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Neuropsychological Functions and SPECT Neuroimaging in Parkinson's Disease

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1. Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder, characterized by motor and non-motor signs. It was Charcot, who first in 1875 pointed out that 'psychic faculties are definitely impaired' and that 'the mind becomes clouded and the memory is lost'. Most patients with PD experience some degree of cognitive impairment, ranging from mild selective deficits to Parkinson's disease dementia (Dubois & Pillon, 1997). PD patients may also spend several years in a transition state called Mild Cognitive Impairment (MCI), which is now recognized as one of the cardinal non-motor manifestations of PD. It is a major cause of disability, and has been shown to be an important predictor for quality of life (Karlsen et al., 1998). Recent studies have reported a 21% prevalence rate of MCI in a large PD population and consider MCI as a risk factor for developing Parkinson's disease Dementia (PDD) (Caviness et al., 2007; Janvin et al., 2006; Levin et al., 1992). The neuropathophysiological basis of cognitive deficits in PD is complicated and includes degeneration of dopaminergic neurons mainly of the nigrostriatal pathway and to a lesser degree the mesocortical and mesolimbic pathways. The striatum is closely interrelated to cortical areas mainly to the frontal lobes. The neuropathophysiological puzzle is further complicated by multiple neurotransmitter deficits including noradrenalin, serotonin and acetylcholine pathway as well as Lewy body- type degeneration in cortical and limbic structures (Mandir & Vaughan, 2000). The direct dopaminergic connections between the ventral tegmental area and the prefrontal cortex may also influence changes in cognition (Cools 2006; Mattay et al., 2002). The pattern of cognitive impairment seen even in early PD mainly resembles that produced by frontal lobe damage, as the basal ganglia and prefrontal cortex are closely interrelated through anatomofunctional circuits (Alexander et al., 1986; Bondi et al., 1993) and include deficits mainly in cognitive flexibility, planning, working memory and learning.

Perfusion brain single photon emission computed tomography (SPECT) provides a well-established means of studying regional cerebral blood flow (rCBF) which is known to reflect cortical function. On the other hand Dopamine Transporter (DAT) SPECT imaging can be used as a marker for the degree of loss of dopaminergic nerve endings. It is well known that SPECT Neuroimaging can assist in the differential diagnosis of parkinsonian and dementia

syndromes and DAT SCAN can also be helpful in differentiating tremors resulting from damage to the nigrostriatal dopaminergic terminals from those due to essential tremor, drug-induced or psychogenic causes (Benamer et al., 2000). SPECT can also be useful in monitoring disease progression as well as providing information about the pathophysiological process.

Numerous studies during the last decade have attempted to investigate differences and associations between cortical perfusion, nigrostriatal dopamine pathway and neuropsychological functions in demented and non demented patients with PD. These studies show a tendency towards increased hypoperfusion in parietal and temporal lobes in PDD as compared to the non demented PD patients (Derejko et al., 2006; Liu et al., 1992; Matsui et al., 2005).There are also conflicting results in the literature regarding PD patients with MCI ranging from either no difference compared to controls (Sawada et al.,1992; Spampinato et al., 1991) to hypoperfusion in the parietal (Wallin et al., 2007) and frontal areas (Antonini et al., 2001; Firbank et al., 2005; Paschali et al., 2009). Regarding rCBF and neuropsychological functions in different stages of PD, as dopaminergic nerve endings degenerate in PD there is progressive cortical hypoperfusion affecting mainly the frontal lobes in the early stages, extending to the parietal and temporal lobes in the late stages of Parkinson's disease. In parallel, neuropsychological performance gradually deteriorates as the disease progresses (Paschali et al., 2010).

In the present chapter we will discuss neuropsychological deficits seen early in the course of Parkinson's disease as well as clinical characteristics of dementia seen later in the course of PD. We will also discuss the underlying neurochemistry of these cognitive impairments and address the concept of heterogeneous nature of the observed cognitive dysfunction in PD as revealed by neuropsychological and neuroimaging studies with a focus on SPECT neuroimaging.

2. Epidemiology of PDD

2.1 Prevalence rates

The prevalence of dementia in PD was reported to range from 2% in early onset cases (Hietanen &Teravainen, 1988) to 81% in an unselected patient population (Martin et al., 1973). In a review of 27 studies, an average prevalence of 40% was found (Cummings JL 1988). Other community based studies have estimated the point prevalence for dementia in PD to be between 28% and 44% (Mayeux et al., 1992).One longitudinal study observed a 52% prevalence rate of dementia with over 4 years follow-up and 60% prevalence rate of dementia with over 12 years follow up in 233 patients with PD (Buter et al., 2008). Another prospective study of 249 patients with PD observed a 65% risk rate of dementia by age 85 years (Mayeux et al., 1990). A further prospective study of 86 patients with PD and 102 age-matched controls estimated that the relative risk for dementia was equal to 5.1 in patients with PD (Hobson et al., 2004). In another study conducted in the general population, the prevalence of dementia among patients with PD was 41% and the association with age was striking, i.e. the prevalence rate was zero in patients below the age of 50 and 69% in patients above 80 years old (Mayeux et al., 1992). The variation noted between different studies is probably due to different methods of cognitive assessment, how dementia was defined, the study populations chosen and the data collection methods.

