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Chapter 1

General Introduction

PARKINSON'S DISEASE

In 1817, James Parkinson described six people that displayed similar motor impairments in “*An essay on the shaking palsy*” [1]. Now, almost 200 years later, the neurodegenerative disease that is presently known as Parkinson’s disease (PD), is diagnosed based on the motor symptoms bradykinesia / hypokinesia, resting tremor, rigidity and postural instability [2, 3]. It is the second most common neurodegenerative disorder, after Alzheimer’s disease, and affects approximately one out of 100 people who are aged older than 60 years [4]. One of the pathological hallmarks of the disease is the progressive degeneration of the dopamine producing neurons in the substantia nigra *pars compacta*, leading to decreased striatal dopamine levels [5, 6]. Upon administering dopamine replacement therapy, and thereby normalizing striatal dopamine levels, brady- / hypokinesia and rigidity are greatly reduced. These observations have led to the general consent that the dopaminergic depletion underlies the motor symptoms in PD. It is important to note that, although dopamine replacement therapy alleviates (some of) the motor and non-motor symptoms of the disease, it does not cure the it. To date, there is no disease-modifying therapy available for PD.

Already in 1918 the German neurologist Frederik Lewy [7] observed in post-mortem tissue that substantia nigra cells of PD patients include pathological microscopic protein aggregates, which have come to be known as Lewy-bodies. These inclusions are not restricted to the midbrain areas, but progress in a predictable topological pattern [8]. In the prodromal phase of the disease (Braak stage I and II), sporadic Lewy-body inclusions are found only in the brainstem, thereby affecting the serotonergic (raphe nucleus), noradrenergic (locus coeruleus) and cholinergic (pedunculopontine nucleus) systems, and are additionally found within the olfactory bulb. In the intermediate phases (Braak stage III and IV), the pathology progresses towards the midbrain areas, affecting the substantia nigra, nucleus basalis of Meynert, and the mesotemporal areas. At this point, patients convert to the symptomatic phase of the illness. In the final phase (Braak stages V and VI), inclusions are found throughout the neo-cortex [9, 10]. From a more clinical perspective, it is increasingly recognized that PD is far more than only a motor disease. Non-motor symptoms include autonomic dysfunction (e.g. constipation, sexual dysfunction, sweating), neuropsychiatric (e.g. depression, anxiety, impulse control disorders, hallucinations, delusions) and sensory symptoms (pain, loss of smell), sleep disturbances (excessive daytime sleepiness, REM sleep behaviour disorder) and cognitive impairments/dementia [11]. PD is therefore no longer regarded as a motor disease, but as a multi-system disorder.

COGNITIVE IMPAIRMENTS IN PARKINSON'S DISEASE

Although James Parkinson initially noted that “the senses and intellects [are] uninjured” [1] the prevalence of cognitive deficits in PD is currently well recognized and are typically found in the mnemonic, visuo-spatial and executive domains [12, 13]. Already at the moment of diagnosis, 19-36% of patients suffers from mild cognitive impairments (MCI) (see Figure 1.1), an intermediate stage between intact cognition and dementia in which impairments are found in some cognitive domains, but not others [14-17] Importantly, cognitive abilities typically deteriorate with increasing disease duration [18]. Ten percent develops Parkinson's disease dementia (PDD) three years after diagnosis, [18-20], seventeen percent after five years [21], 46-78 percent after eight to ten years [22], and up to 80 percent of all patients become demented at the end of the disease [23]. A higher age of onset is typically associated with a faster rate of cognitive decline [17, 18, 20], whereas higher educational level is associated with a slower development of cognitive impairments [24, 25].

