Parkinson's disease

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Chapter 1

General Introduction

In 1817 James Parkinson wrote his Essay on the Shaking Palsy in which he described a disease characterized by a sense of muscle weakness in the limbs with a proneness to trembling, a stooped figure, difficulty walking and intact intellects and senses. At first the disease was known as “paralysie agitante”, however in 1876 Jean-Martin Charcot named it Parkinson’s Disease (PD). According to Charcot “paralysie agitante” was an inappropriate name since studies showed that a sense of weakness in the limbs was not always present and not all patients experienced tremor (Draaisma, 2006).

Nowadays PD is described as a neurodegenerative movement disorder characterized by motor symptoms, such as tremor, rigidity, bradykinesia and akinesia, and non-motor symptoms, such as cognitive impairments, depression, visual hallucinations and autonomic dysfunctions. PD is mainly present in persons aged 50 years and older and has a prevalence of 1.6 per 1000 persons in the European population, which increases with age, without differences between men and women (de Rijk et al., 1997). The incidence of PD ranges from 0.3 per 1000 persons per year in subjects aged 55 to 65 years, to 4.4 per 1000 persons per year in subjects aged 85 years and older (de Lau et al., 2004). The cause of PD is unknown, however it is generally thought that the disease is caused by an interaction between environmental (e.g. exogenous toxins) and genetic factors (Schapira et al., 1992).

1.1 Pathology

Symptoms of PD are mainly related to a progressive degeneration of dopamine producing neurons in the substantia nigra pars compacta (SNc) and to a lesser extent in the ventral tegmental area (VTA). Degeneration of neurons in PD is also found in the locus coeruleus (noradrenaline), raphe nucleus (serotonine), and nucleus basalis of Meynert (acetylcholine). However, these degenerations occur in more severe and later stages of the disease (Dauer & Przedborski, 2003). The SNc and VTA mainly project to the striatum and both interfere with the fronto-striatal circuits. These circuits all have the same basic design: in specific parts of the striatum all circuits receive input from functionally related cortical areas. These striatal regions send projections to distinct parts of the pallidum and the substantia nigra pars reticulata, that in turn projects to a subdivision of the thalamus. The thalamus subsequently projects to the frontal cortical area that feeds into the circuit (Groenewegen & Dongen, 2007). Several parallel, functionally segregated circuits have been defined of which three are most relevant for PD: the “sensorimotor circuit”, the “associative, cognitive circuit” and the “limbic ciruit” (see figure 1.1). These circuits support different functions. The sensorimotor circuit is concerned with movement, and motor symptoms in PD are thought to be related to a dysfunction of this circuit. Cognitive impairments in PD on the

other hand are related to the associative, cognitive circuit which is thought to be mainly involved in cognitive control or executive functions. And finally the limbic circuit is concerned with the emotional and motivational aspects of behavior and has been associated with apathy and depression in PD.

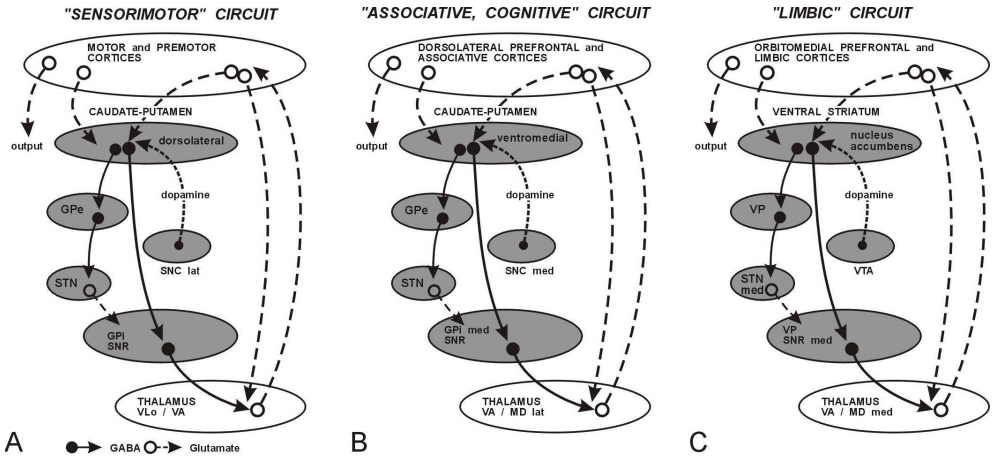

Figure 1.1 Schematic representation of the three main basal ganglia-thalamocortical circuits, each consisting of multiple subcircuits (Groenewegen & Van Dongen, 2007).

Abbreviations: Gpe, external segment of the globus pallidus; Gpi, internal segment of the globus pallidus; lat, lateral; med, medial; MD, mediodorsal thalamic nucleus; SNC, substantia nigra, pars compacta; SNR, substantia nigra, pars reticulata; STN, subthalamic nucleus; VA, ventral anterior thalamic nucleus; VLo, ventral lateral thalamic nucleus, pars oralis; VP, ventral pallidum; VTA, ventral tegmental area.