2.2 Incidence rates

Incidence studies may provide a more accurate estimate of risk of dementia in PD because of their prospective nature. Incidence of dementia was found to be consistently higher in patients with PD than in persons without PD. The number of demented patients was found to be four times higher than expected over a period of 3 years (Mindham et al., 1982). In another prospective study, the incidence of dementia was six times higher in patients with PD than in controls (Aarsland et al., 2001). In a survey of 83 patients and 50 controls, who were free of dementia at baseline, followed over 10 and 14 years, the cumulative incidence rate was 38% and 53% respectively (Hughes et al.,2000; Read et al.,2001).

3. Neuropsychology of Parkinson's disease

3.1 Neuropsychological deficits in PD

Cognitive deficits in PD are found early in the disease process even before initiation of anti-parkinsonian treatment and resemble those commonly attributed to frontal lobe dysfunction. PD patients have been reported to have reduced cognitive speed and increased distractibility, problems in set formation and impairment in set shifting and maintaining, visuoperceptual deficits, deficits in executive functions such as self-directed planning and problem solving and deficits in working memory. Characteristically, Parkinson's disease patients fail to solve a novel task when relying on internal rather than external cues. Memory impairments, mainly depicted in decreased performance in free recall tasks, while recognition memory appears to be intact, are thought to represent defective retrieval strategies, that is inability for active organization of the material to be remembered

Dopamine restoration offers relief from many of the motor symptoms of Parkinson's disease and has also been shown to exert beneficial effects on certain aspects of cognition that involve mainly executive functions, while memory and visuospatial deficits seem to be less dopamine dependent. Moreover, dopaminergic medication may have deleterious effects on certain cognitive functions such as reversal learning. This has led to the formation of the dopamine overdose hypothesis, according to which, dopamine dosing that ameliorates motor symptoms by restoring dopamine concentrations in severely depleted brain areas such as the putamen may impair some aspects of cognition by overdosing other areas, which are less dopaminergically depleted early in the disease such as the caudate nucleus and ventral striatum (Cools et al., 2001.) The pathological basis of cognitive impairments in PD has been attributed to disruption of the "complex loop" which connects the caudate nucleus with the frontal association regions, via the thalamus or to loss of dopaminergic neurons in the ventro-tegmental area affecting meso-cortico-limbic pathways. As cognitive impairment in PD however, is inadequately explained by dopamine loss alone, alternative hypotheses have been raised implicating the underlying frontal cholinergic denervation as outlined in a following section of this chapter.

3.2 Mild cognitive impairment in PD

Parkinson's disease is often associated with mild cognitive impairment (MCI) and dementia. The term mild cognitive impairment is used in Parkinson's disease to include diverse neuropsychological deficits within the executive, mnemonic and visuospatial domains. Cognitive impairment in a single or in multiple domain(s) is common in non-demented patients with PD (Foltynie et al., 2004; Janvin et al., 2003) and more than 50% of patients with PD will develop dementia and cognitive impairment which ultimately affects quality

of life (Schrag et al., 2000). The original MCI definition requires presence of subjective cognitive complaints (preferably by third party), objective evidence of impaired test performance and lack of significant functional impairment (Petersen et al.,1999).The following subtypes of MCI in patients with PD have been described. Amnestic MCI-single domain, amnesticMCI-multiple domain, Non-amnestic MCI-Single domain and Non-amnestic MCI-multiple domain (Aarsland D. et al,. 2010). In a study by Caviness et al., (2007) the majority of their patients had single domain MCI (67%), with either executive dysfunction (39%) or amnestic deficits (22%). Another study showed that the most prevalent subtypes of MCI in PD were single, non-amnestic domain (mostly executive dysfunction) in 44,7%, followed by multiple impaired domains in 39, 5% and single amnestic domain MCI in 15,8% (Janvin et al., 2006). In a recently published multicenter pooled analysis study, one quarter of patients with Parkinson's disease without dementia, had impairments in at least one cognitive domain. The most common MCI subtype was nonamnestic single domain (11,3%), followed by amnestic single domain MCI (8,9%).These results showed that memory impairment also represents an important aspect of cognitive impairment in PD, and deficits in attention-executive functions may not always be the predominant deficits in PD-MCI (Aarsland et al., 2010). Findings from the above studies, underline the necessity that standardized diagnostic criteria for Mild Cognitive Impairment in Parkinson's disease need to be better defined. Based on existing data (Emre et al., 2004) that pharmacological treatment with acetylcholinesterase inhibitors can improve cognitive impairment in PDD, new studies must be performed in order to investigate whether these or other medications can delay the progression from MCI to PDD.

3.3 Risk factors associated with development of PDD

Several risk factors are reported to be associated with PDD. These include age at onset, age at the time of the study, duration of illness, akinetic-rigid syndrome, depression and atypical neurological features (e.g., early occurrence of autonomic nervous system failure, symmetrical disease presentation, and moderate response to dopaminergic treatment). More severe cognitive impairments and higher risk for developing dementia have also been associated with the clinical manifestations of postural instability and gait disorder (Alves et al., 2006). Further, poor performance in verbal fluency tasks was found to be significantly and independently associated with PDD (Jacobs et al., 1995). In summary, up to 40% of patients with Parkinson's disease will develop dementia and the incidence is up to six times higher than aged matched controls. Older age at onset and atypical features seem to be the main risk factors. With regard to neural correlates of cognitive decline in PD the hypothesis has been raised that this might be due to the simultaneous effect of age-related and disease associated neuropathology (Levy, 2007). Furthermore, it has been shown that cognitive status of PD patients correlates with neuropathological stage showing deterioration as the disease process in the brain progresses following an upward path from the brainstem to the neocortex (Braak et al., 2005). However, the extent of cortical alpha-synuclein pathology was not predictive of cognitive impairment in an autopsy series (Parkkinen et al., 2005).

