsychological tests assessing global cognitive abilities, executive functions, attention and short-term memory. They found that patients with PD with both depression and apathy had significantly lower scores on the Controlled Oral Word Association Test and on the Trial Making Test (part B) compared with

patients with PD without these symptoms (Starkstein, Mayberg, Preziosi, et al., 1992). Another recent study investigated the relationship between depression and cognitive dysfunctions in patients with PD without dementia. There were 65 patients with PD with a major depressive disorder, 11 of these having both depression and apathy, and also, 60 patients with PD without depression and apathy. Depression was assessed by the DSM-IV (American Psychiatric Association, 2000) and the HRSD (Hamilton, 1960); apathy was measured by the Apathy Evaluation Scale (Marin, et al., 1991). It was found that patients with both depression and apathy performed significantly worse on the Frontal Assessment Battery, Semantic Fluency Test, Phonological Fluency Test and on a Copying Task when compared with those patients without depression and apathy. Also, patients with apathy performed significantly worse on the Phonological Fluency and Copying Tasks compared with patients with PD with depression. However, there was no significant difference between patients with PD with both depression and apathy and those without on the MMSE scores (Santangelo, Vitale, Trojano, Longo, et al., 2009). Furthermore, patients with AD with both neuropsychiatric symptoms have shown similar executive dysfunction (Nakaaki et al., 2008).

The two studies that suggested the association between cognitive function and both apathy and depression in PD mainly focused on each symptom separately looking at the clinical and cognitive correlates of apathy (Starkstein, Mayberg, Preziosi, et al., 1992) and at the cognitive profile of patients with depression (Santangelo, Vitale, Trojano, Longo, et al., 2009). However, little is known about the cognitive profile of patients who show both neuropsychiatric symptoms together. Thus, the aim of the present study was to obtain a detailed cognitive profile of patients with PD who have both depression and apathy in a sample of non-demented

patients with PD who had had extensive neuropsychological testing. It can be predicted that patients with depression and apathy may have more cognitive impairments than patients without any neuropsychiatric symptoms, particularly in executive functioning.

4.7.2 METHOD

4.3.2.1 SAMPLE

Thirty nine Patients with idiopathic PD (19 male and 20 female) participated in this study. The patients were retrospectively recruited from those identified at a Parkinson outpatient clinic. The patients had been diagnosed based on the UK PD Brain Bank Criteria (Hughes, et al., 1992). All patients had extensive neuropsychological screening, neuropsychiatric assessment using the NPI, structural MRI scanning and neurological examination. All patients were in the mild to mild-moderate disease stage, according to the Hoehn and Yahr staging (Hoehn & Yahr, 1967). None of the patients had a history of psychiatric disorders and the neuropsychiatric symptoms started after the onset of PD. All patients were treated with a combination of levodopa and variable doses of dopamine agonists but none were treated with antidepressants. The mean age of the all sample was 69.38 years (SD= 8.57, range 48-83), their mean education was 10.94 years (SD= 0.51 range 5-18), their mean disease duration was 8.4 years (SD= 5.88) and their mean MMSE score was 28 (SD= 1.78 range 24- 30). The patient sample was divided into two subgroups according to their NPI score for depression and apathy, 22 (56%) patients had both depression and apathy and 17 (44%) patients had no neuropsychiatric symptoms (see figure 4.31).

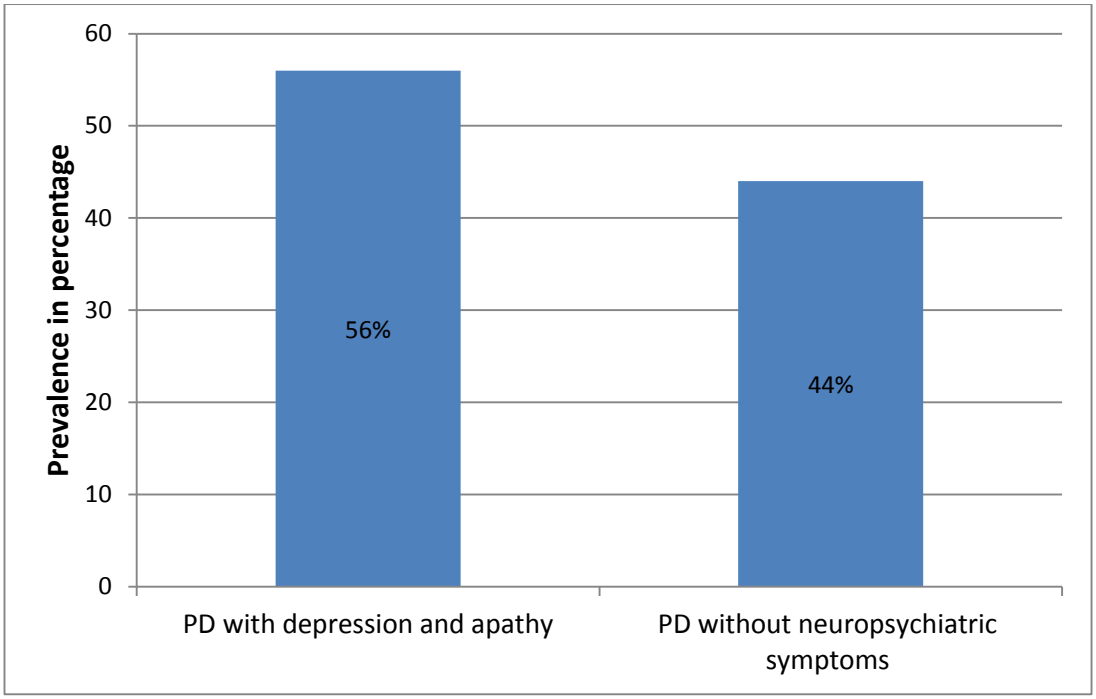

Fig 4.31 Percentage of patients with PD having both depression and apathy and of patients with PD without any neuropsychiatric symptoms

The mean age of the subgroup with depression and apathy was 69.50 years (SD= 9.28, range 49-83), their mean education was 10.00 years (SD= 4.97 range 5-18), their mean disease duration was 7.77 years (SD= 6.8) and their mean MMSE score was 27.5 (SD= 1.99 range 24- 30). The mean age of the subgroup without neuropsychiatric symptoms was 69.24 years (SD= 7.84, range 48-80), their mean education was 10.24 years (SD= 5.7 range 5-18), their mean disease duration was 7.24 years (SD= 5.3) and their mean MMSE score was 28.7 (SD= 1.2 range 27- 30).

4.7.2.2 ASSESSMENTS OF DEPRESSION AND APATHY

Depression and apathy had been assessed using the NPI (Cummings, et al., 1994), and the DSM-IV- TR (American Psychiatric Association, 2000). Each patient and their caregiver had an interview with an experienced psychologist who also completed the NPI. The NPI assesses the presence or absence, severity and frequency of 14 symptom fields. The depression and apathy scores from the NPI were then entered into statistical analyses.

4.7.2.3 NEUROPSYCHOLOGICAL ASSESSMENTS

This study used the same neuropsychological assessments as described in chapter 4, section 4.1.2.3, pages 79-83.

4.7.2.4 STATISTICAL ANALYSES

An independent T-test and a series of independent T-tests were carried out to compare the demographic data and neuropsychological tests of the two subgroups with and without depression and apathy. To account for multiple comparisons, this study set significance level at $p < 0.004$ for all between group comparisons. For group comparisons of demographical data, the significance level was set at a $p < 0.01$.

4.7.3 RESULTS

4.7.3.1 DEMOGRAPHICAL AND MENTAL STATE SCREENING DATA ANALYSES

Independent T-tests were carried out to compare the subgroup with PD with both depression and apathy and that without neuropsychiatric symptoms. There were no significant differences between the two subgroups of patients in age $t(37) = -0.094$, $p > .01$, education $t(37) = 0.138$, $p > .01$, duration of disease $t(37) = -0.268$, $p > .01$. No significant difference was also found between the two subgroup's mean MMSE scores $t(37) = 2.300$, $p > .01$ (see Table 4.37).

Table 4.37 Mean (SD) Age, Education, Duration of disease and MMSE of patients with PD with both depression and apathy and patients with PD without any neuropsychiatric symptoms (NPSS)

	PD with depression and apathy (N = 22)	**PD without NPSS (N = 17)**	***P***
Age	69.50 (9.28)	69.24 (7.84)	.925
Education	10.00 (4.97)	10.24 (5.65)	.891
Duration of disease	7.77 (6.85)	7.24 (5.25)	.790
MMSE	27.45 (1.99)	28.7 (1.16)	.027

4.7.3.2 COGNITIVE PROFILE OF PD PATIENTS WITH AND WITHOUT DEPRESSION AND APATHY

Independent T-tests were also carried out to compare the cognitive performance of patients with PD with depression and apathy with that of patients without any neuropsychiatric symptoms in the neuropsychological tests. Patients with PD with both depression and apathy had lower scores than those without neuropsychiatric symptoms in the Letter Fluency Test $t(37) = 3.34$, $p < .004$. However, there was no significant difference between the two patient subgroups in any of the other neuropsychological tests i.e. Raven's Progressive Matrices $t(37) = 2.24$, $p > .004$, Stroop Test (time) $t(37) = 1.11$, $p > .004$, Stroop Test (error) $t(37) = -1.95$, $p > .004$, TMT $t(37) = 1.65$, $p > .004$, Category Fluency Test $t(37) = 2.53$, $p > .004$ Similarities Test $t(37) = 1.61$, $p > .004$, Rey Complex Figure (copy) $t(37) = 1.95$, $p > .004$, Rey Complex Figure (delayed) $t(37) = 1.60$, $p > .004$, Frontal Assessment Battery $t(37) = -.53$, $p > .004$, Digit Span (forward) $t(37) = -.81$, $p > .004$, Digit Span (backward) $t(37) = -.73$, $p < .004$, Visual-spatial span $t(37) = -1.16$, $p > .004$ and Rey 15-word Memory Test $t(37) = -.19$, $p > .004$ (see table 4.38).

4.7.4 DISCUSSION

The present study showed a higher prevalence of both symptoms (56%) when compared with prior findings of lower prevalence of both depression and apathy (Dujardin, et al., 2007; Kirsch-Darrow, et al., 2006; Levy, 1998; Oguru, et al., 2010; Pedersen, Larsen, et al., 2009; Starkstein, Mayberg, Preziosi, et al., 1992; Ziropadja, et al., 2012). This may be explained by the use of a different scale to assess depression and apathy. A further reason could be that some of those studies involved patients who had been treated with antidepressants, resulting in an inaccurate reflection of the true prevalence of both symptoms. The high prevalence of both

depression and apathy in the patient sample in this study suggests that they are core features of PD.

Table 4.38 Mean (SD) on the neuropsychological tests scores and *P* value for the two subgroups of patients with PD with both depression and apathy and without any neuropsychiatric symptoms (NPSS).

	PD with depression and apathy (N = 22)	**PD without NPSS (N = 17)**	***p***
Raven's Progressive Matrices	20.09 (14.31)	29.12 (9.66)	.032
Stroop test			
Time interference effect	26.28 (23.03)	33.79 (18.07)	.276
Error interference effect	3.39 (4.92)	.97 (1.53)	.059
Trail Making Test	35.55 (48.28)	65.24 (63.95)	.107
Letter Fluency Test	**25.32 (8.99)**	**37.65 (14.01)**	**.002***
Category Fluency Test	28.00 (11.05)	36.71 (10.17)	.016
Similarities Test	13.64 (6.60)	16.59 (4.12)	.115
Rey Complex Figure			
Direct copy	22.84 (9.90)	28.79 (8.85)	.059
Delayed copy	10.09 (6.06)	13.33 (6.52)	.118
Digit Span			
Forward	3.41 (3.07)	2.59 (3.26)	.425
Backward	2.18 (1.92)	1.71 (2.17)	.473
Frontal Assessment Battery	8.14 (7.19)	6.82 (8.42)	.603
Visual-spatial span	2.55 (2.32)	1.65 (2.47)	.252
Rey 15-word Memory Test	4.85 (1.23)	7.09 (2.28)	.098

*Significant difference between PD with both depression and apathy and PD without any neuropsychiatric symptoms $P < 0.004$ (corrected for multiple comparison)

Consistent with previous findings (Santangelo, Vitale, Trojano, Longo, et al., 2009; Starkstein, Mayberg, Preziosi, et al., 1992), the present study found no significant difference in MMSE scores between the two patients' subgroups. However, a recent study reported that patients with PD with both depression and apathy had significantly lower scores on the MMSE compared with patients with PD without those symptoms (Ziropadja, et al., 2012). The difference in findings between this study and the present study may be explained by the inclusion of patients at the more severe stages of the disease by Ziropadja et al. (2012). Several studies have indicated that cognitive impairment is greater with the progression of PD (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Braak, Rub, Jansen Steur, Del Tredici, & de Vos, 2005; Stepkina, Zakharov, & Yakhno, 2010), therefore, our

results could suggest that in early PD, both depression and apathy have a marginal influence on the global level of cognitive functioning.

The main finding of this study indicates that patients with both depression and apathy performed significantly lower than those without neuropsychiatric symptoms on the letter fluency test. This finding suggests that both depression and apathy may be associated with deficits in a specific cognitive domain (executive functioning) in early PD. This result is also in line with the finding of two earlier studies (Santangelo, Vitale, Trojano, Longo, et al., 2009; Starkstein, Mayberg, Preziosi, et al., 1992). The impairment in generating words has been associated with frontal lobe dysfunction (Lezak, et al., 2004); and neuroimaging studies have also found an association between frontal lobe atrophy and depression in PD (Feldmann, et al., 2008; Kostic, et al., 2010; Matsui, et al., 2007; Ring, et al., 1994; Skidmore, et al., 2011) and in patients with PD with apathy (Le Jeune, et al., 2009; Reijnders, et al., 2010; Skidmore, et al., 2011). This evidence can explain the difference between the two groups in the present study. Furthermore, executive dysfunction has been found in patients with AD who developed both depression and apathy (Nakaaki, et al., 2008). No additional significant differences were detected by other neuropsychological tests in the battery.

Santangelo et al., (2009) and Starkstein et al., (1992) found more cognitive impairments than in the present study in their assessment of cognitive functions in patients with PD with depression and apathy. One reason for this difference could be that these studies did not correct for multiple comparisons or for paired correlations in their analysis. Another reason might be their use of a different methodology and an alternative assessment of neuropsychiatric symptoms. Additionally, previous studies did not clarify whether the subgroups of patients with PD without depression

and apathy had no other neuropsychiatric symptoms such as, hallucinations and anxiety. Several studies have found hallucinations and anxiety to be common neuropsychiatric symptoms in PD (Aarsland, et al., 2007; Aarsland, Marsh, et al., 2009; Marsh, & Berk, 2003; Schneider, et al., 2008; Thanvi, et al., 2003; Weintraub, et al., 2008b) and it cannot be ruled out that these symptoms might have been present in the other studies thus influencing cognitive performance and perhaps acting as confounding variables.

4.8 EXPERIMENT 8 – NEUROANATOMICAL CORRELATES OF DEPRESSION AND APATHY IN PD

4.8.1 INTRODUCTION

Previous studies of depression in PD have found that depression is associated with grey and white matter loss in the frontal lobe, particularly, in the orbito-frontal cortex (Feldmann, et al., 2008; Kostic, et al., 2010). Previous studies of apathy in PD have shown that apathy is associated with dysfunctions in the frontal and cingulate cortex (Le Jeune, et al., 2009; Reijnders, et al., 2010). To my knowledge, in the literature the neural correlates of both depression and apathy in patients with PD have not been explored. There are only two imaging studies that have investigated the neuroanatomical correlates of both depression and apathy in AD and in psychiatric populations. Starkstein and colleagues (2009) investigated the association between structural brain changes and the two neuropsychiatric symptoms by using MRI scans, DSM-IV (American Psychiatric Association, 2000) and HRSD (Hamilton, 1960) to assess depression and a 14-item scale to rate apathy. Seventy nine patients with mild to moderate AD participated in this study (40 patients without depression and apathy, 15 patients with only depression, 14 patients with only apathy and 10 patients with both depression and apathy). It was found that patients with only depression had a significantly greater number of right parietal white matter hyperintensities than patients without depression. However, patients with apathy (with or without depression) had a significantly greater number of frontal white matter hyperintensities than patients without apathy. Patients with both depression and apathy had a greater number of white matter hyperintensities in the right parietal lobe compared with other groups. The grey matter and white matter analyses showed no significant differences between the four groups (Starkstein, et

al., 2009). In addition, in the psychiatric literature there is a study which has investigated the neuroanatomical correlates of apathy in 84 older participants with and without major depression (43 patients with depression and 41 normal controls). All participants underwent neuropsychiatric examination, physical examination and an MRI brain scan. Depression was assessed using the DSM-IV (American Psychiatric Association, 2000) and HRSD (Hamilton, 1960) and the Apathy Evaluation Scale (Marin, et al., 1991) was used to assess apathy. The depressed patients had a significantly greater severity of apathy when compared with normal controls. Apathy in elderly depressed participants was significantly associated with grey matter loss in the bilateral orbitofrontal cortex compared with the normal controls. In addition, although the depressed group had more white matter reduction in the left orbitofrontal cortex compared with normal controls, the difference was not significant after adjustment for multiple comparisons (Lavretsky, et al., 2007).

The present study is the first to explore the underlying neuroanatomical damage of both depression and apathy in a sample of patients with PD whose overall cognitive profile was still broadly intact. All patients had mild PD, according to Hoehn and Yahr stages (1967). The NPI was used to assess depression and apathy and SPM8 software was used for group comparison analysis (all patients with PD versus healthy control, PD with depression and apathy versus healthy control, PD without any neuropsychiatric symptoms versus healthy control, and PD with depression and apathy versus PD without any neuropsychiatric symptoms) of 3-dimensional structural MRI scans of the brains of patients with PD and healthy controls. This study was designed to explore grey and white matter deficits which may underlie the occurrence of both neuropsychiatric symptoms in PD.

From previous studies, it can be predicted that patients with PD with depression and apathy may show grey and white matter loss in the frontal lobe and cingulate cortex when compared with patients with PD without any neuropsychiatric symptoms or healthy controls.

4.8.2 METHOD

4.8.2.1 SAMPLE

Thirty seven patients with idiopathic PD (18 male and 19 female) participated in this study. These patients were part of the sample who had taken part in the behavioural study of both depression and apathy. The mean age of all PD patients was 68.0 years (SD= 8.25, range 48-80), their mean education was 11.2 years (SD= 4.67 range 5-18), their mean disease duration was 8.70 years (SD= 5.31) and their mean Mini-Mental State Examination (MMSE) score was 27.95 (SD= 1.72 range 24- 30). The patient sample was divided into two subgroups according to their NPI score for depression and apathy, 15 patients with both depression and apathy and 22 patients without any neuropsychiatric symptoms. The mean age of the patients with both depression and apathy was 70.73 years (SD= 7.73, range 49-80), their mean education was 11.2 years (SD= 4.78 range 5-18), their mean disease duration was 9.87 years (SD= 6.32) and their mean MMSE score was 27.13 (SD= 1.9 range 24- 30). The mean age of patients without any neuropsychiatric symptoms was 66.14 years (SD= 8.5, range 48-80), their mean education was 11.2 years (SD= 4.7 range 5-18), their mean disease duration was 7.9 years (SD= 4.5) and their mean MMSE score was 28.2 (SD= 1.3 range 26- 30). In addition, this imaging study used the same healthy controls who had been involved in the imaging study of depression (see section, 4.4.2.1, page 131).

4.8.2.2 STRUCTURAL MRI SCANNING: ACQUISITION AND ANALYSIS

The acquisition and analysis of structural MRI scanning have already been described in the imaging study of neuropsychiatric symptoms (chapter 4, section 4.2.2.2, pages 99-100). The x, y, z coordinates of significant areas obtained from the analyses were first converted into Talairach coordinates using the mni2tal Matlab routine and then identified using the Talairach Daemon Client (http://www.talairach.org/). Unless otherwise stated a cluster corrected height threshold of $p < 0.001$ was used in all analyses.

4.8.3 RESULTS

4.8.3.1 DEMOGRAPHICAL AND MENTAL STATE SCREENING DATA ANALYSES

Univariate analyses of variance were carried out to compare the three groups (PD with both depression and apathy, PD without any neuropsychiatric symptoms and healthy controls) in age, education, MMSE and disease duration for patients groups. The controls and subgroups of patients with PD showed no significant difference in age [$F(2, 60) = 2.64$, $P > .01$] or education [$F(2, 60) = .28$, $P > .01$], but there was a significant difference in MMSE [$F(2,60) = 25.46$, $p = .000$]. Post hoc (Bonferroni) comparisons showed that there was no significant difference between PD with both depression and apathy and PD without any neuropsychiatric symptoms in MMSE but there was a significant difference between controls and each of the two groups of patients. Also, the two groups of patients with PD did not differ for duration of disease [$F(1, 36) = 2.2$, $P > .01$] (Table 4.39).

Table 4.39 Mean (SD) Age, Education, Duration of disease and MMSE of patients with PD with depression and apathy, patients with PD without any neuropsychiatric symptoms (NPSS), and controls

	PD with depression and apathy (N = 15)	**PD without NPSS (N = 22)**	**Controls (N = 24)**	***P***
Age	70.73 (7.73)	66.1 (8.5)	62.79 (9.77)	.080
Education	11.2 (4.78)	11.2 (4.7)	12.21 (5.49)	.756
Duration of disease	9.87 (6.32)	7.9 (4.5)	__	.277
MMSE	27.13 (1.9)	28.2 (1.4)	30.00 (.000)	.000*

*Significant difference between controls and the two groups of patients (Using Bonferroni Post-hoc test)

4.8.3.2 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF GREY MATTER

All patients with PD versus controls: when compared with healthy controls, patients had significantly less grey matter volume in the right postcentral gyrus, the right supramarginal gyrus, right inferior parietal lobule, right medial frontal gyrus and left anterior cingulate. Significant differences were detected at $p < 0.01$ (Table 4.40 and Figure 4.32).

Table 4.40 Areas of significant grey matter volume value differences between patients with PD and controls

Brain areas	**R/L**	**BA**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
						X	**Y**	**Z**
Postcentral gyrus	R	2	2755	0.000	4.25	51	-27	38
Supramarginal gyrus	R	40			4.19	48	-43	33
Inferior parietal lobule	R	40			3.91	50	-43	43
Medial frontal gyrus	R	10	2028	0.002	3.69	2	52	-3
	R	10			3.46	4	51	12
Anterior cingulate	L	24			3.28	-2	33	0

R = Right L = Left BA = Brodmann Area

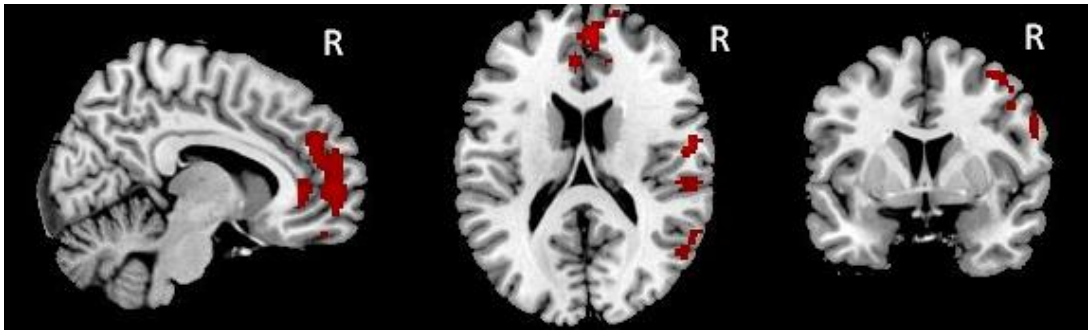

Fig 4.32 Areas of significantly less grey matter volume values in all patients with PD when compared with healthy controls

Patients with PD with depression and apathy versus controls: patients with both neuropsychiatric symptoms had significantly less grey matter volume in the right superior temporal gyrus, the right middle temporal gyrus, right inferior parietal lobule, right medial frontal gyrus, left anterior cingulate, left cuneus and left inferior occipital gyrus when compared with healthy controls (Table 4.41 and Figure 4.33).

Table 4.41 Areas of significant grey matter volume value differences between patients with PD with depression and apathy and controls

Brain areas	**R/L**	**BA**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
						X	**Y**	**Z**
Superior temporal gyrus	R	39	1457	0.000	4.61	55	-57	19
Middle temporal gyrus	R	21			4.09	65	-35	-10
Inferior parietal lobule	R	40			3.97	40	-36	48
Medial frontal gyrus	R	9	1140	0.000	4.42	4	47	14
	R	10			4.05	2	52	-1
Anterior cingulate	L	32			3.92	-4	38	18
Cuneus	L	18	394	0.012	4.06	-18	-99	-0
Inferior occipital gyrus	L	18			4.00	-32	-90	-4
Cuneus	L	17			3.81	-6	-93	3

R = Right L = Left BA = Brodmann Area

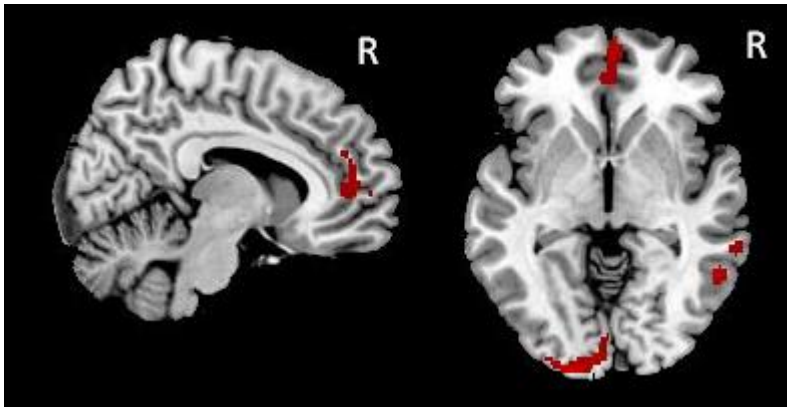

Fig 4.33 Areas of significantly less grey matter volume values in patients with PD with depression and apathy when compared with healthy controls

Patients with PD without any neuropsychiatric symptoms versus controls: patients without neuropsychiatric symptoms had less grey matter volume in the left inferior frontal gyrus and the left middle frontal gyrus when compared with healthy controls (Table 4.42 and Figure 4.34).

Table 4.42 Areas of significant grey matter volume value differences between patients with PD without any neuropsychiatric symptoms and healthy controls.

Brain areas	**R/L**	**BA**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
						X	**Y**	**Z**
Inferior frontal gyrus	L	9	56	0.001	5.28	-51	5	26
Middle frontal gyrus	L	10	71	0.002	4.63	-36	45	5

R = Right L = Left BA = Brodmann Area

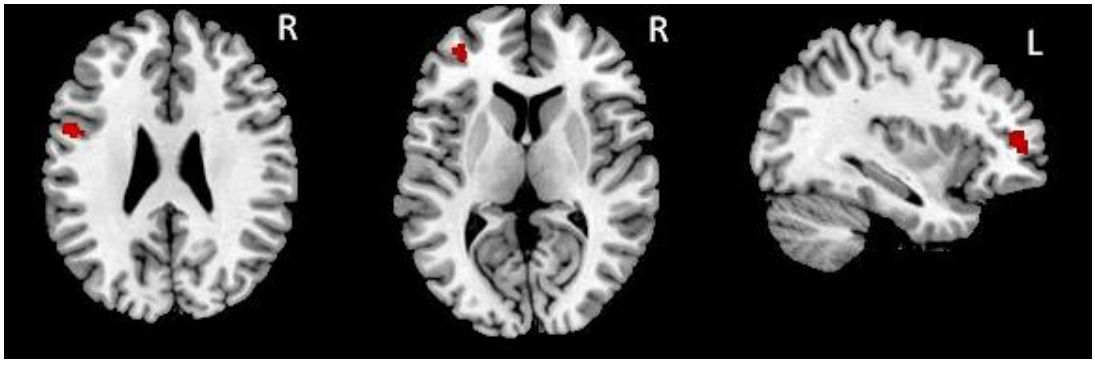

Fig 4.34 Areas of significantly less grey matter volume values in left inferior frontal gyrus and middle frontal gyrus in patients with PD without any neuropsychiatric symptoms when compared with healthy controls

Patients with PD with depression and apathy versus patients with PD without any neuropsychiatric symptoms: there was no significant difference between patients with both depression and apathy and those without any neuropsychiatric symptoms

at the corrected cluster level. However, at the uncorrected cluster level ($p < 0.05$) grey matter volume differences between the two patients subgroups were detected in several brain areas including the left anterior cingulate gyrus, left medial frontal gyrus, right parahippocampal gyrus, right fusiform gyrus, right cerebellum (posterior lobe), right middle occipital gyrus, left inferior parietal lobule, left superior parietal lobule, left superior frontal gyrus, left middle frontal gyrus, left cuneus and right posterior cingulate (Table 4.43 and Figure 4.35).

Table 4.43 Areas of significant grey matter volume value differences between patients with PD with depression and apathy compared with patients with PD without any neuropsychiatric symptoms

Brain areas	**R/L**	**BA**	**Cluster Size**	**Cluster-level *P*-value (uncorrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
						X	**Y**	**Z**
Anterior cingulate gyrus	L	32	3356	0.002	3.22	-2	34	26
Medial frontal gyrus	L	6			3.10	-8	27	35
Parahippocampal gyrus	R	34			2.96	24	3	-15
Fusiform gyrus	R	37	1689	0.018	3.18	36	-49	-8
Cerebellum posterior lobe	R	-			2.88	48	-69	-30
Middle occipital gyrus	R	18			2.84	26	-92	18
Inferior parietal lobule	L	40	1133	0.046	3.15	-32	-54	45
Superior parietal lobule	L	7			2.71	-20	-51	60
Inferior parietal lobule	L	40			2.66	-42	-37	44
Superior frontal gyrus	L	8	1637	0.020	2.93	-18	35	46
Middle frontal gyrus	L	10			2.92	-32	46	25
	L	46			2.87	-46	38	15
Cuneus	L	17	1616	0.020	2.69	-2	-81	10
	L	18			2.62	-2	-93	5
Posterior cingulate	R	30			2.32	20	-59	16

R = Right L = Left BA = Brodmann Area

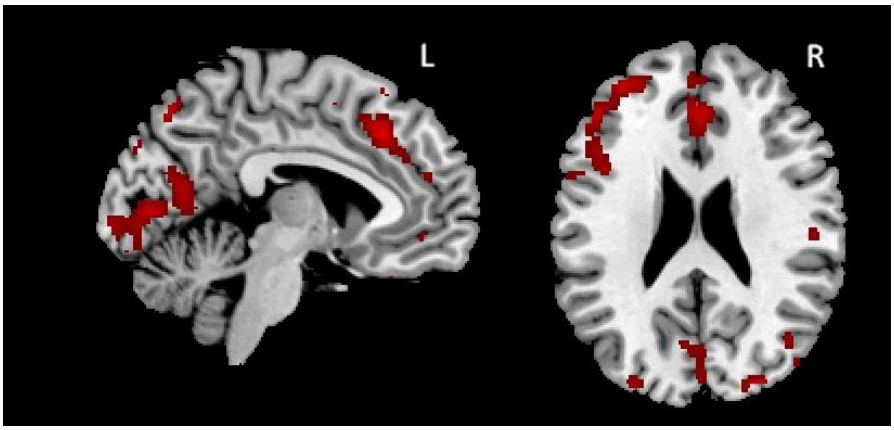

Fig 4.35 Areas of significantly less grey matter volume values in patients with PD with depression and apathy when compared with patients with PD without any neuropsychiatric symptoms

4.8.3.3 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF WHITE MATTER

All patients with PD versus controls: there was no significant difference when the white matter of the whole group with PD (with and without neuropsychiatric symptoms) was compared with that of the healthy controls at both corrected and uncorrected cluster levels.

Patients with PD with depression and apathy versus controls: there was a significant difference in white matter volume between patients with both neuropsychiatric symptoms and healthy controls. Patients with depression and apathy had less white matter volume in the right superior frontal gyrus when compared with controls. Significant difference was found at $p < 0.01$ (Table 4.44 and Figure 4.36).

Table 4.44 Areas of significant white matter volume value differences between patients with PD with both neuropsychiatric symptoms (depression and apathy) and controls.

Brain areas	**R/L**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
					X	**Y**	**Z**
Superior frontal gyrus	R	75	0.027	3.09	26	45	3

R = Right L = Left

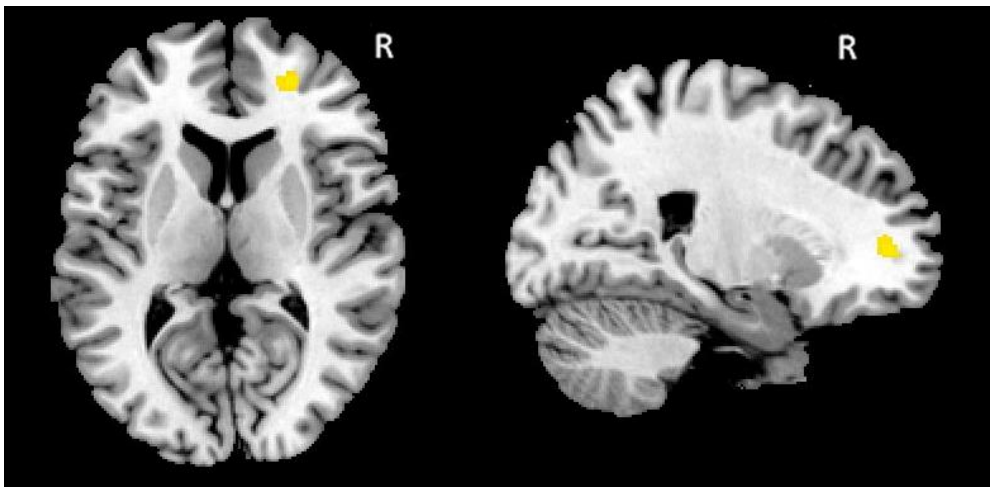

Fig 4.36 Significant less white matter volume values in the right superior frontal gyrus in patients with PD with depression and apathy when compared with healthy controls

Patients with PD without any neuropsychiatric symptoms versus controls: There was no significant difference between patients without any neuropsychiatric symptoms and controls at the corrected cluster level. However, at the uncorrected cluster level patients without neuropsychiatric symptoms had significantly less white matter volume values than controls in the right medial frontal gyrus, left precentral gyrus, left middle frontal gyrus and left anterior cingulate (Table 4.45 and Figure 4.37).

Table 4.45 Areas of significant white matter volume value differences between patients with PD without any neuropsychiatric symptoms and controls.

Brain areas	**R/L**	**Cluster Size**	**Cluster-level *P*-value (uncorrected)**	**Z value at Local Maximum**	**Talairach coordinates**		
					X	**Y**	**Z**
Medial frontal gyrus	R	396	0.000	4.34	20	47	9
Frontal lobe (sub-gyral)	R			3.37	26	28	12
	R			3.32	18	33	-7
Precentral gyrus	L	143	0.017	4.19	-32	-15	43
Middle frontal gyrus	L	110	0.032	3.54	-28	21	28
Frontal lobe (sub-gyral)	L			3.34	-26	34	11
Anterior cingulate	L			3.25	-20	43	3

R = Right L = Left

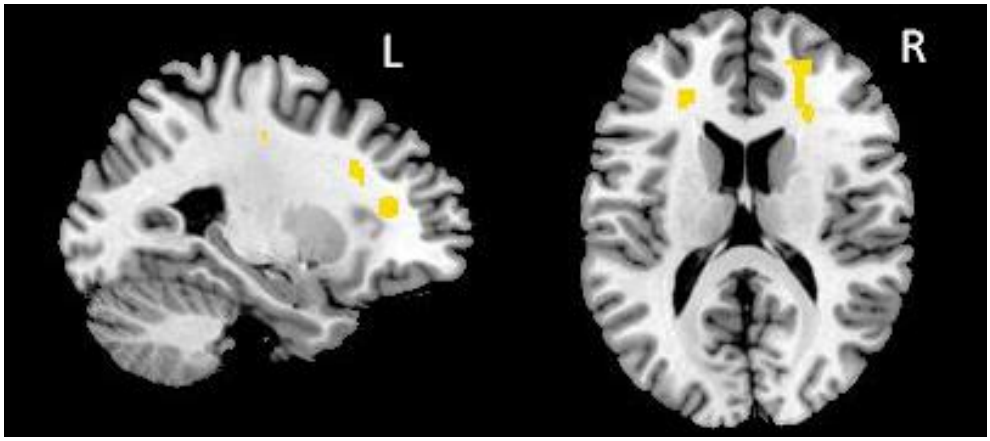

Fig 4.37 Areas of significantly less white matter volume values in patients with PD without any neuropsychiatric symptoms when compared with healthy controls

Patients with PD with depression and apathy versus patients with PD without any neuropsychiatric symptoms: There was no significant difference in white matter

volume values between patients with both depression and apathy and those without any neuropsychiatric symptoms.

4.8.4 DISCUSSION

In this experiment, patients with both depression and apathy showed grey and white matter loss in the frontal lobe which is in line with earlier findings in psychiatric population (Lavretsky, et al., 2007). Further grey matter reductions were identified in structural brain areas including the parietal, temporal lobe, the anterior cingulate cortex. These findings suggest that the underlying neuropathology of both depression and apathy may be better explained by atrophy in cortical brain regions than sub-cortical areas.

The present study showed more brain atrophy in patients with both depression and apathy compared with the earlier report that examined these symptoms in psychiatric population (Lavretsky, et al., 2007). However, Starkstien et al (2009) did not find significant differences between patients with AD with both depression and apathy when compared with those without such symptoms. The difference in findings between the previous studies and the current study may be due to the use of a more refined and homogenous method of segmentation routine in the imaging analyses software (SPM8 in the current study) and in the use of a different scale to assess depression and apathy.

4.8.5 GENERAL DISCUSSION

This study is the first to have explored the cognitive and neuroanatomical correlates of both depression and apathy in patients with PD. The behavioural results showed that patients with both depression and apathy had lower scores than those patients without any neuropsychiatric symptoms on almost all neuropsychological

tests; however significant differences were found on the letter fluency test which is designed to assess executive functions. These behavioural results are supported by the present imaging findings of greater grey and white matter atrophy in frontal cortex. Troyer et al (1998) demonstrated that patients with frontal lobe damage displayed impaired phonemic fluency which has been shown to activate the frontal lobe and anterior cingulate cortex in healthy participants (Ravnkilde, et al., 2002). The latter results may explain the involvement of grey matter loss in the anterior cingulate gyrus in the present study. This area is responsible for the selection of the words which is required when performing the letter fluency task.

Van den et al (2009) reported structural connections between two regions of the parietal-frontal networks, particularly, between the superior parietal and middle/superior frontal regions in both hemispheres. The findings of the present study showed brain atrophy in the same brain regions but mainly in the left hemisphere. Therefore our findings may suggest that dysfunction in parietal-frontal networks may play an important role for the occurrence of both depression and apathy in PD.

According to Braak et al (2004), PD pathology involves deficits in the substantia nigra which is responsible for the production of dopamine. The lack of dopamine neurotransmitter is followed by degeneration of other neurotransmitter systems such as the noradrenergic and serotoninergic brainstem nuclei (Halliday, et al., 1990). Dysfunction of dopaminergic systems also contribute to the presence of neuropsychiatric symptoms (Aarsland, Marsh, et al., 2009; Ring & Serra-Mestres, 2002). For instance, it has been reported that depressed patients with PD showed

dysfunction of a combination of dopaminergic, serotoninergic and noradrenergic pathways in the limbic system (Remy, et al., 2005).

Moreover, the brain regions we identified in this experiment are relevant to those observed in each symptom alone (depression or apathy) in patients with PD. For instance, atrophy in the frontal and temporal lobe, cingulate gyrus and parahippocampal gyrus has been previously reported in patients with PD with depression (Feldmann, et al., 2008). The present study also identified certain brain areas that have previously been observed to be affected in patients with PD with apathy, such as frontal and parietal lobe and cingulate gyrus (Reijnders, et al., 2010). These findings suggest that patients with PD with isolated mood or motivational disorders show differing cortical dysfunction in the early stages of the disease, confirming a different structural basis for the occurrence of depression and apathy in PD.