PD is thus a heterogeneous disorder affecting the motor, cognitive and emotional domains. These different symptoms and impairments are to a large extent the consequence of a common underlying neurodegenerative disease and can therefore not be considered as separate entities, they are associated or overlap. The studies included in this thesis investigate cognitive functioning and depression in PD using neuroimaging and clinical methods.

1.2 Cognition

PD patients show cognitive impairments in the absence of dementia with an estimated prevalence of 36 to 55% (Foltynie et al., 2004; Janvin et al., 2003). Cognitive impairments occur in the early stages of PD (Muslimovic et al., 2005) and are more often observed in

patients with the non-tremor dominant subtype of PD and in patients who are older at disease onset (Muslimovic et al., 2005; Williams-Gray et al., 2007). Longitudinal studies show that cognition declines with the progression of the disease, and 3.5 years after diagnosis 10% of PD patients have developed dementia (Williams-Gray et al., 2007).

In PD cognitive impairments can be found in both automatic and controlled processing. Automatic processes take advantage of previously established and learned relationships between external or internal contexts and behavioral patterns. Controlled processing on the other hand, involves deliberate planning and regulation in new situations where current schemata are not sufficient. It requires maintenance and stabilization of goal representations in working or prospective memory and the flexibility to update these goals when necessary (Cools, 2008). Concerning automatic processing, PD patients show difficulties applying previously learned skills or automaticities. This is most often observed in the motor domain, for example a decreased stride length when walking. To compensate, patients must think about each step if they are to make adequately long steps (Wu & Hallett, 2005). In addition, impairments are also often found in PD when learning new automaticities or skills, i.e. implicit or procedural learning (Myers et al., 2003; Swainson et al., 2000). Particularly, feedback plays an important role: PD patients show impairments when performing feedback-based learning tasks, while they perform equally compared to healthy controls on learning tasks without feedback (Shohamy et al., 2004). In addition, antiparkinsonian medication appears to influence learning based upon feedback in PD: PD patients who do not use antiparkinsonian medication learn better based upon negative feedback, while PD patients who do use antiparkinsonian medication learn better based upon positive feedback[1] (Frank et al., 2004). Unfortunately, not much is known about the processing of positive feedbacks in PD. Previously, neuroimaging studies were focused on investigating the processing of rewards of different magnitudes in PD and showed that reward processing is altered, which was mainly reflected by decreased striatal and increased prefrontal activation (Kunig et al., 2000; Schott et al., 2007). In this context however, not many studies have been performed and previous findings need to be extended. In addition, it is not clear if and to what extent altered positive feedback processing might affect behavior in PD patients. Positive feedback processing may be associated with a behavioral trait called low novelty seeking (NS; Menza et al., 1993a). NS is ‘a heritable tendency toward intense exhilaration or excitement in response to novel stimuli, cues for potential rewards or potential relief of punishment, which leads to frequent exploratory activity in

[1] We are aware of the fact that positive feedback within the theory of systems refers to a stimulus that causes behavior to diverge or move away from the goal, while negative feedback refers to a stimulus that causes behavior to move toward the goal (Forrester, 1968). In this thesis however, positive feedbacks can also be designated as reward, while negative feedbacks can be designated as punishment, following Frank et al. (2004).

pursuit of potential rewards as well as active avoidance of monotony and potential punishment' (Cloninger, 1987). Is it possible that an altered positive feedback processing also alters NS in PD?

Besides impairments within automatic processing, PD patients also show impairments in controlled processing. Cognitive control or executive functions are assumed to have a number of constituent elementary functions, like monitoring, planning, inhibition, set-shifting and divided attention. Declarative memory, working memory and prospective memory also play an important role. In PD, impairments in cognitive flexibility, planning, working memory, inhibition and declarative memory have been reported (Cools et al., 2001; Green et al., 2002; Muslimovic et al., 2005; Schneider, 2007; Van Beilen et al., 2008; Weintraub et al., 2005a). In PD impairments of cognitive control are thus likely to emerge, caused by impairments in more elementary executive functions.

Executive functioning and cognitive control needed in daily life is difficult to assess however, and not all patients with frontal lobe lesions and impairments in executive functioning in daily life show a decreased performance on the tests for executive functions (Shallice & Burgess, 1991). These tests are often structured and offer a standardized method: rules are explained, goals are set and behavior is prompted and stopped (Manchester et al., 2004). In addition, these tests are often aimed at isolating one aspect of the executive functions, such as inhibition or set-shifting, in order to measure that aspect reliably and excluding other influences. Executive functioning in daily life however, requires a collaboration between the many different aspects of the executive functions, without a structured method being offered. To gain more knowledge about the executive impairments that PD patients experience in daily life, unstructured tests are required.

In summary, PD patients show cognitive impairments in the domains of automatic and controlled processing. Specifically, deautomatisation, impairments in learning automaticities or skills and impairments in more elementary executive functions have been observed.