4. Clinical characteristics of PDD

4.1 Executive function

The phenotype of dementia associated with Parkinson's Disease is a dysexecutive syndrome in which executive function (defined as the ability to plan, organize and regulate goal

directed behavior) impairment is the main feature (Litvan et al., 1991; Pillon et al., 1986; Pillon et al., 1991).These deficits include impairment in concept formation and rule finding, problem solving, set elaboration and planning, set shifting and set maintenance. Difficulties are due to shifting attention to novel stimuli, whereas preservative errors are less common (Levin et al., 1991).Verbal fluency has been extensively studied in PDD, where impaired performance is typical (Aarsland et al., 2003; Cahn-Weiner et al., 2002; Paolo et al., 1995).The results of these studies reveal that executive functions are impaired in PDD patients, probably more than in patients with AD.

4.2 Attention

Attention was found to be impaired in demented patients with Parkinson's disease, as shown by measures of attention such as cognitive reaction and vigilance (Litvan et al.,1991).There were also fluctuations in attention similar to those found in patients with dementia with Lewy bodies (Ballard et al., 2002). In a test involving letter cancellation, it was found that PDD and DLB groups were slower and showed more errors than an AD group (Noe et al., 2004). Another study employing a composite index of attention noted greater deficits in PDD than AD patients (Beatty et al., 2003). Finally, when attention was measured in terms of variability in performance over time in a series of reaction time tasks, it showed that 29% of the PDD patients had attentional fluctuations compared to 42% of those with DLB (Ballard et al., 2002). From the above findings, it appears that attention is impaired in PDD and may fluctuate more than AD.

4.3 Memory

Memory, including working memory, long term memory, visuospatial memory and procedural learning is significantly impaired in Parkinson's disease demented patients, but the impairment differs from the amnesia seen in patients with Alzheimer's disease. Memory complaint was reported to be the presenting problem in 67% of PDD patients, compared to 94% with DLB and 100% in AD (Noe et al.,2004).Short term memory has received a little attention, although digit span performance which is more an attentional test, does not appear to distinguish PDD and AD patients (Starkstein et al.,1996). Learning of new information is also impaired, but to a lesser degree than in patients with Alzheimer disease (Helkala et al., 1989; Pillon et al., 1991; Stern et al., 1993). Several studies have shown that demented patients with Parkinson's disease have impaired free recall, similar to Alzheimer's disease, but their recognition is better than free recall, which shows that new information is stored but not accessed (Helkala et al., 1989; Pillon et al.,1993). A very important assumption is that memory in demented patients with Parkinson's disease was related to executive function test scores (Pillon et al., 1993).Therefore, amnesia is not of a temporal-limbic type, because patients are able to store information, but is caused by difficulty with the accessing of memory traces, which reflects a deficiency in strategy, due to a dysexecutive syndrome (Dubois et al., 1997). Both verbal and visual memory are impaired in PDD, and the degree of this impairment is probably less than that seen in AD, and recognition may be less affected than recall in mild to moderate PDD.

4.4 Visuospatial dysfunction

Visuospatial dysfunction was noted in demented patients with Parkinson's disease and this impairment was more severe in demented patients with Parkinson's disease than with

Alzheimer's disease (but similar to DLB) with approximately similar dementia severity (Huber et al.,1989; Stern et al.,1993). Boller et al., (1984) found impairments in visuoperceptual and visuomotor tasks, independent of intellectual impairment; however patients with larger loss in motor function tended to show the largest visuospatial impairment. Visuospatial impairment in PD is seen especially in more complicated tasks, that require planning and strategy, therefore impairments in perceptual motor tasks may be in part due to problems in organization of behavioral-executive problems (Stern et al.,1983).

4.5 Language

Language is also impaired in patients with PDD, but to a lesser degree than Alzheimer's disease (Cummings et al., 1988; Huber et al., 1989).The domain that is reported to be more severe than in patients with Alzheimer's disease is verbal fluency (Huber et al., 1989; Stern et al., 1993). Naming difficulties, decreased information content of spontaneous speech and impaired comprehension of complex sentences were described in demented and non demented patients with PD, but to a lesser degree than Alzheimer's disease (Grossman et al., 1991; Grossman et al., 1992).

4.6 Construction and praxis

Typically, drawing tests are used to assess construction ability and praxis, either copying designs or drawing common objects. The clock drawing test is markedly impaired in PDD (Emre et al., 2004). It should be noted however, that apraxia is not a common feature of PDD, although impaired ideomotor praxis was described (Goldenberg et al., 1986; Huber et al., 1989). Impaired verbal fluency and naming difficulties may not reflect an original involvement of language function but may be related to dysexecutive syndrome (Grossman et al., 1991).