5. CHAPTER FIVE: COGNITIVE IMPAIRMENT IN PD

5.1 EXPERIMENT 9 – NEUROANATOMICAL CORRELATES OF NEUROPSYCHOLOGICAL PERFORMANCE IN NON-DEMENTED PD

5.1.1 INTRODUCTION

In PD cognitive dysfunctions occur at an early stages and mainly include impairments of executive function, memory, visuospatial and attention (Aarsland, Marsh, et al., 2009; Foltynie, et al., 2004; Muslimovic, et al., 2005; Wu, et al., 2012). Wu and others (2012) explored the prevalence of cognitive impairment in 80 non-demented patients with PD in the early and middle stages of the disease. Results showed that 60% of patients had cognitive impairments. More specifically, 30 (63%) patients had executive dysfunction, 27 (56%) patients had memory deficit, eight (17%) patients had visuospatial impairment and seven (15%) patients had attention deficit (Wu, et al., 2012). Furthermore, patients with PD with cognitive impairments have been found to have a higher risk of developing dementia than patients with PD who are cognitively intact (Janvin, Larsen, Aarsland, & Hugdahl, 2006). Additionally, several studies have reported that older age and duration of disease were associated with cognitive decline in PD (Aarsland, Marsh, et al., 2009; Di Biasio et al., 2012; Muslimovic, et al., 2005). It has been suggested that cognitive impairments in non-demented patients with PD reflect a reduction in function in fronto-striatal circuits (which link the frontal lobe to the basal ganglia), particularly, executive dysfunctions (Lewis, et al., 2003; Monchi, et al., 2004; Owen, 2004; Zgaljardic, et al., 2006). Memory dysfunction in PD has been reported to be secondary to retrieval deficit and has also been linked to fronto-striatal dysfunction (Cooper, et al., 1991). Recently a number of imaging studies have started to explore

the underlying mechanisms of cognitive impairments in PD. Some of those studies examined executive dysfunctions in PD while other studies examined different cognitive domains in order to see if there are other brain regions that may contribute to cognitive deficits in PD.

Neuroimaging techniques, particularly structure MRI, are considered as a useful tool to assess the neuroanatomical correlates of cognitive dysfunctions in PD. Most studies used two methods to examine structural MRI changes in PD, these being volumetric Region of Interest and Voxel-based Morphometry (Ibarretxe-Bilbao, et al., 2011). The following paragraphs will review previous imaging studies that have investigated the anatomical changes related to cognitive impairments in PD including general cognitive abilities, executive function, memory, verbal fluency, visuospatial and visuoperceptual functions and facial emotion recognition.

A small number of imaging studies have explored the correlation between grey matter density and global cognitive abilities in patients with PD. An MRI study investigated the correlation between right and left hippocampal volumes and MMSE scores in 20 patients with PD (10 with dementia and 10 without dementia) using an ROI approach (Camicioli, et al., 2003). A significant correlation was found between MMSE scores and the left, but not right hippocampal volume (Camicioli, et al., 2003). Melzer and colleagues (2012) examined grey matter atrophy and cognitive impairments in 96 patients with PD (57 without cognitive impairments, 23 with mild cognitive impairment and 16 with dementia) and 34 matched controls using a VBM approach. Moreover, 39 of the patients with PD were not on anti-parkinsonian medications. MMSE (Molloy & Standish, 1997) and the Movement Disorders Task Force criteria (Emre et al., 2007) were used to classify patients with PD as either

cognitively normal, with mild cognitive impairment or demented. In addition, this study used a variety of neuropsychological tests to assess the four cognitive domains of executive function, attention, learning and memory, and visuospatial/visuoperceptual function (Dalrymple-Alford, et al., 2011).

Global performance for each patient was expressed by an aggregate z score obtained by averaging the standardised scores within each cognitive domain and then taking the mean of these four domain scores. Correlation between grey matter density and continuous measures of cognition was calculated by using a total z score from an average of four cognitive domain scores. Correlation analyses found a significant correlation between total cognitive z scores in the patients group and grey matter density in the bilateral posterior cingulate, precuneus cortex, superior parietal lobule, lateral occipital cortex, superior middle and inferior frontal gyri, precentral gyri, insula cortex, superior and middle temporal gyri, hippocampi, medial thalamic region and left amygdala. Group comparison analyses showed that when compared with healthy controls, patients with PD without cognitive impairments showed no significant grey matter atrophy. In the patients with PD with mild cognitive impairment, grey matter loss was found in several brain regions including the bilateral precentral and postcentral gyrus, precuneus, superior and middle frontal gyrus, superior lateral occipital cortex, right insula, superior and inferior temporal gyrus, bilateral amygdala, caudal hippocampus and right putamen. Patients with PD with dementia showed similar grey matter atrophy as in those patients with mild cognitive impairment but also grey matter loss emerged in other brain areas including the lingual gyrus, posterior cingulate gyrus, prefrontal cortex, bilateral caudate and parahippocampi (Melzer, et al., 2012). However, another structural MRI study (with 32 non-demented patients) found no correlation between grey matter

density and MMSE scores (Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009). Different findings between the two VBM studies may be explained by the use of a different methodology to assess global cognitive abilities and the Melzer et al study having a larger sample size.

A number of VBM studies have explored the association between grey matter density and executive dysfunction in PD. One such study examined brain atrophy as associated with executive function in 43 non-demented patients (aged 65 and older) and 43 matched healthy controls. Executive functions were assessed using the Stroop Test (Stroop, 1935), (Part B) and the Digit Ordering Test (DOT) (Camicioli, et al., 2009). Behavioural results showed that patients had significantly lower scores on TMT B and the Digit Ordering Test but not on the Stroop Test. However, on the composite executive function assessments, patients had significantly lower scores than healthy controls. In addition, there was a significant correlation between grey matter volume values and the executive function composite measures in the bilateral middle temporal gyrus, the bilateral caudate, the left cerebellum, the left precuneus. No significant correlation was found between white matter values and the executive function composite measures (Camicioli, et al., 2009). Another VBM study investigated the neuroanatomical correlates of decision-making impairment in 24 early non-demented patients with PD and 24 healthy controls (Ibarretxe-Bilbao, et al., 2009). This study performed a Region of Interest analyses with ROIs within the orbitofrontal cortex and the amygdala. Decision-making was assessed by the Iowa Gambling Task (Bechara, et al., 1999). Correlation analyses showed that the total scores on the Iowa Gambling Task correlated with the left orbitofrontal cortex but not with the amygdala. However, group comparison analyses showed that patients had grey matter loss in the right amygdala and bilateral orbitofrontal cortex when

compared with healthy controls (Ibarretxe-Bilbao, et al., 2009). A further VBM study (Nagano-Saito et al., 2005) examined the relationship between grey matter density and cognitive impairment in 38 non-demented patients with PD using the Raven Coloured Progressive Matrices to assess executive and visuospatial abilities (Raven, 1962 as cited in Nagano-Saito, et al., 2005). The results showed that the Raven Coloured Progressive Matrices scores were positively correlated with grey matter density in the right middle frontal gyrus (BA 9), left superior frontal gyrus (BA 10), right parahippocampal/fusiform gyrus (BA 37), left parahippocampal gyrus (BA 28) and right insula (Nagano-Saito, et al., 2005). This study suggested that the Raven Coloured Progressive Matrices can act to measure executive and visuospatial functions. However, the Raven Coloured Progressive Matrices should also be considered as a test of abstract reasoning and/or a measure of general intelligence.

Cognitive dysfunction in non-demented patients with PD is not only limited to executive dysfunction. Memory deficit is common in patients with PD. Some MRI studies have suggested that in PD, memory dysfunction may reflect atrophy of medial temporal lobe (Ibarretxe-Bilbao, et al., 2011). Camicioli et al (2003) reported that in patients with PD, left but not right hippocampal volume loss correlated with verbal memory scores. Another study investigated the extent of medial temporal lobe atrophy on MRI in 33 non-demented patients with PD, 31 patients with PD with dementia and 39 healthy controls using a visual scale (Tam, et al., 2005). Cognitive abilities were assessed using the Cambridge Cognitive Examination (Roth, et al., 1986). The results showed that when compared with controls, both patient groups had a significantly greater hippocampal atrophy in both hemispheres. However, there was no correlation between medial temporal lobe atrophy and cognitive impairment in the two patient groups (Tam, et al., 2005). Bruck et al (2004) examined prefrontal

and hippocampal atrophy in 20 non-demented and non-medicated patients with PD and 22 healthy controls using a visual scale. When compared with healthy controls, patients were found to have atrophy in the bilateral prefrontal and hippocampal regions. In addition, atrophy of the left hippocampus correlated negatively with verbal memory scores as measured by the Wechsler Memory Scale-Revised (Wechsler, 1945). Ibarretxe-Bilbao et al (2008) examined the relationship between hippocampal and grey matter density in 44 patients with PD (Nine patients with dementia, 16 with visual hallucination, and 19 without either dementia or visual hallucination) using a VBM approach. The results indicated that delay recall scores for all patients on the Rey's Auditory Verbal Learning Test correlated with grey matter density in the bilateral head of the hippocampus. Moreover, another VBM study examined the brain atrophy associated with memory in non-demented patients with PD (Camicioli, et al., 2009). In this study, memory was measured by the California Verbal Learning Test (CVLT) (Delis, et al., 2002). The results showed that there was a significant correlation between the CVLT long delay free recall and grey matter volume values in the left middle temporal and left fusiform gyrus, the left uncus, the right temporal lobe and the left putamen. However, there was no significant correlation between white matter values and the memory test scores (Camicioli, et al., 2009).

Although previous imaging studies used different MRI analysis techniques, the results emphasised the role of temporal lobe (particularly the hippocampus) in memory dysfunction in patients with PD. However, some of these studies used ROI methods which limited the exploration of other brain regions that may be relevant to in memory dysfunctions in patients with PD.

Verbal fluency impairment has been observed in patients with PD even in the early stages of the disease (Henry & Crawford, 2004a). Verbal fluency includes phonemic and semantic fluency and it has been reported that semantic but not phonemic fluency is found to be a useful predictor of dementia and cognitive decline in patients with PD (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). A contrasting study reported that both phonemic and semantic fluency were significantly impaired in patients with PD when compared with healthy controls (Obeso, et al., 2012). Phonemic and semantic deficits are considered secondary to dysfunctions of the frontal lobe in patients with PD (Ibarretxe-Bilbao, et al., 2011) with a behavioural study finding that both types of fluency are impaired in patients with structural frontal lesion (Henry & Crawford, 2004a). In addition, it has been found that semantic fluency is more impaired than phonemic fluency in patients with temporal damage (Henry & Crawford, 2004b).

Only one VBM study has investigated the neuroanatomical correlates of verbal fluency in 32 non-demented patients with PD (Fourteen of the sample also had visual hallucination; mean age of sample 73.1, mean years of education 7.7, mean duration of the disease 11.7 and patients were in the moderate stage of the disease) (Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009). All patients performed a phonemic task involving those generating words that begin with the letter P. In addition, for the semantic task, all patients were asked to retrieve words that belonged to the category of animals. There was a positive correlation between grey matter density and semantic fluency scores in the right inferior frontal gyrus (BA 10), left rectal gyrus (BA 11), bilateral inferior temporal gyrus (BA 20), left middle temporal gyrus (BA 21), Left superior temporal gyrus (BA 38), right caudate head, right caudate body, left anterior nucleus of the thalamus, bilateral

parahippocampus and bilateral cerebellum. However, there was no correlation between grey matter density and phonemic fluency scores (Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009).

Another VBM study investigated the neuroanatomical substrate of impaired visuoperceptual and visuospatial skills in 36 non-demented patients with PD (Eighteen of the sample also had visual hallucination) (Pereira, Junque, Marti, Ramirez-Ruiz, Bargallo, et al., 2009). Visuoperceptual functions were assessed by Benton's Facial Recognition Test (BFRT) (Benton & Van Allen, 1968). The results showed that performance on this test correlated with grey matter reduction in the left fusiform gyrus (BA 19, 36), left inferior frontal gyrus (BA 47), right parahipocampal gyrus, left middle occipital gyrus (BA 19), right posterior cingulate (BA 29) and left cerebellum. Patients were also evaluated by the Visual Form Discrimination Test (VFDT). This test does not only evaluate visuoperceptual functions but also has a visuospatial component, and a correlation between the VFDT and grey matter reduction was found in the bilateral superior parietal lobule (BA 7, 40), left inferior frontal gyrus (BA 47), left middle frontal gyrus (BA 9) and right superior occipital gyrus (BA 19) (Pereira, Junque, Marti, Ramirez-Ruiz, Bargallo, et al., 2009). This study concluded that visuospatial and visuoperceptual dysfunctions in patients with PD reflect structural grey matter decreases in the frontal and temporo-parietal cortical regions.

A further study of patients with early PD examined the recognition of facial emotion expressions using the Ekman 60 Faces Test by placing a ROI within the orbitofrontal cortex and the amygdala. Correlation analyses showed that the total

scores of the Ekman test correlated with the volume of the bilateral orbitofrontal cortex but not with the amygdala (Ibarretxe-Bilbao, et al., 2009).

However, another study found no grey matter atrophy in newly diagnosed patients with PD (Dalaker, et al., 2009). Dalaker and others (2009) investigated the possible association between grey matter atrophy and mild cognitive impairment in PD patients using VBM. The study compared 31 patients without mild cognitive impairment, 11 patients with mild cognitive impairment and 37 healthy controls. Regression analyses were carried out between grey matter volume values and the cognitive assessments of verbal memory, attention-executive and visuospatial functions. The results showed no significant differences in grey matter volume values between the study groups. In addition, although correlation analyses showed less grey matter volumes to be significantly associated with higher scores on the attention-executive tests in the bilateral medial frontal gyrus, bilateral inferior frontal gyrus and right middle temporal gyrus, the significant correlation disappeared after adding age, gender, education and total intracranial volume as covariates in the model. Furthermore, there was no significant correlation between grey matter volume and scores of performance on the memory or visuospatial tests (Dalaker, et al., 2009). This study also found no significant correlation between grey matter volume and any of the neuropsychological assessments in contrast to other studies that found a significant correlation. This finding can be explained by the inclusion of patients who had a shorter duration of disease (mean 30.8 months), who were not taking any anti-parkinsonian medication, and the inclusion of younger participants (mean 64.4 SD 9.6) than in previous studies.

The hypothesis for the current study is that cognitive impairment in non-demented patients with PD is not limited to the atrophy of fronto-striatal circuits and that atrophy in other brain regions may also contribute to the cognitive impairment in this population. Previous studies had some limitations such as the inclusion of patients with VH (Ibarretxe-Bilbao, et al., 2008; Pereira, Junque, Marti, Ramirez-Ruiz, Bargallo, et al., 2009; Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009) while other studies did not specifically mention the exclusion of neuropsychiatric symptoms. It is important to exclude neuropsychiatric symptoms because several studies have provided evidence of the contribution of neuropsychiatric symptoms to cognitive decline in patients with PD (Costa, et al., 2006; Drijgers, et al., 2010; Dujardin, et al., 2009; Fernandez, et al., 2009; Isella, et al., 2002; Morgante, et al., 2012; Oguru, et al., 2010; Santangelo, Vitale, Trojano, Longo, et al., 2009) and a further study reported that 89% of patients with PD with dementia had at least one neuropsychiatric symptom (as measured by NPI). The most common symptoms were depression (58%), apathy (56%), anxiety (49%) and hallucinations (44%) (Aarsland, et al., 2007). Some studies even included patients with dementia in the correlation analyses (Camicioli, et al., 2003; Ibarretxe-Bilbao, et al., 2008; Melzer, et al., 2012; Nagano-Saito, et al., 2005; Tam, et al., 2005) and some examined only one or two cognitive domains within the same sample and included patients with older age. Thus, to my knowledge the present study is the first to explore the correlation between grey matter volume and cognitive impairments within a sample of non-demented patients with PD without any neuropsychiatric symptoms using an extensive battery of neuropsychological tests to assess multiple cognitive domains.

5.1.2 METHOD

5.1.2.1 SAMPLE

There were twenty three patients with PD (13 male and 10 female) who participated in this study. The patients were retrospectively recruited from a large database from a Parkinson outpatient clinic. The patients had been diagnosed based on the UK PD Brain Bank Criteria (Hughes, et al., 1992). All patients had extensive neuropsychological screening, neuropsychiatric assessment using the NPI, structural MRI scanning and neurological examination. All patients were in the mild to mild-moderate disease stage, according to the Hoehn and Yahr staging (Hoehn & Yahr, 1967). None of the patients had a history of psychiatric disorders. All patients were treated with a combination of levodopa and variable doses of dopamine agonists. According to the NPI none of the patients had any neuropsychiatric symptoms. The mean age of all patients was 64.83 years (SD= 9.19, range 46-79), their mean education was 11.3 years (SD= 4.86 range 5-18), their mean disease duration was 7.61 years (SD= 4.54) and their mean MMSE score was 28.61 (SD= 1.31 range 26-30).

5.1.2.2 NEUROPSYCHOLOGICAL ASSESSMENTS

The present study used extensive neuropsychological assessments to examine several cognitive domains as follows:

Global cognitive abilities: Mini Mental State Examination (MMSE)

Executive ability:
Frontal Assessment Battery (FAB)
Letter Fluency Test
Trail Making Test (TMT)
Stroop Test

Digit Span (Backward): This is part of the Wechsler Adult intelligence scale (WAIS)

Abstract reasoning:

Raven's Progressive Matrices, version 1938 (PM38) (Black and white)

Similarities Test: This is part of the WAIS

Non-verbal memory:

Rey Complex Figure Test (Delay)

Corsi Block-tapping Test (Visual-spatial span)

Verbal memory:

Category Fluency Test (Verbal retrieval of semantic materials)

Digit Span (Forward): This is part of the WAIS

Rey 15-word Memory Test (Delay)

Learning and attention:

Rey 15-word Memory Test (Immediate recall)

Visual-construction:

Rey Complex Figure Test (Copy)

All of these assessments were described in detail previously (chapter 4, section 4.1.2.3, pages 79-83).

5.1.2.3 STRUCTURAL MRI SCANNING: ACQUISITION

The acquisition of structural MRI scanning has been already described in an imaging study reported earlier in this thesis (see chapter 4, section 4.2.2.2, pages 99-100).

5.1.2.4 STATISTICAL ANALYSES

Statistical analyses were carried out using the SPM8 imaging analysis software (Wellcome Centre for Neuroimaging, London, UK). A multiple regression analysis was carried out to investigate linear correlations between grey matter concentration and neuropsychological assessment scores in patients with PD. Age, number of years of education, duration of disease and total intracranial volume were also included in the model as covariates. The x, y, z coordinates of significant areas obtained from the analyses were first converted into Talairach coordinates using the

mni2tal Matlab routine and then identified using the Talairach Daemon Client (http://www.talairach.org/). Unless otherwise stated a cluster corrected height threshold of $p < 0.01$ was used in all analyses.

5.1.3 RESULTS: CORRELATION ANALYSES

5.1.3.1 GLOBAL COGNITIVE ABILITIES

There was no significant positive correlation between grey matter density and the MMSE scores at 0.01 cluster level. However, significant positive correlation was found at 0.05 cluster level in the right middle temporal gyrus (BA 21), right superior temporal gyrus (BA 38), right inferior temporal gyrus (BA 20), bilateral middle frontal gyrus (BA 6/10), left inferior frontal gyrus (BA 44/45) and left cingulate gyrus (BA 32) (See Table 5.1, Figure 5.1 and 5.2).

Table 5.1 Areas of positive correlation between grey matter volume values and MMSE scores in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (uncorrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Middle Temporal Gyrus	R	21	517	0.022	0.79	3.70	48	10	-32
Superior Temporal Gyrus	R	38			0.76	3.46	40	14	-24
Inferior Temporal Gyrus	R	20			0.66	2.79	48	-6	-38
Middle Frontal Gyrus	R	6	1406	0.011	0.76	3.46	26	22	52
Cingulate Gyrus	L	32			0.72	3.16	-2	21	41
	L	32			0.69	2.96	-2	34	26
Middle Frontal Gyrus	L	10	1036	0.004	0.74	3.32	-36	55	5
Inferior Frontal Gyrus	L	44			0.69	2.95	-55	18	16
	L	45			0.68	2.89	-51	26	21

R = Right L = Left BA = Brodmann Area

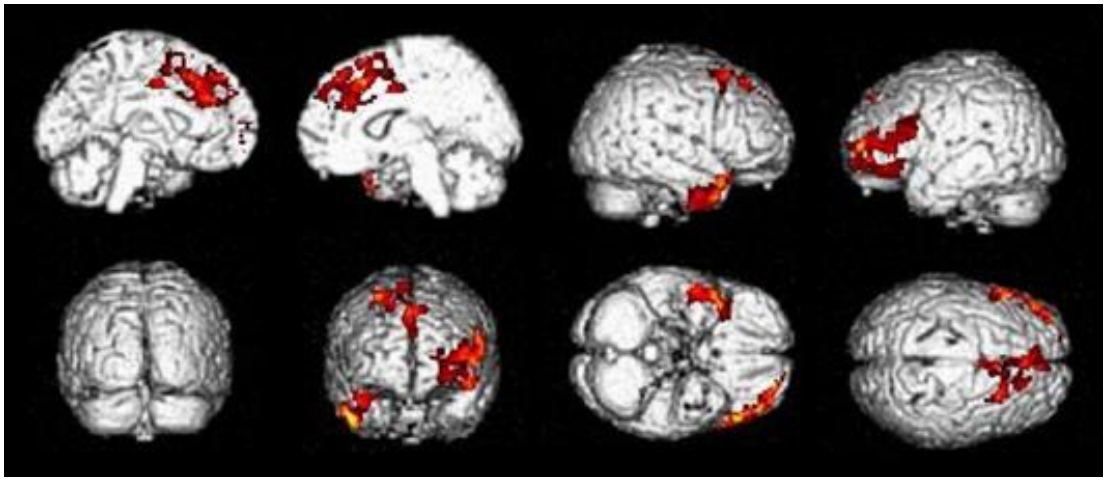

Fig 5.1 Areas of significant positive correlation between grey matter volume values and MMSE scores in the temporal, frontal and cingulate cortex

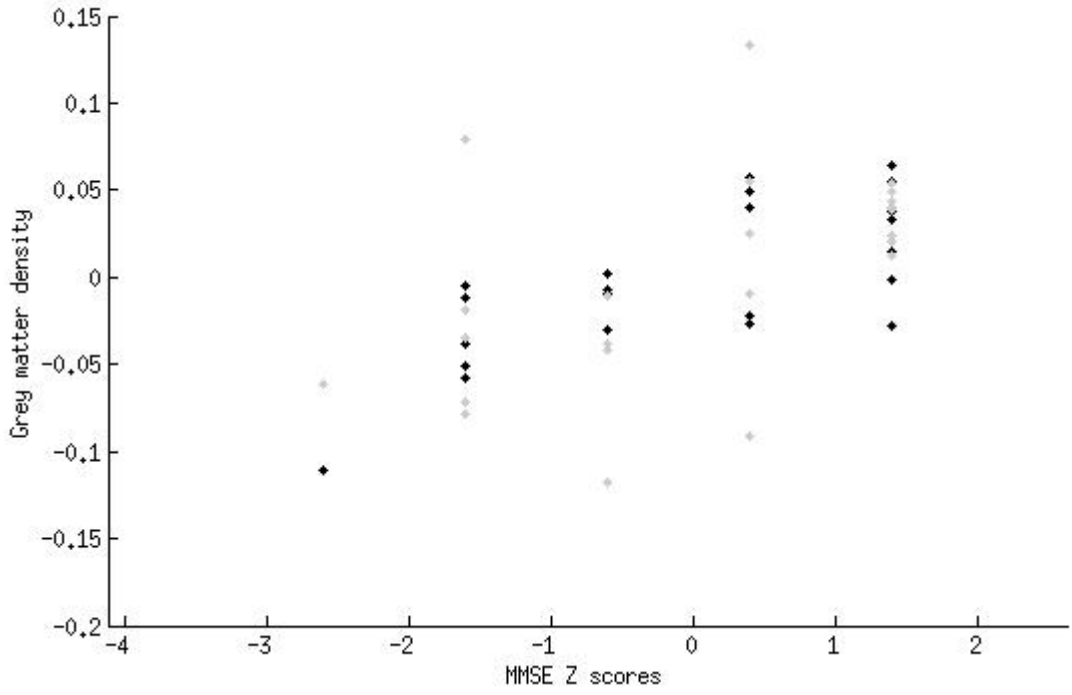

Fig 5.2 Scatterplot showing the positive correlation between grey matter density values and min-mental state examination scores (expressed as z scores) in the most significant cluster (right middle frontal gyrus)

5.1.3.2 EXECUTIVE ABILITY

5.1.3.2.1 FRONTAL ASSESSMENT BATTERY

There was a significant positive correlation between the scores on the Frontal Assessment Battery and grey matter volume values in the bilateral parietal lobe (BA

7) and right occipital lobe (Precuneus) (BA 31) at 0.01 cluster level. Further correlations were found at 0.02 cluster level, those regions include left inferior occipital gyrus (BA 18), left lingual gyrus (BA 18), left middle frontal gyrus (BA 9/6/8), inferior frontal gyrus (BA 45/46) and left precentral gyrus (BA 44) (See Table 5.2, Figure 5.3 and 5.4).

Table 5.2 Areas of positive correlation between grey matter volume values and Frontal Assessment Battery scores in patients with PD without any neuropsychiatric symptoms

Brain areas	**R/L**	**BA**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**r value**	**Z value at Local Maximum**	**Talairach coordinates**		
							X	**Y**	**Z**
Parietal Lobe (Precuneus)	L	7	1758	0.015	0.97	4.74	-12	-76	37
	R	7			0.92	4.00	20	-62	38
Occipital Lobe (Precuneus)	R	31			0.897	3.78	6	-61	27
Inferior Occipital Gyrus	L	18	545	0.047	0.94	4.24	-28	-86	-7
Lingual Gyrus	L	18			0.94	4.17	-8	-74	-5
	L	17			0.88	3.66	-8	-85	1
Middle Frontal Gyrus	L	9	806	0.041	0.89	3.74	-44	27	32
	L	6			0.88	2.78	-28	18	53
	L	8			0.88	2.75	-24	29	37
Inferior Frontal Gyrus	L	45			0.97	3.66	-51	18	3
	L	45			0.92	3.65	-50	26	8
	L	46			0.897	2.73	-50	36	11
Precentral Gyrus	L	44			0.94	2.88	-42	6	7

R = Right L = Left BA = Brodmann Area

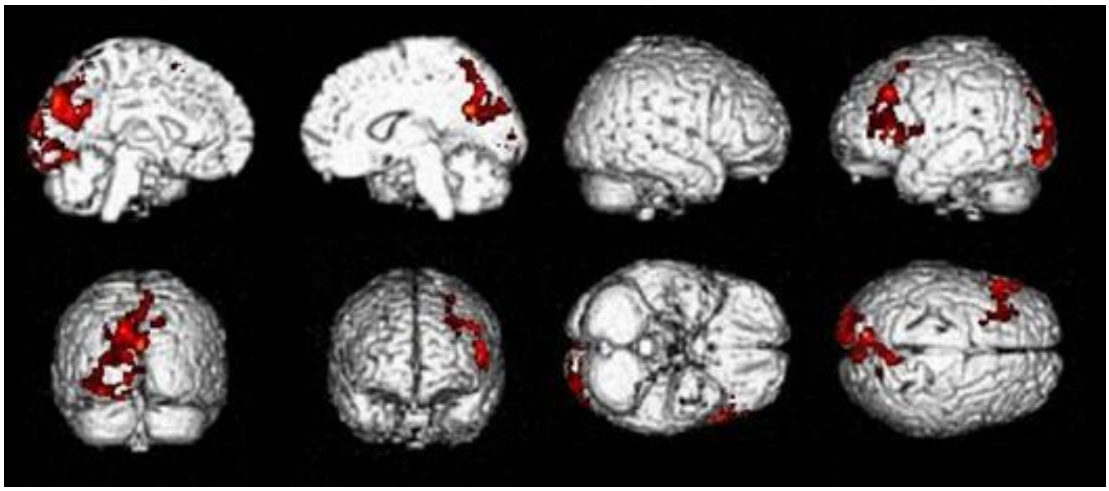

Fig 5.3 Areas of significant positive correlation between grey matter volume values and Frontal Assessment Battery scores

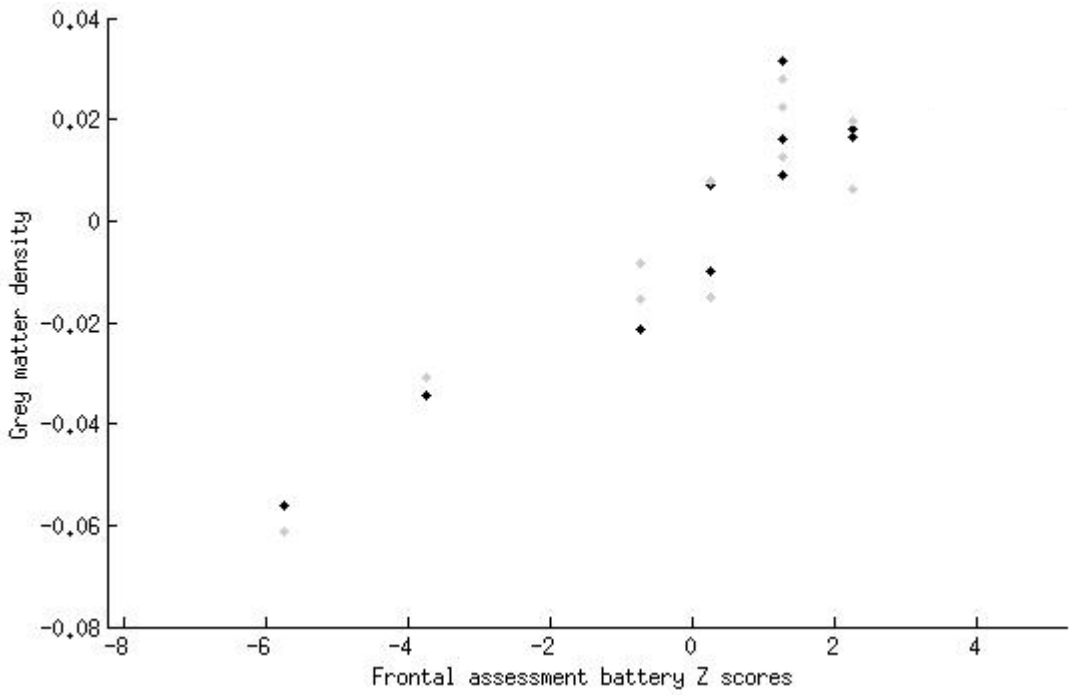

Fig 5.4 Scatterplot showing the positive correlation between grey matter density values and frontal assessment battery scores (expressed as z scores) in the most significant cluster (left precuneus)

5.1.3.2.2 LETTER FLUENCY TEST

There was a significant positive correlation between grey matter volume values and letter fluency scores in the bilateral anterior cingulate (BA 32), left superior frontal gyrus (BA 10) and bilateral medial frontal gyrus (BA 25) (See Table 5.3, Figure 5.5 and 5.6).

Table 5.3 Areas of positive correlation between grey matter volume values and letter fluency scores in patients with PD without any neuropsychiatric symptoms

Brain areas	**R/L**	**BA**	**Cluster Size**	**Cluster-level *P*-value (corrected)**	**r value**	**Z value at Local Maximum**	**Talairach coordinates**		
							X	**Y**	**Z**
Anterior Cingulate	L	32	1029	0.021	0.77	3.52	-6	39	-2
Superior Frontal Gyrus	L	10			0.76	3.40	-10	54	-1
Anterior Cingulate	L	32			0.74	3.29	-8	41	11
	R	32			0.73	3.17	10	41	-5
Medial Frontal Gyrus	R	25			0.69	2.92	10	19	-8
	L	25			0.66	2.75	-4	15	-18

R = Right L = Left BA = Brodmann Area

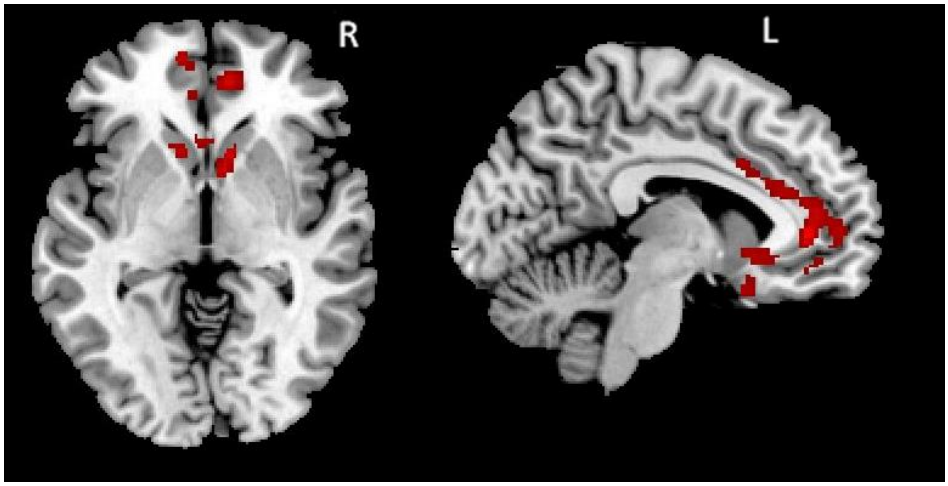

Fig 5.5 Regions with significant positive correlation with the letter fluency score in the frontal and cingulate cortex

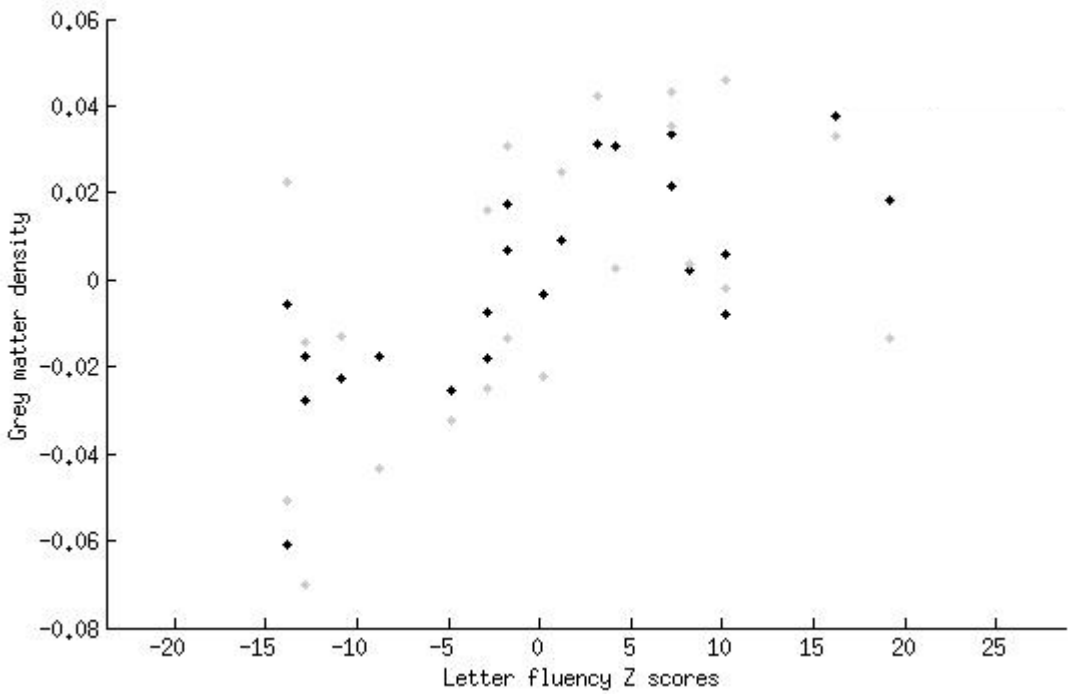

Fig 5.6 Scatterplot showing the positive correlation between grey matter density values and letter fluency test scores (expressed as z scores) in the most significant cluster (left superior frontal gyrus)

5.1.3.2.3 TRAIL MAKING TEST (PART A)

A significant negative correlation was found between grey matter volume values and trail making score (Part A) in the right postcentral gyrus (BA 7), right

parietal lobe (BA 40), medial frontal gyrus bilaterally (BA 10/11/25), anterior cingulate bilaterally (BA 32) (See Table 5.4, Figure 5.7 and 5.8).

Table 5.4 Areas of negative correlation between grey matter volume values and TMT A scores in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Postcentral Gyrus	R	7	328	0.034	- 0.89	4.45	14	-45	65
Parietal Lobe (Sub-Gyral)	R	40			- 0.86	4.16	26	-36	57
Medial Frontal Gyrus	L	10	830	0.026	- 0.77	3.37	-2	49	9
	L	11			- 0.76	3.32	-2	30	-15
Anterior Cingulate	R	32			- 0.75	3.19	2	39	-2
Medial Frontal Gyrus	L	10			- 0.75	3.19	-2	55	10
Anterior Cingulate	L	32			- 0.75	3.19	-2	37	-4
	R	32			- 0.73	3.10	4	39	4
Medial Frontal Gyrus	R	25			- 0.66	2.67	10	19	-18

R = Right L = Left BA = Brodmann Area

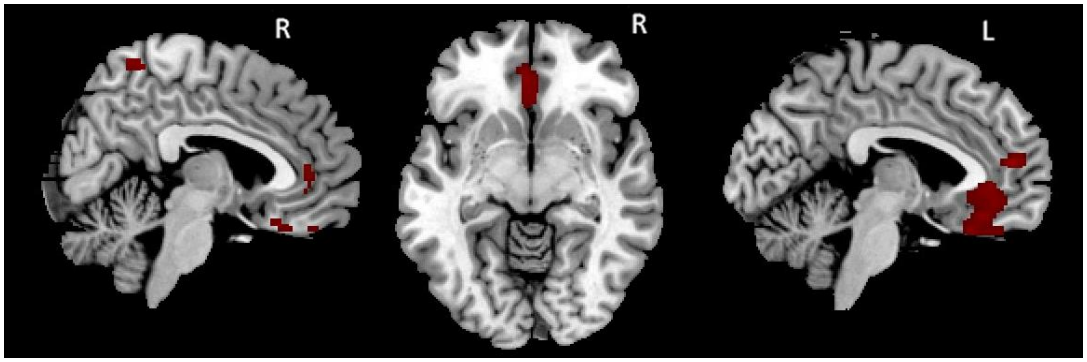

Fig 5.7 Regions with significant negative correlation with Trail Making Test (Part A)

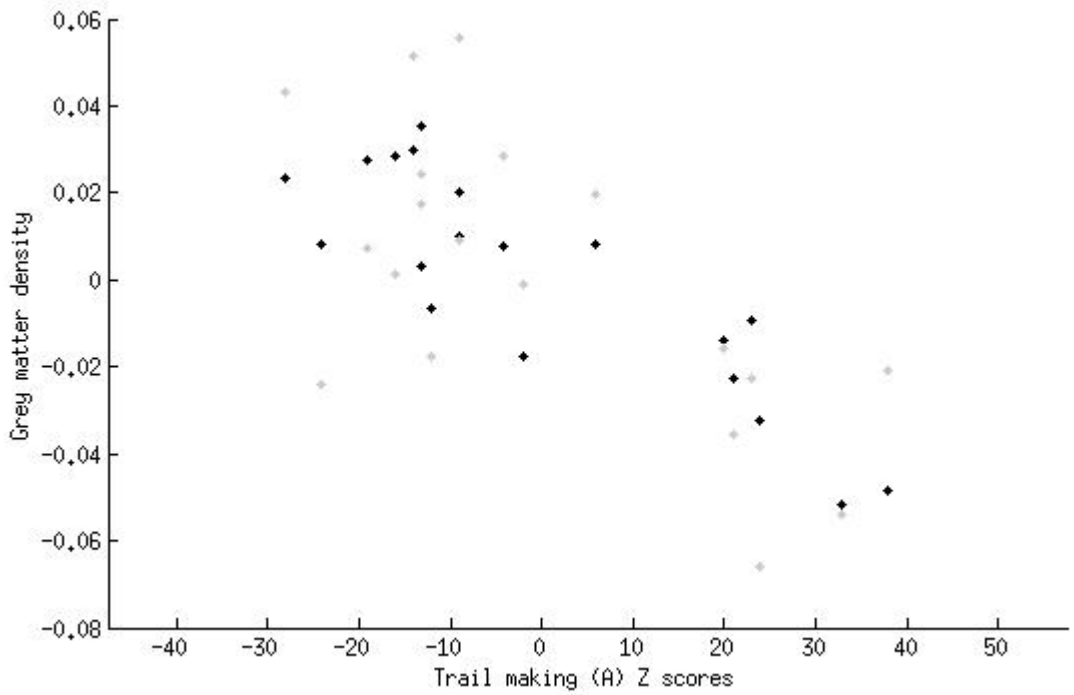

Fig 5.8 Scatterplot showing the negative correlation between grey matter density values and Trail making test part (A) scores (expressed as z scores) in the most significant cluster (left medial frontal gyrus)

5.1.3.2.4 TRAIL MAKING TEST (PART B)

Correlation analysis showed a significant negative correlation between grey matter volume values and trail making score (Part B) in the bilateral medial frontal gyrus (BA 10/11/25), bilateral superior frontal gyrus (BA 10/11), right middle frontal gyrus (BA 10), right inferior frontal gyrus (BA 10), bilateral anterior cingulate (BA 32), bilateral superior temporal gyrus (BA 22), bilateral middle temporal gyrus (BA 21) and right inferior temporal gyrus (BA 20) (See Table 5.5, Figure 5.9 and 5.10).