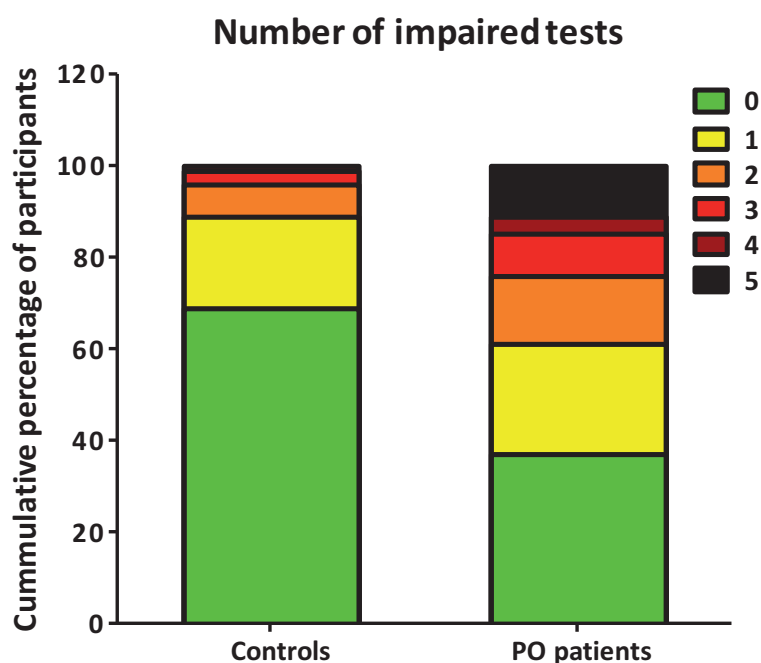


Figure 1.1 Bar graph showing the number of neuropsychological tests on which healthy controls (N=70) and newly diagnosed patients with Parkinson's disease (N=115) displayed impaired performance. A test score was categorized as impaired when it was at least two standard deviations below the mean score of the normative sample. This graph illustrates the large heterogeneity in cognitive performance between PD patients in the early disease stage. Whereas the majority of the patients scores within the normal range, about 25% already suffers from cognitive dysfunction (defined as impaired performance on at least three neuropsychological tests). Darker colours indicate more affected cognitive domains.

Figure adapted from Table 2 in Muslimovic et al. (2005), *Neurology*.

Executive functions are described as the abilities that are involved in goal-directed behaviour and allow us to shift attentional resources and adapt to diverse situations while at the same time inhibiting inappropriate responses in a constantly changing environment [26]. Although optimal performance on tasks that measure executive functions is still often associated with an optimal functioning of the (dorsal) prefrontal cortex, the role of parietal and striatal areas, and the interaction between them, is increasingly recognized [27, 28]. Three frequently postulated aspects of executive functions are i) shifting, ii) updating, and iii) inhibition [29] and numerous studies that employed tasks that measured these cognitive constructs have reported deficits in PD patients [12, 13]. Executive dysfunction in PD is frequently explained by the classical model of the basal ganglia [5, 6] (see Figure 1.2), that states that multiple loops project from the (pre)frontal cortex to sub-regions of the basal ganglia, and back to the cortex through the thalamus. Fine-tuning between excitation and inhibition within these cortico-basal ganglia-thalamo-cortical loops is primarily mediated through the excitatory direct, and inhibitory indirect, pathways. Striatal neurons belonging to the direct pathway express D1 dopamine receptors, whereas neurons belonging to the indirect pathway express D2 dopamine receptors [30]. It is widely held that in PD, due to the degeneration of the nigro-striatal projections, D1 receptors are hypo-excited, leading to i) increased activity of striatal indirect-pathway neurons, and ii) decreased activity of direct-pathway neurons [31]. As a net result, the thalamus and (pre)frontal cortex are hypo-excited [32, 33], leading to the impaired executive functions, such as working memory deficits (see e.g. [34]). Anatomically, the dorsal striatum, which is associated with motor functions and cognition, is primarily affected by the degeneration of the nigro-striatal pathway, whereas functions of the ventral striatum, which is associated with limbic processes and receives dopaminergic projections from the ventral tegmental area, are relatively spared. This distinction has been further corroborated by behavioural studies showing that dopamine replacement therapy improves behavioural performance on executive tasks that rely on the dorsal prefrontal cortex [35, 36], but impairs performance that relies on the relatively spared ventral prefrontal areas [37], thus leading to the dopamine “overdose hypothesis” [38]. Also disturbances in other neurotransmitters, such as serotonin [39, 40], norepinephrine [41, 42] and acetylcholine [43], and the interaction between them [44], are increasingly recognized to contribute to cognitive and executive dysfunctions in PD.