5. Neuropsychiatric manifestations in PD

5.1 Depression and anxiety

Symptoms of depression and anxiety are common in Parkinson's disease. Approximately 30-40% of patients with PD have depressive symptoms, with lower prevalence rates in population based studies (Leentjens et al 2008; Reijnders et al., 2008). Anxiety also affects up to 40% of patients with PD (Leentjens et al., 2008; Menza et al., 1993; Richard 2005). Depression and anxiety can be off-period phenomena and respond to antiparkinsonian medication (Maricle et al., 1995; Nissenbaum et al., 1987; Siemers et al., 1993; Witjas et al., 2002).The pathophysiology of these symptoms is complex and probably includes dopaminergic, serotonergic and noradrenergic mechanisms. The raphe nuclei and locus coeruleus are structures which appear to be involved in depression, early in the course of Parkinson's disease (Braak et al., 2004). There is also clear evidence that dopaminergic dysfunction also plays a role. Dopaminergic projections from the ventral tegmentum of the midbrain to the medial temporal and orbitofrontal regions are affected in post mortem studies (Torack & Morris, 1988).There is also evidence that limbic noradrenergic/dopaminergic pathways are dysfunctional in PD patients with depression compared to those without (Remy et al.,2005). The main characteristics of depression are low mood and lack of interest or pleasure, one of which is required for a diagnosis of depression in most classifications. Other features are altered appetite or sleep, weight

change, loss of libido, reduced memory, psychomotor retardation, loss of energy, feelings of guilt, and suicidal ideation which can overlap with the symptoms of PD, making diagnosis of depression in PD difficult (Gotham et al., 1986; Myslobodsky et al, 2001).The most common anxiety disorders in PD are panic attacks which are often noted during off-periods, generalized anxiety disorder, simple and social phobias. Outside off-periods, anxiety may be part of an underlying depressive disorder (Mondolo et al., 2007). The most commonly used diagnostic classification for depression and anxiety is the DSM IV-TR . For screening purposes the Hamilton depression scale, Beck depression inventory, Hospital anxiety and depression scale and Geriatric depression scale have been shown to be valid in depression of PD. However, it's very important to remember that diagnosis of depression should only be made using clinical criteria rather than scales. Several rating scales for anxiety have been used in patients with PD, but their validity needs to be assessed further (Leentjens et al., 2008). Regarding the management of these symptoms, the first important issue, is to determine whether the depression and/or anxiety symptoms occur during off-periods. If so, then the adjustment of antiparkinsonian medication is required. In most cases with mild depression, which are the majority, non-pharmacological intervention is the treatment of choice, ranging from counseling - patient education to cognitive-behavioral therapy (Cole & Vaughan, 2005).The most useful first step in treatment is the optimization of the existing dopaminergic medication. Other pharmacological agents used for depression of PD include tricyclic antidepressants, tricyclic-related drugs (trazodone), selective serotonin reuptake inhibitors (SSRI), the serotonin and noradrenaline re-uptake inhibitors (SNRI) venlafaxine, the selective noradrenaline re-uptake inhibitor reboxetine and the presynaptic alpha2 adrenoreceptor antagonist mirtazapine.

5.2 Apathy and fatigue

Apathy and fatigue are two common non motor manifestations in PD, which contribute to disability and are attributed to basal ganglia pathology and disturbances in frontal-subcortical connections (Dujardin et al., 2007). Reported prevalence for apathy ranges from 17% to 70% (Isella et al.,2002; Levy et al.,1998;Starkstein et al.,1992) and is influenced by the extend of cognitive impairment and depressive symptoms in the sample and the tools used (Pluck & Brown,2002; Shulman, 2000). Apathy in the absence of depression occurs in 4-30% of cases, whereas reported prevalence for depression in the absence of apathy is 6-28% and for combination of apathy-depression is 12-47% (Aarsland et al., 1999; Dujardin et al., 2007; Isella et al., 2002). Fatigue is reported in up to 1/3 of patients with PD (Friedmann et al., 2007), and has a prevalence rate of 32-58%. However, fatigue outcome is influenced by the definitions of fatigue and the assessment tool that was used (Alves et al., 2004). Fatigue is also associated with depression, cognitive deficits and daytime sleepiness (Rochester et al., 2004). Apathy refers to a set of behavioral, emotional and cognitive features with reduced interest and motivation in goal-directed behaviors (Marin, 1997). The impact of apathy is considerable, the patient is inactive and this leads to greater functional decline and disability (Aarsland et al., 1999).The role of depression and cognitive impairment in apathy is considerable. There are conflicting reports in the literature whether apathy and depression combined are more common than apathy without depression or depression without apathy (Isella et al., 2002). Fatigue can be classified as peripheral and central (Voon & Lang, 2004). Peripheral fatigue is a physiological phenomenon that involves lack of energy associated with muscular fatigue, and is measured objectively by decreased force generation or the