Table 5.5 Areas of negative correlation between grey matter volume values and TMT B scores in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Medial Frontal Gyrus	R	11	919	0.028	- 0.91	4.76	10	61	-15
Superior Frontal Gyrus	L	11			- 0.82	3.78	-14	61	-15
	R	10			- 0.79	3.53	12	66	-7
Middle Frontal Gyrus	R	10			- 0.76	3.31	34	58	-8
Medial Frontal Gyrus	L	10			- 0.76	3.26	-4	62	-6
Anterior Cingulate	R	32			- 0.75	2.91	10	33	-10
Inferior Frontal Gyrus	R	10			- 0.73	2.75	42	52	1
Medial Frontal Gyrus	L	25			- 0.73	2.63	-2	19	-14
Anterior Cingulate	L	32			- 0.72	2.45	-2	25	-10
Superior Temporal Gyrus	R	22	1070	0.003	- 0.89	4.50	48	-12	-8
Middle Temporal Gyrus	R	21			- 0.83	3.83	67	-33	-2
Inferior Temporal Gyrus	R	20			- 0.82	3.75	61	-32	-17
Middle Temporal Gyrus	L	21	526	0.033	- 0.84	3.88	-63	-43	-5
Superior Temporal Gyrus	L	22			- 0.80	3.58	-63	-25	-2
Middle Temporal Gyrus	L	37			- 0.73	3.10	-59	-49	-8

R = Right L = Left BA = Brodmann Area

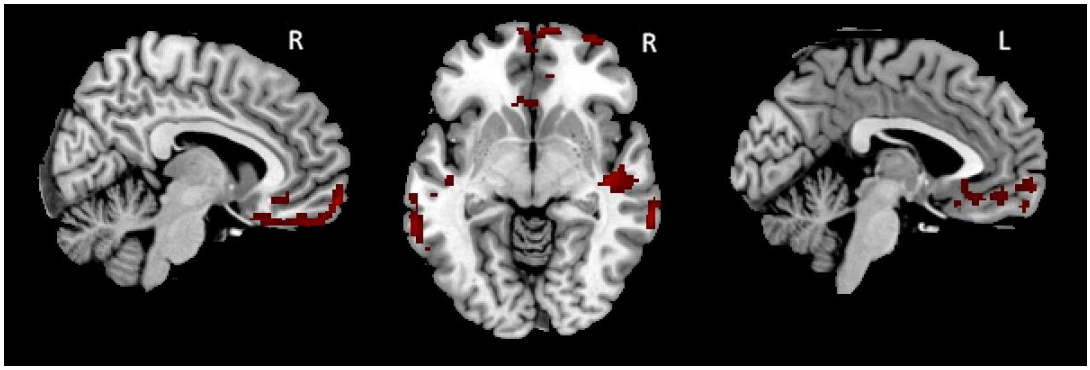

Fig 5.9 Regions with significant negative correlation with Trail Making Test (Part B)

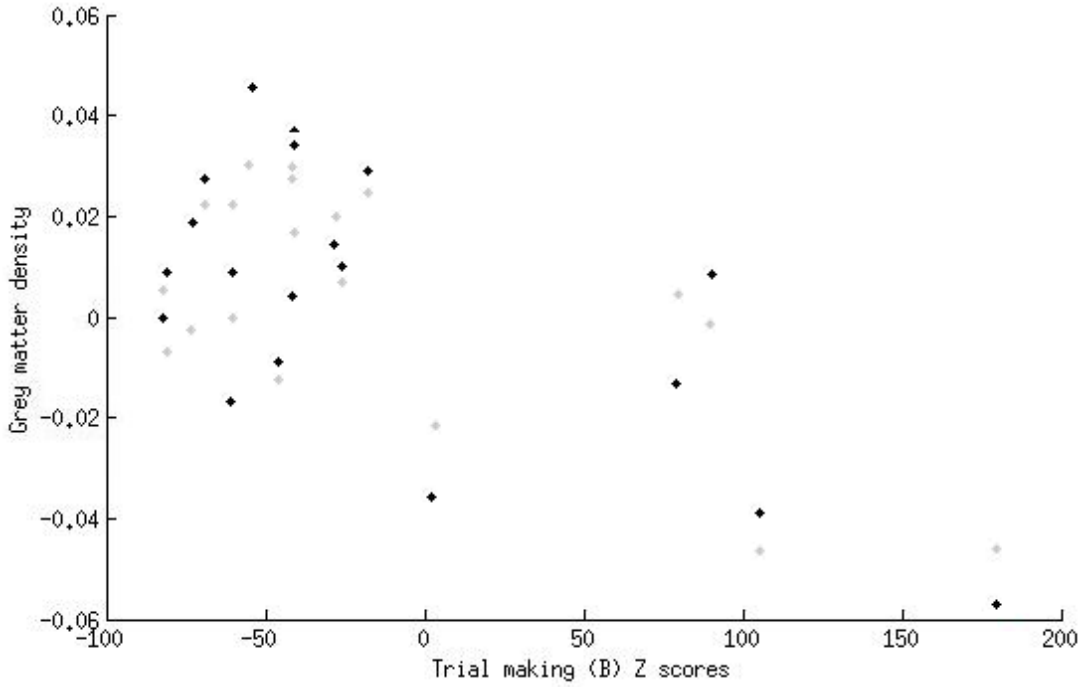

Fig 5.10 Scatterplot showing the negative correlation between grey matter density values and Trail making test part (B) scores (expressed as z scores) in the most significant cluster (right superior temporal gyrus)

5.1.3.2.5 STROOP TEST

Time interference scores were used in this analysis. Significant negative correlations were found between grey matter volume values and time interference score in the right superior temporal gyrus (BA 38), right inferior temporal gyrus (BA 20), right middle temporal gyrus (BA 21), bilateral inferior frontal gyrus (BA 11/47), bilateral middle frontal gyrus (BA 11), left superior frontal gyrus (BA 10/11), left caudate head and body (See Table 5.6, Figure 5.11 and 5.12).

Table 5.6 Areas of negative correlation between grey matter volume values and Stroop (Time) scores in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Superior Temporal Gyrus	R	38	199	0.032	- 0.78	3.62	36	12	-24
Inferior Temporal Gyrus	R	20			- 0.72	3.15	48	-2	-32
Middle Temporal Gyrus	R	21			- 0.69	2.98	55	1	-25
Inferior Frontal Gyrus	R	47	249	0.026	- 0.74	3.32	32	22	-18
Frontal Lobe (Sub Gyral)	R	10			- 0.68	2.88	42	39	-2
Middle Frontal Gyrus	R	11			- 0.68	2.87	26	30	-15
Caudate Head	L		160	0.024	- 0.74	3.27	-12	17	-1
Caudate Body	L				- 0.73	3.23	-14	14	9
Middle Frontal Gyrus	L	11	79	0.024	- 0.697	3.00	-24	30	-17
Inferior Frontal Gyrus	L	11			- 0.62	2.55	-16	36	-19
	L	47			- 0.59	2.38	-24	18	-19
Superior Frontal Gyrus	L	11	68	0.031	- 0.66	2.78	-12	57	-16
	L	10			- 0.61	2.49	-26	60	-10

R = Right L = Left BA = Brodmann Area

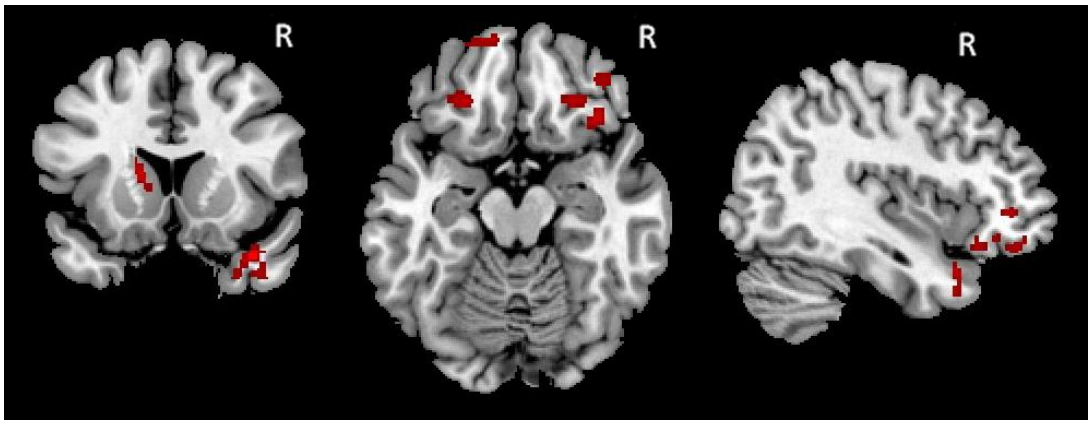

Fig 5.11 Areas of significant negative correlation between grey matter volume values and Stroop Test (Time interference score) in frontal and temporal cortex

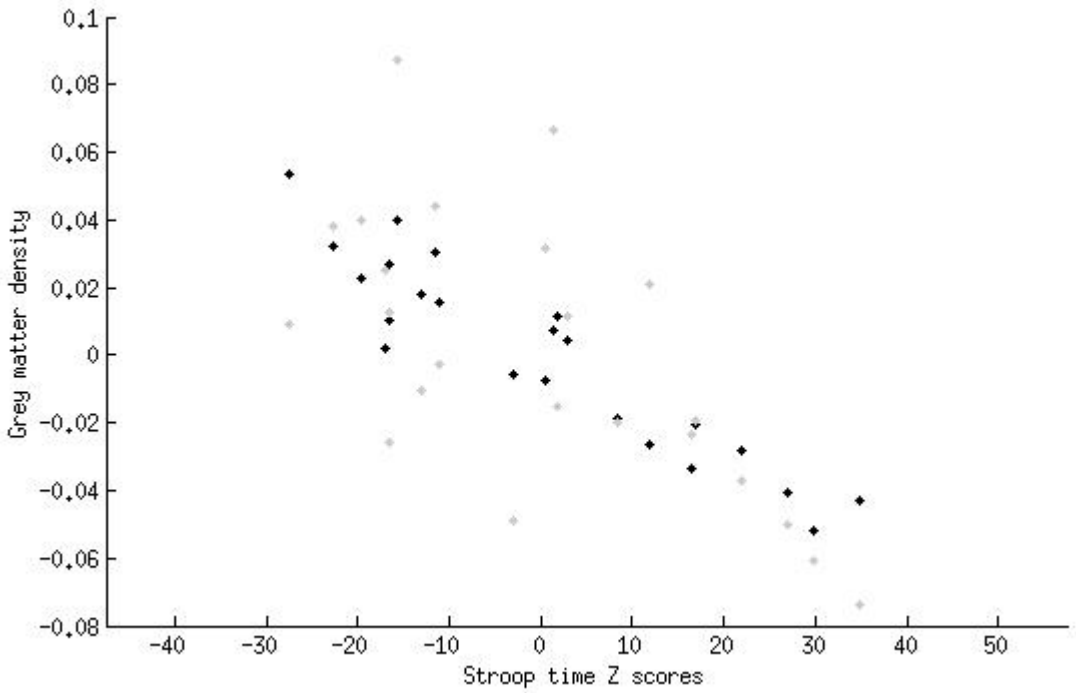

Fig 5.12 Scatterplot showing the negative correlation between grey matter density values and Stroop time scores (expressed as z scores) in the most significant cluster (right inferior frontal gyrus)

5.1.3.2.6 DIGIT SPAN BACKWARDS

There were significant positive correlations between grey matter volume values and digit span (backwards) score in several brain regions including the left superior temporal gyrus (BA 38), left limbic lobe (Uncus) (BA 28), middle temporal gyrus bilaterally (BA 21/39), left inferior parietal lobule (BA 40), parietal lobe (Precuneus) bilaterally (BA 19/7), right superior parietal lobule (BA 7), right postcentral gyrus (BA 5), right supramarginal gyrus (BA 40), left superior frontal gyrus (BA 10) and left middle frontal gyrus (BA 10) (See Table 5.7, Figure 5.13 and 5.14).

Table 5.7 Areas of positive correlation between grey matter volume values and digit span (backwards) score in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Superior Temporal Gyrus	L	38	686	0.032	0.991	4.82	-30	14	-28
Limbic Lobe (Uncus)	L	28			0.92	3.58	-16	7	-24
Middle Temporal Gyrus	L	21			0.91	3.48	-53	4	-29
Inferior Parietal Lobule	L	40	1153	0.014	0.98	4.43	-42	-50	49
Parietal Lobe (Precuneus)	L	19			0.98	4.28	-42	-74	35
	L	7			0.98	4.14	-22	-58	49
	R	7	805	0.024	0.98	4.35	28	-68	37
Superior Parietal Lobule	R	7			0.98	4.30	28	-62	42
Middle Temporal Gyrus	R	39			0.96	4.08	44	-67	24
Parietal Lobe (Precuneus)	R	7	914	0.023	0.98	4.33	18	-48	56
Postcentral Gyrus	R	5			0.96	4.08	30	-42	59
Supramarginal Gyrus	R	40			0.95	3.89	53	-37	33
Superior Frontal Gyrus	L	10	411	0.041	0.94	3.74	-20	64	-10
	L	10			0.92	3.52	-18	64	2
Middle Frontal Gyrus	L	10			0.91	3.49	-32	60	-1

R = Right L = Left BA = Brodmann Area

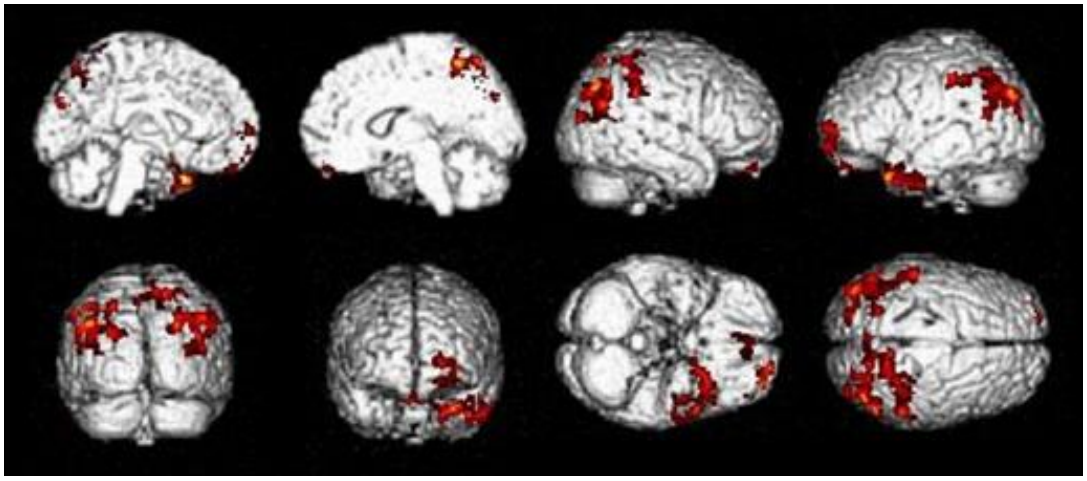

Fig 5.13 Regions with significant positive correlation with digit span (backwards) score

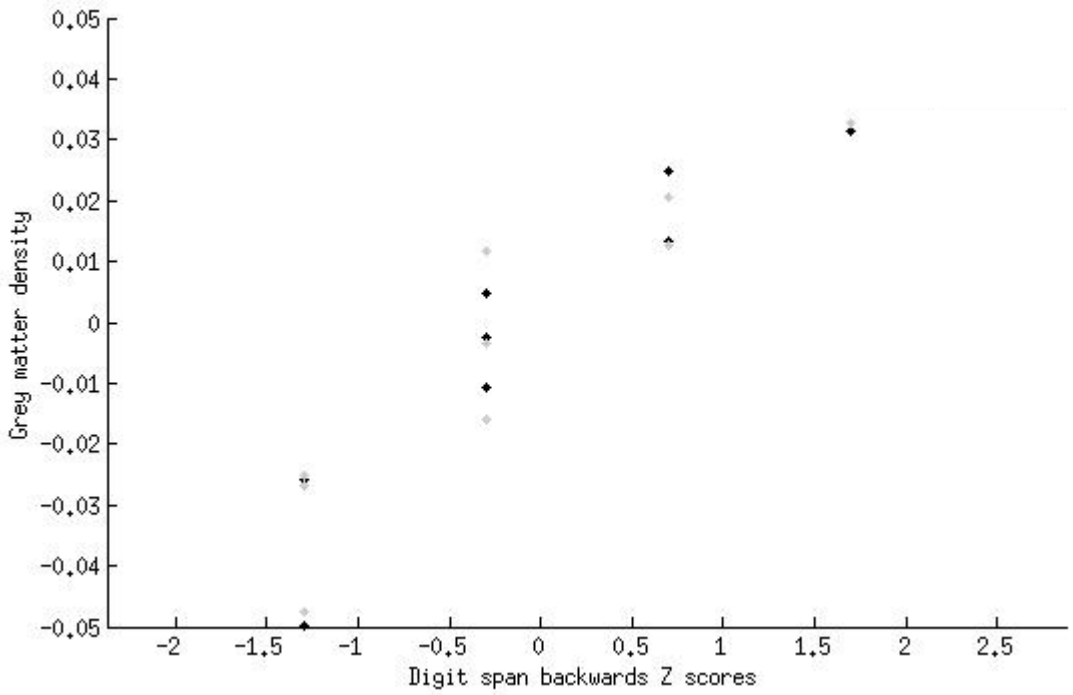

Fig 5.14 Scatterplot showing the positive correlation between grey matter density values and digit span backwards scores (expressed as z scores) in the most significant cluster (left inferior parietal lobule)

5.1.3.3 ABSTRACT REASONING

5.1.3.3.1 RAVEN'S PROGRESSIVE MATRICES, VERSION 1938 (PM38) (BLACK AND WHITE)

A significant positive correlation between grey matter volume values and Raven's Progressive Matrices score was found in the bilateral middle frontal gyrus (BA 10/11), right superior frontal gyrus (BA 10/6), right medial frontal gyrus (BA 6), right limbic lobe (Uncus) (BA 36), left middle temporal gyrus (BA 21) and left superior temporal gyrus (BA 22) (See Table 5.8, Figure 5.15 and 5.16).

Table 5.8 Areas of positive correlation between grey matter volume values and Raven's Progressive Matrices score in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Middle Frontal Gyrus	R	11	165	0.024	0.82	3.99	26	48	-9
Superior Frontal Gyrus	R	10			0.78	3.62	18	56	-6
Middle Frontal Gyrus	L	11	138	0.037	0.79	3.66	-24	46	-9
	L	10			0.75	3.39	-24	49	5
Limbic Lobe (Uncus)	R	36	75	0.025	0.77	3.49	32	1	-29
Middle Temporal Gyrus	L	21	99	0.029	0.76	3.42	-50	-12	-11
Superior Temporal Gyrus	L	22			0.73	3.25	-48	-20	-2
Superior Frontal Gyrus	R	6	130	0.024	0.75	3.40	10	9	59
Medial Frontal Gyrus	R	6			0.74	3.28	16	3	61

R = Right L = Left BA = Brodmann Area

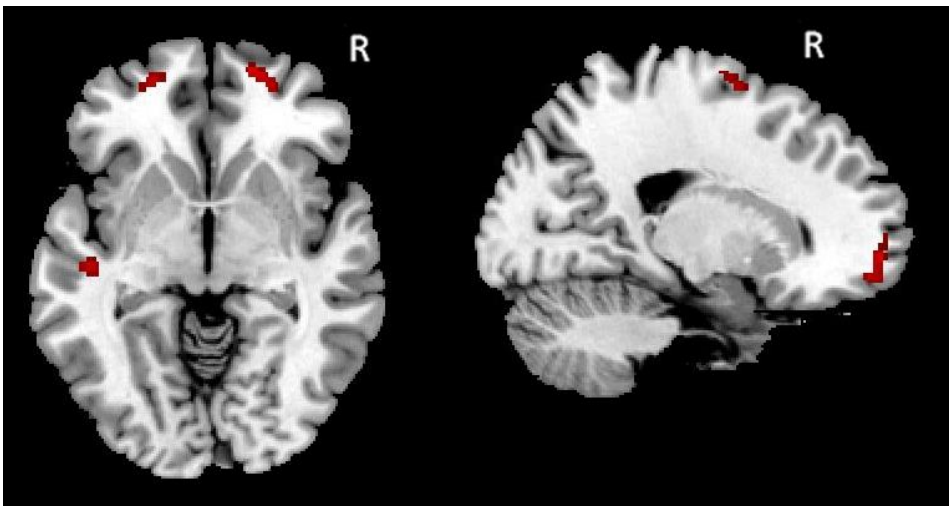

Fig 5.15 Areas of significant positive correlation between grey matter volume values and Raven's Progressive Matrices score in frontal and temporal cortex

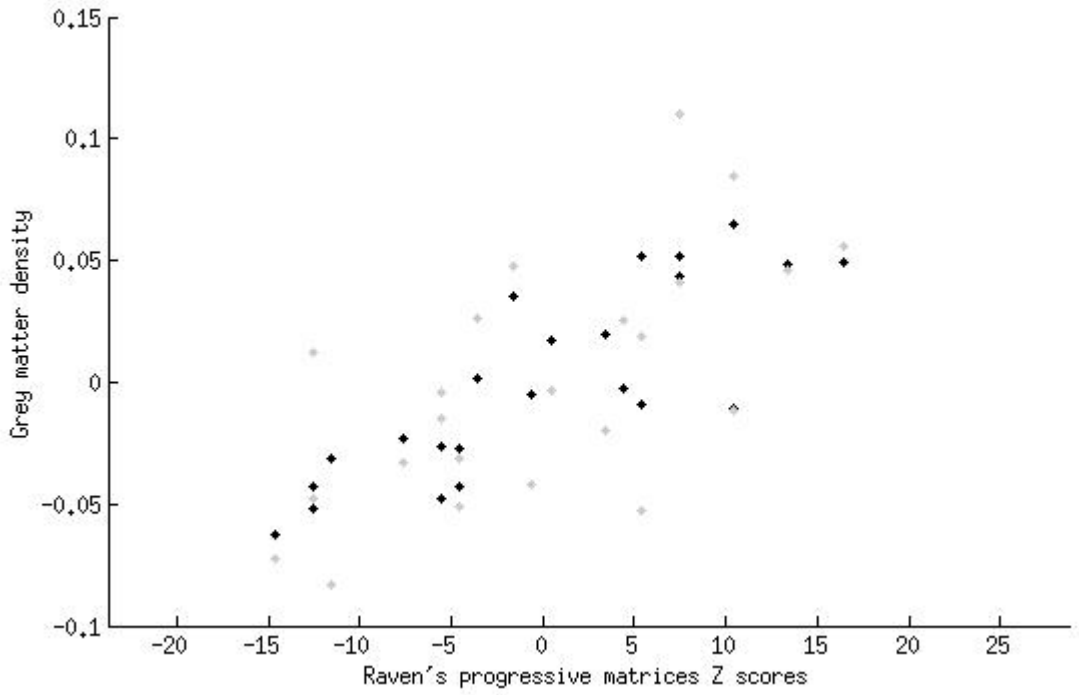

Fig 5.16 Scatterplot showing the positive correlation between grey matter density values and Raven's progressive matrices test scores (expressed as z scores) in the most significant cluster (right middle frontal gyrus)

5.1.3.3.2 SIMILARITIES TEST

There was no significant positive correlation between grey matter volume values and similarities score at 0.01 cluster level but significant correlations were found at 0.05 cluster level in the left middle temporal gyrus (BA 21/38), bilateral limbic lobe (Uncus) (BA 28), right inferior temporal gyrus (BA 20), right superior temporal gyrus (BA 38), left medial frontal gyrus (BA 6) and left cingulate gyrus (BA 24) (See Table 5.9, Figure 5.17 and 5.18).

Table 5.9 Areas of positive correlation between grey matter volume values and similarities test score in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (uncorrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Middle Temporal Gyrus	L	21	1081	0.015	0.73	3.17	-44	-1	-25
Limbic Lobe (Uncus)	L	28			0.67	2.80	-22	2	-29
Middle Temporal Gyrus	L	38			0.67	2.78	-32	2	-39
Limbic Lobe (Uncus)	R	28	699	0.023	0.66	2.77	20	8	-29
Inferior Temporal Gyrus	R	20			0.63	2.60	46	-11	-28
Superior Temporal Gyrus	R	38			0.63	2.59	44	19	-16
Medial Frontal Gyrus	L	6	155	0.046	0.62	2.54	-2	18	43
Cingulate Gyrus	L	24			0.499	2.39	-2	7	33

R = Right L = Left BA = Brodmann Area

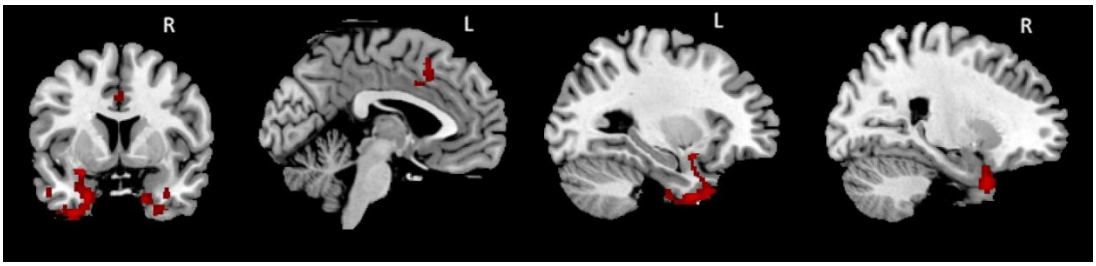

Figure 5.17 Areas of significant positive correlation between grey matter volume values and similarities score

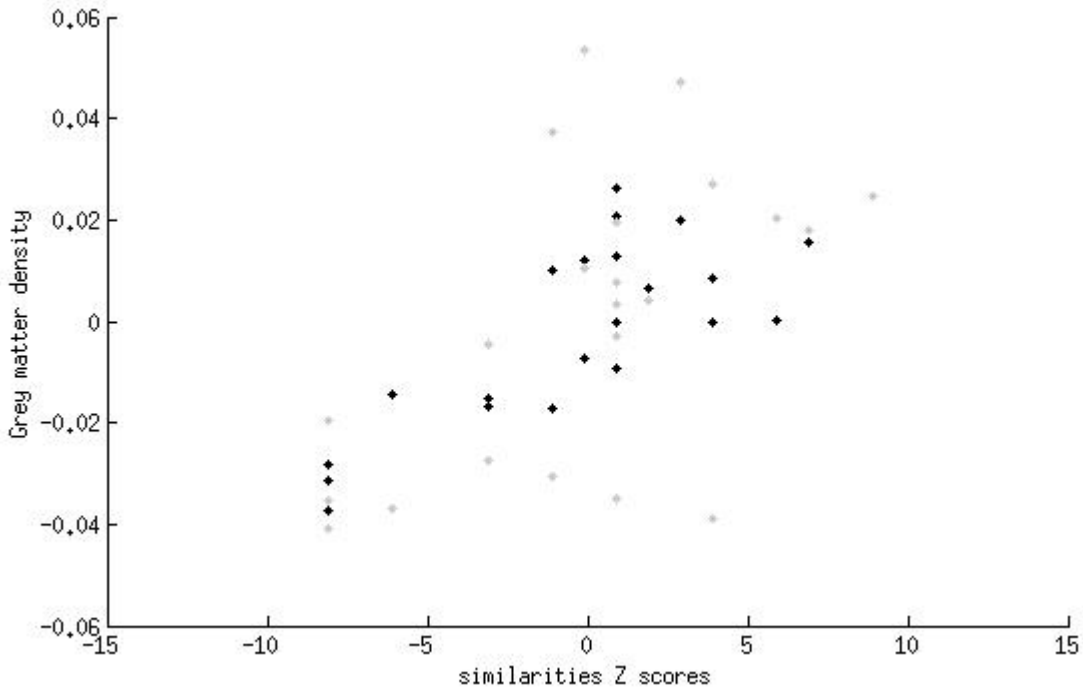

Fig 5.18 Scatterplot showing the positive correlation between grey matter density values and similarities test scores (expressed as z scores) in the most significant cluster (left middle temporal gyrus)

5.1.3.4 NON-VERBAL MEMORY

5.1.3.4.1 REY COMPLEX FIGURE TEST (DELAY)

Significant positive correlation was found between grey matter volume values and Rey Figure (Delay) score in several brain regions including the right postcentral gyrus (BA 43), right insula, left cerebellum anterior and posterior lobe, left superior frontal gyrus (BA 6), left medial frontal gyrus (BA 6), left amygdala, right parahippocampal gyrus (BA 28), right limbic lobe (Uncus) (BA 28) and right hippocampus (See Table 5.10, Figure 5.19 and 20).

Table 5.10 Areas of positive correlation between grey matter volume values and Rey Figure (Delay) scores in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Postcentral Gyrus	R	43	121	0.023	0.82	3.83	51	-11	21
Insula	R				0.71	3.06	38	-13	21
Precentral Gyrus	R	6			0.67	2.80	48	-4	28
Cerebellum Anterior Lobe	L		190	0.024	0.78	3.52	-16	-55	-21
Cerebellum Posterior Lobe	L		174	0.019	0.77	3.47	-24	-47	-43
	L				0.74	3.23	-32	-43	-40
Superior Frontal Gyrus	L	6	104	0.031	0.75	3.29	-8	12	51
	L	6			0.69	2.93	-8	11	58
Medial Frontal Gyrus	L	6			0.62	2.51	-8	3	57
Amygdala	L		146	0.017	0.74	3.25	-24	-5	-23
Parahippocampal Gyrus	R	28	141	0.016	0.71	3.05	20	-13	-21
Limbic Lobe (Uncus)	R	28			0.70	2.97	22	-13	-28
Hippocampus	R				0.60	2.41	30	-14	-18

R = Right L = Left BA = Brodmann Area

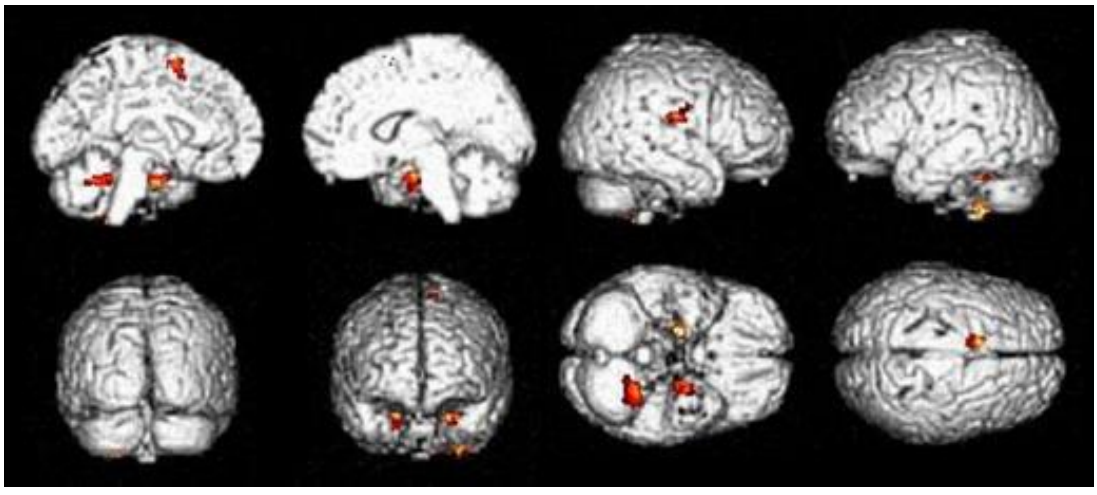

Fig 5.19 Regions with significant positive correlation with Rey Figure (Delay) scores

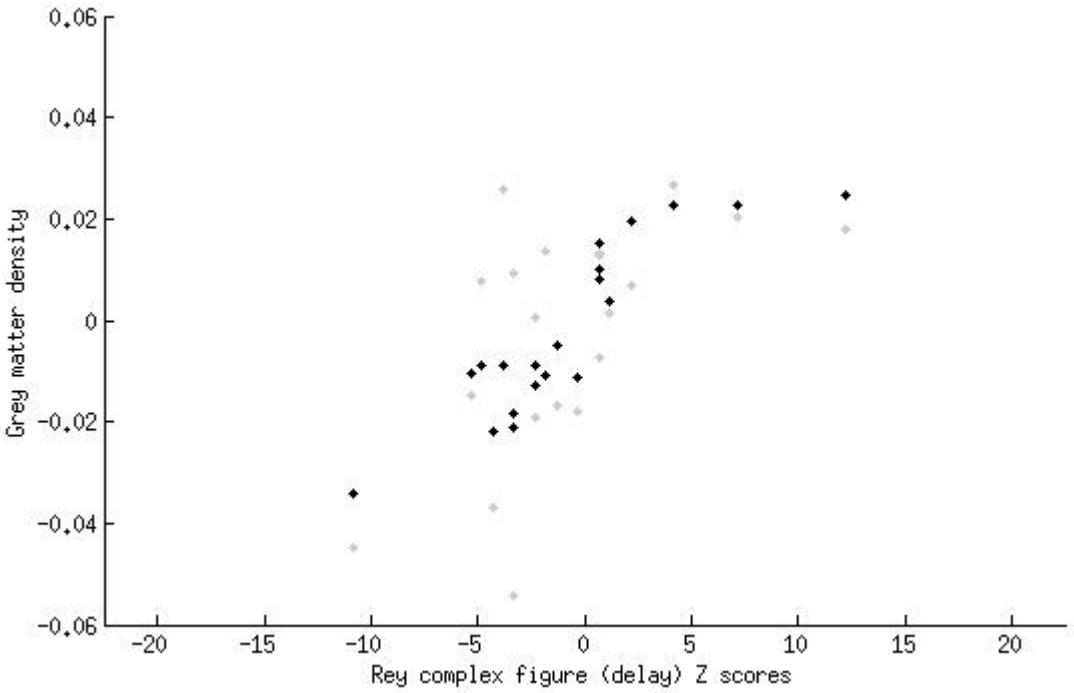

Fig 5.20 Scatterplot showing the positive correlation between grey matter density values and Rey complex figure test (delay) scores (expressed as z scores) in the most significant cluster (right parahippocampal gyrus)

5.1.3.4.2 CORSI BLOCK-TAPPING TEST (VISUAL-SPATIAL SPAN)

There was no significant correlation between grey matter volume values and Corsi scores.

5.1.3.5 VERBAL MEMORY

5.1.3.5.1 CATEGORY FLUENCY TEST (VERBAL RETRIEVAL OF SEMANTIC MATERIALS)

Significant positive correlations were found between grey matter volume values and category fluency score in the superior temporal gyrus bilaterally (BA 38), right precentral gyrus (BA 4/6), right middle frontal gyrus (BA 6), left anterior cingulate (BA 24) and cingulate gyrus bilaterally (BA 24/32) (See Table 5.11, Figure 5.21 and 5.22).

Table 5.11 Areas of positive correlation between grey matter volume values and category fluency score in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Superior Temporal Gyrus	R	38	173	0.020	0.82	3.87	36	12	-29
	R	38			0.67	2.84	30	6	-34
Precentral Gyrus	R	4	80	0.036	0.77	3.45	38	-15	56
Middle Frontal Gyrus	R	6			0.73	3.18	26	-14	62
Precentral Gyrus	R	6			0.66	2.73	34	-18	62
Anterior Cingulate	L	24	310	0.018	0.76	3.41	-2	26	23
Cingulate Gyrus	R	24			0.69	2.93	2	4	35
	L	32			0.63	2.59	-8	11	34
Superior Temporal Gyrus	L	38	136	0.017	0.75	3.32	-34	10	-34
	L	38			0.597	2.41	-24	4	-32

R = Right L = Left BA = Brodmann Area

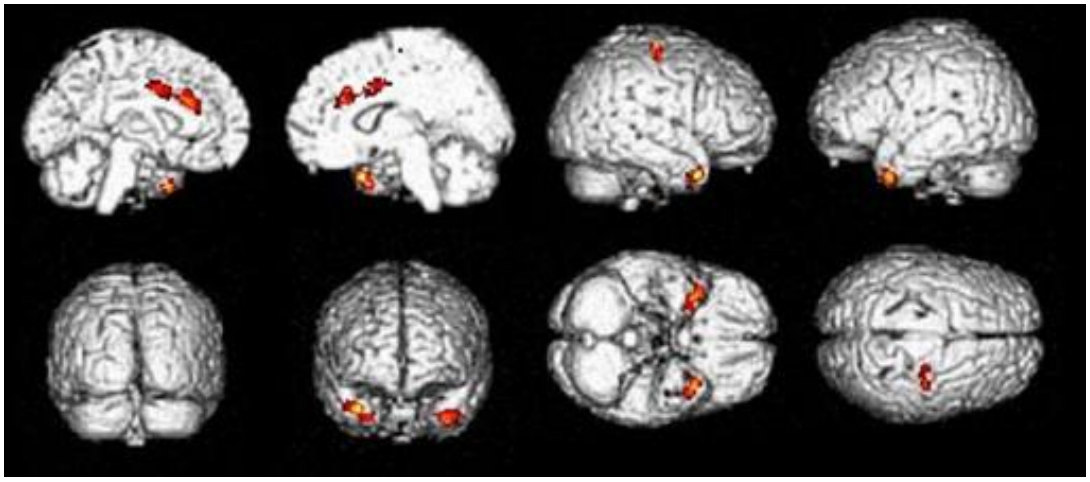

Fig 5.21 Areas of significant positive correlation between grey matter volume values and category fluency score in the temporal, frontal and cingulate cortex

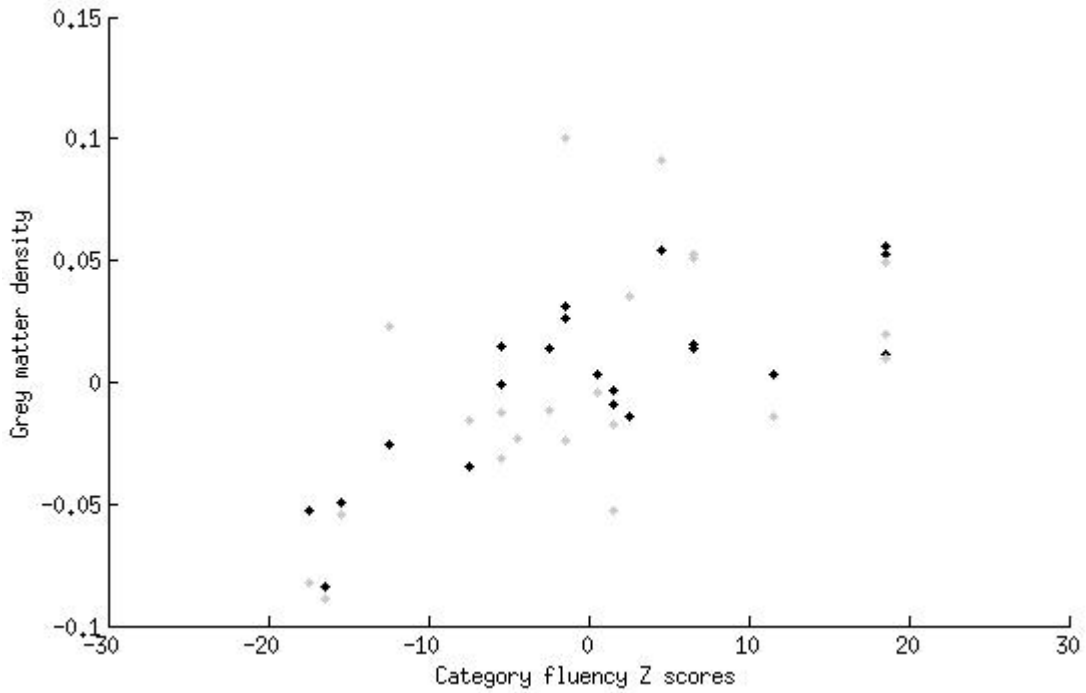

Fig 5.22 Scatterplot showing the positive correlation between grey matter density values and category fluency test scores (expressed as z scores) in the most significant cluster (left superior temporal gyrus)

5.1.3.5.2 DIGIT SPAN FORWARDS

There was no significant positive correlation between grey matter volume values and digit span (forwards) at 0.01 cluster level. However, significant correlations were found at 0.05 cluster level in several brain regions including the bilateral postcentral gyrus (BA 3), right supramarginal gyrus (BA 40), right inferior parietal lobule (BA 40), bilateral precuneus (BA 7/39), right paracentral lobule (BA 5), bilateral inferior temporal gyrus (BA 20), bilateral temporal lobe (BA 20/21), left middle temporal gyrus (BA 21), left superior temporal gyrus (BA 39), left precentral gyrus (BA 6), right medial frontal gyrus (BA 6) and right middle frontal gyrus (BA 9/46) (See Table 5.12, Figure 5.23 and 5.24).