1.3 Depression

Depression is a common non-motor symptom in PD. It has a prevalence of approximately 40% (Cummings & Masterman, 1999) and has been shown to be more common in PD than in other chronic, disabling disorders (Ehmann et al., 1990). Depression is thus not merely a psychological reaction to having PD. Indeed, the incidence of depression rises in the last three years preceding the diagnosis of PD (Leentjens et al., 2003b), suggesting that the risk factor for depression is already present before the motor symptoms of PD become apparent.

Neuroimaging studies report that depressed PD patients show a decreased dopaminergic and noradrenergic transporter binding ([^{11}C]RTI-32 Positron Emission Tomography; PET) in the locus coeruleus, anterior cingulate cortex, thalamus, amygdala and ventral striatum compared to non-depressed PD patients (Remy et al., 2005). Also a decreased dopamine transporter availability in the left putamen has been associated with depression in PD (Weintraub et al., 2005b). At a neurochemical level depressed PD patients thus appear to be more severely affected.

The diagnosis of depression can in general be based upon the diagnostic criteria of the DSM-IV-TR (American Psychiatric Association, 2000; see table 1.1). However, although no specific symptomatology has been identified for depression in PD (Leentjens, 2004), and affective symptoms of depression (e.g. depressed mood or loss of interest and pleasure in activities) appear to be the most important symptoms for establishing the diagnosis of depression in PD (Leentjens et al., 2003a), this diagnosis may be difficult to establish. This is mainly caused by the fact that somatic symptoms also significantly contribute to the diagnosis of depression in PD (Leentjens et al., 2003a). This documents an overlap of symptoms of depression and PD. Non-depressed PD patients can show cognitive impairments (Dubois & Pillon, 1997), sleep disorders (Stocchi et al., 1998), fatigue (Alves et al., 2004) and apathy (Kirsch-Darrow et al., 2006), which are inherent to the disease and can be dissociated from depression in PD. These symptoms can however also be part of a major depression (see table 1.1). Consequently, depression can be overrated and underrated in PD. For clinical purposes it is therefore important to evaluate the depression scale rating scores on item level and considering which items are likely to be confounded by somatic symptoms or cognitive impairments.

Depression can have a negative influence on cognition in PD. In elderly patients with depression, without PD, cognitive impairments have been observed. These patients show impairments in set-shifting, inhibition and initiation and also have difficulties applying adequate strategies (Baudic et al., 2004). Concerning patients with PD and depression it can therefore be hypothesized that depression exacerbates cognitive impairments in PD.

Several studies were focused on the influence of depression on cognition in PD (Boller et al., 1998; Costa et al., 2006; Cubo et al., 2000; Kuzis et al., 1997; Norman et al., 2002; Silberman et al., 2007; Starkstein et al., 1990a; Troster et al., 1995; Uekermann et al., 2003) and generally it was reported that depression exacerbates cognitive impairments in PD. However, only a few of the studies focused on this subject used an extensive neuropsychological battery and much controversy remains. One study reported that depressed PD patients showed more memory and language impairments that non-depressed

PD patients (Troster et al., 1995), while another reported that depressed PD patients showed impairments in concept formation and set-switching compared to non-depressed PD patients (Kuzis et al., 1997). Also, it has been suggested that mild depressive symptoms exacerbate cognitive impairments in PD (Uekermann et al., 2003), while in other studies it was reported that minor depression does not significantly affect cognitive functions in PD (Costa et al., 2006). Attempts should therefore be taken to resolve these discrepancies.

Table 1.1 DSM-IV-TR criteria for major depressive disorder (American Psychiatric Association, 2000)

A.	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one symptom is either (1) depressed mood or (2) loss of interest or pleasure. • Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others • Markedly diminished interest or pleasure in all, or nearly all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others) • Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day • Insomnia or hypersomnia nearly every day • Psychomotor agitation or retardation nearly every day • Fatigue or loss of energy nearly every day • Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day • Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) • Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B.	The symptoms do no meet the criteria for a ‘mixed episode’.
C.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D.	The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.
E.	The symptoms are not better accounted for by ‘bereavement’, i.e. after the loss of a loved one.

1.5 Outline of thesis

Motor and non-motor symptoms in PD can not be considered as separate entities, they are associated or overlap. This thesis is focused on the nature of cognitive impairments and depression in PD. In chapter 2 it is investigated whether overlapping symptoms of depression and PD are associated with the striatal dopaminergic dysfunction typical for PD, using FDOPA-PET. Chapter 3 consists of an empirical study regarding the overlap of

motor symptoms of PD and symptoms of depression. In Chapter 4 studies focused on automatic and controlled processing in PD are reviewed using a comprehensive mental schema framework. In chapter 5 and 6 studies are described focused on cerebral activation patterns during positive feedback processing (using fMRI) and the associations with the behavioral trait NS. Chapter 7 consists of an empirical study regarding controlled behavior in non-depressed PD patients, specifically focusing on the initiation of behavior, everyday planning and multi-tasking, using a relatively unstructured multiple component visual-motor task. In chapter 8 a study is described focused on the influence of depression on cognition in PD. Finally, in Chapter 9 the results of these studies are integrated and suggestions for future research are given.