inability to sustain repetitive movements (Lou et al., 2001). Central fatigue is generally described as an abnormal degree of persistent tiredness, weakness or exhaustion that can be mental, physical or both in the absence of motor and physical impairment (Lou et al., 2001). Physical fatigue represents the sense of physical exhaustion and lack of energy to perform physical tasks despite the ability to do so. Mental fatigue refers to the effects experienced during and after prolonged periods of demanding cognitive activities that require sustained mental efficiency. Fatigue exerts its main effects on quality of life, depression, and disability in PD and is the major determinant of work-related disability (Martinez-Martin et al., 2006; Zesiewicz et al., 2007). For apathy and fatigue, co-existence of depression and cognitive deficits and their overlap with motor signs of PD, contribute to diagnostic challenges. For apathy, Marin's criteria of reduced goal-directed behavior, cognition and emotional concomitants of goal-directed behavior are the most widely used (Marin, 1997). Distinguishing apathy from depression requires evidence for emotional features such as low mood, reduced levels of pleasure, guilt and anxiety in patients with a concurrent depressive disorder. A number of fatigue-rating scales have been developed for the general population and for specific conditions (Dittner et al.,2004).The Parkinson's fatigue scale was developed as a disease specific scale and is widely used (Brown et al.,2005).Treatments for both apathy and fatigue include illness education to families and patients about depression, fatigue, apathy and cognitive decline in PD, behavioral strategies to maximize executive functions and use of medication to treat mood disorders and cognitive impairment. It's very important to know that improvement of comorbid conditions may be sufficient to relieve apathy and fatigue. Non pharmacological strategies with an individualized daily schedule and structure with varied activities and group therapy help to maintain a satisfactory activity level. Possible medications include dopamine agonists, psychostimulants, modafinil and testosterone (Campbell & Duffy, 1997; Friedman et al., 2007).

5.3 Hallucinations and psychosis

The main psychotic symptoms noted in PD include, visuoperceptual symptoms such as visual hallucinations, illusions, and delusions. Auditory hallucinations may also occur but usually together with visual hallucinations. Psychotic symptoms may be mild or severe, occur either in combination or alone, may be accompanied by behavioral disturbances and require hospitalization. Psychotic features may affect up to 50% of patients with PD (Graham et al.,1997) and when present, tend to be persistent and progressive (Factor et al.,2003).The typical visual hallucinations consist of persons, familiar or not, and less often animals or objects. They are usually complex and stereotype and often occur in dim light, and at night. The neuropsychiatric symptoms in PD tend to cluster into distinct syndromes. It's very important, for the clinician to examine for these phenomena because these symptoms are not always reported voluntarily. Some patients may deny or refuse to report these symptoms, therefore the clinician should also ask relatives. There are several rating scales that can be utilized, although no one is generally accepted. Item 2 of UPDRS subscale 1 and the neuropsychiatric inventory are most often used. More detailed assessments can be made using specific scales such as the Parkinson psychosis rating scale. Psychotic symptoms develop from extrinsic and intrinsic factors. It was previously considered that visual hallucinations in patients with Parkinson's disease were caused by dopaminergic medications. However, it is now generally accepted that although dopaminergic drugs and especially dopamine agonists, can contribute to psychosis, other factors may be more

important such as dementia, visuospatial impairment, old age and advanced disease stage. It is now well known that psychotic symptoms may occur during the night and are associated with sleep disturbances and vivid dreams that may lead to hallucinations. Non pharmacological approaches such as information about the nature of these phenomena may help. A cognitive approach is also very useful, such as distraction or re-directing attention. Improvement of light conditions and visual aids may also help (Diederich et al., 2003). It's crucial to search for general medical conditions such as infection, pain, metabolic disorders, dehydration, and recent changes in medication. Concerning the pharmacological approach for psychotic symptoms in patients with PD, the reduction of dose or number of drugs may reduce these symptoms without worsening the motor condition. For example anticholinergic drugs must be withdrawn first. It is better to withdraw selegiline first, amantadine and dopamine agonists before changing the L-dopa dose. The drug that is recommended is clozapine, which has been shown to reduce visual hallucinations without worsening motor features. Other agents such as risperidone and olanzapine are less effective and with a higher risk for worsening motor symptoms, cognitive decline and confusion (Miyasaki et al., 2006). Finally, initial open label reports on quetiapine were promising although two placebo controlled trials were negative.

5.4 Sleep disorders

Between 60-98% of patients with Parkinson's disease experience a sleep disorder (Stacy, 2002). These disorders include excessive daytime sleepiness, sleep attacks, advanced sleep phase syndrome, early morning awakenings and Rapid Eye Movement Sleep Behavior Disorder (RBD). Advanced stages of PD are associated with circadian rhythm disruption. Only few of these sleep disorders are treatable with dopaminergic therapy, and in fact, many are the side effects of treatment. The pathophysiological mechanism of circadian rhythm disruption in PD is not fully understood, and is complicated by the concomitant use of PD medications, as well as other medications such as antidepressants and stimulants, which are known to disrupt sleep architecture. RBD may respond to night-time clonazepam or melatonin (Gagnon et al., 2006). Modafinil 200-400mg per day is effective in treatment of excessive daytime sleepiness and the sedative effects of anti parkinsonian medications (Adler et al., 2003). Finally, nocturnal administration of sodium oxybate has been found to improve excessive daytime sleepiness and fatigue in patients with Parkinson's disease (Ondo et al., 2008).