Table 5.12 Areas of positive correlation between grey matter volume values and digit span (forwards) score in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (uncorrected)	r value	Z value at Local Maximum	Talairach coordinates X	Y	Z
Postcentral Gyrus	R	3	1571	0.002	0.98	4.47	32	-34	50
Supramarginal Gyrus	R	40			0.95	3.89	46	-37	39
Inferior Parietal Lobule	R	40			0.95	3.87	44	-54	38
Inferior temporal Gyrus	L	20	1572	0.002	0.96	4.02	-53	-47	-13
Temporal Lobe (Sub-Gyrus)	L	21			0.96	4.00	-46	-5	-13
Middle Temporal Gyrus	L	21			0.94	3.76	-46	1	-19
Temporal Lobe (Sub-Gyrus)	R	20	469	0.008	0.95	3.89	38	-11	-20
Inferior Temporal Gyrus	R	20			0.74	2.57	40	-8	-40
	R	20			0.73	2.51	30	-4	-42
Precentral Gyrus	L	6	955	0.002	0.95	3.89	-20	-16	63
	L	6			0.95	3.84	-42	-6	39
Postcentral Gyrus	L	3			0.88	3.27	-40	-27	51
Precuneus	R	7	1437	0.002	0.94	3.76	8	-69	53
Medial Frontal Gyrus	R	6			0.93	3.64	2	2	48
Paracentral Lobule	R	5			0.91	3.45	10	-38	46
Superior Temporal Gyrus	L	39	1807	0.002	0.93	3.63	-46	-48	13
Precuneus	L	7			0.92	3.59	-14	-64	31
	L	31			0.90	3.43	-24	-65	25
Middle Frontal Gyrus	R	9	299	0.008	0.92	3.59	51	13	34
	R	46			0.89	3.33	48	23	26
	R	46			0.98	3.10	50	32	15

R = Right L = Left BA = Brodmann Area

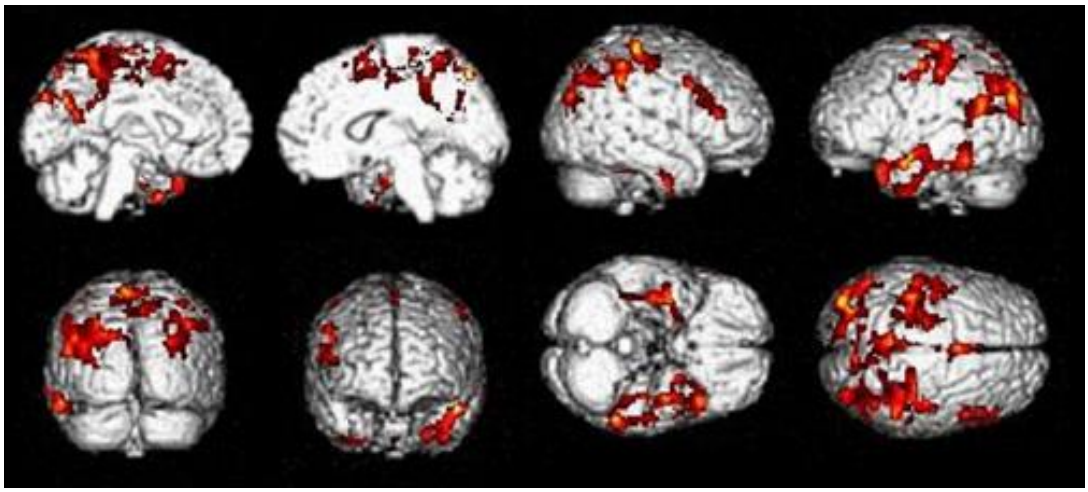

Fig 5.23 Areas of significant positive correlation between grey matter volume values and digit span (forwards) score

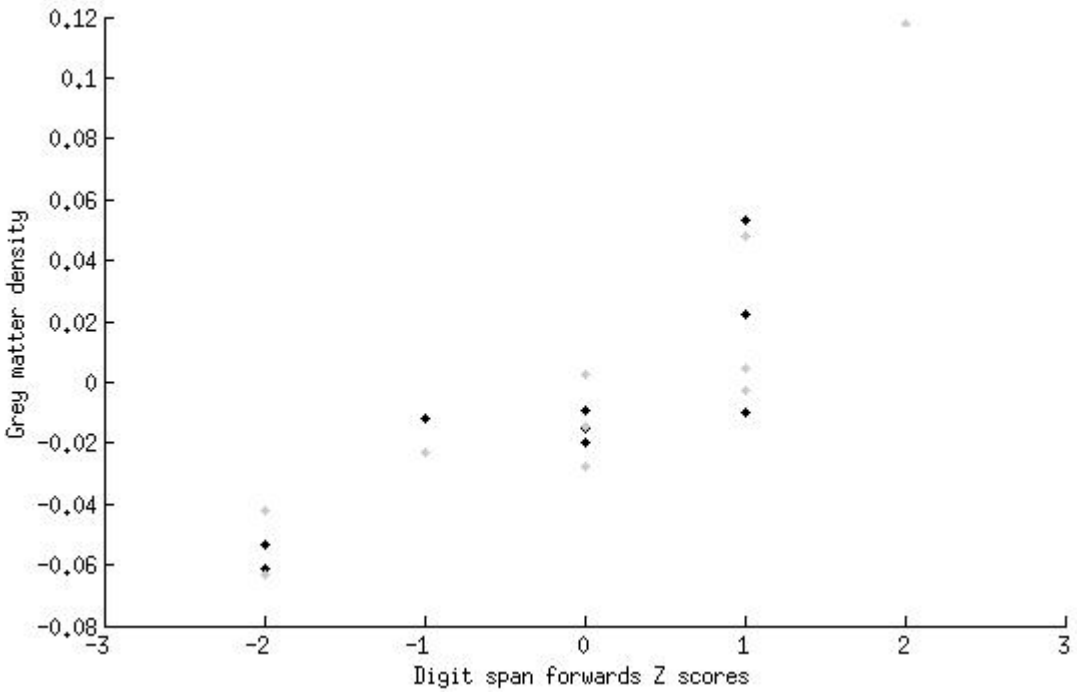

Fig 5.24 Scatterplot showing the positive correlation between grey matter density values and digit span forwards scores (expressed as z scores) in the most significant cluster (left superior temporal gyrus)

5.1.3.5.3 REY 15-WORD MEMORY TEST (DELAY)

Significant positive correlations were found between grey matter volume values and Rey 15 words (Delay) in left cerebellum (Posterior Lobe), bilateral anterior cingulate (BA 32/24), right medial frontal gyrus (BA 9), right superior frontal gyrus (BA 9), left postcentral gyrus (BA 3), bilateral caudate head and left parahippocampal gyrus (BA 34) (See Table 5.13, Figure 5.25 and 5.26).

Table 5.13 Areas of positive correlation between grey matter volume values and Rey 15 words (Delay) score in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Cerebellum Posterior Lobe	L		113	0.013	0.97	4.97	-48	-52	-21
Anterior Cingulate	L	32	159	0.042	0.87	3.69	-12	41	7
Medial Frontal Gyrus	R	9			0.84	3.48	4	45	16
	R	9			0.83	3.37	4	53	14
Postcentral Gyrus	L	3	26	0.038	0.85	3.56	-61	-18	30
Superior Frontal Gyrus	R	9	27	0.041	0.82	3.36	12	58	25
Anterior Cingulate	L	32	42	0.028	0.80	3.24	-12	44	-9
	R	32	27	0.036	0.80	3.21	12	45	-2
	L	24	114	0.013	0.79	3.14	-2	26	15
Caudate Head	L		40	0.029	0.73	2.82	-8	10	3
	L				0.65	2.41	-6	17	-3
Anterior Cingulate	R	24	35	0.045	0.71	2.72	6	21	-3
Caudate Head	R				0.70	2.68	10	14	3
Parahippocampal Gyrus	L	34	20	0.047	0.67	2.42	-20	-1	-10

R = Right L = Left BA = Brodmann Area

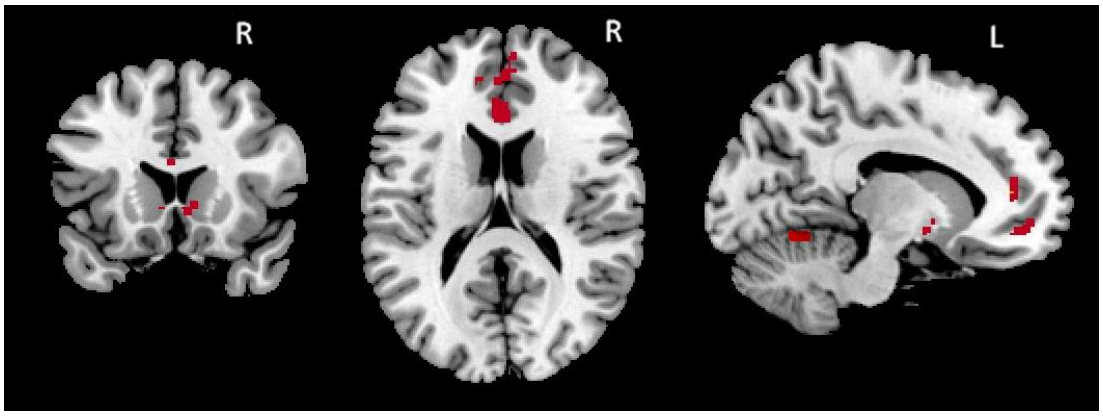

Fig 5.25 Areas of significant positive correlation between grey matter volume values and Rey 15 words (Delay)

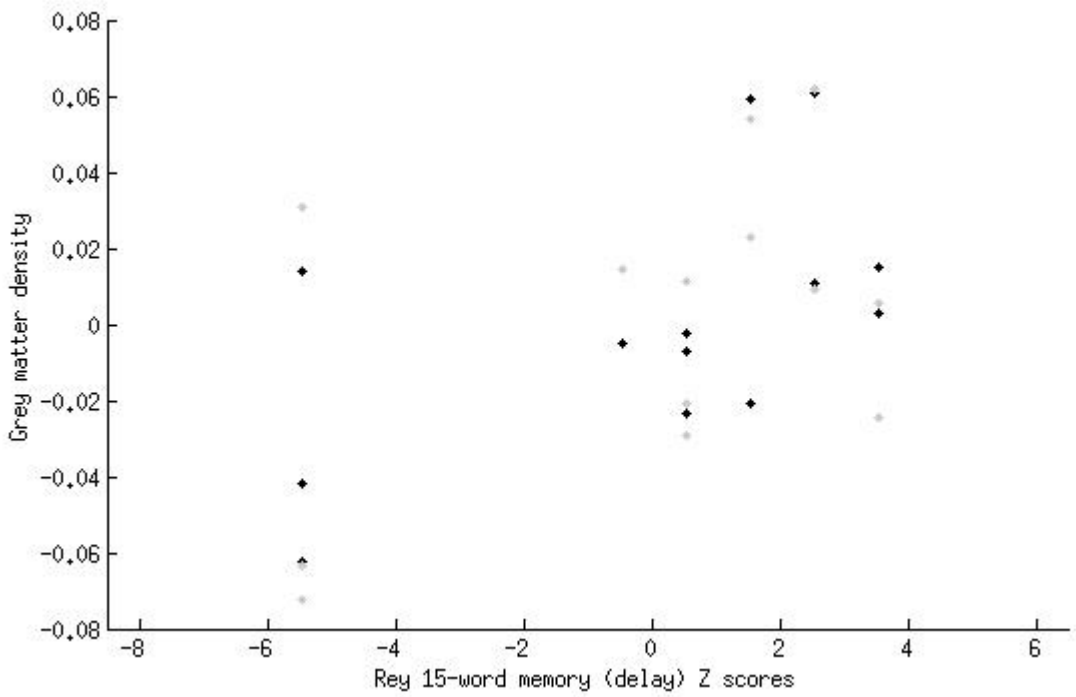

Fig 5.26 Scatterplot showing the positive correlation between grey matter density values and Rey 15-word memory test (delay) scores (expressed as z scores) in the most significant cluster (left anterior cingulate)

5.1.3.6 LEARNING AND ATTENTION

5.1.3.6.1 REY 15-WORD MEMORY TEST (IMMEDIATE RECALL)

Significant positive correlations were present between grey matter volume values and RAVLT (Immediate recall) score in the left superior frontal gyrus (BA 9), right caudate body, superior temporal gyrus bilaterally (BA 22/38) and left caudate head (See Table 5.14, Figure 5.27 and 5.28).

Table 5.14 Areas of positive correlation between grey matter volume values and Rey 15 words (Immediate recall) score in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Superior Frontal Gyrus	L	9	30	0.036	0.94	4.41	-44	36	28
Caudate Body	R		54	0.042	0.90	3.97	10	10	7
	R				0.84	3.46	10	2	11
Superior Temporal Gyrus	L	22	71	0.029	0.81	3.27	-63	-17	3
	L	22			0.79	3.16	-57	-6	4
	R	38	51	0.037	0.77	3.04	55	13	-9
Caudate Head	L		31	0.034	0.75	2.94	-8	19	-3
	L				0.73	2.82	-10	14	3

R = Right L = Left BA = Brodmann Area

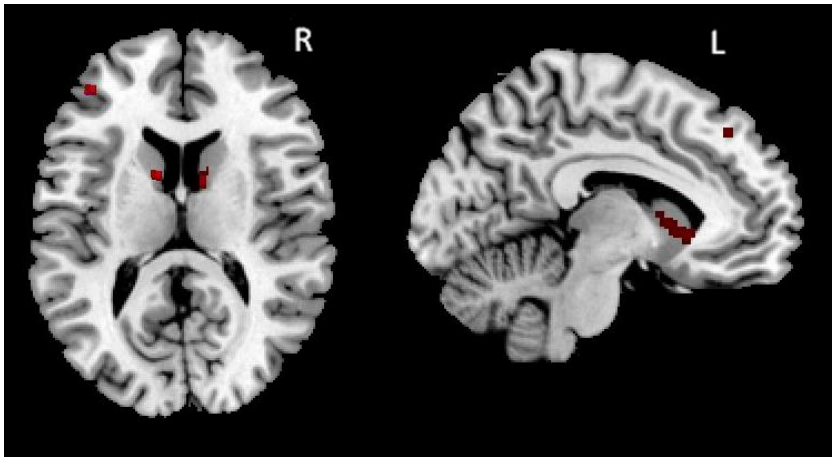

Fig 5.27 Areas of significant positive correlation between grey matter volume values and Rey 15 words (Immediate recall) score in the frontal and temporal cortex

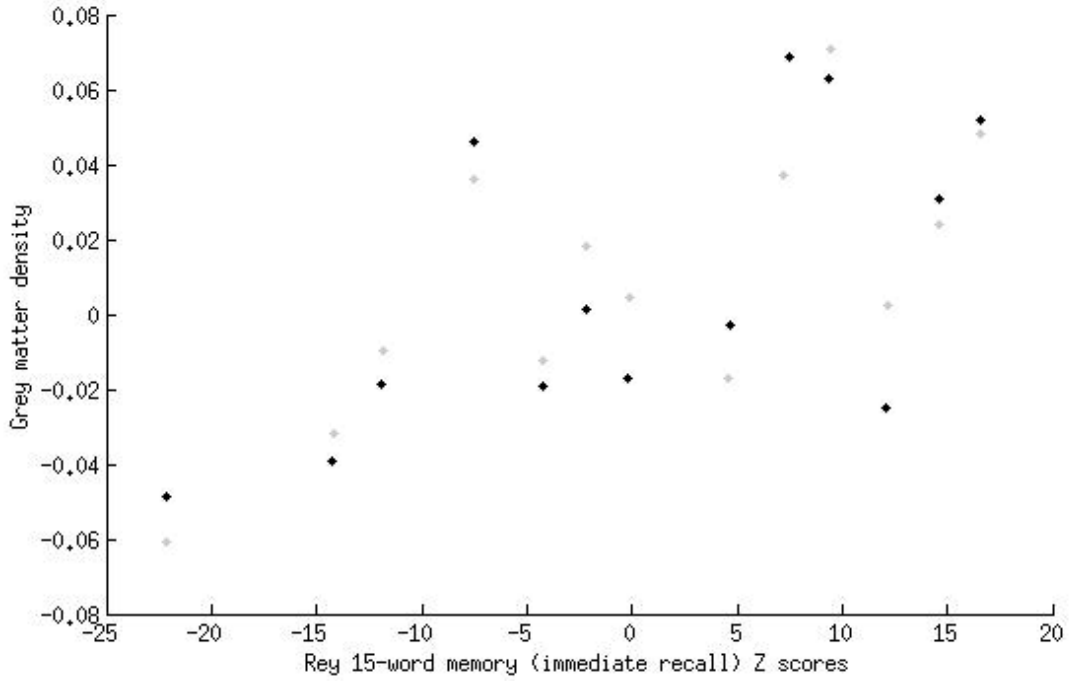

Fig 5.28 Scatterplot showing the positive correlation between grey matter density values and Rey 15-word memory test (immediate recall) scores (expressed as z scores) in the most significant cluster (left superior temporal gyrus)

5.1.3.7 VISUAL-CONSTRUCTION

5.1.3.7.1 REY COMPLEX FIGURE TEST (COPY)

Significant positive correlations between grey matter volume values and Rey Figure (Copy) score were found in posterior areas of the brain which are the right thalamus, right substania nigra, right limbic lobe (Uncus) (BA 34), left inferior

temporal gyrus (BA 20), right insula, left inferior parietal lobule (BA 40), right postcentral gyrus (BA 43), right precuneus (BA 19), right superior parietal lobule (BA 7) and left middle occipital gyrus (BA 37) (See Table 5.15, Figure 5.29 and 5.30).

Table 5.15 Areas of positive correlation between grey matter volume values and Rey Complex Figure (Copy) score in patients with PD without any neuropsychiatric symptoms

Brain areas	R/L	BA	Cluster Size	Cluster-level *P*-value (corrected)	r value	Z value at Local Maximum	Talairach coordinates		
							X	Y	Z
Thalamus	R		117	0.039	0.78	3.53	4	-23	12
Substania Nigra	R				0.67	2.78	14	-25	-4
Thalamus	R				0.65	2.65	8	-29	-2
Inferior Temporal Gyrus	L	20	36	0.033	0.78	3.49	-50	-6	-33
Inferior Parietal Lobule	L	40	37	0.033	0.77	3.47	-44	-55	34
Postcentral Gyrus	R	43	63	0.033	0.72	3.06	50	-19	18
Insula	R				0.62	2.49	38	-17	17
Middle Occipital Gyrus	L	37	39	0.033	0.71	3.06	-57	-63	-7
Limbic Lobe (Uncus)	R	34	43	0.031	0.69	2.90	14	-5	-20
Precuneus	R	19	38	0.047	0.66	2.75	32	-68	37
Superior Parietal Lobule	R	7			0.65	2.65	28	-72	44
Precuneus	R	19			0.61	2.47	28	-78	37

R = Right L = Left BA = Brodmann Area

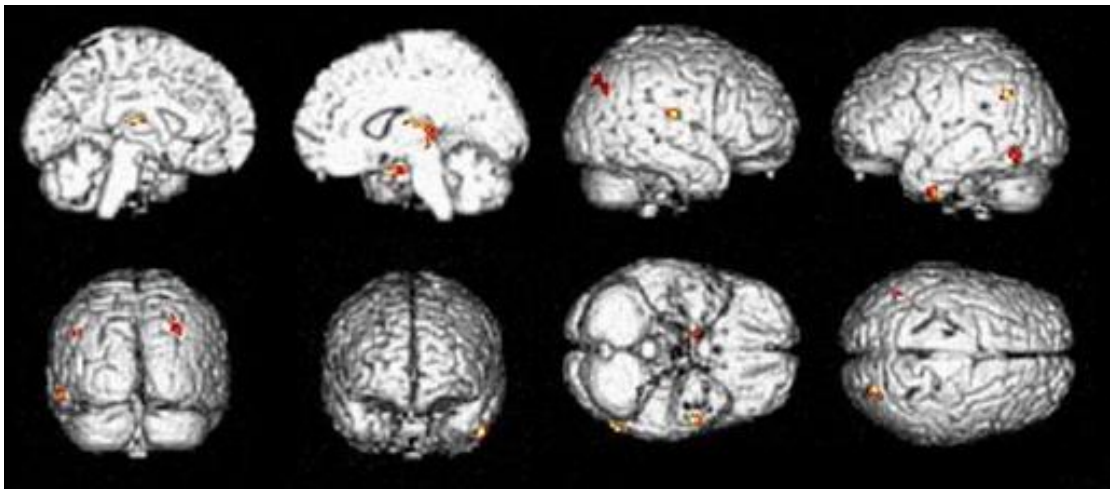

Fig 5.29 Regions with significant positive correlation with Rey Complex Figure (Copy) score

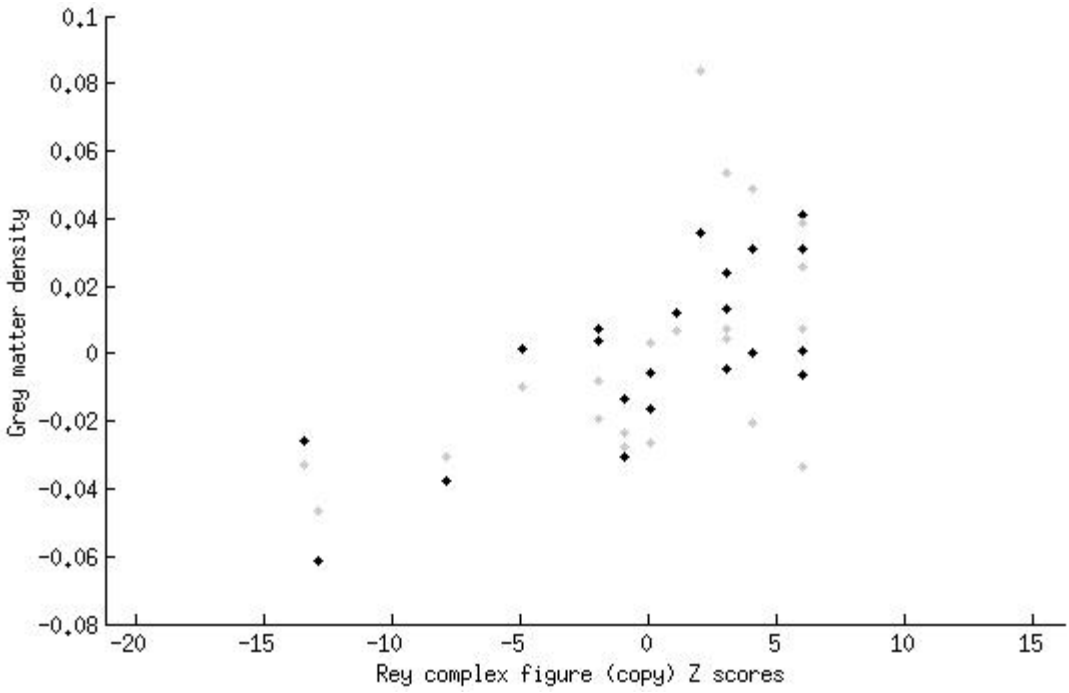

Fig 5.30 Scatterplot showing the positive correlation between grey matter density values and Rey complex figure (copy) scores (expressed as z scores) in the most significant cluster (right limbic lobe, uncus)

5.1.4 DISCUSSION

5.1.4.1 GLOBAL COGNITIVE ABILITIES

The current study identified some structural brain areas that are associated with global cognitive impairments including the frontal, temporal cortex and the cingulate gyrus which is in line with a previous VBM study (Melzer, et al., 2012). However, the previous study found more brain areas to be correlated with global cognitive abilities than the present study, which could be due to the larger sample size, the inclusion of patients with dementia or the use of different measurements to assess global cognitive abilities. Pereira and others (2009) did not find a correlation between grey matter density and MMSE scores which is not consistent with the present findings. Pereira et al (2009) used a significant cluster level of 0.001 which can explain the different findings between this and the present result as the present

study found no correlation between grey matter volume values and MMSE scores at 0.01, while a significant correlation was found at 0.05 cluster level. Our results, therefore, suggest that subtle deficits in frontal, temporal lobe and the cingulate gyrus might influence the overall level of global cognitive function in the early stages of PD.

5.1.4.2 EXECUTIVE ABILITY

The present findings showed that an association between grey matter volume and executive function performance is commonly found in the frontal, parietal, temporal cortex and anterior cingulate gyrus. These results may provide evidence of the involvement of non-frontal brain regions in executive dysfunction in non-demented PD which is in line with earlier findings (Camicioli, et al., 2009; Ibarretxe-Bilbao, et al., 2009; Nagano-Saito, et al., 2005). Seeley et al (2007) reported that functional connectivity in the frontal-parietal network was associated with working memory and control processes tasks in healthy participants. In our study, the association between the frontal-parietal regions and executive function performance was identified by the FAB, TMT and Digit Span backward tests. The involvement of frontal-parietal areas in executive dysfunction has also been reported in other studies. For instance, Matsui et al (2006) found that in non-demented patients with PD with low FAB scores, there was reduced perfusion in the left parietal lobe. Earlier behavioural studies demonstrated that FAB is not only correlated with frontal lobe functions but also reflects skills associated with a variety of other areas of the brain (Cohen et al., 2012; Lima, Meireles, Fonseca, Castro, & Garrett, 2008; Paviour et al., 2005). However, it might be possible that the more extensive correlation of this test which is assumed to tap only executive functions might reflect the actual multicomponential nature of the test. Unfortunately, this hypothesis cannot be tested

because of the lack of access to the original patient notes since the FAB sub-scores were not included in the database. In addition, the association between the frontal-parietal regions and digit span backwards has been reported previously in patients with neurodegenerative disease (Amici et al., 2007). Digit span backwards has been considered more effortful than digit span forwards and has a working memory component (Lezak, et al., 2012). In healthy participants, digit span backwards activated several brain regions including the bilateral superior temporal gyrus, left middle temporal gyrus, bilateral inferior parietal lobule, right precuneus, right superior parietal lobule, right supramarginal gyrus, bilateral superior frontal gyrus and bilateral middle frontal gyrus (Gerton et al., 2004). Taken together, these findings suggest that in patients with PD without dementia, dysfunction of functional and structural processes in frontal-parietal regions may result in impairments in executive functioning as reflected by decreased FAB and digit span backward scores.

Furthermore, lower digit span backward scores correlated with less grey matter in the temporal lobe, a region not usually associated with working memory skills but rather with visual processing (Ungerleider & Haxby, 1994). A possible explanation might be that when performing the digit span backwards, visualisation of the digit sequence is one of the strategies that could be used by the participant (Wager & Smith, 2003).

Although TMT is designed to assess frontal function, there is evidence to indicate that TMT is sensitive to impairment in multiple cognitive domains. For instance, the association between TMT (part B) and middle/medial/superior frontal gyrus and middle/superior temporal gyrus in the present study is in line with the

findings of a previous fMRI study which reported brain activation in the same areas when healthy participants performed the TMT (Zakzanis, Mraz, & Graham, 2005). A recent fMRI study has also found that in healthy subjects TMT (Part B minus part A) activated frontal cortex, occipital cortex, insula and the cerebellum (Ruscheweyh et al., 2012). The present findings support the idea that TMT (part B) is not sensitive to frontal functioning only, but that other brain areas such as the left temporal lobe (middle and superior temporal gyrus) also contribute to poor performance in this test. Therefore, our results provide structural evidence for the sensitivity of TMT damage in non-frontal regions. Additionally, in the present study, part B was found to be associated with more brain regions than part A. These results are consistent with the nature of the TMT test as part B is a more complex task than part A (Lezak, et al., 2012).

The association between lower grey matter volume in anterior cingulate gyrus and executive function performance was detected by the letter fluency and TMT tests. The letter fluency task requires the participant to initiate extensive searches for suitable words. The association between the anterior cingulate cortex and the letter fluency task has been reported by previous fMRI studies in healthy participants (Abrahams, et al., 2003; Ravnkilde, et al., 2002; Senhorini et al., 2011). The anterior cingulate cortex is linked to conflict monitoring, motivation and response initiation (Matsui, et al., 2006), therefore, our findings suggest that dysfunction of the anterior cingulate gyrus may result in lower scores on the letter fluency task. However, the present finding contrasts with a previous VBM study that found no correlation between letter fluency scores and grey matter volume values in patients with PD (Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009). Different demographic and clinical characteristics of PD patients (such as including

patients with visual hallucinations in the Pereira et al study) between the present study and the contrasting study can explain the difference in findings.

Significant negative correlations were found between grey matter volume values and the Stroop time interference score in the frontal, temporal cortex and caudate nuclei. Only two structural MRI studies have investigated the association between grey matter volume values and the Stroop Test in healthy participants. The first study showed a correlation between grey matter density and the Stroop score in the left insula, bilateral lateral prefrontal cortex, right middle temporal gyrus, right superior temporal gyrus, left occipital cortex and the left cerebellum (Ruscheweyh, et al., 2012). The second study found an association between grey matter volume values and the Stroop Test in the right hemisphere including the cerebellum, anterior cingulate cortex and inferior frontal gyrus (Takeuchi, et al., 2012). We can note that the findings of both VBM studies are inconsistent with each other with the exception of the involvement of the frontal cortex. However, although both studies examined normal participants, the first study included only older people (50 – 58 years of age) with a larger sample size (367 participants) whereas the second study included younger people (Mean age = 21.6 years, SD = 1.57), with a small sample size of 118 participants.

The present findings are partially supported by the Ruscheweyh et al (2012) study, particularly the association between Stroop scores and the inferior frontal gyrus and the middle/superior temporal gyrus. Furthermore, the present findings are in line with earlier fMRI and PET studies (using healthy participants) that reported an association between the Stroop Test and the bilateral inferior and middle frontal gyrus (Banich et al., 2000), right inferior temporal gyrus (Bush et al., 1998), right

superior temporal gyrus (Carter, Mintun, & Cohen, 1995) and the left caudate nuclei (Zysset, Schroeter, Neumann, & von Cramon, 2007). The current findings suggest that executive dysfunction in patients with PD reflects impairment in frontal and non-frontal regions such as temporal lobe and caudate nuclei. Indeed, structural and functional MRI studies reported that the right inferior frontal gyrus was found to be consistently associated with the Stroop task (Laird et al., 2005; Takeuchi, et al., 2012). This region had the largest cluster size associated with scores on the Stroop Test in the present study, suggesting that the right inferior frontal gyrus might be responsible for response inhibition and interference resolution; therefore, atrophy in this particular brain area may result in poorer performance on the Stroop Test.

5.1.4.3 ABSTRACT REASONING

The present study revealed that the middle/superior frontal, middle temporal and limbic lobe were associated with verbal and non-verbal abstract reasoning abilities. These findings are partially supported by a previous VBM study that found an association between grey matter density and Raven's Coloured Progressive Matrices scores in the middle and superior frontal gyrus and limbic lobe in patients with PD (Nagano-Saito, et al., 2005). In healthy participants most of the functional MRI studies have demonstrated frontal activation when performing RPM (Geake & Hansen, 2010; Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997; Wendelken, Nakhabenko, Donohue, Carter, & Bunge, 2008) while others have reported activation in the middle temporal gyrus (Prabhakaran, et al., 1997) and the superior temporal gyrus (Esposito, Kirkby, Van Horn, Ellmore, & Berman, 1999). Moreover, Chase et al (1984) reported an increase in glucose metabolism in the frontal and temporal lobes when normal participants performed the Similarities Test.

The above findings, as corroborated by other structural and functional studies, suggest that damage in the identified brain areas may cause impaired performance in abstract reasoning tasks in early PD.

5.1.4.4 NON-VERBAL MEMORY

The current study also reported that the frontal, limbic lobe (including the hippocampus) and cerebellum correlated with the Rey Complex Figure (Delayed), as this test is considered a non-verbal memory test which also involves a visuospatial component (Carlesimo et al., 2012). Behavioural studies reported that memory and visuospatial impairments are common in patients with PD (Aarsland, Marsh, et al., 2009; Wu, et al., 2012). The involvement of the limbic cortex, particularly the hippocampus suggests that atrophy of this brain area may result in low performance in the Rey Complex Figure (delayed) in non-demented PD. This suggestion is supported by a diffusion tensor imaging study that found an association between reduced hippocampal volume and Rey complex figure (delayed) performance in non-demented patients with PD (Carlesimo, et al., 2012). On the other hand, the present study could not find a significant correlation between grey matter volume values and Corsi Block-tapping scores. This result could be explained by small sample size used for this correlation analysis, as only a subset of 10 out of 23 non-demented PD patients without neuropsychiatric symptoms completed the Corsi Block-tapping Test.

5.1.4.5 VERBAL MEMORY

The present study showed that verbal memory scores were associated with the frontal, temporal lobe, anterior cingulate gyrus, caudate nucleus and the parahippocampus gyrus. This finding indicated that these structural brain areas may

be relevant to verbal memory deficits in PD. For instance, poor semantic fluency task performance has been linked to atrophy of the frontal and temporal lobe in patients with PD (Pereira, Junque, Marti, Ramirez-Ruiz, Bartres-Faz, et al., 2009). Although structural and functional imaging studies have found that frontal lobe damage is associated with letter fluency impairment while temporal lobe damage has more of an effect on category fluency performance (Birn et al., 2010; Gourovitch et al., 2000), patients also tend to rely on frontal functions when switching between sub-categories when they perform the semantic fluency task. This explanation may support the involvement of the frontal cortex in the present findings. The current study found an association between parahippocampus volume and memory performance on the Rey 15 words Test (Delayed recall). This finding is consistent with previous reports that also linked poor memory performance with hippocampal dysfunction in PD (Carlesimo, et al., 2012; Ibarretxe-Bilbao, et al., 2008).

The role of the caudate nucleus in memory impairment in PD patients has also been reported. Using a radial distance mapping technique, Apostolova et al (2010) found trend-level significant differences in the right lateral caudate in non-demented patients with PD when compared with healthy controls.

The present finding of digit span forward is consistent with a previous fMRI study that found similar patterns of activation when healthy participants performed the digit span forwards. Brain activation included the right supramarginal gyrus, bilateral inferior parietal lobule, left middle and inferior temporal gyrus, bilateral superior temporal gyrus and right medial frontal gyrus (Gerton, et al., 2004). Previous behavioural studies have reported that non-demented patients with PD have memory and attention deficits (Foltynie, et al., 2004; Muslimovic, et al., 2005; Wu,

et al., 2012), and the present finding provides evidence of structural brain regions that have an association with memory and attention tasks.

5.1.4.6 LEARNING AND ATTENTION

This study assessed learning and attention abilities and found significant positive correlations between grey matter volume values and RAVLT (Immediate recall) scores in the left superior frontal gyrus, caudate nucleus and superior temporal gyrus bilaterally. The association between frontal lobe and learning ability has been reported previously, by studies in which patients with frontal lesions performed significantly lower than patients with non-frontal lesions on the RAVLT (Immediate recall) (Eslinger & Grattan, 1994) and on a different measurement using the California Verbal Learning Test (Alexander, Stuss, & Fansabedian, 2003).

Deficit in the frontal lobe may reflect the role of working memory and attention when encoding information. The involvement of the caudate nucleus observed in the present study may be the basis for the learning difficulties experienced by patients with PD, since this brain region has been reported to play an important role in learning in healthy participants (Haruno et al., 2004; Seger & Cincotta, 2005). Patients with AD seem to have a slightly different pattern of association with performance on the RAVLT (immediate recall) compared with patients with PD. Using a ROI approach (the regions being: the hippocampus, medial temporal gyrus, inferior temporal gyrus, temporal pole, superior frontal gyrus, superior parietal lobule, precuneus, inferior frontal sulcus/caudal middle frontal gyrus, angular gyrus and supramarginal gyrus), Wolk and Dickerson (2011) found that in mild patients with AD the RAVLT (immediate recall) was associated with the hippocampus, medial temporal gyrus, temporal pole and caudal middle

frontal gyrus. The present results suggest that learning difficulty in non-demented patients with PD may be associated with atrophy in areas which are also concerned with semantic processing and perhaps working memory; interestingly, both these skills are required in the context of the RAVLT (immediate recall).

5.1.4.7 VISUAL-CONSTRUCTION

The last cognitive domain assessed in the current study was visual-construction ability. Significant positive correlations between grey matter volume values and Rey's Complex Figure Task (copy) scores were found in the posterior part of the brain including occipital, parietal lobe and limbic structures. This finding highlighted the contribution of the parietal and occipital regions in the Rey Complex Figure (copy) Task, which may reflect difficulty in the spatial organization of the figure (Lezak, et al., 2012). In addition, this test is associated with two brain regions in the basal ganglia, which are the right substantia nigra and right thalamus. The substantia nigra has a crucial role in PD pathology; the symptoms of PD reflect a deficit in this area (Braak, et al., 2004). One of the important functional roles of the substantia nigra is motor planning (Nicola, Surmeier, & Malenka, 2000) which could explain the association between this brain region and Rey's Complex Figure (copy). Furthermore, the Rey's Complex Figure has been found to be a useful measurement to distinguish patients with mild cognitive impairment from healthy subjects (Kasai et al., 2006).

The main finding of the present study was that cognitive impairment in non-demented PD patients is not limited to the reduction of fronto-striatal circuits. These findings provide a useful insight into the brain regions that correlate with general cognitive abilities as well as specific cognitive domains in non-demented patients

with PD. Our findings could have clinical implications or may be useful to differentiate cognitive decline in patients with PD from that caused by other neurodegenerative conditions.

6. CHAPTER SIX: GENERAL DISCUSSION

In general, non-motor symptoms play a major role in the course of PD, because these symptoms have a strong impact on patients' everyday life and may lead to early admittance in nursing homes. In addition, it has been observed that some of these non-motor symptoms i.e. neuropsychiatric symptoms and cognitive impairments occur even in the early stages of the disease. However, the investigation of these aspects is still challenging. Previous research has used different methodologies to explore these symptoms and has produced inconsistent results. The present project has tried to control various methodological shortcomings that were identified in previous studies, in an attempt to obtain a clearer picture of the biological breakdown leading to their early appearance of cognitive deficits in PD.