6. SPECT neuroimaging

Perfusion brain single photon emission computed tomography (SPECT) provides a well-established means of studying regional cerebral blood flow (rCBF) which is known to reflect cortical function. On the other hand Dopamine Transporter (DAT) SPECT imaging can be used as a marker for the degree of loss of dopaminergic nerve endings. It is well known that SPECT Neuroimaging can assist in the differential diagnosis of parkinsonian and dementia syndromes and DAT SCAN can also be helpful in differentiating tremors resulting from damage to the nigrostriatal dopaminergic terminals from those due to essential tremor, drug-induced or psychogenic causes (Benamer et al., 2000). SPECT can also be useful in monitoring disease progression as well as providing information about the pathophysiological process in PD (Burn et al., 2003). Numerous studies during the last

decade have attempted to investigate differences and associations between cortical perfusion, nigrostriatal dopamine pathway and neuropsychological functions in demented and non demented patients with PD. These studies show a tendency towards increased hypoperfusion in parietal and temporal lobes in PDD as compared to the non demented PD patients (Derejko et al., 2006; Liu et al., 1992; Matsui et al., 2005).There are also conflicting results in the literature regarding PD patients with MCI ranging from either no difference compared to controls (Sawada et al., 1992; Spampinato et al.,1991) or to hypoperfusion in the parietal (Wallin et al.,2007) and frontal areas (Antonini et al.,2001; Firbank et al.,2005; Paschali et al.,2009). Regarding rCBF and neuropsychological functions in different stages of PD, as dopaminergic nerve endings degenerate in PD there is progressive cortical hypoperfusion affecting mainly the frontal lobes in the early stages, extending to the parietal and temporal lobes in the late stages of Parkinson's disease. In parallel, neuropsychological performance gradually deteriorates as the disease progresses (Paschali et al., 2010).

7. Studies investigating correlations between cortical perfusion, nigrostriatal dopamine pathway and neuropsychological functions in PD patients

A study using 18F fluorodeoxyglucose positron emission tomography and neuropsychological tests identified a cognitive network associated with hypermetabolism of the medial and anterior temporal lobe, pons and cerebellum, concomitant to metabolic decreases in the parieto-occipital cortex that was related to mnemonic and visuospatial deficits in non-demented PD patients (Mentis, et al., 2002)

Another FDG-PET study in non-demented PD patients revealed a correlation of performance on tests of memory, visuospatial function and perceptual motor speed with a cognitive pattern characterized by metabolic reductions in frontal and parietal association areas and relative increases in the cerebellar vermis and dentate nuclei which was not altered by routine antiparkinsonian treatment (Huang, et al., 2007)

Marie et al. (1995) found verbal working memory performance to correlate positively with resting brain glucose metabolism in the dorsolateral prefrontal cortex. The same group in another study reported a correlation between working memory functions and striatal uptake of [^{11}C]-S-nomifensine, a radioligand for the presynaptic dopamine and noradrenaline transporters (Marie et al., 1999). Holthoff-Deto et al. (1997) found that deficits in paired associate learning in a subgroup of moderately to severe PD patients was shown to correlate with [^{18}F] dopa binding in the caudate nucleus. Further, Muller et al. (2000) found impaired prefrontal cognitive functions and preserved short-term memory, in a combined neuropsychological and neuroimaging study of twenty PD patients without dementia or depression. DAT density in the putamen as evaluated by [^{123}I]β-CIT SPECT was related to the severity of motor deficits and cognitive functions correlated with the integrity of both striatal compartments. The authors concluded that the striatum is part of a neuronal network mediating prefrontal cognitive tasks. Another study by Antonini et al (2001) found significant decrements in frontal lobe perfusion in PD patients without cognitive impairment. This data is consistent with the presence of reduced frontal lobe activity and may be related to reduced dopaminergic input from the basal ganglia to this region. Conversely, in the demented group, the study found more diffused cortical perfusion defects involving the temporal and parietal cortex. This finding is consistent with the neuropathological finding that neocortical cholinergic activity is depleted in patients with

PDD. In a longitudinal of 44 consecutive patients at an early stage of PD by Dujardin and colleagues (2004), 3 years after diagnosis, a proportion of patients showed reduced overall cognitive efficiency, a subcorticofrontal syndrome and more severe motor symptoms as measured by the motor UPDRS score. At the time of diagnosis, best predictors of this progression were specific cognitive scores, such as the interference index from the Stroop word-colour test and the number of animal nouns named on the semantic word fluency task, as well as more general variables such as the educational level and the MMSE score. Other indices that contributed to a lesser extent were specific cognitive scores, such as delayed recall in the Grober&Buschke test, the Mattis DRS score and SPECT measurements such as the left Temporal-Insular, Left Temporal-Parietal-Occipital, Right Temporal-Insular and Left lenticular nucleus regional cerebral blood flow.

In another study, Osaki et al (2005) identified regions with a reduced regional cerebral blood flow using the 3D-Stereotactic Surface Projection [^{123}I] IMP-SPECT in cases for which the original diagnosis was PD. Multiple hypoperfusion areas were also observed in this analysis. There were significant correlations between clinical manifestations and regional hypoperfusion, namely between the presence of dementia and the bilateral posterior cingulated areas, and between fluctuating cognition and the bilateral parietal association areas, medial parietal lobes and dorsal occipital lobes. Derejko and colleagues (2006) observed significantly greater bilateral temporal and left parietal decrease of regional cerebral blood flow in PDD patients as compared to a group without cognitive impairment. This pattern of perfusion deficits described as 'a posterior' type of hypoperfusion resembles the one mostly described in Alzheimer's disease, except that defects were often unilateral, whereas predominantly bilateral defects are seen in AD. Hypoperfusion within the left temporal cortex with additional hyperperfusion in the ipsilateral thalamus were the most significant factors associated with cognitive decline and dementia.