6.1 NEUROPSYCHIATRIC SYMPTOMS

From the literature, we noted that none of the reports explored the cognitive and neuroanatomical correlates of multiple neuropsychiatric symptoms. Other articles have looked at specific neuropsychiatric symptom, but failed to control for the other various neuropsychiatric symptoms which may have affected their results. Therefore, we thought that using the NPI as a tool to explore the neuropsychiatric profile of patients with PD would help us to exclude other symptoms when exploring a particular feature. Furthermore, unlike previous work, in the present study an extensive neuropsychological battery was used to explore multiple cognitive domains. Using this approach could provide a clearer picture of the cognitive skills which might have deteriorated in non-demented PD patients who develop neuropsychiatric symptoms. The underlying mechanism of neuropsychiatric symptoms is still unclear. Although there are several published studies which have investigated the neural correlates of neuropsychiatric symptoms using different

approaches, little is known about the structural brain areas that may associate with these symptoms. We have found that a VBM approach offers a suitable way to explore grey and white matter volume changes as it has been championed for its powerful approach for unbiased hypothesis testing across the whole brain (Luo & Nichols, 2003).

In chapter four, we hypothesised that neuropsychiatric symptoms (in general or as a specific symptom) may have an association with deficits in a particular cognitive domain and may also be associated with structural loss in specific brain areas. There are several reasons why we expected to find more cognitive decline in the abilities that depend on frontal lobe functions. Firstly, PD pathology causes pathophysiological deficits in the frontal cortex which could explain possible cognitive decline. Secondly, in the psychiatric population previous imaging studies identified an association between neuropsychiatric symptoms and dysfunction of the frontal cortex. Earlier studies have also reported executive dysfunctions in patients with PD who developed neuropsychiatric symptoms.

At the inception of this project, we were interested in exploring the cognitive and neural correlates of neuropsychiatric symptoms in general. We found that patients with multiple neuropsychiatric symptoms may be at a higher risk of developing executive dysfunction and possibly memory, attention and global cognitive impairments. In addition, VBM analyses identified deficits in two brain networks that may underlie the presence of multiple neuropsychiatric symptoms: the first involving the frontal lobe, insula and the basal ganglia and the second linking the anterior cingulate gyrus and the insula. These findings suggest that dysfunction/disconnection of cortical and sub-cortical regions may contribute to the occurrence of neuropsychiatric symptoms in non-demented patients with PD.

It has been reported that delusional misidentification is associated more frequently with damage in the right hemisphere rather than the left hemisphere in patients with neurological disease (Roane et al. 1998). Alexander et al (1979) suggested that damage to right hemisphere causes difficulty in recognition or identification, especially when memory is impaired. When these deficiencies occur in the context of frontal lobe dysfunction, judgment is diminished and delusional misidentification may occur. A VBM study (Bruen et al. 2011) found that in PD patients, delusions were associated with lower grey matter volume in predominantly right frontal and limbic structures. Frontal lobe atrophy, which produces a disturbance in judgment, self-awareness (Stuss, 1991 as cited in Roane et al. 1998), and relatedness to elements in the environment such as persons, places and objects (Feinberg and Roane, 1997), may also be responsible for the presence of delusional misidentification in PD.

In patients with AD delusions were associated with atrophy in the right frontoparietal regions (Bruen et al. 2008). It seems, therefore, that dysfunction in the right frontal lobe may give a significant contribution to the presence of delusional symptoms. Structural damage in the frontal lobe probably disrupts the functional role of this region in the assessment of mental contents and veridical reality checking (Shanks and Venneri, 2004).

Although the incidence of symptoms of delusion were low in the present sample, it is possible that delusional misidentifications might associate with content-related confabulations and delusional memories. The research to support this notion comes from the involvement of the frontal lobe areas in personal episodic memory retrieval. Moreover, behavioural studies have provided evidence of the association

between confabulations and delusional memories and failure of personal episodic memory retrieval in patients with AD (Cooper et al. 2006; Lee et al. 2007).

Experiments 3 and 4 explored the cognitive and neural correlates of depression which is the most common neuropsychiatric symptom. Behavioural findings suggested that non-demented patients with PD who experience depression also display attention and short term memory impairments. Moreover, some brain areas (bilateral inferior frontal gyrus, right rectal gyrus and the right parahippocampal gyrus) were identified as possible neural correlates underlying depression in non-demented PD patients. The present findings strongly suggest diagnostic and therapeutic implications. For instance, specialists who deal with patients with PD should be aware that depressive symptoms can occur in the early stages of PD and provide interventions that may help to treat or mitigate the effects of those symptoms. In so doing, patients with PD could avoid further cognitive decline and, more importantly, the development of neuropsychological impairments or, as this study suggests, attention and short term memory deficits.

Clinicians need to be aware of these specific cognitive impairments in patients with PD who have already developed depressive symptoms, as this can have practical implications for patient treatment and could provide useful information for patients, families in terms of implementing effective coping strategies. In addition, detecting brain regions whose structure is associated with depression may have an important impact on future research. The present findings provide a unique interpretational pattern because they are based on a combination of both neuropsychological and imaging techniques in exploring depression in PD. The use of this kind of methodology can provide a better understanding of both the cognitive and the neural correlates of depression in the early stages of PD.

Experiments 5 and 6 explored the cognitive and neural correlates of apathy which is the second most common neuropsychiatric symptom in PD. The present finding on apathy provides evidence of an association between specific cognitive decline and brain atrophy in patients with apathy. Neuropsychological findings emphasise that patients with apathy have cognitive impairment, particularly, executive function deficits. In addition, imaging results identified loss of volume in brain regions that are consistent with the cognitive finding and this may underlie the occurrence of apathy in PD patients including the inferior frontal gyrus, anterior cingulate cortex, insula and the cerebellum. The current findings have several implications for patients with PD, their families and clinicians. For example, increasing awareness of the potential presence of apathy while the symptom is still mild may help treatment of this symptom before it begins to have an even greater negative effect on the cognitive abilities of patients.

Compared to the profile of patients with depression, apathy seems to have a stronger impact on cognitive skills. Patients with apathy showed a different cognitive profile relative to patients with depression. Apathy was associated with executive dysfunctions while depression was associated with attention and short term memory deficits. Furthermore, a prior study has demonstrated that apathy is associated with dementia and cognitive impairments in patients with PD (Dujardin, et al., 2009). Apathy, therefore, appears to be a risk factor for more severe global cognitive impairment in this patient population. This represents a negative prognostic indicator and could, therefore, be useful as a clinical indicator of dementia risk in PD. Patients' caregivers could also benefit from the current findings by having greater insight into the disease. In addition, identifying brain structures that associate with apathy could provide useful information for future studies.

The experiments (7 and 8) in chapter four explored the cognitive and neural correlates of co-existing symptoms of depression and apathy. There are a number of reasons to justify why these symptoms were studied in conjunction. Firstly, several studies demonstrated that depression and apathy occur at the same time (Aarsland, et al., 1999; Cubo, et al., 2012; Dujardin, et al., 2007; Kirsch-Darrow, et al., 2006; Oguru, et al., 2010; Pedersen, Larsen, et al., 2009; Santangelo, Vitale, Trojano, Longo, et al., 2009; Starkstein, Mayberg, Preziosi, et al., 1992). Secondly, as far as I know, only two studies have investigated the cognitive profile of depression and apathy in patients with PD and the conclusions of these studies focused on either apathy or depression but not both symptoms simultaneously. For instance, the study by Starkstein and others (1992) aimed at examining the clinical and cognitive correlates of apathy and the dissociation between apathy and depression, whereas, the other study focused more on investigating the relationship between depression and cognitive dysfunctions in PD patients (Santangelo, Vitale, Trojano, Longo, et al., 2009). Moreover, both studies examined only a small number of patients who developed both depression and apathy.

The current findings of both depression and apathy indicated that patients with both neuropsychiatric symptoms have executive dysfunctions. Moreover, the imaging results suggest that dysfunction of a more extensive parietal-frontal network might underlie the occurrence of both depression and apathy in PD. The implications mentioned earlier concerning the study of apathy could also apply to this study in terms of both detection of these symptoms in the early stages and treatment, as the presence of these symptoms together is associated with more extensive structural impairment and most likely their presence represent greater risk of developing

dementia. These findings could also provide a better understanding of both symptoms for patients and their families, and could be used for research purposes.

We expected to find increased cognitive impairments in patients with both depression and apathy compared with those patients who only developed apathy. However, patients with both symptoms appeared to have milder executive function deficits (they had poor performance on only one executive test, letter fluency) when compared with patients without any neuropsychiatric symptoms. Experiment 5 showed that patients with only apathy had significantly lower scores on two of the executive function tests (letter fluency and Stroop test) when compared with patients with no symptoms. In explanation, we found that patients included in the apathy study had higher scores on the apathy subscale of the NPI than patients included in the depression and apathy study. This means that they had a more severe form of apathy which also caused more severe cognitive impairments in patients with apathy only.

The prevalence of neuropsychiatric symptoms in other neurodegenerative disorders causing dementia is said to range from 56% to 88% (Bergh and Selbaek 2012); in particular, about 78% of patients with AD had one or more neuropsychiatric symptoms (Tatsch et al. 2006). In addition, several reports have revealed that the most common symptom in mild AD was apathy followed by depression (Tatsch et al. 2006; Bruen et al. 2008; van Vlie et al. 2012; Tunnard et al. 2010), while in our study with PD depression was more common than apathy. However, in both groups of patients psychotic symptoms were less common. On the other hand, patients with Dementia with Lewy Bodies (DLB) are more likely to develop both mood and psychotic symptoms even in the early stages of the disease. For instance, Johnson et al. (2011) found that the most common symptoms in

patients with DLB were apathy (73%), anxiety (64%) and hallucinations (55%). Similarly another study also showed that apathy and hallucinations were the most common symptoms in the early stages of DLB (Ricci et al. 2009). This study emphasised that patients with DLB developed more symptoms than patients with AD. Therefore, although the neuropsychiatric symptoms are common in neurodegenerative disorders, there are differences in terms of the most common symptoms depending of the type of the disease.

The cognitive profile of AD patients with apathy showed that these patients had lower performance on tests of globe cognitive ability, executive function, verbal fluency, and memory (Bruen et al. 2008; Grossi et al. 2012). The presence of executive dysfunction in AD patients with apathy is supported by a study that found these patients had significantly lower scores on tests of verbal fluency than patients without apathy (Drijgers et al. 2011). A study of AD patients with depression showed that these patients had impairment in attention and memory skills (Jean et al. 2005), while another report found an association between depression and executive dysfunction in the early stages of AD (Lonie et al. 2008). In addition, it has been reported that AD patients with both depression and apathy had significantly lower total score on the FAB than patients with either depression or apathy alone (Nakaaki et al. 2008). Ricci et al. (2009) compared the cognitive profile of patients with DLB and AD in the early stages of the disease who developed neuropsychiatric symptoms using extensive neuropsychological assessments. They found that patients with DLB performed significantly worse on tests of attention and executive functions, whereas AD patients had significantly lower scores on tests of long-term memory (Ricci et al. 2009). Further studies have also examined the cognitive profile of patients with PD, DLB and multiple system atrophy who had neuropsychiatric symptoms (Kao et al.

2009; Perri et al, 2013). The results showed that the DLB group had the most cognitive deficit, followed by the multiple system atrophy group, and then the PD group. The DLB and MSA groups had worse executive functions and visuospatial abilities than the PD group, while patients with DLB had more severe memory deficits than both the PD and the MSA groups (Kao et al. 2009). A recent published study indicated that hallucinations were correlated with severity of visuospatial deficits in patients with DLB (Perri et al. 2013).

From the above data, it appears that patients with PD and neuropsychiatric symptoms have a distinguishable cognitive profile from that of patients with AD or DLB. While the present study showed that patients with multiple symptoms had significantly more executive dysfunction, studies of patients with AD have indicated that neuropsychiatric symptoms in patients with this condition are associated with deficits in long-term memory while in patients with DLB are associated with more extensive cognitive impairment including deficits of attention, memory, executive functions and visuospatial skills. In terms of specific behavior disturbance, the present study indicated that depression was associated with attention and short-term memory impairment in PD, while in studies of AD depression has been found in association with deficits of attention, long-term memory and executive functions. For apathy, our study showed that this symptom was associated with executive dysfunction. In studies of AD, however, apathy was related with greater global cognitive decline including memory and executive functions. These findings could have diagnostic and therapeutic implications in terms of better understanding the cognitive and behavioural correlates of each neurodegenerative disease.

In imaging studies with AD patients apathy was found associated with atrophy in the bilateral inferior frontal gyrus (Bruen et al. 2008), bilateral middle

frontal gyrus (Bruen et al. 2008; Vasconcelos, et al., 2011; Apostolova et al. 2007), right superior frontal gyrus (Bruen et al. 2008), right orbitofrontal gyrus, left inferior temporal gyrus (Vasconcelos, et al., 2011), left orbitofrontal gyrus (Tunnard et al. 2010), bilateral anterior cingulate (Bruen et al. 2008, Tummard et al. 2010; Apostolova et al. 2007), left caudate nucleus and putamen (Bruen et al. 2008). Imaging studies of depression in AD found an association between this symptom and atrophy in the left inferior temporal gyrus (Son et al. 2013), the right orbitofrontal gyrus, the inferior frontal gyrus bilaterally and the right middle frontal gyrus (Kang et al. 2012). A recent published study showed that depression in mild AD and DLB was associated with atrophy in the prefrontal and temporal regions (Lebedev et al. 2013).

Although these findings have indicated that there are underlying similarities in brain atrophy in different neurodegenerative conditions which are relevant for the appearance of specific behavioural disturbances. These include atrophy in orbitofrontal structures in major depressive disorders and anterior cingulate cortex in apathy; there are, however, other brain areas that are implicated in the appearance of specific neuropsychiatric symptoms within specific diseases. These findings suggest that the underlying mechanisms of depression and apathy in PD may involve other brain areas that were not observed in patients with other neurodegenerative diseases who developed these symptoms, and these rather than been essential contributors may reflect ancillary disease specific dysfunction or differences in level of disease severity across studies, which might not have been factored in and accounted for in the analyses.

The present study only explored the cognitive and neural correlates of PD patients at a mild stage. This could be considered a limitation of the current study regarding the full development of neuropsychiatric symptomatology. In addition, the depression and apathy study included only patients with mild apathy which may have impacted on the final results. While we acknowledge this limitation, it is also the case that at a milder stage of the disease symptoms appears in isolation and, although milder, the findings are not contaminated by the possible effect of comorbidities related to the presence of a range of other symptoms.

Future studies may explore the cognitive and neural correlates of those patients with PD who have more severe depression and apathy. Moreover, other studies may explore the cognitive and neural correlates at the moderate and advanced stages of the disease. In addition, future investigation could explore the cognitive and neural correlates of anxiety in patients with PD and compare them with patients without any neuropsychiatric features or healthy controls. Only two studies have examined the cognitive correlates of anxiety in PD (Bogdanova & Cronin-Golomb, 2012; Foster, et al., 2010) but neither of them compared patients with anxiety versus patients without any neuropsychiatric symptoms or healthy controls. Furthermore, the underlying neurobiological mechanisms of anxiety in PD have not yet been explored, which is something that could add a further dimension to the investigation and clarification of the causes of neuropsychiatric symptoms in PD.

6.2 COGNITIVE IMPAIRMENT IN PD

Experiment 9 was designed to explore the associations between grey matter volume loss and cognitive impairments in non-demented patients with PD. It has been thought that cognitive decline in non-demented patients with PD results from

the atrophy of fronto-striatal circuits. However, we hypothesised that other brain areas may contribute to cognitive impairment in PD. In the last decade, various imaging studies have attempted to examine such hypotheses; however, limitations were identified in these studies such as the inclusion of lack of screening for the presence of neuropsychiatric symptoms and the investigation of limited cognitive domains. Additionally, we noted that some earlier reports focused only on examining the limbic areas and the temporal cortex. Therefore, in experiment 9 we used the NPI to exclude a wide range of neuropsychiatric symptoms. This may have contributed to more focused findings. Further, we used an extensive battery of neuropsychological tests to evaluate multiple cognitive domains. Finally, we thought that the best way to test our hypothesis was to use a whole brain approach which could help the identification of any brain areas that might be associated with the decline of global cognitive skills or of specific cognitive abilities.

The present research revealed that global cognitive skills measured by the MMSE correlated with grey matter volume values in the frontal and temporal lobe and cingulate cortex. Therefore, abnormalities in these brain regions may be responsible for the overall cognitive decline in non-demented patients with PD, suggesting that grey matter degeneration in the identified regions might be indicative of a critical point in the early stages of progression towards mild cognitive impairments and dementia.

The association between executive dysfunctions (assessed by different tests: FAB, letter fluency test, TMT, Stroop test and digit span backwards) and grey matter volumes were mainly found in the frontal, parietal, temporal lobes and the anterior cingulate gyrus. These findings indicate that deficits of executive abilities are not restricted to atrophy in fronto-striatal circuits as previously reported (Lewis, et al.,

2003; Monchi, et al., 2004; Owen, 2004; Zgaljardic, et al., 2006), but other brain regions may contribute to the executive impairments in non-demented patients with PD.

The lower performance on the verbal and non-verbal abstract reasoning tasks was associated with the middle/superior frontal, middle temporal and limbic lobe. Therefore, volume loss in these regions may have an important role for the impairment of the conceptualisation ability as well as verbal reasoning skills in non-demented PD.

It is well known that hippocampus and parahippocampal gyrus changes play a crucial role in memory dysfunctions. Our study also found that these brain areas were associated with memory task scores. Importantly, the results from this experiment point out that the involvement of atrophy in either left or right medial temporal structures, which had different patterns of association in verbal and non-verbal memory, implying that volume loss in the identified brain areas may play a vital role in memory deficits in PD.

The current study also found that RAVLT (immediate recall) scores were correlated with grey matter volume values in the frontal, temporal lobe and the caudate nucleus, suggesting that atrophy in these regions may reflect deficits in learning and attention abilities in PD. In particular, some studies demonstrated that frontal lobe atrophy is linked to encoding difficulty (Eslinger & Grattan, 1994), while temporal lobe atrophy might reflect the contribution of semantic processing in a learning task (Alexander, et al., 2003). In addition, the present findings showed that visual-constructional scores (as measured by Rey's Complex Figure task - Copy) associated with areas located in the posterior part of the brain. These are areas

important in visuospatial and visuoperceptual processing and are central to the impairments observed in the spatial organization of the figure.

In conclusion, this study has investigated the brain regions that are associated with the different cognitive domains of global cognitive skills, executive functions, abstract reasoning, memory, visual-constructional abilities and learning and attentional abilities. According to the present results, each cognitive domain was found to be associated with dysfunction to particular configurations of brain areas. This information can be most useful to distinguish patterns of brain regions associated with cognitive consequences of typical PD from profiles of atrophy and cognition due to other overlapping neurodegenerative diseases. Finally, the present findings provide key data for generating new working hypotheses for future research in this field.

7. REFERENCE

Aarons, S., Peisah, C., & Wijeratne, C. (2012). Neuropsychiatric effects of Parkinson's disease treatment. *Australasian journal on ageing, 31*(3), 198-202. doi: 10.1111/j.1741-6612.2012.00632.x

Aarsland, D., Andersen, K., Larsen, J. P., Lolk, A., & Kragh-Sorensen, P. (2003). Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Archives of Neurology, 60*(3), 387-392.

Aarsland, D., Andersen, K., Larsen, J. P., Perry, R., Wentzel-Larsen, T., Lolk, A., & Kragh-Sorensen, P. (2004). The rate of cognitive decline in Parkinson disease. [Comparative Study]. *Archives of Neurology, 61*(12), 1906-1911. doi: 10.1001/archneur.61.12.1906

Aarsland, D., Bronnick, K., Alves, G., Tysnes, O. B., Pedersen, K. F., Ehrt, U., & Larsen, J. P. (2009). The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry, 80*(8), 928-930. doi: DOI 10.1136/jnnp.2008.166959

Aarsland, D., Bronnick, K., Ehrt, U., De Deyn, P. P., Tekin, S., Emre, M., & Cummings, J. L. (2007). Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. [Research Support, Non-U.S. Gov't]. *Journal of neurology, neurosurgery, and psychiatry, 78*(1), 36-42. doi: 10.1136/jnnp.2005.083113

Aarsland, D., Larsen, J. P., Lim, N. G., Janvin, C., Karlsen, K., Tandberg, E., & Cummings, J. L. (1999). Range of neuropsychiatric disturbances in patients with Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry, 67*(4), 492-496.

Aarsland, D., Larsen, J. P., Tandberg, E., & Laake, K. (2000). Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *Journal of the American Geriatrics Society, 48*(8), 938-942.

Aarsland, D., Litvan, I., & Larsen, J. P. (2001). Neuropsychiatric symptoms of patients with progressive supranuclear palsy and Parkinson's disease. *The Journal of neuropsychiatry and clinical neurosciences, 13*(1), 42-49.

Aarsland, D., Marsh, L., & Schrag, A. (2009). Neuropsychiatric symptoms in Parkinson's disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Movement disorders : official journal of the Movement Disorder Society, 24*(15), 2175-2186. doi: 10.1002/mds.22589.

Aarsland, D., Pahlhagen, S., Ballard, C. G., Ehrt, U., & Svenningsson, P. (2012). Depression in Parkinson disease--epidemiology, mechanisms and management. [Research Support, Non-U.S. Gov't Review]. *Nature reviews. Neurology, 8*(1), 35-47. doi: 10.1038/nrneurol.2011.189

Abbas, N., Lucking, C. B., Ricard, S., Durr, A., Bonifati, V., De Michele, G., . . . Brice, A. (1999). A wide variety of mutations in the parkin gene are responsible for autosomal recessive parkinsonism in Europe. French Parkinson's Disease Genetics Study Group and the European Consortium on Genetic Susceptibility in Parkinson's Disease. [Research Support, Non-U.S. Gov't]. *Human molecular genetics, 8*(4), 567-574.

Abou-Sleiman, P. M., Healy, D. G., Quinn, N., Lees, A. J., & Wood, N. W. (2003). The role of pathogenic DJ-1 mutations in Parkinson's disease. [Comparative Study Research Support, Non-U.S. Gov't]. *Annals of Neurology, 54*(3), 283-286. doi: 10.1002/ana.10675

Abrahams, S., Goldstein, L. H., Simmons, A., Brammer, M. J., Williams, S. C. R., Giampietro, V. P., . . . Leigh, P. N. (2003). Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. *Human brain mapping, 20*(1), 29-40. doi: Doi 10.1002/Hbm.10126

Adler, T. (2009). Pesticides and Parkinson's disease: the legacy of contaminated well water. [Comment News]. *Environmental health perspectives, 117*(12), A553.

Ahearn, D. J., McDonald, K., Barraclough, M., & Leroi, I. (2012). An exploration of apathy and impulsivity in Parkinson disease. *Current gerontology and geriatrics research, 2012*, 390701. doi: 10.1155/2012/390701

Albanese, A. (2003). Diagnostic criteria for Parkinson's disease. *Neurological Sciences, 24*, S23-S26.

Alexander, M. P., Stuss, D. T., & Benson, D. F. (1979). Capgras syndrome: a reduplicative phenomenon. [Case Reports]. *Neurology, 29*(3), 334-339.

Alexander, M. P., Stuss, D. T., & Fansabedian, N. (2003). California Verbal Learning Test: performance by patients with focal frontal and non-frontal lesions. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Brain : a journal of neurology, 126*(Pt 6), 1493-1503.

Alexopoulos, G. S., Abrams, R. C., Young, R. C., & Shamoian, C. A. (1988). Cornell Scale for Depression in Dementia. [Research Support, Non-U.S. Gov't]. *Biological Psychiatry, 23*(3), 271-284.

Allcock, L. M., Ullyart, K., Kenny, R. A., & Burn, D. J. (2004). Frequency of orthostatic hypotension in a community based cohort of patients with Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry, 75*(10), 1470-1471. doi: 10.1136/jnnp.2003.029413

Allman, J. M., Hakeem, A., Erwin, J. M., Nimchinsky, E., & Hof, P. (2001). The anterior cingulate cortex. The evolution of an interface between emotion and cognition. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Annals of the New York Academy of Sciences, 935*, 107-117.

American Psychiatric association. (1980). *Diagnostic and Statistical Manual of Mental Disorders. Third edition. Washington, DC: American Psychiatric.*

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th., text rev. ed.). Washington, DC: Author.

Amici, S., Ogar, J., Brambati, S. M., Miller, B. L., Neuhaus, J., Dronkers, N. L., & Gorno-Tempini, M. L. (2007). Performance in specific language tasks correlates with regional volume changes in progressive aphasia. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Cognitive and behavioral neurology : official journal of the Society for Behavioral and Cognitive Neurology, 20*(4), 203-211. doi: 10.1097/WNN.0b013e31815e6265

Apostolova, L. G., Akopyan, G. G., Partiali, N., Steiner, C. A., Dutton, R. A., Hayashi, K. M., . . . Thompson, P. M. (2007). Structural correlates of apathy in Alzheimer's disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *Dementia and geriatric cognitive disorders, 24*(2), 91-97. doi: 10.1159/000103914

Apostolova, L. G., Beyer, M., Green, A. E., Hwang, K. S., Morra, J. H., Chou, Y. Y., . . . Thompson, P. M. (2010). Hippocampal, Caudate, and Ventricular Changes in Parkinson's Disease with and Without Dementia. *Movement Disorders, 25*(6), 687-695. doi: Doi 10.1002/Mds.22799

Apostolova, L. G., & Cummings, J. L. (2008). Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Dementia and geriatric cognitive disorders, 25*(2), 115-126. doi: 10.1159/000112509

Appleby, B. S., Duggan, P. S., Regenberg, A., & Rabins, P. V. (2007). Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: A meta-analysis of ten years' experience. *Movement Disorders, 22*(12), 1722-1728. doi: Doi 10.1002/Mds.21551

Appollonio, I., Leone, M., Isella, V., Piamarta, F., Consoli, T., Villa, M. L., . . . Nichelli, P. (2005). The Frontal Assessment Battery (FAB): normative values in an Italian population sample. [Comparative Study]. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 26*(2), 108-116. doi: 10.1007/s10072-005-0443-4

Arai, H., Furuya, T., Mizuno, Y., & Mochizuki, H. (2006). Inflammation and infection in Parkinson's disease. [Review]. *Histology and histopathology, 21*(6), 673-678.

Arnulf, I. (2006). Sleep and wakefulness disturbances in Parkinson's disease. *Journal of Neural Transmission-Supplement*(70), 357-360.

Ascherio, A., Chen, H., Weisskopf, M. G., O'Reilly, E., McCullough, M. L., Calle, E. E., . . . Thun, M. J. (2006). Pesticide exposure and risk for Parkinson's disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Annals of Neurology, 60*(2), 197-203. doi: 10.1002/ana.20904

Ballmaier, M., Sowell, E. R., Thompson, P. M., Kumar, A., Narr, K. L., Lavretsky, H., . . . Toga, A. W. (2004). Mapping brain size and cortical gray matter changes in elderly depression. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. *Biological Psychiatry, 55*(4), 382-389. doi: 10.1016/j.biopsych.2003.09.004

Baltadjieva, R., Giladi, N., Gruendlinger, L., Peretz, C., & Hausdorff, J. M. (2006). Marked alterations in the gait timing and rhythmicity of patients with de novo Parkinson's disease. [Comparative Study]. *The European journal of neuroscience, 24*(6), 1815-1820. doi: 10.1111/j.1460-9568.2006.05033.x

Bandopadhyay, R., Kingsbury, A. E., Cookson, M. R., Reid, A. R., Evans, I. M., Hope, A. D., . . . Lees, A. J. (2004). The expression of DJ-1 (PARK7) in normal human CNS and idiopathic Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Brain : a journal of neurology, 127*(Pt 2), 420-430. doi: 10.1093/brain/awh054

Banich, M. T., Milham, M. P., Atchley, R. A., Cohen, N. J., Webb, A., Wszalek, T., . . . Brown, C. (2000). Prefrontal regions play a predominant role in imposing an attentional 'set': evidence from fMRI. [Research Support, Non-U.S. Gov't]. *Brain research. Cognitive brain research, 10*(1-2), 1-9.

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Phan, K. L. (2007). Amygdala-frontal connectivity during emotion regulation. [Research Support, N.I.H., Extramural]. *Social cognitive and affective neuroscience, 2*(4), 303-312. doi: 10.1093/scan/nsm029

Barbas, N. R. (2006). Cognitive, affective, and psychiatric features of Parkinson's disease. *Clinics in Geriatric Medicine, 22*(4), 773-+. doi: DOI 10.1016/j.cger.2006.06.004

Baron, J. A. (1986). Cigarette smoking and Parkinson's disease. [Research Support, Non-U.S. Gov't Review]. *Neurology, 36*(11), 1490-1496.

Bartels, A. L., Balash, Y., Gurevich, T., Schaafsma, J. D., Hausdorff, J. M., & Giladi, N. (2003). Relationship between freezing of gait (FOG) and other features of Parkinson's: FOG is not correlated with bradykinesia. *Journal of Clinical Neuroscience, 10*(5), 584-588. doi: Doi 10.1016/S0967-5868(03)00192-9

Bechara, A., Damasio, H., Damasio, A. R., & Lee, G. P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 19*(13), 5473-5481.

Beck, A. T., & Steer, R. A. (1990). Beck Anxiety Inventory Manual. San Antonio, The Psychological Corporation.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiatry, 4*, 561-571.

Benedict, R. H. B., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test Revised: Normative data and analysis of inter-form and test-retest reliability. *Clinical Neuropsychologist, 12*(1), 43-55. doi: DOI 10.1076/clin.12.1.43.1726

Benoit, M., Koulibaly, P. M., Migneco, O., Darcourt, J., Pringuey, D. J., & Robert, P. H. (2002). Brain perfusion in Alzheimer's disease with and without apathy: a SPECT study with statistical parametric mapping analysis. *Psychiatry research, 114*(2), 103-111.

Benoit, M., & Robert, P. H. (2011). Imaging correlates of apathy and depression in Parkinson's disease. *Journal of the neurological sciences*. doi: 10.1016/j.jns.2011.07.006

Benton, A. (1968). Differential behavioral effects in frontal lobe disease. Neuropsyhologia, 6, 53-60.

Benton, A., Hamsher, K. d., Varney, N., & Spreen, O. (1994). *Contributions to neuropsychological assessment* (2nd ed.). New York: Oxford University Press.

Benton, A. L., Hamsher, K., Varney, N. R., & Spreen, O. (1983). Contributions to neuropsychological assessment. New York: Oxford University Press.

Benton, A. L., & Van Allen, M. W. (1968). Impairment in facial recognition in patients with cerebral disease. Trans Am Neurol Assoc, 93:38–42.

Berg, D., Schweitzer, K. J., Leitner, P., Zimprich, A., Lichtner, P., Belcredi, P., . . . Gasser, T. (2005). Type and frequency of mutations in the LRRK2 gene in familial and sporadic Parkinson's disease*. *Brain : a journal of neurology, 128*(Pt 12), 3000-3011. doi: 10.1093/brain/awh666

Bhidayasiri, R., Wannachai, N., Limpabandhu, S., Choeytim, S., Suchonwanich, Y., Tananyakul, S., . . . Asawavichienjinda, T. (2011). A national registry to determine the distribution and prevalence of Parkinson's disease in Thailand: implications of urbanization and pesticides as risk factors for Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Neuroepidemiology, 37*(3-4), 222-230. doi: 10.1159/000334440

Birn, R. M., Kenworthy, L., Case, L., Caravella, R., Jones, T. B., Bandettini, P. A., & Martin, A. (2010). Neural systems supporting lexical search guided by letter and semantic category cues: a self-paced overt response fMRI study of verbal fluency. [Research Support, N.I.H., Intramural]. *Neuroimage, 49*(1), 1099-1107. doi: 10.1016/j.neuroimage.2009.07.036

Biundo, R., Formento-Dojot, P., Facchini, S., Vallelunga, A., Ghezzo, L., Foscolo, L., . . . Antonini, A. (2011). Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. *Journal of the neurological sciences, 310*(1-2), 64-69. doi: 10.1016/j.jns.2011.08.001

Biver, F., Goldman, S., Delvenne, V., Luxen, A., De Maertelaer, V., Hubain, P., . . . Lotstra, F. (1994). Frontal and parietal metabolic disturbances in unipolar depression. *Biological Psychiatry, 36*(6), 381-388.

Blackinton, J. G., Anvret, A., Beilina, A., Olson, L., Cookson, M. R., & Galter, D. (2007). Expression of PINK1 mRNA in human and rodent brain and in Parkinson's disease. [Research Support, N.I.H., Extramural Research Support, N.I.H., Intramural Research Support, Non-U.S. Gov't]. *Brain research, 1184*, 10-16. doi: 10.1016/j.brainres.2007.09.056

Bloem, B. R., Hausdorff, J. M., Visser, J. E., & Giladi, N. (2004). Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Movement disorders : official journal of the Movement Disorder Society, 19*(8), 871-884. doi: 10.1002/mds.20115

Bogdanova, Y., & Cronin-Golomb, A. (2012). Neurocognitive correlates of apathy and anxiety in Parkinson's disease. *Parkinson's disease, 2012*, 793076. doi: 10.1155/2012/793076

Bond, A., & Lader, M. (1974). Use of Analog Scales in Rating Subjective Feelings. *British Journal of Medical Psychology, 47*(Sep), 211-218.

Bonifati, V., Rizzu, P., van Baren, M. J., Schaap, O., Breedveld, G. J., Krieger, E., . . . Heutink, P. (2003). Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. [Research Support, Non-U.S. Gov't]. *Science, 299*(5604), 256-259. doi: 10.1126/science.1077209

Booij, J., Speelman, J. D., Horstink, M. W. I. M., & Wolters, E. C. (2001). The clinical benefit of imaging striatal dopamine transporters with [I-123]FP-CIT SPET in differentiating patients with presynaptic parkinsonism from those with other forms of parkinsonism. *European Journal of Nuclear Medicine, 28*(3), 266-272.

Bora, E., Fornito, A., Pantelis, C., & Yucel, M. (2012). Gray matter abnormalities in Major Depressive Disorder: A meta-analysis of voxel based morphometry studies. *Journal of Affective Disorders, 138*(1-2), 9-18. doi: DOI 10.1016/j.jad.2011.03.049

Braak, H., Del Tredici, K., Rub, U., de Vos, R. A., Jansen Steur, E. N., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Neurobiology of Aging, 24*(2), 197-211.

Braak, H., Ghebremedhin, E., Rub, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. [Research Support, Non-U.S. Gov't Review]. *Cell and tissue research, 318*(1), 121-134. doi: 10.1007/s00441-004-0956-9

Braak, H., Rub, U., Jansen Steur, E. N., Del Tredici, K., & de Vos, R. A. (2005). Cognitive status correlates with neuropathologic stage in Parkinson disease. [Research Support, Non-U.S. Gov't]. *Neurology, 64*(8), 1404-1410. doi: 10.1212/01.WNL.0000158422.41380.82

Brain Research Trust. (2013). Parkinson's disease, Retrieved January 03, 2013 from http://www.brt.org.uk/parkinsons-disease

Brauer, S. G., Woollacott, M., & Shumway-Cook, A. (2002). The influence of a concurrent cognitive task on the compensatory stepping response to a perturbation in balance-impaired and healthy elders. [Research Support, U.S. Gov't, P.H.S.]. *Gait & posture, 15*(1), 83-93.

Bremner, J. D., Vythilingam, M., Vermetten, E., Nazeer, A., Adil, J., Khan, S., . . . Charney, D. S. (2002). Reduced volume of orbitofrontal cortex in major depression. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *Biological Psychiatry, 51*(4), 273-279.

Brodaty, H., & Moore, C. M. (1997). The Clock Drawing Test for dementia of the Alzheimer's type: A comparison of three scoring methods in a memory disorders clinic. [Comparative Study]. *International journal of geriatric psychiatry, 12*(6), 619-627.

Bronnick, K., Emre, M., Tekin, S., Haugen, S. B., & Aarsland, D. (2011). Cognitive Correlates of Visual Hallucinations in Dementia Associated with Parkinson's Disease. *Movement Disorders, 26*(5), 824-829. doi: Doi 10.1002/Mds.23525

Brown, T. P., Rumsby, P. C., Capleton, A. C., Rushton, L., & Levy, L. S. (2006). Pesticides and Parkinson's disease--is there a link? [Research Support, Non-U.S. Gov't Review]. *Environmental health perspectives, 114*(2), 156-164.

Bruck, A., Kurki, T., Kaasinen, V., Vahlberg, T., & Rinne, J. O. (2004). Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. [Research Support, Non-U.S. Gov't]. *Journal of neurology, neurosurgery, and psychiatry, 75*(10), 1467-1469. doi: 10.1136/jnnp.2003.031237

Bruen, P. D., Plebani, M., Dojot, P. F., Trevisan, M., Shanks, M. F., Antonini, A., & Venneri, A. (2011). *The Neural and Psychological Correlates of Delusions and Hallucinations in Parkinson's Disease*. Paper presented at the Neurology. <Go to ISI>://000288149302505

Bruen, P. D., McGeown, W. J., Shanks, M. F., & Venneri, A. (2008). Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimers disease. *Brain, 131*, 2455-2463. doi: Doi 10.1093/Brain/Awn151

Burbulla, L. F., & Kruger, R. (2011). Converging environmental and genetic pathways in the pathogenesis of Parkinson's disease. [Research Support, Non-U.S. Gov't Review]. *Journal of the neurological sciences, 306*(1-2), 1-8. doi: 10.1016/j.jns.2011.04.005

Burn, D. J. (2002). Depression in Parkinson's disease. [Review]. *European journal of neurology : the official journal of the European Federation of Neurological Societies, 9 Suppl 3*, 44-54.

Bush, G., Whalen, P. J., Rosen, B. R., Jenike, M. A., McInerney, S. C., & Rauch, S. L. (1998). The counting Stroop: an interference task specialized for functional neuroimaging--validation study with functional MRI. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Human brain mapping, 6*(4), 270-282.

Butterfield, L. C., Cimino, C. R., Oelke, L. E., Hauser, R. A., & Sanchez-Ramos, J. (2010). The independent influence of apathy and depression on cognitive functioning in Parkinson's disease. *Neuropsychology, 24*(6), 721-730. doi: 10.1037/a0019650

Butterfield, P. G., Valanis, B. G., Spencer, P. S., Lindeman, C. A., & Nutt, J. G. (1993). Environmental antecedents of young-onset Parkinson's disease. [Research Support, U.S. Gov't, P.H.S.]. *Neurology, 43*(6), 1150-1158.

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, A., & Venneri, A. (2002). Una versione abbreviata del test di Stroop. Dati normativi nella popolazione italiana. *Nuova Riv Neurol, 12*, 111-115.

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002a). Rey-Osterrieth complex figure: normative values in an Italian population sample. *Neurol Sci, 22*, 443-447.

Caffarra, P., Vezzadini, G., Zonato, F., Copelli, S., & Venneri, A. (2003). A normative study of a shorter version of Raven's progressive matrices 1938. *Neurological Sciences, 24*(5), 336-339. doi: DOI 10.1007/s10072-003-0185-0.

Calne, D. B., & Langston, J. W. (1983). Aetiology of Parkinson's disease. *Lancet, 2*(8365-66), 1457-1459.

Camicioli, R., Gee, M., Bouchard, T. P., Fisher, N. J., Hanstock, C. C., Emery, D. J., & Martin, W. R. (2009). Voxel-based morphometry reveals extra-nigral atrophy patterns associated with dopamine refractory cognitive and motor impairment in parkinsonism. [Research Support, Non-U.S. Gov't]. *Parkinsonism & Related Disorders, 15*(3), 187-195. doi: 10.1016/j.parkreldis.2008.05.002

Camicioli, R., Howieson, D., Lehman, S., & Kaye, J. (1997). Talking while walking: The effect of a dual task in aging and Alzheimer's disease. *Neurology, 48*(4), 955-958.

Camicioli, R., Moore, M. M., Kinney, A., Corbridge, E., Glassberg, K., & Kaye, J. A. (2003). Parkinson's disease is associated with hippocampal atrophy. *Movement Disorders, 18*(7), 784-790. doi: Doi 10.1002/Mds.10444

Camicioli, R., Oken, B. S., Sexton, G., Kaye, J. A., & Nutt, J. G. (1998). Verbal fluency task affects gait in Parkinson's disease with motor freezing. [Clinical Trial Comparative Study Controlled Clinical Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Journal of Geriatric Psychiatry and Neurology, 11*(4), 181-185.

Caparros-Lefebvre, D., Pecheux, N., Petit, V., Duhamel, A., & Petit, H. (1995). Which factors predict cognitive decline in Parkinson's disease? [Research Support, Non-U.S. Gov't]. *Journal of neurology, neurosurgery, and psychiatry, 58*(1), 51-55.

Cardoso, E. F., Maia, F. M., Fregni, F., Myczkowski, M. L., Melo, L. M., Sato, J. R., . . . Amaro, E. (2009). Depression in Parkinson's disease: Convergence from voxel-based morphometry and functional magnetic resonance imaging in the limbic thalamus. *Neuroimage, 47*(2), 467-472. doi: DOI 10.1016/j.neuroimage.2009.04.059

Carlesimo, G. A., Piras, F., Assogna, F., Pontieri, F. E., Caltagirone, C., & Spalletta, G. (2012). Hippocampal abnormalities and memory deficits in Parkinson disease: a multimodal imaging study. [Research Support, Non-U.S. Gov't]. *Neurology, 78*(24), 1939-1945. doi: 10.1212/WNL.0b013e318259e1c5

Carlson, P., Thase, M., Bogers, W., Kupfer, D., & Drevets, W. C. (2005). Medial thalamic metabolism is increased in depression, and decreases with treatment. *Neuroimage, 26*, S28.

Carter, C. S., Mintun, M., & Cohen, J. D. (1995). Interference and facilitation effects during selective attention: an H215O PET study of Stroop task performance. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Neuroimage, 2*(4), 264-272. doi: 10.1006/nimg.1995.1034

Chartier-Harlin, M. C., Kachergus, J., Roumier, C., Mouroux, V., Douay, X., Lincoln, S., . . . Destee, A. (2004). alpha-synuclein locus duplication as a cause of familial Parkinson's disease. *Lancet, 364*(9440), 1167-1169.

Chase, T. N., Fedio, P., Foster, N. L., Brooks, R., Di Chiro, G., & Mansi, L. (1984). Wechsler Adult Intelligence Scale performance. Cortical localization by fluorodeoxyglucose F 18-positron emission tomography. [Comparative Study]. *Archives of Neurology, 41*(12), 1244-1247.

Chaudhuri, K. R., & Schapira, A. H. (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurology, 8*(5), 464-474. doi: S1474-4422(09)70068-7 [pii] 10.1016/S1474-4422(09)70068-7

Chen, R. C., Chang, S. F., Su, C. L., Chen, T. H., Yen, M. F., Wu, H. M., . . . Liou, H. H. (2001). Prevalence, incidence, and mortality of PD: a door-to-door survey in Ilan county, Taiwan. [Research Support, Non-U.S. Gov't]. *Neurology, 57*(9), 1679-1686.

Clarimon, J., Xiromerisiou, G., Eerola, J., Gourbali, V., Hellstrom, O., Dardiotis, E., . . . Singleton, A. B. (2005). Lack of evidence for a genetic association between FGF20 and Parkinson's disease in Finnish and Greek patients. *Bmc Neurology, 5*. doi: Artn 11 Doi 10.1186/1471-2377-5-11

Clark, L. N., Afridi, S., Mejia-Santana, H., Harris, J., Louis, E. D., Cote, L. J., . . . Marder, K. (2004). Analysis of an early-onset Parkinson's disease cohort for DJ-1 mutations. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Movement disorders : official journal of the Movement Disorder Society, 19*(7), 796-800. doi: 10.1002/mds.20131

Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Archives of General Psychiatry, 50*(12), 975-990.

Coene, E. H. (2000). What is Parkinson Disease? In R. K. Griffiths, Coene, E. H. (Ed.), *Parkinson's Disease: Self Care Manual* (pp. 13-32). Amsterdam: September Foundation.

Cohen, O. S., Vakil, E., Tanne, D., Molshatzki, N., Nitsan, Z., & Hassin-Baer, S. (2012). The Frontal Assessment Battery as a Tool for Evaluation of Frontal Lobe Dysfunction in Patients With Parkinson Disease. *Journal of Geriatric Psychiatry and Neurology, 25*(2), 71-77. doi: Doi 10.1177/0891988712445087

Colloby, S. J., Firbank, M. J., Thomas, A. J., Vasudev, A., Parry, S. W., & O'Brien, J. T. (2011). White matter changes in late-life depression: a diffusion tensor imaging study. [Research Support, Non-U.S. Gov't]. *Journal of Affective Disorders, 135*(1-3), 216-220. doi: 10.1016/j.jad.2011.07.025

Comella, C. (2003). Sleep episodes in Parkinson's disease: more questions remain. *Sleep Medicine, 4*(4), 267-268. doi: Doi 10.1016/S1389-9457(03)00116-3

Comella, C. L., Morrissey, M., & Leurgans, S. (2000). Excessive daytime sleepiness in Parkinson's disease is associated with male gender and dopamine agonist therapy. *Annals of Neurology, 48*(3), 432-432.

Cookson, M. R., & Bandmann, O. (2010). Parkinson's disease: insights from pathways. [Research Support, N.I.H., Intramural Research Support, Non-U.S. Gov't Review]. *Human molecular genetics, 19*(R1), R21-27. doi: 10.1093/hmg/ddq167

Cookson, M. R., Hardy, J., & Lewis, P. A. (2008). Genetic neuropathology of Parkinson's disease. *International journal of clinical and experimental pathology, 1*(3), 217-231.

Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E. V. (1991). Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Brain : a journal of neurology, 114 (Pt 5)*, 2095-2122.

Cooper, J. M., Shanks, M. F., & Venneri, A. (2006). Provoked confabulations in Alzheimer's disease. [Comparative Study Research Support, Non-U.S. Gov't]. *Neuropsychologia, 44*(10), 1697-1707. doi: 10.1016/j.neuropsychologia.2006.03.029

Cornford, M. E., Chang, L., & Miller, B. L. (1995). The neuropathology of parkinsonism: an overview. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Brain and cognition, 28*(3), 321-341. doi: 10.1006/brcg.1995.1261

Costa, A., Peppe, A., Carlesimo, G. A., Pasqualetti, P., & Caltagirone, C. (2006). Major and minor depression in Parkinson's disease: a neuropsychological investigation. [Comparative Study]. *European journal of neurology : the official journal of the European Federation of Neurological Societies, 13*(9), 972-980. doi: 10.1111/j.1468-1331.2006.01406.x

Costa, F. H., Rosso, A. L., Maultasch, H., Nicaretta, D. H., & Vincent, M. B. (2012). Depression in Parkinson's disease: diagnosis and treatment. *Arquivos de neuro-psiquiatria, 70*(8), 617-620.

Cramer, C. K., Friedman, J. H., & Amick, M. M. (2010). Olfaction and apathy in Parkinson's disease. *Parkinsonism & Related Disorders, 16*(2), 124-126. doi: 10.1016/j.parkreldis.2009.09.004

Cruto, C., Freitas, J., Carvalheiras, G., Mendes, A., & Lima, A. B. (2011). HIV infection and Parkinson's disease: is there a causal relationship? *Journal of Neurology, 258*, 86-86.

Cubo, E., Benito-Leon, J., Coronell, C., & Armesto, D. (2012). Clinical correlates of apathy in patients recently diagnosed with Parkinson's disease: the ANIMO study. [Multicenter Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neuroepidemiology, 38*(1), 48-55. doi: 10.1159/000334314

Cubo, E., Bernard, B., Leurgans, S., & Raman, R. (2000). Cognitive and motor function in patients with Parkinson's disease with and without depression. [Clinical Trial]. *Clinical neuropharmacology, 23*(6), 331-334.

Cummings, J. L. (1992). Depression and Parkinson's disease: a review. *Am J Psychiatry, 149*(4), 443-454.

Cummings, J. L. (1997). The neuropsychiatric inventory: Assessing psychopathology in dementia patients. *Neurology, 48*(5), S10-S16.

Cummings, J. L. (1999). Understanding Parkinson disease. *JAMA, 281*(4), 376-378. doi: jed80123 [pii]

Cummings, J. L., & Masterman, D. L. (1999). Depression in patients with Parkinson's disease. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *International journal of geriatric psychiatry, 14*(9), 711-718.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology, 44*(12), 2308-2314.

Dalaker, T. O., Larsen, J. P., Bergsland, N., Beyer, M. K., Alves, G., Dwyer, M. G., . . . Zivadinov, R. (2009). Brain atrophy and white matter hyperintensities in early Parkinson's disease(a). [Multicenter Study Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 24*(15), 2233-2241. doi: 10.1002/mds.22754

Dalrymple-Alford, J. C., Livingston, L., MacAskill, M. R., Graham, C., Melzer, T. R., Porter, R. J., . . . Anderson, T. J. (2011). Characterizing mild cognitive impairment in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society, 26*(4), 629-636. doi: 10.1002/mds.23592

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in cognitive sciences, 3*(1), 11-21.

de Boer, A. G., Wijker, W., Speelman, J. D., & de Haes, J. C. (1996). Quality of life in patients with Parkinson's disease: development of a questionnaire. *Journal of neurology, neurosurgery, and psychiatry, 61*(1), 70-74.

de Rijk, M. C., Tzourio, C., Breteler, M. M., Dartigues, J. F., Amaducci, L., Lopez-Pousa, S., . . . Rocca, W. A. (1997). Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry, 62*(1), 10-15.

Delis, C. E., & Kaplan, E. (2001). The Delis Kaplan Executive Function System – trial making test. The psychological Corporation.

Delis, C. E., Kramer, J. H., & Kaplan, E. e. a. (2002). California verbal learning test-second edition. The Psychological Corporation.

Della Sala, S., Baddeley, A., Papagno, C., & Spinnler, H. (1995). Dual-task paradigm: a means to examine the central executive. *Annals of the New York Academy of Sciences, 769*, 161-171.

Deng, H., Le, W. D., Zhang, X., Pan, T. H., & Jankovic, J. (2005). G309D and W437OPA PINK1 mutations in Caucasian Parkinson's disease patients. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. *Acta Neurologica Scandinavica, 111*(6), 351-352. doi: 10.1111/j.1600-0404.2005.00383.x

Di Biasio, F., Vanacore, N., Fasano, A., Modugno, N., Gandolfi, B., Lena, F., . . . Ruggieri, S. (2012). Neuropsychology, neuroimaging or motor phenotype in diagnosis of Parkinson's disease-dementia: which matters most? [Clinical Trial Comparative Study Validation Studies]. *Journal of Neural Transmission, 119*(5), 597-604. doi: 10.1007/s00702-011-0733-3

Dick, F. D., De Palma, G., Ahmadi, A., Scott, N. W., Prescott, G. J., Bennett, J., . . . Felice, A. (2007). Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. *Occupational and Environmental Medicine, 64*(10), 666-672. doi: DOI 10.1136/oem.2006.027003

Dickson, D. W., Braak, H., Duda, J. E., Duyckaerts, C., Gasser, T., Halliday, G. M., . . . Litvan, I. (2009). Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. [Review]. *Lancet Neurology, 8*(12), 1150-1157. doi: 10.1016/S1474-4422(09)70238-8

Diederich, N. J., Raman, R., Leurgans, S., & Goetz, C. G. (2002). Progressive worsening of spatial and chromatic processing deficits in Parkinson disease. [Research Support, Non-U.S. Gov't]. *Archives of Neurology, 59*(8), 1249-1252.

Dissanayaka, N. N., Sellbach, A., Matheson, S., O'Sullivan, J. D., Silburn, P. A., Byrne, G. J., . . . Mellick, G. D. (2010). Anxiety disorders in Parkinson's disease: prevalence and risk factors. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 25*(7), 838-845. doi: 10.1002/mds.22833

Dissanayaka, N. N., Sellbach, A., Silburn, P. A., O'Sullivan, J. D., Marsh, R., & Mellick, G. D. (2011). Factors associated with depression in Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Journal of Affective Disorders, 132*(1-2), 82-88. doi: 10.1016/j.jad.2011.01.021

Djamshidian, A., Jha, A., O'Sullivan, S. S., Silveira-Moriyama, L., Jacobson, C., Brown, P., . . . Averbeck, B. B. (2010). Risk and learning in impulsive and nonimpulsive patients with Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society, 25*(13), 2203-2210. doi: 10.1002/mds.23247

Dodd, M. L., Klos, K. J., Bower, J. H., Geda, Y. E., Josephs, K. A., & Ahlskog, J. E. (2005). Pathological gambling caused by drugs used to treat Parkinson disease. [Clinical Trial Comparative Study]. *Archives of Neurology, 62*(9), 1377-1381. doi: 10.1001/archneur.62.9.noc50009

Drevets, W. C. (1999). Prefrontal cortical-amygdalar metabolism in major depression. *Advancing from the Ventral Striatum to the Extended Amygdala, 877*, 614-637.

Drevets, W. C., Price, J. L., Simpson, J. R., Todd, R. D., Reich, T., Vannier, M., & Raichle, M. E. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature, 386*(6627), 824-827.

Drijgers, R. L., Dujardin, K., Reijnders, J. S., Defebvre, L., & Leentjens, A. F. (2010). Validation of diagnostic criteria for apathy in Parkinson's disease. [Validation Studies]. *Parkinsonism & Related Disorders, 16*(10), 656-660. doi: 10.1016/j.parkreldis.2010.08.015

Drijgers, R. L., Verhey, F. R., Leentjens, A. F., Kohler, S., & Aalten, P. (2011). Neuropsychological correlates of apathy in mild cognitive impairment and Alzheimer's disease: the role of executive functioning. *International psychogeriatrics / IPA, 23*(8), 1327-1333. doi: 10.1017/S1041610211001037

Driver-Dunckley, E., Samanta, J., & Stacy, M. (2003). Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology, 61*(3), 422-423.

Dubois, B., & Pillon, B. (1997). Cognitive deficits in Parkinson's disease. [Review]. *Journal of Neurology, 244*(1), 2-8.

Dubois, B., Pillon, B., Sternic, N., Lhermitte, F., & Agid, Y. (1990). Age-Induced Cognitive Disturbances in Parkinsons-Disease. *Neurology, 40*(1), 38-41.

Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000). The FAB - A frontal assessment battery at bedside. *Neurology, 55*(11), 1621-1626.

Dujardin, K., Sockeel, P., Delliaux, M., Destee, A., & Defebvre, L. (2009). Apathy may herald cognitive decline and dementia in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society, 24*(16), 2391-2397. doi: 10.1002/mds.22843

Dujardin, K., Sockeel, P., Devos, D., Delliaux, M., Krystkowiak, P., Destee, A., & Defebvre, L. (2007). Characteristics of apathy in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society, 22*(6), 778-784. doi: 10.1002/mds.21316

Durso, R., Isaac, K., Perry, L., Saint-Hilaire, M., & Feldman, R. G. (1993). Age influences magnitude but not duration of response to levodopa. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *Journal of neurology, neurosurgery, and psychiatry, 56*(1), 65-68.

Duvoisin, R. C. (1991). *Parkinson's Disease A Guide for Patient and Family* (Third Edition ed.). New York: Raven Press.

Edwards, E. R., Spira, A. P., Barnes, D. E., & Yaffe, K. (2009). Neuropsychiatric symptoms in mild cognitive impairment: differences by subtype and progression to dementia. [Multicenter Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *International journal of geriatric psychiatry, 24*(7), 716-722. doi: 10.1002/gps.2187

Elizan, T. S., Madden, D. L., Noble, G. R., Herrmann, K. L., Gardner, J., Schwartz, J., . . . Yahr, M. D. (1979). Viral antibodies in serum and CSF of Parkinsonian patients and controls. [Research Support, U.S. Gov't, P.H.S.]. *Archives of Neurology, 36*(9), 529-534.

Ellison, J. M., Harper, D. G., Berlow, Y., & Zeranski, L. (2008). Beyond the "C" in MCI: noncognitive symptoms in amnestic and non-amnestic mild cognitive impairment. [Research Support, Non-U.S. Gov't]. *CNS spectrums, 13*(1), 66-72

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., . . . Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. [Review]. *Movement disorders : official journal of the Movement Disorder Society, 22*(12), 1689-1707; quiz 1837. doi: 10.1002/mds.21507

Eng, M. L., & Welty, T. E. (2010). Management of hallucinations and psychosis in Parkinson's disease. [Review]. *The American journal of geriatric pharmacotherapy, 8*(4), 316-330. doi: 10.1016/j.amjopharm.2010.08.004

Eslinger, P. J., & Grattan, L. M. (1994). Altered serial position learning after frontal lobe lesion. [Research Support, U.S. Gov't, P.H.S.]. *Neuropsychologia, 32*(6), 729-739.

Esposito, G., Kirkby, B. S., Van Horn, J. D., Ellmore, T. M., & Berman, K. F. (1999). Context-dependent, neural system-specific neurophysiological concomitants of ageing: mapping PET correlates during cognitive activation. [Comparative Study]. *Brain : a journal of neurology, 122 (Pt 5)*, 963-979.

Even, C., & Weintraub, D. (2012). Is depression in Parkinson's Disease (PD) a specific entity? *Journal of Affective Disorders, 139*(2), 103-112. doi: DOI 10.1016/j.jad.2011.07.002

Factor, S. A., Molho, E. S., Podskalny, G. D., & Brown, D. (1995). Parkinson's disease: drug-induced psychiatric states. [Case Reports Research Support, Non-U.S. Gov't Review]. *Advances in neurology, 65*, 115-138.

Factor, S. A., & Weiner, W. J. (1991). Prior history of head trauma in Parkinson's disease. [Comparative Study Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 6*(3), 225-229. doi: 10.1002/mds.870060306

Fahn, S. (1995). The freezing phenomenon in parkinsonism. [Review]. *Advances in neurology, 67*, 53-63.

Fall, P. A., Fredrikson, M., Axelson, O., & Granerus, A. K. (1999). Nutritional and occupational factors influencing the risk of Parkinson's disease: A case-control study in southeastern Sweden. *Movement Disorders, 14*(1), 28-37.

Fang, F., Wirdefeldt, K., Jacks, A., Kamel, F., Ye, W., & Chen, H. (2012). CNS infections, sepsis and risk of Parkinson's disease. *International journal of epidemiology*. doi: 10.1093/ije/dys052

Farabaugh, A. H., Locascio, J. J., Yap, L., Weintraub, D., McDonald, W. M., Agoston, M., . . . Fava, M. (2009). Pattern of depressive symptoms in Parkinson's disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *Psychosomatics, 50*(5), 448-454. doi: 10.1176/appi.psy.50.5.448

Fearnley, J. M., & Lees, A. J. (1991). Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain : a journal of neurology, 114 (Pt 5)*, 2283-2301.

Feil, D., Razani, J., Boone, K., & Lesser, I. (2003). Apathy and cognitive performance in older adults with depression. *International journal of geriatric psychiatry, 18*(6), 479-485. doi: Doi 10.1002/Gps.869

Feinberg, T. E., & Roane, D. M. (1997). Anosognosia, completion and confabulation: The neutral-personal dichotomy. *Neurocase, 3*(1), 73-85. doi: Doi 10.1080/13554799708404037

Feldmann, A., Illes, Z., Kosztolanyi, P., Illes, E., Mike, A., Kover, F., . . . Nagy, F. (2008). Morphometric changes of gray matter in Parkinson's disease with depression: a voxel-based morphometry study. *Movement Disorders, 23*(1), 42-46. doi: Doi 10.1002/Mds.21765

Feldman, H., Scheltens, P., Scarpini, E., Hermann, N., Mesenbrink, P., Mancione, L., . . . Ferris, S. (2004). Behavioral symptoms in mild cognitive impairment. *Neurology, 62*(7), 1199-1201.

Fenelon, G. (2008). Psychosis in Parkinson's disease: phenomenology, frequency, risk factors, and current understanding of pathophysiologic mechanisms. [Review]. *CNS spectrums, 13*(3 Suppl 4), 18-25.

Fenelon, G., & Alves, G. (2010). Epidemiology of psychosis in Parkinson's disease. [Review]. *Journal of the neurological sciences, 289*(1-2), 12-17. doi: 10.1016/j.jns.2009.08.014

Fenelon, G., Mahieux, F., Huon, R., & Ziegler, M. (2000). Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. [Case Reports]. *Brain : a journal of neurology, 123 (Pt 4)*, 733-745.

Fernandez-Calle, P., Jimenez-Jimenez, F. J., Molina, J. A., Cabrera-Valdivia, F., Vazquez, A., Garcia Urra, D., . . . Codoceo, R. (1993). Serum levels of ascorbic acid (vitamin C) in patients with Parkinson's disease. [Comparative Study Research Support, Non-U.S. Gov't]. *Journal of the neurological sciences, 118*(1), 25-28.

Fernandez, H. H., See, R. H., Gary, M. F., Bowers, D., Rodriguez, R. L., Jacobson, C., & Okun, M. S. (2009). Depressive Symptoms in Parkinson Disease Correlate With Impaired Global and Specific Cognitive Performance. *Journal of Geriatric Psychiatry and Neurology, 22*(4), 223-227. doi: Doi 10.1177/0891988709335792

Firestone, J. A., Smith-Weller, T., Franklin, G., Swanson, P., Longstreth, W. T., Jr., & Checkoway, H. (2005). Pesticides and risk of Parkinson disease: a population-based case-control study. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. *Archives of Neurology, 62*(1), 91-95. doi: 10.1001/archneur.62.1.91

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research, 12*(3), 189-198.

Foltynie, T., Brayne, C. E., Robbins, T. W., & Barker, R. A. (2004). The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. [Research Support, Non-U.S. Gov't]. *Brain : a journal of neurology, 127*(Pt 3), 550-560. doi: 10.1093/brain/awh067

Foster, P. S., Drago, V., Yung, R. C., Skidmore, F. M., Skoblar, B., Shenal, B. V., . . . Heilman, K. M. (2010). Anxiety affects working memory only in left hemibody onset Parkinson disease patients. *Cognitive and behavioral neurology : official journal of the Society for Behavioral and Cognitive Neurology, 23*(1), 14-18. doi: 10.1097/WNN.0b013e3181cc8be9

Fowler, J. S., Volkow, N. D., Wang, G. J., Pappas, N., Logan, J., MacGregor, R., . . . Cilento, R. (1996). Inhibition of monoamine oxidase B in the brains of smokers. [Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Nature, 379*(6567), 733-736. doi: 10.1038/379733a0

Fowler, J. S., Wang, G. J., Volkow, N. D., Franceschi, D., Logan, J., Pappas, N., . . . Garza, V. (1999). Smoking a single cigarette does not produce a measurable reduction in brain MAO B in non-smokers. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco, 1*(4), 325-329.

Frank, C., Pari, G., & Rossiter, J. (2006). Approach to diagnosis of Parkinson disease. *Canadian Family Physician Journal, 52*, 862-868.

Friedman, J. H. (2010). Parkinson's disease psychosis 2010: a review article. [Review]. *Parkinsonism & Related Disorders, 16*(9), 553-560. doi: 10.1016/j.parkreldis.2010.05.004

Frodl, T., Scheuerecker, J., Albrecht, J., Kleemann, A. M., Muller-Schunk, S., Koutsouleris, N., . . . Meisenzahl, E. (2009). Neuronal correlates of emotional processing in patients with major depression. *World J Biol Psychiatry, 10*(3), 202-208. doi: 783517756 [pii] 10.1080/15622970701624603

Fuchs, J., Nilsson, C., Kachergus, J., Munz, M., Larsson, E. M., Schule, B., . . . Farrer, M. J. (2007). Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neurology, 68*(12), 916-922. doi: 10.1212/01.wnl.0000254458.17630.c5

Funayama, M., Hasegawa, K., Kowa, H., Saito, M., Tsuji, S., & Obata, F. (2002). A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1. [Research Support, Non-U.S. Gov't]. *Annals of Neurology, 51*(3), 296-301.

Funayama, M., Li, Y., Tsoi, T. H., Lam, C. W., Ohi, T., Yazawa, S., . . . Hattori, N. (2008). Familial Parkinsonism with digenic parkin and PINK1 mutations. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 23*(10), 1461-1465. doi: 10.1002/mds.22143

Gallagher, D. A., & Schrag, A. (2012). Psychosis, apathy, depression and anxiety in Parkinson's disease. [Review]. *Neurobiology of disease, 46*(3), 581-589. doi: 10.1016/j.nbd.2011.12.041

Galletly, R., & Brauer, S. G. (2005). Does the type of concurrent task affect preferred and cued gait in people with Parkinson's disease? *Australian Journal of Physiotherapy, 51*(3), 175-180.

Gandhi, S., Muqit, M. M., Stanyer, L., Healy, D. G., Abou-Sleiman, P. M., Hargreaves, I., . . . Revesz, T. (2006). PINK1 protein in normal human brain and Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Brain : a journal of neurology, 129*(Pt 7), 1720-1731. doi: 10.1093/brain/awl114

Gatto, N. M., Cockburn, M., Bronstein, J., Manthripragada, A. D., & Ritz, B. (2009). Well-water consumption and Parkinson's disease in rural California. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *Environmental health perspectives, 117*(12), 1912-1918. doi: 10.1289/ehp.0900852

Geake, J. G., & Hansen, P. C. (2010). Functional neural correlates of fluid and crystallized analogizing. *Neuroimage, 49*(4), 3489-3497. doi: 10.1016/j.neuroimage.2009.09.008

Gelb, D. J., Oliver, E., & Gilman, S. (1999). Diagnostic criteria for Parkinson disease. *Archives of Neurology, 56*(1), 33-39.

Gerschlager, W., Bencsits, G., Pirker, W., et al. (2002). [123]b-CIT SPECT distinguishes vascular parkinsonism from Parkinsion's disease. *Movement Disorders, 17*(5), 18-23.

Gerton, B. K., Brown, T. T., Meyer-Lindenberg, A., Kohn, P., Holt, J. L., Olsen, R. K., & Berman, K. F. (2004). Shared and distinct neurophysiological components of the digits forward and backward tasks as revealed by functional neuroimaging. [Comparative Study]. *Neuropsychologia, 42*(13), 1781-1787. doi: 10.1016/j.neuropsychologia.2004.04.023

Giasson, B. I., Covy, J. P., Bonini, N. M., Hurtig, H. I., Farrer, M. J., Trojanowski, J. Q., & Van Deerlin, V. M. (2006). Biochemical and pathological characterization of Lrrk2. *Annals of Neurology, 59*(2), 315-322. doi: Doi 10.1002/Ana.20791

Gibb, W. R., & Lees, A. J. (1988). The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. [Research Support, Non-U.S. Gov't Review]. *Journal of neurology, neurosurgery, and psychiatry, 51*(6), 745-752.

Gibb, W. R., & Lees, A. J. (1991). Anatomy, pigmentation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry, 54*(5), 388-396.

Giladi, N. (2001). Freezing of gait. Clinical overview. [Review]. *Advances in neurology, 87*, 191-197.

Giladi, N., McMahon, D., Przedborski, S., Flaster, E., Guillory, S., Kostic, V., & Fahn, S. (1992). Motor blocks in Parkinson's disease. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Neurology, 42*(2), 333-339.

Giladi, N., Treves, T. A., Simon, E. S., Shabtai, H., Orlov, Y., Kandinov, B., . . . Korczyn, A. D. (2001). Freezing of gait in patients with advanced Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Journal of Neural Transmission, 108*(1), 53-61.

Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., & Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. [Clinical Trial]. *Italian journal of neurological sciences, 17*(4), 305-309.

Goetz, C. G., & Stebbins, G. T. (1993). Risk factors for nursing home placement in advanced Parkinson's disease. *Neurology, 43*(11), 2227-2229.

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., . . . UPDRS, M. D. S. (2008). Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results. *Movement Disorders, 23*(15), 2129-2170. doi: Doi 10.1002/Mds.22340

Golbe, L. I., Farrell, T. M., & Davis, P. H. (1988). Case-control study of early life dietary factors in Parkinson's disease. *Archives of Neurology, 45*(12), 1350-1353.

Goldin, P. R., McRae, K., Ramel, W., & Gross, J. J. (2008). The neural bases of emotion regulation: reappraisal and suppression of negative emotion. [Research Support, N.I.H., Extramural]. *Biological Psychiatry, 63*(6), 577-586. doi: 10.1016/j.biopsych.2007.05.031

Goodglass, H., & Kaplan, E. (1983). Assessment of aphasia and related disorders (2nd ed.). Philadelphia: Lea and Febiger.

Gourovitch, M. L., Kirkby, B. S., Goldberg, T. E., Weinberger, D. R., Gold, J. M., Esposito, G., . . . Berman, K. F. (2000). A comparison of rCBF patterns during letter and semantic fluency. [Clinical Trial Comparative Study]. *Neuropsychology, 14*(3), 353-360.

Greene, J. G., Smith, R., Gardiner, M., & Timbury, G. C. (1982). Measuring behavioural disturbance of elderly demented patients in the community and its effects on relatives: a factor analytic study. [Research Support, Non-U.S. Gov't]. *Age and ageing, 11*(2), 121-126.

Grosset, D. (2008). Dopamine agonists and therapy compliance. [Review]. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 29 Suppl 5*, S375-376. doi: 10.1007/s10072-008-1050-y

Grossi, D., Santangelo, G., Barbarulo, A. M., Vitale, C., Castaldo, G., Proto, M. G., . . . Trojano, L. (2012). Apathy and related executive syndromes in dementia associated with Parkinson's disease and in Alzheimer's disease. *Behavioural neurology*. doi: 10.3233/BEN-129023

Grossi, D., Trojano, L., Pellecchia, M. T., Amboni, M., Fragassi, N. A., & Barone, P. (2005). Frontal dysfunction contributes to the genesis of hallucinations in non-demented Parkinsonian patients. *International journal of geriatric psychiatry, 20*(7), 668-673. doi: 10.1002/gps.1339

Halkias, I. A., Haq, I., Huang, Z., & Fernandez, H. H. (2007). When should levodopa therapy be initiated in patients with Parkinson's disease? [Review]. *Drugs & aging, 24*(4), 261-273.

Halliday, G. M., Li, Y. W., Blumbergs, P. C., Joh, T. H., Cotton, R. G., Howe, P. R., . . . Geffen, L. B. (1990). Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Annals of Neurology, 27*(4), 373-385. doi: 10.1002/ana.410270405

Halliday, G. M., & McCann, H. (2010). The progression of pathology in Parkinson's disease. [Review]. *Annals of the New York Academy of Sciences, 1184*, 188-195. doi: 10.1111/j.1749-6632.2009.05118.x

Hamilton, M. (1960). A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry, 23*, 56-62.

Hancock, D. B., Martin, E. R., Stajich, J. M., Jewett, R., Stacy, M. A., Scott, B. L., . . . Scott, W. K. (2007). Smoking, caffeine, and nonsteroidal anti-inflammatory drugs in families with Parkinson disease. *Archives of Neurology, 64*(4), 576-580.

Hardy, J., Lewis, P., Revesz, T., Lees, A., & Paisan-Ruiz, C. (2009). The genetics of Parkinson's syndromes: a critical review. [Review]. *Current opinion in genetics & development, 19*(3), 254-265. doi: 10.1016/j.gde.2009.03.008

Harris, M. A., Tsui, J. K., Marion, S. A., Shen, H., & Teschke, K. (2012). Association of Parkinson's disease with infections and occupational exposure to possible vectors. *Movement disorders : official journal of the Movement Disorder Society, 27*(9), 1111-1117. doi: 10.1002/mds.25077

Haruno, M., Kuroda, T., Doya, K., Toyama, K., Kimura, M., Samejima, K., . . . Kawato, M. (2004). A neural correlate of reward-based behavioral learning in caudate nucleus: a functional magnetic resonance imaging study of a stochastic decision task. [Research Support, Non-U.S. Gov't]. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 24*(7), 1660-1665. doi: 10.1523/JNEUROSCI.3417-03.2004

Hatano, T., Kubo, S., Sato, S., & Hattori, N. (2009). Pathogenesis of familial Parkinson's disease: new insights based on monogenic forms of Parkinson's disease. [Research Support, Non-U.S. Gov't Review]. *Journal of neurochemistry, 111*(5), 1075-1093. doi: 10.1111/j.1471-4159.2009.06403.x

Hausdorff, J. M., Balash, J., & Giladi, N. (2002). Cognitive challenge increases gait variability and fall risk in patients with Parkinson's disease. *Journal of the American Geriatrics Society, 50*(4), S48-S49.

Hausdorff, J. M., Balash, J., & Giladi, N. (2003). Effects of cognitive challenge on gait variability in patients with Parkinson's disease. [Research Support, U.S. Gov't, P.H.S.]. *Journal of Geriatric Psychiatry and Neurology, 16*(1), 53-58.

Hausdorff, J. M., Yogev, G., Springer, S., Simon, E. S., & Giladi, N. (2005). Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Experimental Brain Research, 164*(4), 541-548. doi: DOI 10.1007/s00221-005-2280-3

Hauser, R. A. (2010). Early Pharmacologic Treatment in Parkinson's Disease. *American Journal of Managed Care, 16*(4), S100-S107.

Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science, 293*(5539), 2425-2430. doi: 10.1126/science.1063736

Heaton, R. K., Chelune, G. J., & Talley, J. L., et al. (1993). Wisconsin Card Sorting Test. Manual revised and espanded. Odessa, FL: Psychological Assessment Resources.

Hellenbrand, W., Boeing, H., Robra, B. P., Seidler, A., Vieregge, P., Nischan, P., . . . Ulm, G. (1996). Diet and Parkinson's disease. II: A possible role for the past intake of specific nutrients. Results from a self-administered food-frequency questionnaire in a case-control study. [Research Support, Non-U.S. Gov't]. *Neurology, 47*(3), 644-650.

Henry, J. D., & Crawford, J. R. (2004a). A meta-analytic review of verbal fluency performance following focal cortical lesions. [Meta-Analysis]. *Neuropsychology, 18*(2), 284-295. doi: 10.1037/0894-4105.18.2.284

Henry, J. D., & Crawford, J. R. (2004b). Verbal fluency deficits in Parkinson's disease: a meta-analysis. [Comparative Study Meta-Analysis]. *Journal of the International Neuropsychological Society : JINS, 10*(4), 608-622. doi: 10.1017/S1355617704104141

Hering, R., Strauss, K. M., Tao, X., Bauer, A., Woitalla, D., Mietz, E. M., . . . Riess, O. (2004). Novel homozygous p.E64D mutation in DJ1 in early onset Parkinson disease (PARK7). [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Human mutation, 24*(4), 321-329. doi: 10.1002/humu.20089

Herishanu, Y. O., Goldsmith, J. R., Abarbanel, J. M., & Weinbaum, Z. (1989). Clustering of Parkinson's disease in southern Israel. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 16*(4), 402-405.

Hertzman, C., Wiens, M., Bowering, D., Snow, B., & Calne, D. (1990). Parkinson's disease: a case-control study of occupational and environmental risk factors. [Research Support, Non-U.S. Gov't]. *American journal of industrial medicine, 17*(3), 349-355.

Hindle, J. V. (2010). Ageing, neurodegeneration and Parkinson's disease. [Review]. *Age and ageing, 39*(2), 156-161. doi: 10.1093/ageing/afp223

Hirtz, D., Thurman, D. J., Gwinn-Hardy, K., Mohamed, M., Chaudhuri, A. R., & Zalutsky, R. (2007). How common are the "common" neurologic disorders? *Neurology, 68*(5), 326-337.

Hobson, P., & Meara, J. (2004). Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 19*(9), 1043-1049. doi: 10.1002/mds.20216

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology, 17*(5), 427-442.

Hofman, A., Collette, H. J., & Bartelds, A. I. (1989). Incidence and risk factors of Parkinson's disease in The Netherlands. [Research Support, Non-U.S. Gov't]. *Neuroepidemiology, 8*(6), 296-299.

Holroyd, S., Currie, L., & Wooten, G. F. (2001). Prospective study of hallucinations and delusions in Parkinson's disease. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Journal of neurology, neurosurgery, and psychiatry, 70*(6), 734-738.

Holtzer, R., Verghese, J., Xue, X., & Lipton, R. B. (2006). Cognitive processes related to gait velocity: results from the Einstein Aging Study. [Comparative Study Research Support, N.I.H., Extramural]. *Neuropsychology, 20*(2), 215-223. doi: 10.1037/0894-4105.20.2.215

Huang, C., Ravdin, L. D., Nirenberg, M. J., Piboolnurak, P., Severt, L., Maniscalco, J. S., . . . Henchcliffe, C. (2013). Neuroimaging Markers of Motor and Nonmotor Features of Parkinson's Disease: An [F]Fluorodeoxyglucose Positron Emission Computed Tomography Study. *Dementia and geriatric cognitive disorders, 35*(3-4), 183-196. doi: 10.1159/000345987

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of Clinical-Diagnosis of Idiopathic Parkinsons-Disease - a Clinicopathological Study of 100 Cases. *Journal of Neurology Neurosurgery and Psychiatry, 55*(3), 181-184.

Hughes, T. A., Ross, H. F., Musa, S., Bhattacherjee, S., Nathan, R. N., Mindham, R. H., & Spokes, E. G. (2000). A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Neurology, 54*(8), 1596-1602.

Ibanez, P., Bonnet, A. M., Debarges, B., Lohmann, E., Tison, F., Pollak, P., . . . Genetic, F. P. s. D. (2004). Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. *Lancet, 364*(9440), 1169-1171.

Ibarretxe-Bilbao, N., Junque, C., Marti, M. J., & Tolosa, E. (2011). Brain structural MRI correlates of cognitive dysfunctions in Parkinson's disease. *Journal of the neurological sciences, 310*(1-2), 70-74. doi: DOI 10.1016/j.jns.2011.07.054

Ibarretxe-Bilbao, N., Junque, C., Tolosa, E., Marti, M. J., Valldeoriola, F., Bargallo, N., & Zarei, M. (2009). Neuroanatomical correlates of impaired decision-making and facial emotion recognition in early Parkinson's disease. [Research Support, Non-U.S. Gov't]. *The European journal of neuroscience, 30*(6), 1162-1171. doi: 10.1111/j.1460-9568.2009.06892.x

Ibarretxe-Bilbao, N., Ramirez-Ruiz, B., Tolosa, E., Marti, M. J., Valldeoriola, F., Bargallo, N., & Junque, C. (2008). Hippocampal head atrophy predominance in Parkinson's disease with hallucinations and with dementia. [Research Support, Non-U.S. Gov't]. *Journal of Neurology, 255*(9), 1324-1331. doi: 10.1007/s00415-008-0885-8

Isella, V., Melzi, P., Grimaldi, M., Iurlaro, S., Piolti, R., Ferrarese, C., . . . Appollonio, I. (2002). Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society, 17*(2), 366-371.

Jang, H., Boltz, D. A., Webster, R. G., & Smeyne, R. J. (2009). Viral parkinsonism. [Review]. *Biochimica et biophysica acta, 1792*(7), 714-721. doi: 10.1016/j.bbadis.2008.08.001

Jankovic, J. (2006). An update on the treatment of Parkinson's disease. [Research Support, Non-U.S. Gov't Review]. *The Mount Sinai journal of medicine, New York, 73*(4), 682-689.

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *Journal of Neurology Neurosurgery and Psychiatry, 79*(4), 368-376. doi: DOI 10.1136/jnnp.2007.131045

Jankovic, J., McDermott, M., Carter, J., Gauthier, S., Goetz, C., Golbe, L., . . . et al. (1990). Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. [Research Support, U.S. Gov't, P.H.S.]. *Neurology, 40*(10), 1529-1534.

Janson, A. M., Fuxe, K., & Goldstein, M. (1992). Differential effects of acute and chronic nicotine treatment on MPTP-(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced degeneration of nigrostriatal dopamine neurons in the black mouse. [Research Support, Non-U.S. Gov't]. *The Clinical investigator, 70*(3-4), 232-238.

Janvin, C. C., Larsen, J. P., Aarsland, D., & Hugdahl, K. (2006). Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Movement disorders : official journal of the Movement Disorder Society, 21*(9), 1343-1349. doi: 10.1002/mds.20974

Jean, L., Simard, M., van Reekum, R., & Clarke, D. E. (2005). Differential cognitive impairment in subjects with geriatric depression who will develop Alzheimer's disease and other dementias: a retrospective study. *International psychogeriatrics / IPA, 17*(2), 289-301.

Jimenez-Jimenez, F. J., Mateo, D., & Gimenez-Roldan, S. (1992). Exposure to well water and pesticides in Parkinson's disease: a case-control study in the Madrid area. *Movement disorders : official journal of the Movement Disorder Society, 7*(2), 149-152. doi: 10.1002/mds.870070209

Johnson, D. K., Watts, A. S., Chapin, B. A., Anderson, R., & Burns, J. M. (2011). Neuropsychiatric profiles in dementia. [Comparative Study Randomized Controlled Trial Research Support, N.I.H., Extramural]. *Alzheimer disease and associated disorders, 25*(4), 326-332. doi: 10.1097/WAD.0b013e31820d89b6

Jones-Gotman, M., & Milner, B. (1977). Design fluency: the invention of nonsense drawings after focal cortical lesions. Neuropsychologia, 15, 653-674.