In a study by Firbank et al (2005) the aim was to monitor perfusion changes over a one-year period in subjects with PDD compared to a group with DLB, and also healthy controls, and to relate any perfusion changes to cognitive impairment or motor functioning. The authors hypothesized that cortical (parieto-occipital) changes would be associated with worsening of cognitive function, and basal ganglia changes with progression of motor features. The main finding of this study was a bilateral increase in perfusion in the putamen of DLB patients over a year, and a correlation between increased striatal perfusion and worsening motor symptoms in both PDD and DLB. The authors postulate, that this is associated with continued dopaminergic degeneration, a process which may appear more pronounced in DLB because of the relatively more intact nigrostriatal dopaminergic system at the baseline scan compared to PDD, perhaps due to the shorter duration of Parkinsonism. In another study by Colloby et al (2005), the authors investigated the progression of dopaminergic degeneration in patients with DLB, PD and PDD and healthy controls using serial SPECT imaging with ^{123}I-FP-CIT, a marker for dopamine transport, using a semi-automated region of interest approach. This study found that serial FP-CIT over 1 year demonstrated progressive dopaminergic loss compared with controls in DLB, PD and PDD, and showed that serial dopaminergic SPECT may be useful in monitoring disease progression in DLB, PD as well as PDD. Dementia severity and motor impairment were predictors of percentage decline, suggesting that dopaminergic loss may play an important role in the development of cognitive as well as motor features.

In another study comparing SPECT findings between patients with PD and DLB by Chang et al (2008), significant perfusion differences in bilateral temporal areas were noted between the DLB and PD groups, with a lower perfusion index in the DLB group. On the other hand, Rossi and colleagues (2009) concluded that neither FP-CIT nor ECD-SPECT investigations were able to discriminate between DLB and PDD in vivo. These findings might support the theory that PDD and DLB share clinical and neurobiological characteristics within a Parkinson-Dementia spectrum. Moreover, the perfusional cortical pattern of both PDD and DLB is unrelated to dopaminergic impairment evaluated either clinically or by means of ^{123}I-FP-CIT SPECT and it may be due to different neurochemical systems impairment. Wallin et al (2007) note in their study that reductions of cortical blood flow in PD patients with cognitive impairment indicate cortical brain dysfunction. In the PDD group, the regional cerebral blood flow reductions were extensive and bilaterally symmetric, involving both anterior and posterior brain regions. In the PD-MCI group, individual variations were seen, but a nonsignificant reduction in the posterior brain regions was the most prominent finding. These findings suggest once more that there is an associatiom between the degree of cognitive impairment and the magnitude of cortical brain dysfunction in PD patients. In addition, hypoperfusion in the left inferior parietal lobule and supramarginal gyrus has been reported in a small group of PD-MCI patients with low performance in the frontal assessment battery (Matsui et al., 2006).

In another study by Nobili et al (2009), that investigated cortical dysfunction in PD-MCI patients, the authors found a posterior parietal-occipital hypoperfusion pattern in PD-MCI, maximally expressed in the comparison with both healthy subjects and common amnestic MCI patients, and more slightly in comparison with cognitively unimpaired PD patients. These findings are consistent with the hypothesis that PD patients with MCI of the amnestic type may be at high risk of developing PDD, by sharing a similar posterior pattern of cortical dysfunction. Finally, a recent study by Nobili and colleagues (2010) showed that the associations between nigrostriatal and cognitive functions are different for the nigro-caudate and for the nigro-putaminal endings in PD, whereas in the control group nigrostriatal and cognitive functions are not correlated. In de novo PD patients, the nigro-caudate dysfunction is significantly correlated to executive functions. This result is in keeping with other studies, highlighting the relationships between nigro-caudate impairment and executive dysfunction in PD. In this study, the motor severity of the disease was not correlated to executive functions and just marginally to caudate uptake.

A PET study using an alpha4beta2*-nAChR-specific radioligand provided in vivo evidence that there is a broad reduction of alpha4beta2*-nAChR availability in patients with PD without clinically manifest dementia or depression compared with healthy volunteers. Reduced alpha4beta2*-nAChR binding in patients with PD within the subcortical and cortical regions was associated with the severity of mild cognitive or depressive symptoms (Meyer et al., 2009)

8. Studies contributing to the neuropsychological and SPECT neuroimaging literature in PD conducted at the University of Patras Medical School

In our first study (Paschali et al., 2009) we examined relationships between neuropsychological functions and brain single photon emission computed tomography (SPECT) regional cerebral blood flow observed at presurgical evaluation for deep brain stimulation (DBS) of the subthalamic nucleus (STN) in advanced PD patients. Twenty

advanced non-demented PD patients, candidates for DBS surgery, underwent perfusion brain SPECT study and neuropsychological assessment prior to surgery (range 30-50 days). Patients were further assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr (H&Y) scale. During all assessments patients were on standard medication. Neurogam Software, which permits voxel by voxel analysis, was used to compare the brain perfusion of PD patients with a normal database adjusted for sex and age. Neuropsychological scores were compared to age, education and sex- adjusted normative databases. Our results indicated that the distribution of rCBF showed significant differences when compared to an age and sex-adjusted normative database. We found impaired blood flow in 17 (85%) of our patients in the left prefrontal lobe, in 14 (70%) in the right prefrontal lobe and in 11 (55%) in the left frontal and right parietal lobes. Neuropsychological testing revealed that 18 (90%) of our patients had significant impairments in measures of executive functions (set-shifting) and 15 (75%) in response inhibition. Furthermore we found significant correlations between measures of visual attention, executive functions and the right frontal lobe region. The presence of widespread blood flow reduction was observed mainly in the frontal lobes of non-demented patients with advanced PD. Furthermore, performance on specific cognitive measures was highly related to perfusion brain SPECT findings. Frontal lobe dysfunctions in PD have also been reported from other studies as mentioned above. In a recent review by Zgaljardic et al., (2003), frontostriatal circuit impairments in PD were described and it was suggested that the anterior cingulated cortex was related to conflict monitoring, motivation, response initiation and apathy. Moreover, they showed that the dorsolateral prefrontal cortex was related to working memory, set shifting, conditioned associate learning, set maintenance and memory retrieval, while the orbitofrontal cortex was related to stimulus-driven behavior, disinhibition, and impulse control.