Kagi, G., Bhatia, K. P., & Tolosa, E. (2010). The role of DAT-SPECT in movement disorders. [Research Support, Non-U.S. Gov't Review]. *Journal of neurology, neurosurgery, and psychiatry, 81*(1), 5-12. doi: 10.1136/jnnp.2008.157370

Kang, J. Y., Lee, J. S., Kang, H., Lee, H. W., Kim, Y. K., Jeon, H. J., . . . Lee, D. S. (2012). Regional cerebral blood flow abnormalities associated with apathy and depression in Alzheimer disease. [Research Support, Non-U.S. Gov't]. *Alzheimer disease and associated disorders, 26*(3), 217-224. doi: 10.1097/WAD.0b013e318231e5fc

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). The Boston Naming Test (2nd ed.). Philadelphia: Lea and Febiger.

Kasai, M., Meguro, K., Hashimoto, R., Ishizaki, J., Yamadori, A., & Mori, E. (2006). Non-verbal learning is impaired in very mild Alzheimer's disease (CDR 0.5): normative data from the learning version of the Rey-Osterrieth Complex Figure Test. *Psychiatry and Clinical Neurosciences, 60*(2), 139-146. doi: 10.1111/j.1440-1819.2006.01478.x

Katzen, H. L., Levin, B. E., & Llabre, M. L. (1998). Age of disease onset influences cognition in Parkinson's disease. [Clinical Trial]. *Journal of the International Neuropsychological Society : JINS, 4*(3), 285-290.

Kegeles, L. S., Malone, K. M., Slifstein, M., Ellis, S. P., Xanthopoulos, E., Keilp, J. G., . . . Mann, J. J. (2003). Response of cortical metabolic deficits to serotonergic challenge in familial mood disorders. *American Journal of Psychiatry, 160*(1), 76-82.

Kenborg, L., Lassen, C. F., Lander, F., & Olsen, J. H. (2012). Parkinson's disease among gardeners exposed to pesticides--a Danish cohort study. *Scandinavian journal of work, environment & health, 38*(1), 65-69. doi: 10.5271/sjweh.3176

Khan, N. L., Brooks, D. J., Pavese, N., Sweeney, M. G., Wood, N. W., Lees, A. J., & Piccini, P. (2002). Progression of nigrostriatal dysfunction in a parkin kindred: an [18F]dopa PET and clinical study. [Research Support, Non-U.S. Gov't]. *Brain : a journal of neurology, 125*(Pt 10), 2248-2256.

Khan, N. L., Graham, E., Critchley, P., Schrag, A. E., Wood, N. W., Lees, A. J., . . . Quinn, N. (2003). Parkin disease: a phenotypic study of a large case series. [Research Support, Non-U.S. Gov't]. *Brain : a journal of neurology, 126*(Pt 6), 1279-1292.

Khan, N. L., Katzenschlager, R., Watt, H., Bhatia, K. P., Wood, N. W., Quinn, N., & Lees, A. J. (2004). Olfaction differentiates parkin disease from early-onset parkinsonism and Parkinson disease. [Research Support, Non-U.S. Gov't]. *Neurology, 62*(7), 1224-1226.

Khedr, E. M., Al Attar, G. S., Kandil, M. R., Kamel, N. F., Abo Elfetoh, N., & Ahmed, M. A. (2012). Epidemiological study and clinical profile of Parkinson's disease in the Assiut Governorate, Egypt: a community-based study. *Neuroepidemiology, 38*(3), 154-163. doi: 10.1159/000335701

Kirsch-Darrow, L., Fernandez, H. H., Marsiske, M., Okun, M. S., & Bowers, D. (2006). Dissociating apathy and depression in Parkinson disease. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neurology, 67*(1), 33-38. doi: 10.1212/01.wnl.0000230572.07791.22

Kjaer, T. W., Nowak, M., & Lou, H. C. (2002). Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. [Clinical Trial Research Support, Non-U.S. Gov't]. *Neuroimage, 17*(2), 1080-1086.

Klein, C., & Schlossmacher, M. G. (2007). Parkinson disease, 10 years after its genetic revolution: multiple clues to a complex disorder. [Review]. *Neurology, 69*(22), 2093-2104. doi: 10.1212/01.wnl.0000271880.27321.a7

Klein, C., Schumacher, K., Jacobs, H., Hagenah, J., Kis, B., Garrels, J., . . . Kramer, P. L. (2000). Association studies of Parkinson's disease and parkin polymorphisms. [CommentLetter Research Support, Non-U.S. Gov't]. *Annals of Neurology, 48*(1), 126-127.

Klein, R. J., Zeiss, C., Chew, E. Y., Tsai, J. Y., Sackler, R. S., Haynes, C., . . . Hoh, J. (2005). Complement factor H polymorphism in age-related macular degeneration. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Science, 308*(5720), 385-389. doi: 10.1126/science.1109557

Klepac, N., Hajnsek, S., & Trkulja, V. (2010). Cognitive Performance in Nondemented Nonpsychotic Parkinson Disease Patients With or Without a History of Depression Prior to the Onset of Motor Symptoms. *Journal of Geriatric Psychiatry and Neurology, 23*(1), 15-26. doi: Doi 10.1177/0891988709351831

Klepac, N., Trkulja, V., & Relja, M. (2008). Nondemented Parkinson disease patients: is cognitive performance associated with depressive difficulties? *Cognitive and behavioral neurology : official journal of the Society for Behavioral and Cognitive Neurology, 21*(2), 87-91. doi: 10.1097/WNN.0b013e3181799da6

Kokmen, E., Smith, G. E., Petersen, R. C., Tangalos, E., & Ivnik, R. C. (1991). The short test of mental status. Correlations with standardized psychometric testing. [Research Support, U.S. Gov't, P.H.S.]. *Archives of Neurology, 48*(7), 725-728.

Kostic, V. S., Agosta, F., Petrovic, I., Galantucci, S., Spica, V., Jecmenica-Lukic, M., & Filippi, M. (2010). Regional patterns of brain tissue loss associated with depression in Parkinson disease. *Neurology, 75*(10), 857-863.

Kruger, R., Kuhn, W., Muller, T., Woitalla, D., Graeber, M., Kosel, S., . . . Riess, O. (1998). Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. [Letter Research Support, Non-U.S. Gov't]. *Nature genetics, 18*(2), 106-108. doi: 10.1038/ng0298-106

Kulisevsky, J., Pagonabarraga, J., Pascual-Sedano, B., Garcia-Sanchez, C., Gironell, A., & Study, T. G. (2008). Prevalence and Correlates of Neuropsychiatric Symptoms in Parkinson's Disease Without Dementia. *Movement Disorders, 23*(13), 1889-1896. doi: Doi 10.1002/Mds.22246

Kumar, M., & Jangra, M. (2012). Does cigarette smoking provoke Parkinson's disease? *International Journal of Nutrition, Pharmacology, Neurological Diseases 2*(1), 16-19. doi: 10.4103/2231-0738.93126

Kuzis, G., Sabe, L., Tiberti, C., Leiguarda, R., & Starkstein, S. E. (1997). Cognitive functions in major depression and Parkinson disease. [Research Support, Non-U.S. Gov't]. *Archives of Neurology, 54*(8), 982-986.

Lai, B. C. L., Marion, S. A., Teschke, K., & Tsui, J. K. C. (2002). Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism & Related Disorders, 8*(5), 297-309.

Laird, A. R., McMillan, K. M., Lancaster, J. L., Kochunov, P., Turkeltaub, P. E., Pardo, J. V., & Fox, P. T. (2005). A comparison of label-based review and ALE meta-analysis in the Stroop task. [Comparative StudyResearch Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. *Human brain mapping, 25*(1), 6-21. doi: 10.1002/hbm.20129

Lamberti, P., Armenise, S., Castaldo, V., de Mari, M., Iliceto, G., Tronci, P., & Serlenga, L. (1997). Freezing gait in Parkinson's disease. *European Neurology, 38*(4), 297-301.

Lauterbach, E. C. (2005). The neuropsychiatry of Parkinson's disease. [Review]. *Minerva medica, 96*(3), 155-173.

Lavretsky, H., Ballmaier, M., Pham, D., Toga, A., & Kumar, A. (2007). Neuroanatomical characteristics of geriatric apathy and depression: A magnetic resonance imaging study. *American Journal of Geriatric Psychiatry, 15*(5), 386-394.

Le Jeune, F., Drapier, D., Bourguignon, A., Peron, J., Mesbah, H., Drapier, S., . . . Verin, M. (2009). Subthalamic nucleus stimulation in Parkinson disease induces apathy: a PET study. [Clinical Trial]. *Neurology, 73*(21), 1746-1751. doi: 10.1212/WNL.0b013e3181c34b34

Lebedev, A. V., Beyer, M. K., Fritze, F., Westman, E., Ballard, C., & Aarsland, D. (2013). Cortical Changes Associated with Depression and Antidepressant Use in Alzheimer and Lewy Body Dementia: An MRI Surface-based Morphometric Study. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. doi: 10.1016/j.jagp.2013.02.004

Lee, A. H., & Weintraub, D. (2012). Psychosis in Parkinson's disease without dementia: common and comorbid with other non-motor symptoms. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *Movement disorders : official journal of the Movement Disorder Society, 27*(7), 858-863. doi: 10.1002/mds.25003

Lee, E., Meguro, K., Hashimoto, R., Meguro, M., Ishii, H., Yamaguchi, S., & Mori, E. (2007). Confabulations in episodic memory are associated with delusions in Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology, 20*(1), 34-40. doi: 10.1177/0891988706292760

Lee, F. J., & Liu, F. (2008). Genetic factors involved in the pathogenesis of Parkinson's disease. [Review]. *Brain research reviews, 58*(2), 354-364. doi: 10.1016/j.brainresrev.2008.02.001

Lee, W. J., Tsai, C. F., Gauthier, S., Wang, S. J., & Fuh, J. L. (2012). The association between cognitive impairment and neuropsychiatric symptoms in patients with Parkinson's disease dementia. *International psychogeriatrics / IPA, 24*(12), 1980-1987. doi: 10.1017/S1041610212001317

Leentjens, A. F. G., Van den Akker, M., Metsemakers, J. F. M., Lousberg, R., & Verhey, F. R. J. (2003). Higher incidence of depression preceding the onset of Parkinson's disease: A register study. *Movement Disorders, 18*(4), 414-418. doi: Doi 10.1002/Mds.10387

Lees, A. (2005). Alternatives to levodopa in the initial treatment of early Parkinson's disease. [Review]. *Drugs & aging, 22*(9), 731-740.

Lehouezec, J., & Benowitz, N. L. (1991). Basic and Clinical Psychopharmacology of Nicotine. *Clinics in Chest Medicine, 12*(4), 681-699.

Leroi, I., Harbishettar, V., Andrews, M., McDonald, K., Byrne, E. J., & Burns, A. (2011). Carer burden in apathy and impulse control disorders in Parkinson's disease. *International journal of geriatric psychiatry*. doi: 10.1002/gps.2704

Leroi, I., Pantula, H., McDonald, K., & Harbishettar, V. (2012). Neuropsychiatric symptoms in Parkinson's disease with mild cognitive impairment and dementia. *Parkinson's disease, 2012*, 308097. doi: 10.1155/2012/308097

Lesage, S., Durr, A., Tazir, M., Lohmann, E., Leutenegger, A. L., Janin, S., . . . St, F. P. s. D. G. (2006). LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. *New England Journal of Medicine, 354*(4), 422-423.

Leverenz, J. B., Quinn, J. F., Zabetian, C., Zhang, J., Montine, K. S., & Montine, T. J. (2009). Cognitive impairment and dementia in patients with Parkinson disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Current topics in medicinal chemistry, 9*(10), 903-912.

Levy, G. (2007). The relationship of Parkinson disease with aging. *Archives of Neurology, 64*(9), 1242-1246.

Levy, G., Tang, M. X., Cote, L. J., Louis, E. D., Alfaro, B., Mejia, H., . . . Marder, K. (2000). Motor impairment in PD - Relationship to incident dementia and age. *Neurology, 55*(4), 539-544.

Levy, L., Cummings, L., Fairbanks, A., Masterman, D., Miller, L., Craig, H., . . . Litvan, I. (1998). Apathy Is Not Depression. *The Journal of neuropsychiatry and clinical neurosciences, 10*, 314-319.

Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. [Research Support, Non-U.S. Gov't Review]. *Cerebral cortex, 16*(7), 916-928. doi: 10.1093/cercor/bhj043

Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2003). Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. [Clinical Trial Controlled Clinical Trial Research Support, Non-U.S. Gov't]. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 23*(15), 6351-6356.

Lewis, S. J., Shine, J. M., Duffy, S., Halliday, G., & Naismith, S. L. (2012). Anterior cingulate integrity: executive and neuropsychiatric features in Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 27*(10), 1262-1267. doi: 10.1002/mds.25104

Lezak, M., Howieson, D., Bigler, E., & Tranel, D. (2012). *Neuropsychological Assessment* (5th ed.): New York: Oxford University Press.

Lezak, M., Howieson, D., & Lorind, D. (2004). *Neuropsychological assessment* (4th ed.): New York: Oxford University Press.

Li, W., Liu, J., Skidmore, F., Liu, Y., Tian, J., & Li, K. (2010). White matter microstructure changes in the thalamus in Parkinson disease with depression: A diffusion tensor MR imaging study. *AJNR Am J Neuroradiol, 31*(10), 1861-1866. doi: ajnr.A2195 [pii] 10.3174/ajnr.A2195

Lima, C. F., Meireles, L. P., Fonseca, R., Castro, S. L., & Garrett, C. (2008). The Frontal Assessment Battery (FAB) in Parkinson's disease and correlations with formal measures of executive functioning. [Research Support, Non-U.S. Gov't]. *Journal of Neurology, 255*(11), 1756-1761. doi: 10.1007/s00415-008-0024-6

Liou, H. H., Tsai, M. C., Chen, C. J., Jeng, J. S., Chang, Y. C., Chen, S. Y., & Chen, R. C. (1997). Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. [Research Support, Non-U.S. Gov't]. *Neurology, 48*(6), 1583-1588.

Liu, B., Gao, H. M., & Hong, J. S. (2003). Parkinson's disease and exposure to infectious agents and pesticides and the occurrence of brain injuries: role of neuroinflammation. [Review]. *Environmental health perspectives, 111*(8), 1065-1073.

Logroscino, G., Marder, K., Cote, L., Tang, M. X., Shea, S., & Mayeux, R. (1996). Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Annals of Neurology, 39*(1), 89-94. doi: 10.1002/ana.410390113

Lohmann, E., Thobois, S., Lesage, S., Broussolle, E., du Montcel, S. T., Ribeiro, M. J., . . . Brice, A. (2009). A multidisciplinary study of patients with early-onset PD with and without parkin mutations. [Research Support, N.I.H., ExtramuralResearch Support, Non-U.S. Gov't]. *Neurology, 72*(2), 110-116. doi: 10.1212/01.wnl.0000327098.86861.d4

Lonie, J. A., Tierney, K. M., Herrmann, L. L., Donaghey, C., O'Carroll, R. E., Lee, A., & Ebmeier, K. P. (2009). Dual task performance in early Alzheimer's disease, amnestic mild cognitive impairment and depression. [Research Support, Non-U.S. Gov't]. *Psychological medicine, 39*(1), 23-31. doi: 10.1017/S0033291708003346

Louis, E. D., & Bennett, D. A. (2007). Mild Parkinsonian signs: An overview of an emerging concept. [Research Support, N.I.H., Extramural Review]. *Movement disorders : official journal of the Movement Disorder Society, 22*(12), 1681-1688. doi: 10.1002/mds.21433

Lucking, C. B., Durr, A., Bonifati, V., Vaughan, J., De Michele, G., Gasser, T., . . . Stu, F. P. D. G. (2000). Association between early-onset Parkinson's disease and mutations in the parkin gene. *New England Journal of Medicine, 342*(21), 1560-1567.

Luo, W. L., & Nichols, T. E. (2003). Diagnosis and exploration of massively univariate neuroimaging models. *Neuroimage, 19*(3), 1014-1032.

Ma, N., Li, L., Shu, N., Liu, J., Gong, G., He, Z., . . . Jiang, T. (2007). White matter abnormalities in first-episode, treatment-naive young adults with major depressive disorder. [Comparative Study Research Support, Non-U.S. Gov't]. *The American journal of psychiatry, 164*(5), 823-826. doi: 10.1176/appi.ajp.164.5.823

Malouin, F., Richards, C. L., Jackson, P. L., Dumas, F., & Doyon, J. (2003). Brain activations during motor imagery of locomotor-related tasks: a PET study. [Research Support, Non-U.S. Gov't]. *Human brain mapping, 19*(1), 47-62. doi: 10.1002/hbm.10103

Marder, K., Tang, M. X., Cote, L., Stern, Y., & Mayeux, R. (1995). The Frequency and Associated Risk-Factors for Dementia in Patients with Parkinsons-Disease. *Archives of Neurology, 52*(7), 695-701.

Marek, K., Innis, R., van Dyck, C., Fussell, B., Early, M., Eberly, S., . . . Seibyl, J. (2001). [I-123]beta-CIT SPECT imaging assessment of the rate of Parkinson's disease progression. *Neurology, 57*(11), 2089-2094.

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the Apathy Evaluation Scale. [Research Support, U.S. Gov't, P.H.S.]. *Psychiatry research, 38*(2), 143-162.

Marin, R. S., Butters, M. A., Mulsant, B. H., Pollock, B. G., & Reynolds, C. F., 3rd. (2003). Apathy and executive function in depressed elderly. [Research Support, U.S. Gov't, P.H.S.]. *Journal of Geriatric Psychiatry and Neurology, 16*(2), 112-116.

Marquis, S., Moore, M. M., Howieson, D. B., Sexton, G., Payami, H., Kaye, J. A., & Camicioli, R. (2002). Independent predictors of cognitive decline in healthy elderly persons. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Archives of Neurology, 59*(4), 601-606.

Marsden, C. D. (1983). Neuromelanin and Parkinson's disease. *Journal of neural transmission. Supplementum, 19*, 121-141.

Marsh, L. (2000). Neuropsychiatric aspects of Parkinson's disease. *Psychosomatics, 41*(1), 15-23.

Marsh, L., & Berk, A. (2003). Neuropsychiatric aspects of Parkinson's disease: Recent advances. *Current Science Inc, 5*, 68-76.

Martyn, C. N., & Osmond, C. (1995). Parkinson's disease and the environment in early life. [Research Support, Non-U.S. Gov't]. *Journal of the neurological sciences, 132*(2), 201-206.

Masalha, R., Kordysh, E., Alpert, G., Hallak, M., Morad, M., Mahajnah, M., . . . Herishanu, Y. (2010). The prevalence of Parkinson's disease in an Arab population, Wadi Ara, Israel. [Research Support, Non-U.S. Gov't]. *The Israel Medical Association journal : IMAJ, 12*(1), 32-35.

Mata, I. F., Wedemeyer, W. J., Farrer, M. J., Taylor, J. P., & Gallo, K. A. (2006). LRRK2 in Parkinson's disease: protein domains and functional insights. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Trends in neurosciences, 29*(5), 286-293. doi: 10.1016/j.tins.2006.03.006

Matsui, H., Nishinaka, K., Oda, M., Niikawa, H., Komatsu, K., Kubori, T., & Udaka, F. (2007). Depression in Parkinson's disease - Diffusion tensor imaging study. *Journal of Neurology, 254*(9), 1170-1173. doi: DOI 10.1007/s00415-006-0236-6

Matsui, H., Udaka, F., Miyoshi, T., Hara, N., Tamura, A., Oda, M., . . . Kameyama, M. (2006). Frontal assessment battery and brain perfusion image in Parkinson's disease. *Journal of Geriatric Psychiatry and Neurology, 19*(1), 41-45. doi: 10.1177/0891988705284714

Mattis, S. (1988). Dementia Rating Scale. Odessa, FL: Psychological Assessment Resources.

Maurizi, C. P. (2010). Influenza caused epidemic encephalitis (encephalitis lethargica): the circumstantial evidence and a challenge to the nonbelievers. [Case Reports Historical Article]. *Medical hypotheses, 74*(5), 798-801. doi: 10.1016/j.mehy.2009.12.012

Mayeux, R., Denaro, J., Hemenegildo, N., Marder, K., Tang, M. X., Cote, L. J., & Stern, Y. (1992). A Population-Based Investigation of Parkinsons-Disease with and without Dementia - Relationship to Age and Gender. *Archives of Neurology, 49*(5), 492-497.

Mayeux, R., Tang, M. X., Marder, K., Cote, L. J., & Stern, Y. (1994). Smoking and Parkinson's disease. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Movement disorders : official journal of the Movement Disorder Society, 9*(2), 207-212. doi: 10.1002/mds.870090215

McCann, S. J., LeCouteur, D. G., Green, A. C., Brayne, C., Johnson, A. G., Chan, D., . . . Pond, S. M. (1998). The epidemiology of Parkinson's disease in an Australian population. [Research Support, Non-U.S. Gov't]. *Neuroepidemiology, 17*(6), 310-317.

Mcgeer, P. L., Mcgeer, E. G., & Suzuki, J. S. (1977). Aging and Extrapyramidal Function. *Archives of Neurology, 34*(1), 33-35.

Meireles, J., & Massano, J. (2012). Cognitive impairment and dementia in Parkinson's disease: clinical features, diagnosis, and management. *Frontiers in neurology, 3*, 88. doi: 10.3389/fneur.2012.00088

Mellon, A. F., Appleton, R. E., Gardner-Medwin, D., & Aynsley-Green, A. (1991). Encephalitis lethargica-like illness in a five-year-old. [Case Reports]. *Developmental medicine and child neurology, 33*(2), 158-161.

Melzer, T. R., Watts, R., MacAskill, M. R., Pitcher, T. L., Livingston, L., Keenan, R. J., . . . Anderson, T. J. (2012). Grey matter atrophy in cognitively impaired Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry, 83*(2), 188-194. doi: DOI 10.1136/jnnp-2011-300828

Middleton, F. A., & Strick, P. L. (1994). Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Science, 266*(5184), 458-461.

Migneco, O., Benoit, M., Koulibaly, P. M., Dygai, I., Bertogliati, C., Desvignes, P., . . . Darcourt, J. (2001). Perfusion brain SPECT and statistical parametric mapping analysis indicate that apathy is a cingulate syndrome: a study in Alzheimer's disease and nondemented patients. *Neuroimage, 13*(5), 896-902. doi: 10.1006/nimg.2000.0741

Mizuno, Y., Hattori, N., Kubo, S. I., Sato, S., Nishioka, K., Hatano, T., . . . Mochizuki, H. (2008). Progress in the pathogenesis and genetics of Parkinson's disease. *Philosophical Transactions of the Royal Society B-Biological Sciences, 363*(1500), 2215-2227. doi: DOI 10.1098/rstb.2008.2273

Molloy, D. W., & Standish, T. I. (1997). A guide to the standardized Mini-Mental State Examination. [Comparative Study]. *International psychogeriatrics / IPA, 9 Suppl 1*, 87-94; discussion 143-150.

Monchi, O., Petrides, M., Doyon, J., Postuma, R. B., Worsley, K., & Dagher, A. (2004). Neural bases of set-shifting deficits in Parkinson's disease. *Journal of Neuroscience, 24*(3), 702-710. doi: Doi 10.1523/Jneurosci.4860-03.2004

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. [Comparative Study]. *The British journal of psychiatry : the journal of mental science, 134*, 382-389.

Moore, D. J., & Dawson, T. M. (2008). Value of genetic models in understanding the cause and mechanisms of Parkinson's disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Current neurology and neuroscience reports, 8*(4), 288-296.

Moore, S. T., MacDougall, H. G., & Ondo, W. G. (2008). Ambulatory monitoring of freezing of gait in Parkinson's disease. [Research Support, U.S. Gov't, Non-P.H.S.]. *Journal of neuroscience methods, 167*(2), 340-348. doi: 10.1016/j.jneumeth.2007.08.023

Morano, A., Jimenez-Jimenez, F. J., Molina, J. A., & Antolin, M. A. (1994). Risk-factors for Parkinson's disease: case-control study in the province of Caceres, Spain. [Comparative Study Review]. *Acta Neurologica Scandinavica, 89*(3), 164-170.

Morens, D. M., Grandinetti, A., Waslien, C. I., Park, C. B., Ross, G. W., & White, L. R. (1996). Case-control study of idiopathic Parkinson's disease and dietary vitamin E intake. [Comparative Study Multicenter Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Neurology, 46*(5), 1270-1274.

Moretti, R., Torre, P., Antonello, R. M., Rosin, M. V., Esposito, F., Furman, M. R., & Bellini, G. (2012). Apathy: a complex symptom specific to the clinical pattern of presentation of Parkinson's disease? *American journal of Alzheimer's disease and other dementias, 27*(3), 196-201. doi: 10.1177/1533317512445502

Morgante, L., Colosimo, C., Antonini, A., Marconi, R., Meco, G., Pederzoli, M., . . . Barone, P. (2012). Psychosis associated to Parkinson's disease in the early stages: relevance of cognitive decline and depression. *Journal of neurology, neurosurgery, and psychiatry, 83*(1), 76-82. doi: 10.1136/jnnp-2011-300043

Morioka, S., Sakata, K., Yoshida, S., Nakai, E., Shiba, M., Yoshimura, N., & Hashimoto, T. (2002). Incidence of Parkinson disease in Wakayama, Japan. [Research Support, Non-U.S. Gov't]. *Journal of epidemiology / Japan Epidemiological Association, 12*(6), 403-407.

Murata, M. (2009). Levodopa in the early treatment of Parkinson's disease. *Parkinsonism & Related Disorders, 15*, S17-S20.

Muslimovic, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. [Comparative Study Research Support, Non-U.S. Gov't]. *Neurology, 65*(8), 1239-1245. doi: 10.1212/01.wnl.0000180516.69442.95

Nagai, M., Kishi, K., & Kato, S. (2007). Insular cortex and neuropsychiatric disorders: A review of recent literature. *European Psychiatry, 22*(6), 387-394. doi: DOI 10.1016/j.eurpsy.2007.02.006

Nagano-Saito, A., Washimi, Y., Arahata, Y., Iwai, K., Kawatsu, S., Ito, K., . . . Kachi, T. (2004). Visual hallucination in Parkinson's disease with FDG PET. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 19*(7), 801-806. doi: 10.1002/mds.20129

Nagano-Saito, A., Washimi, Y., Arahata, Y., Kachi, T., Lerch, J. P., Evans, A. C., . . . Ito, K. (2005). Cerebral atrophy and its relation to cognitive impairment in Parkinson disease. [Comparative Study Research Support, Non-U.S. Gov't]. *Neurology, 64*(2), 224-229. doi: 10.1212/01.WNL.0000149510.41793.50

Nakaaki, S., Murata, Y., Sato, J., Shinagawa, Y., Hongo, J., Tatsumi, H., . . . Furukawa, T. A. (2008). Association between apathy/depression and executive function in patients with Alzheimer's disease. *International Psychogeriatrics, 20*(5), 964-975. doi: Doi 10.1017/S1041610208007308

Neckelmann, G., Specht, K., Lund, A., Ersland, L., Smievoll, A. I., Neckelmann, D., & Hugdahl, K. (2006). Mr morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. [Controlled Clinical Trial Research Support, Non-U.S. Gov't]. *The International journal of neuroscience, 116*(1), 9-23. doi: 10.1080/00207450690962244

Nelson, H. N. (1976). A modified card-sorting test sensitive to frontal lobe defects. Cortex, 12, 313-324.

Nicola, S. M., Surmeier, J., & Malenka, R. C. (2000). Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. *Annu Rev Neurosci 23*, 185–215. doi: doi:10.1146/annurev.neuro.23.1.185

Norman, S., Troster, A. I., Fields, J. A., & Brooks, R. (2002). Effects of depression and Parkinson's disease on cognitive functioning. *Journal of Neuropsychiatry and Clinical Neurosciences, 14*(1), 31-36.

Noyce, A. J., Bestwick, J. P., Silveira-Moriyama, L., Hawkes, C. H., Giovannoni, G., Lees, A. J., & Schrag, A. (2012). Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Annals of Neurology*. doi: 10.1002/ana.23687

Nuti, A., Ceravolo, R., Dell'Agnello, G., Gambaccini, G., Bellini, G., Kiferle, L., . . . Bonuccelli, U. (2004). Environmental factors and Parkinson's disease: a case-control study in the Tuscany region of Italy. *Parkinsonism & Related Disorders, 10*(8), 481-485. doi: 10.1016/j.parkreldis.2004.01.008

Nuti, A., Ceravolo, R., Piccinni, A., Dell'Agnello, G., Bellini, G., Gambaccini, G., . . . Bonuccelli, U. (2004). Psychiatric comorbidity in a population of Parkinson's disease patients. *European Journal of Neurology, 11*(5), 315-320.

Obeso, I., Casabona, E., Bringas, M. L., Alvarez, L., & Jahanshahi, M. (2012). Semantic and phonemic verbal fluency in Parkinson's disease: Influence of clinical and demographic variables. [Research Support, Non-U.S. Gov't]. *Behavioural neurology, 25*(2), 111-118.

Oguru, M., Tachibana, H., Toda, K., Okuda, B., & Oka, N. (2010). Apathy and Depression in Parkinson Disease. *Journal of Geriatric Psychiatry and Neurology, 23*(1), 35-41.

Oishi, N., Udaka, F., Kameyama, M., Sawamoto, N., Hashikawa, K., & Fukuyama, H. (2005). Regional cerebral blood flow in Parkinson disease with nonpsychotic visual hallucinations. [Comparative Study Research Support, Non-U.S. Gov't]. *Neurology, 65*(11), 1708-1715. doi: 10.1212/01.wnl.0000187116.13370.e0

Okuma, Y. (2006). Freezing of gait in Parkinson's disease. [Review]. *Journal of Neurology, 253 Suppl 7*, VII27-32. doi: 10.1007/s00415-006-7007-2

Ostergaard, K. (1977). The concentration of cadmium in renal tissue from smokers and non-smokers. *Acta medica Scandinavica, 202*(3), 193-195.

Ott, B. R., Lafleche, G., Whelihan, W. M., Buongiorno, G. W., Albert, M. S., & Fogel, B. S. (1996). Impaired awareness of deficits in Alzheimer disease. *Alzheimer disease and associated disorders, 10*(2), 68-76.

Owen, A. M. (2004). Cognitive dysfunction in Parkinson disease: The role of frontostriatal circuitry. *Neuroscientist, 10*(6), 525-537. doi: Doi 10.1177/1073858404266776

Ozelius, L. J., Senthil, G., Saunders-Pullman, R., Ohmann, E., Deligtisch, A., Tagliati, M., . . . Bressman, S. B. (2006). LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. [Letter]. *The New England journal of medicine, 354*(4), 424-425. doi: 10.1056/NEJMc055509

Ozer, F., Meral, H., Hanoglu, L., Ozturk, O., Aydemir, T., Cetin, S., . . . Tiras, R. (2007). Cognitive impairment patterns in Parkinson's disease with visual hallucinations. *Journal of Clinical Neuroscience, 14*(8), 742-746. doi: DOI 10.1016/j.jocn.2006.05.006

Paelecke-Habermann, Y., Pohl, J., & Leplow, B. (2005). Attention and executive functions in remitted major depression patients. *Journal of Affective Disorders, 89*(1-3), 125-135. doi: 10.1016/j.jad.2005.09.006

Paisan-Ruiz, C., Jain, S., Evans, E. W., Gilks, W. P., Simon, J., van der Brug, M., . . . Singleton, A. B. (2004). Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron, 44*(4), 595-600.

Pallone, J. A. (2007). Introduction to Parkinson's disease. [Review]. *Disease-a-month : DM, 53*(4), 195-199. doi: 10.1016/j.disamonth.2007.05.001

Paradiso, S., Lamberty, G. J., Garvey, M. J., & Robinson, R. G. (1997). Cognitive impairment in the euthymic phase of chronic unipolar depression. [Comparative Study Research Support, U.S. Gov't, Non-P.H.S.]. *The Journal of nervous and mental disease, 185*(12), 748-754.

Park, A., & Stacy, M. (2009). Non-motor symptoms in Parkinson's disease. *Journal of Neurology, 256*, S293-S298. doi: DOI 10.1007/s00415-009-5240-1

Parkinson's UK. (2013). What is Parkinson's? Retrieved January 03, 2013 from http://www.parkinsons.org.uk/about_parkinsons/what_is_parkinsons.aspx

Paviour, D. C., Winterburn, D., Simmonds, S., Burgess, G., Wilkinson, L., Fox, N. C., . . . Jahanshahi, M. (2005). Can the frontal assessment battery (FAB) differentiate bradykinetic rigid syndromes? Relation of the FAB to formal neuropsychological testing. *Neurocase, 11*(4), 274-282. doi: Doi 10.1080/13554790590962933

Pedersen, K. F., Alves, G., Aarsland, D., & Larsen, J. P. (2009). Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. *Journal of neurology, neurosurgery, and psychiatry, 80*(11), 1279-1282. doi: 10.1136/jnnp.2008.170043

Pedersen, K. F., Alves, G., Bronnick, K., Aarsland, D., Tysnes, O. B., & Larsen, J. P. (2010). Apathy in drug-naive patients with incident Parkinson's disease: the Norwegian ParkWest study. [Multicenter Study Research Support, Non-U.S. Gov't]. *Journal of Neurology, 257*(2), 217-223. doi: 10.1007/s00415-009-5297-x

Pedersen, K. F., Larsen, J. P., Alves, G., & Aarsland, D. (2009). Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. *Parkinsonism & Related Disorders, 15*(4), 295-299. doi: 10.1016/j.parkreldis.2008.07.006

Pereira, J. B., Junque, C., Marti, M. J., Ramirez-Ruiz, B., Bargallo, N., & Tolosa, E. (2009). Neuroanatomical substrate of visuospatial and visuoperceptual impairment in Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 24*(8), 1193-1199. doi: 10.1002/mds.22560

Pereira, J. B., Junque, C., Marti, M. J., Ramirez-Ruiz, B., Bartres-Faz, D., & Tolosa, E. (2009). Structural brain correlates of verbal fluency in Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Neuroreport, 20*(8), 741-744. doi: 10.1097/WNR.0b013e328329370b

Perry, D. C., Mao, D. Y., Gold, A. B., McIntosh, J. M., Pezzullo, J. C., & Kellar, K. J. (2007). Chronic nicotine differentially regulates alpha 6-and beta 3-containing nicotinic cholinergic receptors in rat brain. *Journal of Pharmacology and Experimental Therapeutics, 322*(1), 306-315. doi: DOI 10.1124/jpet.107.121228

Petrovic, I. N., Stefanova, E., Kozic, D., Semnic, R., Markovic, V., Daragasevic, N. T., & Kostic, V. S. (2012). White matter lesions and depression in patients with Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Journal of the neurological sciences, 322*(1-2), 132-136. doi: 10.1016/j.jns.2012.07.021

Picard, F., Hirsch, E., Salmon, E., Marescaux, C., & Collard, M. (1996). Post-encephalitic extra-pyramidal syndrome associating akinesia and stereotyped movements responsive to L-dopa. *Revue Neurologique, 152*(4), 267-271.

Pihlajamaki, M., Tanila, H., Hanninen, T., Kononen, M., Laakso, M., Partanen, K., . . . Aronen, H. J. (2000). Verbal fluency activates the left medial temporal lobe: A functional magnetic resonance imaging study. *Annals of Neurology, 47*(4), 470-476.

Piovezan, M. R., Teive, H. A., Piovesan, E. J., Mader, M. J., & Werneck, L. C. (2007). Cognitive function assessment in idiopathic Parkinson's disease. *Arquivos de neuro-psiquiatria, 65*(4A), 942-946.

Plotnik, M., Giladi, N., Balash, Y., Peretz, C., & Hausdorff, J. M. (2005). Is freezing of gait in Parkinson's disease related to asymmetric motor function? [Clinical Trial Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. *Annals of Neurology, 57*(5), 656-663. doi: 10.1002/ana.20452

Pluck, G. C., & Brown, R. G. (2002). Apathy in Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Journal of neurology, neurosurgery, and psychiatry, 73*(6), 636-642.

Poewe, W. (2008). Non-motor symptoms in Parkinson's disease. *European Journal of Neurology, 15 Suppl 1*, 14-20. doi: ENE2056 [pii] 10.1111/j.1468-1331.2008.02056.x

Poewe, W. (2009). Treatments for Parkinson disease--past achievements and current clinical needs. [Historical Article Review]. *Neurology, 72*(7 Suppl), S65-73. doi: 10.1212/WNL.0b013e31819908ce

Poewe, W., & Scherfler, C. (2003). Role of dopamine transporter imaging in investigation of parkinsonian syndromes in routine clinical practice. *Movement Disorders, 18*, S16-S21. doi: Doi 10.1002/Mds.10573

Poletti, M., & Bonuccelli, U. (2012). Impulse control disorders in Parkinson' disease: the role of personality and cognitive status. *Journal of Neurology, 259*(11), 2269-2277. doi: 10.1007/s00415-012-6506-6

Poletti, M., Lucetti, C., Del Dotto, P., Berti, C., Logi, C., & Bonuccelli, U. (2012). Relationship between neuropsychiatric symptoms and cognitive performance in de novo Parkinson's disease. *The Journal of neuropsychiatry and clinical neurosciences, 24*(4), E22-23. doi: 10.1176/appi.neuropsych.11100243

Polymeropoulos, M. H., Lavedan, C., Leroy, E., Ide, S. E., Dehejia, A., Dutra, A., . . . Nussbaum, R. L. (1997). Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Science, 276*(5321), 2045-2047.

Poulopoulos, M., Levy, O. A., & Alcalay, R. N. (2012). The neuropathology of genetic Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society, 27*(7), 831-842. doi: 10.1002/mds.24962

Prabhakaran, V., Smith, J. A., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1997). Neural substrates of fluid reasoning: an fMRI study of neocortical activation during performance of the Raven's Progressive Matrices Test. [Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Cognitive psychology, 33*(1), 43-63. doi: 10.1006/cogp.1997.0659

Perri, R., Monaco, M., Fadda, L., Caltagirone, C., & Carlesimo, G. A. (2013). Neuropsychological Correlates of Behavioral Symptoms in Alzheimer's Disease, Frontal Variant of Frontotemporal, Subcortical Vascular, and Lewy Body Dementias: A Comparative Study. *Journal of Alzheimer's disease : JAD*. doi: 10.3233/JAD-131337

Quik, M. (2004). Smoking, nicotine and Parkinson's disease. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Trends in neurosciences, 27*(9), 561-568. doi: 10.1016/j.tins.2004.06.008

Qureshi, S. U., Amspoker, A. B., Calleo, J. S., Kunik, M. E., & Marsh, L. (2012). Anxiety Disorders, Physical Illnesses, and Health Care Utilization in Older Male Veterans With Parkinson Disease and Comorbid Depression. *Journal of Geriatric Psychiatry and Neurology*. doi: 10.1177/0891988712466458

Raja, M., & Bentivoglio, A. R. (2012). Impulsive and compulsive behaviors during dopamine replacement treatment in Parkinson's Disease and other disorders. [Review]. *Current drug safety, 7*(1), 63-75.

Rajput, A. H. (1984). Epidemiology of Parkinsons-Disease. *Canadian Journal of Neurological Sciences, 11*(1), 156-159.

Rajput, A. H., Offord, K. P., Beard, C. M., & Kurland, L. T. (1984). Epidemiology of Parkinsonism - Incidence, Classification, and Mortality. *Annals of Neurology, 16*(3), 278-282.

Rajput, A. H., Uitti, R. J., Stern, W., Laverty, W., O'Donnell, K., O'Donnell, D., . . . Dua, A. (1987). Geography, drinking water chemistry, pesticides and herbicides and the etiology of Parkinson's disease. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 14*(3 Suppl), 414-418.