In our second study (Paschali et al., 2010), we investigated differences and associations between cortical perfusion, nigrostriatal dopamine pathway and neuropsychological functions in different stages of PD. We recruited 53 non-demented PD patients divided into four groups according to the Hoehn and Yahr staging system and 20 healthy controls who were used in the comparison of the neuropsychological findings. Each patient underwent two separate brain single photon emission computed tomography (SPECT) studies (perfusion and dopamine transporter binding) as well as neuropsychological evaluation. Perfusion images of each patient were quantified and compared with a normative database provided by the Neurogam software manufacturers. Mean values obtained from the cortical areas and neuropsychological measures in the different groups were also compared by analysis of covariance (ANCOVA) controlling for disease duration and educational level. We found cognitive deficits especially in the late PD stages (HY 3, 4, 5) compared to the early stages (HY 1, 2) and associations between cognitive decrements and cortical perfusion deterioration mainly in the frontal and posterior cortical areas. Compared with controls, PD patients showed impairments of cognition and cerebral perfusion that increased with clinical severity. Furthermore, we found a significant correlation between the performance on the phonemic fluency task and regional cerebral blood flow in the left frontal lobe. Dopamine transporter binding in the left caudate nucleus significantly correlated with blood flow in the left dorsolateral prefrontal cortex, but not with measures of executive functions. We reached the conclusion that there are significant cognitive and perfusion deficits associated with PD progression, implying a multifactorial neurodegeneration process apart

from dopamine depletion in the substantia nigra pars compacta. As dopaminergic nerve endings degenerate in PD, there is a progressive cortical hypoperfusion affecting mainly the frontal lobes in the early stages, extending to the parietal and temporal lobes in the late stages of the disease. In parallel, neuropsychological performance gradually deteriorates as the disease progresses. The findings of this study support the multifactorial degeneration process in PD, as the degeneration of the nigrosrtiatal pathway of dopamine alone, cannot explain the perfusion and cognitive deficits in PD progression

9. Conclusions

DAT reduction correlates with dopamine neuron loss in the substantia nigra and striatum which is characteristic for PD. Neuropsychological deficits in the disease cannot be explained by dopamine loss alone as indicated by neuroimaging studies using DAT radiotracers. Thus further evidence is provided through these studies that additional changes occur in the brains of PD patients. Studies of regional cerebral blood flow in PD as an indicator of cognitive impairment show a more diffuse reduction in cortical metabolism as a result of disease progression and transition to dementia. On the other hand the identification of certain metabolic brain networks associated with cognitive functions in non-demented PD patients may provide a tool in clinical trials targeting the progression of non-motor manifestations of the disease and the possible efficacy of new drugs to be tested in PD. The differential diagnosis between PDD and other parkinsonian syndromes with dementia may be assisted but is not yet clearly established by PET and SPECT. The recent development of novel radioligands for use in PET studies point to the role of other neurotransmitter deficits such as the cholinergic deficit in cognitive impairment in PD. SPECT neuroimaging may therefore be useful not only in understanding the pathophysiology of the disease and cognitive impairment but also for clinical monitoring in research studies in PD.

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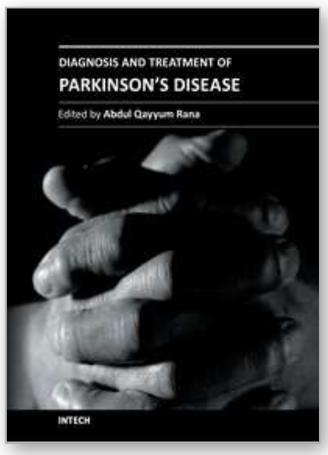

Diagnosis and Treatment of Parkinson's Disease
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Parkinson's disease is diagnosed by history and physical examination and there are no laboratory investigations available to aid the diagnosis of Parkinson's disease. Confirmation of diagnosis of Parkinson's disease thus remains a difficulty. This book brings forth an update of most recent developments made in terms of biomarkers and various imaging techniques with potential use for diagnosing Parkinson's disease. A detailed discussion about the differential diagnosis of Parkinson's disease also follows as Parkinson's disease may be difficult to differentiate from other mimicking conditions at times. As Parkinson's disease affects many systems of human body, a multimodality treatment of this condition is necessary to improve the quality of life of patients. This book provides detailed information on the currently available variety of treatments for Parkinson's disease including pharmacotherapy, physical therapy and surgical treatments of Parkinson's disease. Postoperative care of patients of Parkinson's disease has also been discussed in an organized manner in this text. Clinicians dealing with day to day problems caused by Parkinson's disease as well as other healthcare workers can use beneficial treatment outlines provided in this book.

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