Ramirez-Ruiz, B., Junque, C., Marti, M. J., Valldeoriola, F., & Tolosa, E. (2007). Cognitive changes in Parkinson's disease patients with visual hallucinations. *Dementia and geriatric cognitive disorders, 23*(5), 281-288. doi: Doi 10.1159/000100850

Ramirez-Ruiz, B., Marti, M. J., Tolosa, E., Falcon, C., Bargallo, N., Valldeoriola, F., & Junque, C. (2008). Brain response to complex visual stimuli in Parkinson's patients with hallucinations: a functional magnetic resonance imaging study. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 23*(16), 2335-2343. doi: 10.1002/mds.22258

Ransmayr, G. (2007). [Clinical criteria of Parkinson's disease]. [Comparative Study Review]. *Therapeutische Umschau. Revue therapeutique, 64*(1), 5-8. doi: 10.1024/0040-5930.64.1.5

Ravnkilde, B., Videbech, P., Rosenberg, R., Gjedde, A., & Gade, A. (2002). Putative tests of frontal lobe function: a PET-study of brain activation during Stroop's Test and verbal fluency. *Journal of Clinical and Experimental Neuropsychology, 24*(4), 534-547. doi: 10.1076/jcen.24.4.534.1033

Reijnders, J. S., Ehrt, U., Weber, W. E., Aarsland, D., & Leentjens, A. F. (2008). A systematic review of prevalence studies of depression in Parkinson's disease. [Review]. *Movement disorders : official journal of the Movement Disorder Society, 23*(2), 183-189; quiz 313. doi: 10.1002/mds.21803

Reijnders, J. S., Scholtissen, B., Weber, W. E., Aalten, P., Verhey, F. R., & Leentjens, A. F. (2010). Neuroanatomical correlates of apathy in Parkinson's disease: A magnetic resonance imaging study using voxel-based morphometry. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 25*(14), 2318-2325. doi: 10.1002/mds.23268

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. Pereceptual and Motor Skills, 8, 271-276.

Remy, P., Doder, M., Lees, A., Turjanski, N., & Brooks, D. (2005). Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain, 128*, 1314-1322. doi: Doi 10.1093/Brain/Awh445

Rey, A. (1964). L'examen Clinique en psychologie. *Paris: Presses Universitaires de France*.

Rezak, M. (2007). Current pharmacotherapeutic treatment options in Parkinson's disease. [Review]. *Disease-a-month : DM, 53*(4), 214-222. doi: 10.1016/j.disamonth.2007.05.002

Ricci, M., Guidoni, S. V., Sepe-Monti, M., Bomboi, G., Antonini, G., Blundo, C., & Giubilei, F. (2009). Clinical findings, functional abilities and caregiver distress in the early stage of dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). *Archives of Gerontology and Geriatrics, 49*(2), e101-104. doi: 10.1016/j.archger.2008.10.001

Ring, H. A., Bench, C. J., Trimble, M. R., Brooks, D. J., Frackowiak, R. S. J., & Dolan, R. J. (1994). Depression in Parkinsons-Disease - a Positron Emission Study. *British Journal of Psychiatry, 165*, 333-339.

Ring, H. A., & Serra-Mestres, J. (2002). Neuropsychiatry of the basal ganglia. [Review]. *Journal of neurology, neurosurgery, and psychiatry, 72*(1), 12-21.

Roane, D. M., Rogers, J. D., Robinson, J. H., & Feinberg, T. E. (1998). Delusional misidentification in association with parkinsonism. [Case Reports]. *The Journal of neuropsychiatry and clinical neurosciences, 10*(2), 194-198.

Robert, G., Le Jeune, F., Lozachmeur, C., Drapier, S., Dondaine, T., Peron, J., . . . Drapier, D. (2012). Apathy in patients with Parkinson disease without dementia or depression A PET study. *Neurology, 79*(11), 1155-1160.

Rojo, A., Aguilar, M., Garolera, M. T., Cubo, E., Navas, I., & Quintana, S. (2003). Depression in Parkinson's disease: clinical correlates and outcome. *Parkinsonism & Related Disorders, 10*(1), 23-28.

Rosenberg, P. B., Mielke, M. M., Appleby, B., Oh, E., Leoutsakos, J. M., & Lyketsos, C. G. (2011). Neuropsychiatric symptoms in MCI subtypes: the importance of executive dysfunction. [Research Support, N.I.H., Extramural]. *International journal of geriatric psychiatry, 26*(4), 364-372. doi: 10.1002/gps.2535

Ross, C. A., & Smith, W. W. (2007). Gene-environment interactions in Parkinson's disease. *Parkinsonism & Related Disorders, 13*, S309-S315.

Ross, O. A., Toft, M., Whittle, A. J., Johnson, J. L., Papapetropoulos, S., Mash, D. C., . . . Dickson, D. W. (2006). Lrrk2 and Lewy body disease. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Annals of Neurology, 59*(2), 388-393. doi: 10.1002/ana.20731

Roth, M., Tym, E., Mountjoy, C. Q., Huppert, F. A., Hendrie, H., Verma, S., & Goddard, R. (1986). Camdex - a Standardized Instrument for the Diagnosis of Mental Disorder in the Elderly with Special Reference to the Early Detection of Dementia. *British Journal of Psychiatry, 149*, 698-709. doi: DOI 10.1192/bjp.149.6.698

Royall, D. R., Mahurin, R. K., & Gray, K. F. (1992). Bedside assessment of executive cognitive impairment: the executive interview. [Research Support, Non-U.S. Gov't]. *Journal of the American Geriatrics Society, 40*(12), 1221-1226.

Ruscheweyh, R., Deppe, M., Lohmann, H., Wersching, H., Korsukewitz, C., Duning, T., . . . Knecht, S. (2012). Executive performance is related to regional gray matter volume in healthy older individuals. *Human brain mapping*. doi: 10.1002/hbm.22146

Santangelo, G., Trojano, L., Barone, P., Errico, D., Grossi, D., & Vitale, C. (2012). Apathy in Parkinson's disease: Diagnosis, neuropsychological correlates, pathophysiology and treatment. *Behavioural neurology*. doi: 10.3233/BEN-129025

Santangelo, G., Vitale, C., Trojano, L., Longo, K., Cozzolino, A., Grossi, D., & Barone, P. (2009). Relationship between depression and cognitive dysfunctions in Parkinson's disease without dementia. *Journal of Neurology, 256*(4), 632-638. doi: 10.1007/s00415-009-0146-5

Santangelo, G., Vitale, C., Trojano, L., Verde, F., Grossi, D., & Barone, P. (2009). Cognitive dysfunctions and pathological gambling in patients with Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 24*(6), 899-905. doi: 10.1002/mds.22472

Schaafsma, J. D., Balash, Y., Gurevich, T., Bartels, A. L., Hausdorff, J. M., & Giladi, N. (2003). Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. *European journal of neurology : the official journal of the European Federation of Neurological Societies, 10*(4), 391-398.

Schapira, A. H. V. (2011). Mitochondrial Pathology in Parkinson's Disease. *Mount Sinai Journal of Medicine, 78*(6), 872-881. doi: Doi 10.1002/Msj.20303

Scheider, W. L., Hershey, L. A., Vena, J. E., Holmlund, T., Marshall, J. R., & Freudenheim. (1997). Dietary antioxidants and other dietary factors in the etiology of Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society, 12*(2), 190-196. doi: 10.1002/mds.870120209

Schiesling, C., Kieper, N., Seidel, K., & Kruger, R. (2008). Review: Familial Parkinson's disease--genetics, clinical phenotype and neuropathology in relation to the common sporadic form of the disease. [Research Support, Non-U.S. Gov't Review]. *Neuropathology and applied neurobiology, 34*(3), 255-271. doi: 10.1111/j.1365-2990.2008.00952.x

Schmahmann, J. D., Weilburg, J. B., & Sherman, J. C. (2007). The neuropsychiatry of the cerebellum - insights from the clinic. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Cerebellum, 6*(3), 254-267. doi: 10.1080/14734220701490995

Schneider, F., Althaus, A., Backes, V., & Dodel, R. (2008). Psychiatric symptoms in Parkinson's disease. [Review]. *European archives of psychiatry and clinical neuroscience, 258 Suppl 5*, 55-59. doi: 10.1007/s00406-008-5012-4

Schrag, A., Hovris, A., Morley, D., Quinn, N., & Jahanshahi, M. (2006). Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. *Parkinsonism & Related Disorders, 12*(1), 35-41. doi: DOI 10.1016/j.parkreldis.2005.06.011

Schuurman, A. G., van den Akker, M., Ensinck, K. T. J. L., Metsemakers, J. F. M., Knottnerus, J. A., Leentjens, A. F. G., & Buntinx, F. (2002). Increased risk of Parkinson's disease after depression - A retrospective cohort study. *Neurology, 58*(10), 1501-1504.

Schwarz, J., Odin, P., Buhmann, C., Csoti, I., Jost, W., Wullner, U., & Storch, A. (2011). Depression in Parkinson's disease. [Review]. *Journal of Neurology, 258*(Suppl 2), S336-338. doi: 10.1007/s00415-011-6048-3

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., . . . Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 27*(9), 2349-2356. doi: 10.1523/JNEUROSCI.5587-06.2007

Seger, C. A., & Cincotta, C. M. (2005). The roles of the caudate nucleus in human classification learning. [Comparative Study Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 25*(11), 2941-2951. doi: 10.1523/JNEUROSCI.3401-04.2005

Seidler, A., Hellenbrand, W., Robra, B. P., Vieregge, P., Nischan, P., Joerg, J., . . . Schneider, E. (1996). Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. [Comparative Study Research Support, Non-U.S. Gov't]. *Neurology, 46*(5), 1275-1284.

Selbaek, G., Engedal, K., & Bergh, S. (2013). The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review. [Review]. *Journal of the American Medical Directors Association, 14*(3), 161-169. doi: 10.1016/j.jamda.2012.09.027

Semchuk, K. M., Love, E. J., & Lee, R. G. (1991). Parkinson's disease and exposure to rural environmental factors: a population based case-control study. [Research Support, Non-U.S. Gov't]. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 18*(3), 279-286.

Semchuk, K. M., Love, E. J., & Lee, R. G. (1993). Parkinson's disease: a test of the multifactorial etiologic hypothesis. [Research Support, Non-U.S. Gov't]. *Neurology, 43*(6), 1173-1180.

Senard, J. M., Rai, S., Lapeyre-Mestre, M., Brefel, C., Rascol, O., Rascol, A., & Montastruc, J. L. (1997). Prevalence of orthostatic hypotension in Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry, 63*(5), 584-589.

Senhorini, M. C. T., Cerqueira, C. T., Schaufelberger, M. S., Almeida, J. C., Amaro, E., Sato, J. R., . . . Busatto, G. F. (2011). Brain activity patterns during phonological verbal fluency performance with varying levels of difficulty: A functional magnetic resonance imaging study in Portuguese-speaking healthy individuals. *Journal of Clinical and Experimental Neuropsychology, 33*(8), 864-873. doi: Doi 10.1080/13803395.2011.561299

Shanks, M. F., & Venneri, A. (2004). Thinking through delusions in Alzheimer's disease. [Editorial]. *The British journal of psychiatry : the journal of mental science, 184*, 193-194.

Sheridan, P. L., & Hausdorff, J. M. (2007). The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer's disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Dementia and geriatric cognitive disorders, 24*(2), 125-137. doi: 10.1159/000105126

Shin, S., Lee, J. E., Hong, J. Y., Sunwoo, M. K., Sohn, Y. H., & Lee, P. H. (2012). Neuroanatomical substrates of visual hallucinations in patients with non-demented Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Journal of neurology, neurosurgery, and psychiatry, 83*(12), 1155-1161. doi: 10.1136/jnnp-2012-303391

Shulman, L. M. (2000). Apathy in patients with Parkinson's disease. *International Review of Psychiatry, 12*(4), 298-306. doi: Doi 10.1080/09540260020002523

Silberman, C. D., Laks, J., Capitao, C. F., Rodrigues, C. S., Moreira, I., Vasconcellos, L. F., & Engelhardt, E. (2007). Frontal functions in depressed and nondepressed Parkinson's disease patients: impact of severity stages. *Psychiatry research, 149*(1-3), 285-289. doi: 10.1016/j.psychres.2006.04.020

Simth, A. (1973). Symbol Digit Modalities Test. Manual. Los Angeles: Western Psychological Services.

Sipetic, S. B., Vlajinac, H. D., Maksimovic, J. M., Marinkovic, J. M., Dzoljic, E. D., Ratkov, I. S., & Kostic, V. S. (2012). Cigarette smoking, coffee intake and alcohol consumption preceding Parkinson's disease: a case-control study. *Acta Neuropsychiatrica, 24*(2), 109-114. doi: DOI 10.1111/j.1601-5215.2011.00593.x

Skidmore, F. M., Yang, M., Baxter, L., von Deneen, K., Collingwood, J., He, G., . . . Liu, Y. (2011). Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease. *Neuroimage*. doi: 10.1016/j.neuroimage.2011.07.012

Smargiassi, A., Mutti, A., De Rosa, A., De Palma, G., Negrotti, A., & Calzetti, S. (1998). A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy. [Research Support, Non-U.S. Gov't]. *Neurotoxicology, 19*(4-5), 709-712.

Sockeel, P., Dujardin, K., Devos, D., Deneve, C., Destee, A., & Defebvre, L. (2006). The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. [Comparative Study]. *Journal of neurology, neurosurgery, and psychiatry, 77*(5), 579-584. doi: 10.1136/jnnp.2005.075929

Son, J. H., Han, D. H., Min, K. J., & Kee, B. S. (2013). Correlation between gray matter volume in the temporal lobe and depressive symptoms in patients with Alzheimer's disease. *Neuroscience letters, 548*, 15-20. doi: DOI 10.1016/j.neulet.2013.05.021

Spinnler, H., & Tognoni, G. . (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Ital J Neurol Sci, 6*, 1-120.

Spira, P. J., Sharpe, D. M., Halliday, G., Cavanagh, J., & Nicholson, G. A. (2001). Clinical and pathological features of a Parkinsonian syndrome in a family with an Ala53Thr alpha-synuclein mutation. [Research Support, Non-U.S. Gov't]. *Annals of Neurology, 49*(3), 313-319.

Stacy, M. (1999). Managing late complications of Parkinson's disease. [Review]. *The Medical clinics of North America, 83*(2), 469-481, vii.

Stamey, W., Davidson, A., & Jankovic, J. (2008). Shoulder pain: a presenting symptom of Parkinson disease. [Comment Letter]. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases, 14*(4), 253-254. doi: 10.1097/RHU.0b013e3181826d43

Starkstein, S. E., Mayberg, H. S., Leiguarda, R., Preziosi, T. J., & Robinson, R. G. (1992). A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Journal of neurology, neurosurgery, and psychiatry, 55*(5), 377-382.

Starkstein, S. E., Mayberg, H. S., Preziosi, T. J., Andrezejewski, P., Leiguarda, R., & Robinson, R. G. (1992). Reliability, validity, and clinical correlates of apathy in Parkinson's disease. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *The Journal of neuropsychiatry and clinical neurosciences, 4*(2), 134-139.

Starkstein, S. E., Merello, M., Jorge, R., Brockman, S., Bruce, D., Petracca, G., & Robinson, R. G. (2008). A validation study of depressive syndromes in Parkinson's disease. *Mov Disord, 23*(4), 538-546. doi: 10.1002/mds.21866

Starkstein, S. E., Mizrahi, R., Capizzano, A. A., Acion, L., Brockman, S., & Power, B. D. (2009). Neuroimaging Correlates of Apathy and Depression in Alzheimer's Disease. *Journal of Neuropsychiatry and Clinical Neurosciences, 21*(3), 259-265.

Starkstein, S. E., Preziosi, T. J., Berthier, M. L., Bolduc, P. L., Mayberg, H. S., & Robinson, R. G. (1989). Depression and cognitive impairment in Parkinson's disease. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Brain : a journal of neurology, 112 (Pt 5)*, 1141-1153.

Stefanova, E., Potrebic, A., Ziropadja, L., Maric, J., Ribaric, I., & Kostic, V. S. (2006). Depression predicts the pattern of cognitive impairment in early Parkinson's disease. *Journal of the neurological sciences, 248*(1-2), 131-137. doi: 10.1016/j.jns.2006.05.031

Stepkina, D. A., Zakharov, V. V., & Yakhno, N. N. (2010). Cognitive impairments in progression of Parkinson's disease. *Neuroscience and behavioral physiology, 40*(1), 61-67. doi: 10.1007/s11055-009-9223-6

Stern, G., & Lees, A. (1982). *Parkinson's Disease The Facts*. New York Toronto: Oxford University Press.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psycology, 18*, 643-662.

Takahashi, M., Yamada, T., Nakajima, S., Nakajima, K., Yamamoto, T., & Okada, H. (1995). The substantia nigra is a major target for neurovirulent influenza A virus. [Research Support, Non-U.S. Gov't]. *The Journal of experimental medicine, 181*(6), 2161-2169.

Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Nagase, T., . . . Kawashima, R. (2012). Regional gray and white matter volume associated with Stroop interference: evidence from voxel-based morphometry. [Research Support, Non-U.S. Gov't]. *Neuroimage, 59*(3), 2899-2907. doi: 10.1016/j.neuroimage.2011.09.064

Tam, C. W., Burton, E. J., McKeith, I. G., Burn, D. J., & O'Brien, J. T. (2005). Temporal lobe atrophy on MRI in Parkinson disease with dementia: a comparison with Alzheimer disease and dementia with Lewy bodies. [Comparative Study Research Support, Non-U.S. Gov't]. *Neurology, 64*(5), 861-865. doi: 10.1212/01.WNL.0000153070.82309.D4

Tandberg, E., Larsen, J. P., & Karlsen, K. (1998). A community-based study of sleep disorders in patients with Parkinson's disease. [Comparative Study]. *Movement disorders : official journal of the Movement Disorder Society, 13*(6), 895-899. doi: 10.1002/mds.870130606

Tanner, C. M. (1989). The role of environmental toxins in the etiology of Parkinson's disease. [Review]. *Trends in neurosciences, 12*(2), 49-54.

Tanner, C. M., Chen, B., Wang, W. Z., Peng, M. L., Liu, Z. L., Liang, X. L., . . . Schoenberg, B. S. (1987). Environmental factors in the etiology of Parkinson's disease. [Research Support, Non-U.S. Gov't Review]. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 14*(3 Suppl), 419-423.

Tatsch, M. F., Bottino, C. M., Azevedo, D., Hototian, S. R., Moscoso, M. A., Folquitto, J. C., . . . Louza, M. R. (2006). Neuropsychiatric symptoms in Alzheimer disease and cognitively impaired, nondemented elderly from a community-based sample in Brazil: prevalence and relationship with dementia severity. [Research Support, Non-U.S. Gov't]. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 14*(5), 438-445. doi: 10.1097/01.JGP.0000218218.47279.db

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1988). Idiopathic Parkinson's disease: revised concepts of cognitive and affective status. [Research Support, Non-U.S. Gov't Review]. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 15*(2), 106-113.

Taylor, A. E., Saint-Cyr, J. A., Lang, A. E., & Kenny, F. T. (1986). Parkinson's disease and depression. A critical re-evaluation. *Brain : a journal of neurology, 109 (Pt 2)*, 279-292.

Taylor, C. A., Saint-Hilaire, M. H., Cupples, L. A., Thomas, C. A., Burchard, A. E., Feldman, R. G., & Myers, R. H. (1999). Environmental, medical, and family history risk factors for Parkinson's disease: A new England-based case control study. *American Journal of Medical Genetics, 88*(6), 742-749.

Taylor, K. S., Counsell, C. E., Harris, C. E., Gordon, J. C., & Smith, W. C. (2006). Pilot study of the incidence and prognosis of degenerative Parkinsonian disorders in Aberdeen, United Kingdom: methods and preliminary results. [Research Support, Non-U.S. Gov't]. *Movement disorders : official journal of the Movement Disorder Society, 21*(7), 976-982. doi: 10.1002/mds.20866

Taylor, W. D., Steffens, D. C., McQuoid, D. R., Payne, M. E., Lee, S. H., Lai, T. J., & Krishnan, K. R. (2003). Smaller orbital frontal cortex volumes associated with functional disability in depressed elders. [Research Support, U.S. Gov't, P.H.S.]. *Biological Psychiatry, 53*(2), 144-149.

Taymans, J. M., Van den Haute, C., & Baekelandt, V. (2006). Distribution of PINK1 and LRRK2 in rat and mouse brain. [Comparative Study Research Support, Non-U.S. Gov't]. *Journal of neurochemistry, 98*(3), 951-961. doi: 10.1111/j.1471-4159.2006.03919.x

Tham, A., Engelbrektson, K., Mathe, A. A., Johnson, L., Olsson, E., & Aberg-Wistedt, A. (1997). Impaired neuropsychological performance in euthymic patients with recurring mood disorders. *The Journal of clinical psychiatry, 58*(1), 26-29.

Thanvi, B. R., Lo, T. C., & Harsh, D. P. (2005). Psychosis in Parkinson's disease. [Review]. *Postgraduate Medical Journal, 81*(960), 644-646. doi: 10.1136/pgmj.2004.032029

Thanvi, B. R., Munshi, S. K., Vijaykumar, N., & Lo., T. C. N. (2003). Neuropsychiatric non-motor aspects of Parkinson's disease. *Postgraduate Medical Journal 79*, 561-565.

Thiessen, B., Rajput, A. H., Laverty, W., & Desai, H. (1990). Age, Environments, and the Number of Substantia-Nigra Neurons. *Parkinsons Disease : Anatomy, Pathology, and Therapy, 53*, 201-206.

Thurstone, L. L., & Thurstone, T. G. (1962). Primary Mental Abilities. Chicago: Science Research Associates.

Totaro, R., Marini, C., Pistoia, F., Sacco, S., Russo, T., & Carolei, A. (2005). Prevalence of Parkinson's disease in the L'Aquila district, central Italy. *Acta Neurologica Scandinavica, 112*(1), 24-28. doi: DOI 10.1111/j.1600-0404.2005.00426.x

Trivedi, S. C., Subramanyam, A. A., Pinto, C., & Gambhire, D. D. (2013). Neuropsychiatric symptoms in mild cognitive impairment: An analysis and its impact on caregiving. *Indian journal of psychiatry, 55*(2), 154-160. doi: 10.4103/0019-5545.111454

Troster, A. I., Paolo, A. M., Lyons, K. E., Glatt, S. L., Hubble, J. P., & Koller, W. C. (1995). The influence of depression on cognition in Parkinson's disease: a pattern of impairment distinguishable from Alzheimer's disease. [Research Support, U.S. Gov't, P.H.S.]. *Neurology, 45*(4), 672-676.

Troster, A. I., Stalp, L. D., Paolo, A. M., Fields, J. A., & Koller, W. C. (1995). Neuropsychological impairment in Parkinson's disease with and without depression. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Archives of Neurology, 52*(12), 1164-1169.

Troyer, A. K., Moscovitch, M., Winocur, G., Alexander, M. P., & Stuss, D. (1998). Clustering and switching on verbal fluency: the effects of focal frontal- and temporal-lobe lesions. [Research Support, Non-U.S. Gov't]. *Neuropsychologia, 36*(6), 499-504.

Tunnard, C., Whitehead, D., Hurt, C., Wahlund, L. O., Mecocci, P., Tsolaki, M., . . . Simmons, A. (2011). Apathy and cortical atrophy in Alzheimer's disease. [Research Support, Non-U.S. Gov't]. *International journal of geriatric psychiatry, 26*(7), 741-748. doi: 10.1002/gps.2603

Uc, E. Y., Rizzo, M., Anderson, S. W., Qian, S., Rodnitzky, R. L., & Dawson, J. D. (2005). Visual dysfunction in Parkinson disease without dementia. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neurology, 65*(12), 1907-1913. doi: 10.1212/01.wnl.0000191565.11065.11

Uekermann, J., Daum, I., Peters, S., Wiebel, B., Przuntek, H., & Muller, T. (2003). Depressed mood and executive dysfunction in early Parkinson's disease. [Comparative Study Research Support, Non-U.S. Gov't]. *Acta Neurologica Scandinavica, 107*(5), 341-348.

Uhl, G. R., Walther, D., Mash, D., Faucheux, B., & Javoy-Agid, F. (1994). Dopamine transporter messenger RNA in Parkinson's disease and control substantia nigra neurons. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Annals of Neurology, 35*(4), 494-498. doi: 10.1002/ana.410350421

Ungerleider, L. G., & Haxby, J. V. (1994). 'What' and 'where' in the human brain. [Review]. *Current opinion in neurobiology, 4*(2), 157-165.

Valente, E. M., Abou-Sleiman, P. M., Caputo, V., Muqit, M. M., Harvey, K., Gispert, S., . . . Wood, N. W. (2004). Hereditary early-onset Parkinson's disease caused by mutations in PINK1. [Research Support, Non-U.S. Gov't]. *Science, 304*(5674), 1158-1160. doi: 10.1126/science.1096284

van den Heuvel, M. P., Mandl, R. C., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. [Research Support, Non-U.S. Gov't]. *Human brain mapping, 30*(10), 3127-3141. doi: 10.1002/hbm.20737

van der Vegt, J. P., van Nuenen, B. F., Bloem, B. R., Klein, C., & Siebner, H. R. (2009). Imaging the impact of genes on Parkinson's disease. [Research Support, Non-U.S. Gov't Review]. *Neuroscience, 164*(1), 191-204. doi: 10.1016/j.neuroscience.2009.01.055

van Duijn, C. M., Dekker, M. C., Bonifati, V., Galjaard, R. J., Houwing-Duistermaat, J. J., Snijders, P. J., . . . Heutink, P. (2001). Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. [Research Support, Non-U.S. Gov't]. *American Journal of Human Genetics, 69*(3), 629-634. doi: 10.1086/322996

van Iersel, M. B., Ribbers, H., Munneke, M., Borm, G. F., & Rikkert, M. G. O. (2007). The effect of cognitive dual tasks on balance during walking in physically fit elderly people. *Archives of physical medicine and rehabilitation, 88*(2), 187-191. doi: DOI 10.1016/j.apmr.2006.10.031

Van Maele-Fabry, G., Hoet, P., Vilain, F., & Lison, D. (2012). Occupational exposure to pesticides and Parkinson's disease: a systematic review and meta-analysis of cohort studies. [Research Support, Non-U.S. Gov't]. *Environment international, 46*, 30-43. doi: 10.1016/j.envint.2012.05.004

van Tol, M. J., van der Wee, N. J., van den Heuvel, O. A., Nielen, M. M., Demenescu, L. R., Aleman, A., . . . Veltman, D. J. (2010). Regional brain volume in depression and anxiety disorders. [Research Support, Non-U.S. Gov't]. *Archives of General Psychiatry, 67*(10), 1002-1011. doi: 10.1001/archgenpsychiatry.2010.121

Varanese, S., Perfetti, B., Ghilardi, M. F., & Di Rocco, A. (2011). Apathy, but not depression, reflects inefficient cognitive strategies in Parkinson's disease. *PloS one, 6*(3), e17846. doi: 10.1371/journal.pone.0017846

Vasconcelos, L. D., Jackowski, A. P., de Oliveira, M. O., Flor, Y. M. R., Bueno, O. F. A., & Brucki, S. M. D. (2011). Voxel-based morphometry findings in Alzheimer's disease: neuropsychiatric symptoms and disability correlations - preliminary results. *Clinics, 66*(6), 1045-1050. doi: Doi 10.1590/S1807-59322011000600021

van Vliet, D., de Vugt, M. E., Aalten, P., Bakker, C., Pijnenburg, Y. A., Vernooij-Dassen, M. J., . . . Verhey, F. R. (2012). Prevalence of neuropsychiatric symptoms in young-onset compared to late-onset Alzheimer's disease - part 1: findings of the two-year longitudinal NeedYD-study. [Comparative Study Research Support, Non-U.S. Gov't]. *Dementia and geriatric cognitive disorders, 34*(5-6), 319-327. doi: 10.1159/000342824

Veldman, B. A., Wijn, A. M., Knoers, N., Praamstra, P., & Horstink, M. W. (1998). Genetic and environmental risk factors in Parkinson's disease. [Research Support, Non-U.S. Gov't Review]. *Clinical neurology and neurosurgery, 100*(1), 15-26.

Venneri, A., McGeown, W. J., Hietanen, H. M., Guerrini, C., Ellis, A. W., & Shanks, M. F. (2008). The anatomical bases of semantic retrieval deficits in early Alzheimer's disease. [Research Support, Non-U.S. Gov't]. *Neuropsychologia, 46*(2), 497-510. doi: 10.1016/j.neuropsychologia.2007.08.026

Venneri, A., Molinari, M. A., Pentore, R., Cotticelli, B., Nichelli, P., & Caffarra, P. (1993). Shortened Stroop Color-Word Test - Its Application in Alzheimers-Disease. *Alzheimers Disease and Related Disorders : Selected Communications, 87*, 81-82 474.

Vieregge, P., von Maravic, C., & Friedrich, H. J. (1992). Life-style and dietary factors early and late in Parkinson's disease. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 19*(2), 170-173.

Vilas, D., Pont-Sunyer, C., & Tolosa, E. (2012). Impulse control disorders in Parkinson's disease. [Review]. *Parkinsonism & Related Disorders, 18 Suppl 1*, S80-84. doi: 10.1016/S1353-8020(11)70026-8

Vitale, C., Santangelo, G., Trojano, L., Verde, F., Rocco, M., Grossi, D., & Barone, P. (2011). Comparative neuropsychological profile of pathological gambling, hypersexuality, and compulsive eating in Parkinson's disease. [Comparative Study]. *Movement disorders : official journal of the Movement Disorder Society, 26*(5), 830-836. doi: 10.1002/mds.23567

Voon, V., & Fox, S. H. (2007). Medication-related impulse control and repetitive behaviors in Parkinson disease. [Review]. *Archives of Neurology, 64*(8), 1089-1096. doi: 10.1001/archneur.64.8.1089

Voon, V., Hassan, K., Zurowski, M., de Souza, M., Thomsen, T., Fox, S., . . . Miyasaki, J. (2006). Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. [Controlled Clinical Trial]. *Neurology, 67*(7), 1254-1257. doi: 10.1212/01.wnl.0000238503.20816.13

Voon, V., Mehta, A. R., & Hallett, M. (2011). Impulse control disorders in Parkinson's disease: recent advances. [Research Support, N.I.H., Intramural Research Support, Non-U.S. Gov't Review]. *Current opinion in neurology, 24*(4), 324-330. doi: 10.1097/WCO.0b013e3283489687

Voon, V., Reynolds, B., Brezing, C., Gallea, C., Skaljic, M., Ekanayake, V., . . . Hallett, M. (2010). Impulsive choice and response in dopamine agonist-related impulse control behaviors. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Psychopharmacology, 207*(4), 645-659. doi: 10.1007/s00213-009-1697-y

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: a meta-analysis. [Meta-Analysis Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S. Review]. *Cognitive, affective & behavioral neuroscience, 3*(4), 255-274.

Wang, A., Costello, S., Cockburn, M., Zhang, X., Bronstein, J., & Ritz, B. (2011). Parkinson's disease risk from ambient exposure to pesticides. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *European journal of epidemiology, 26*(7), 547-555. doi: 10.1007/s10654-011-9574-5

Wang, W. Z., Fang, X. H., Cheng, X. M., Jiang, D. H., & Lin, Z. J. (1993). A Case-Control Study on the Environmental Risk-Factors of Parkinsons-Disease in Tianjin, China. *Neuroepidemiology, 12*(4), 209-218.

Wang YS, S. Y., Wu ZY, He YX, Zhang BZ. (1991). Parkinson's disease in China. *Chin Med J, 104:960–4.*

Waragai, M., Wei, J., Fujita, M., Nakai, M., Ho, G. J., Masliah, E., . . . Hashimoto, M. (2006). Increased level of DJ-1 in the cerebrospinal fluids of sporadic Parkinson's disease. [Research Support, Non-U.S. Gov't]. *Biochemical and biophysical research communications, 345*(3), 967-972. doi: 10.1016/j.bbrc.2006.05.011

Wechsler, D. (1945). A standardized memory scale for clinical use. Journal of Psychology, 19, 87-95.

Wechsler, D. (1981). WAIS-R manual. New York: Psychological Corporation.

Wechsler, D. (1997a). Wechsler Adult Intelligence Scale-III. *San Antonio: The Psychological Corporation.*

Weiland-Fiedler, P., Erickson, K., Waldeck, T., Luckenbaugh, D. A., Pike, D., Bonne, O., . . . Neumeister, A. (2004). Evidence for continuing neuropsychological impairments in depression. [Clinical Trial]. *Journal of Affective Disorders, 82*(2), 253-258. doi: 10.1016/j.jad.2003.10.009

Weiner, W. J. (2008). Early diagnosis of Parkinson's disease and initiation of treatment. [Review]. *Reviews in neurological diseases, 5*(2), 46-53; quiz 54-45.

Weintraub, D., & Stern, MD. (2005). Psychiatric complications in parkinson disease. *Am J Geriatr psychiatry, 13*, 844-851.

Weintraub, D., Comella, C. L., & Horn, S. (2008a). Parkinson's disease--Part 2: Treatment of motor symptoms. *Am J Manag Care, 14*(2 Suppl), S49-58. doi: 10176 [pii]

Weintraub, D., Comella, C. L., & Horn, S. (2008b). Parkinson's disease--Part 3: Neuropsychiatric symptoms. *Am J Manag Care, 14*(2 Suppl), S59-69. doi: 10177 [pii]

Weintraub, D., Koester, J., Potenza, M. N., Siderowf, A. D., Stacy, M., Voon, V., . . . Lang, A. E. (2010). Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. [Research Support, Non-U.S. Gov't]. *Archives of Neurology, 67*(5), 589-595. doi: 10.1001/archneurol.2010.65

Weintraub, D., Moberg, PJ., Duda, JE., Katz, IR., & Sten, MB. (2004). Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. *J Am Geriatr Soc, 52*, 784-788.

Weintraub, D., Morales, K. H., Moberg, P. J., Bilker, W. B., Balderston, C., Duda, J. E., . . . Stern, M. B. (2005). Antidepressant studies in Parkinson's disease: A review and meta-analysis. *Movement Disorders, 20*(9), 1161-1169. doi: Doi 10.1002/Mds.20555

Wendelken, C., Nakhabenko, D., Donohue, S. E., Carter, C. S., & Bunge, S. A. (2008). "Brain is to thought as stomach is to ??": investigating the role of rostrolateral prefrontal cortex in relational reasoning. [Comparative Study]. *Journal of cognitive neuroscience, 20*(4), 682-693. doi: 10.1162/jocn.2008.20055

West, R. (1991). Parkinson’s disease. (Office of Health Economics, London).

Williams-Gray, C. H., Foltynie, T., Brayne, C. E., Robbins, T. W., & Barker, R. A. (2007). Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. [Research Support, Non-U.S. Gov't Review]. *Brain : a journal of neurology, 130*(Pt 7), 1787-1798. doi: 10.1093/brain/awm111

Willis, A. W., Schootman, M., Kung, N., & Racette, B. A. (2012). Epidemiology and neuropsychiatric manifestations of Young Onset Parkinson's Disease in the United States. *Parkinsonism & Related Disorders*. doi: 10.1016/j.parkreldis.2012.09.014

Wolk, D. A., & Dickerson, B. C. (2011). Fractionating verbal episodic memory in Alzheimer's disease. [Research Support, N.I.H., ExtramuralResearch Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Neuroimage, 54*(2), 1530-1539. doi: 10.1016/j.neuroimage.2010.09.005

Wolters, E. (2009). Non-motor extranigral signs and symptoms in Parkinson's disease. *Parkinsonism Relat Disord, 15 Suppl 3*, S6-12. doi: S1353-8020(09)70770-9 [pii] 10.1016/S1353-8020(09)70770-9

Wolters, E. C., & Berendse, H. W. (2001). Management of psychosis in Parkinson's disease. *Current opinion in neurology, 14*(4), 499-504. doi: Doi 10.1097/00019052-200108000-00011

Wright, J. M., & Keller-Byrne, J. (2005). Environmental determinants of Parkinson's disease. *Archives of environmental health, 60*(1), 32-38.

Wu, Q., Chen, L., Zheng, Y. F., Zhang, C. X., Huang, L. H., Guo, W. Y., . . . Pei, Z. (2012). Cognitive impairment is common in Parkinson's disease without dementia in the early and middle stages in a Han Chinese cohort. *Parkinsonism & Related Disorders, 18*(2), 161-165. doi: DOI 10.1016/j.parkreldis.2011.09.009

Yang, Y., Gehrke, S., Imai, Y., Huang, Z., Ouyang, Y., Wang, J. W., . . . Lu, B. (2006). Mitochondrial pathology and muscle and dopaminergic neuron degeneration caused by inactivation of Drosophila Pink1 is rescued by Parkin. [Research Support, Non-U.S. Gov't]. *Proceedings of the National Academy of Sciences of the United States of America, 103*(28), 10793-10798. doi: 10.1073/pnas.0602493103

Yogev-Seligmann, G., Hausdorff, J. M., & Giladi, N. (2008). The role of executive function and attention in gait. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Movement disorders : official journal of the Movement Disorder Society, 23*(3), 329-342; quiz 472. doi: 10.1002/mds.21720

Yogev, G., Giladi, N., Peretz, C., Springer, S., Simon, E. S., & Hausdorff, J. M. (2005). Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? [Comparative Study Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. *The European journal of neuroscience, 22*(5), 1248-1256. doi: 10.1111/j.1460-9568.2005.04298.x

Young, K. A., Holcomb, L. A., Yazdani, U., Hicks, P. B., & German, D. C. (2004a). Elevated neuron number in the limbic thalamus on major depression. *American Journal of Psychiatry, 161*(7), 1270-1277.

Zahodne, L. B., Marsiske, M., Okun, M. S., & Bowers, D. (2012). Components of depression in Parkinson disease. *Journal of Geriatric Psychiatry and Neurology, 25*(3), 131-137. doi: 10.1177/0891988712455236

Zakzanis, K. K., Mraz, R., & Graham, S. J. (2005). An fMRI study of the Trail Making Test. [Research Support, Non-U.S. Gov't]. *Neuropsychologia, 43*(13), 1878-1886. doi: 10.1016/j.neuropsychologia.2005.03.013

Zarranz, J. J., Alegre, J., Gomez-Esteban, J. C., Lezcano, E., Ros, R., Ampuero, I., . . . de Yebenes, J. G. (2004). The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. [Case Reports Research Support, Non-U.S. Gov't]. *Annals of Neurology, 55*(2), 164-173. doi: 10.1002/ana.10795

Zayed, J., Ducic, S., Campanella, G., Panisset, J. C., Andre, P., Masson, H., & Roy, M. (1990). [Environmental factors in the etiology of Parkinson's disease]. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 17*(3), 286-291.

Zgaljardic, D. J., Borod, J. C., Foldi, N. S., Mattis, P. J., Gordon, M. F., Feigin, A., & Eidelberg, D. (2006). An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Journal of Clinical and Experimental Neuropsychology, 28*(7), 1127-1144. doi: 10.1080/13803390500246910

Zgaljardic, D. J., Borod, J. C., Foldi, N. S., Rocco, M., Mattis, P. J., Gordon, M. F., . . . Eidelberg, D. (2007). Relationship between self-reported apathy and executive dysfunction in nondemented patients with Parkinson disease. *Cognitive and Behavioral Neurology, 20*(3), 184-192.

Ziemssen, T., & Reichinann, H. (2007). Non-motor dysfunction in Parkinson's disease. *Parkinsonism & Related Disorders, 13*(6), 323-332. doi: DOI 10.1016/j.parkreldis.2006.12.014

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica, 67*(6), 361-370.

Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., . . . Gasser, T. (2004). Mutations in LRRK2 cause autosomal-dominant Parkinsonism with pleomorphic pathology. *Neuron, 44*(4), 601-607.

Ziropadja, L., Stefanova, E., Petrovic, M., Stojkovic, T., & Kostic, V. S. (2012). Apathy and depression in Parkinson's disease: the Belgrade PD study report. [Research Support, Non-U.S. Gov't]. *Parkinsonism & Related Disorders, 18*(4), 339-342. doi: 10.1016/j.parkreldis.2011.11.020

Zysset, S., Schroeter, M. L., Neumann, J., & von Cramon, D. Y. (2007). Stroop interference, hemodynamic response and aging: an event-related fMRI study. *Neurobiology of Aging, 28*(6), 937-946. doi: 10.1016/j.neurobiolaging.2006.05.008