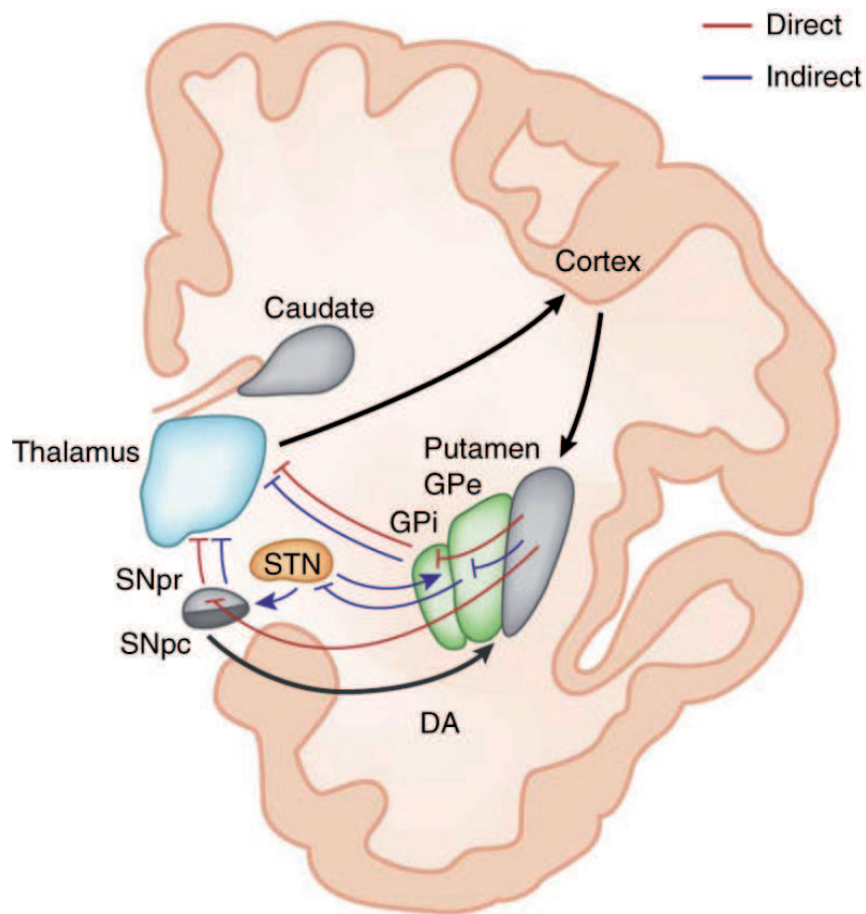


Figure 1.2 Schematic representation of the direct and indirect pathway in the classical model of the basal ganglia that was first described by Alexander et al. (1986). Under normal conditions, dopamine arising from the substantia nigra *pars compacta* activates D1-expressing striatal neurons of the direct pathway (red lines) and inhibits D2-expressing striatal neurons of the indirect pathway (blue lines). The output nuclei of the globus pallidus *interna* and substantia nigra *pars reticulata* project to the thalamus, which in turn sends efferents that complete the cortico-basal ganglia-thalamo-cortical loop. In Parkinson's disease, the degeneration of the dopamine producing cells of the substantia nigra *pars compacta* leads to a hypo-excitation of the striatal D1 dopamine receptors, and a hyper-excitation of the D2 dopamine receptors. This, in turn, leads to an imbalance between the two pathways, and, consequently, to a hyper-inhibition of thalamic neurons projecting to the cortex. This model is often used to explain how the degeneration of the nigro-striatal pathway can lead to the typical parkinsonian symptoms.

Alexander et al. (1986) described five loops, which all follow a different trajectory; the motor, oculomotor, dorsolateral prefrontal cortex, lateral orbitofrontal, and anterior cingulate loop. Only the (oculo)motor loops are shown in this illustration. The dorsolateral prefrontal cortex loop is thought to be involved in cognition.

Abbreviations: *DA* dopamine, *SNpr* substantia nigra pars reticulata, *SNpc* substantia nigra pars compacta, *GPi* globus pallidus interna, *GPe* globus pallidus externa, *STN* sub-thalamic nucleus Image adapted from Calabresi et al., 2014, *Nature Neuroscience Reviews*.

Whereas at the onset of PD the cognitive impairments are thought to arise primarily from functional changes (i.e. changes induced by the degeneration of neurotransmitter producing nuclei), in the later stages also structural changes are presumed to start playing a part. Numerous structural MRI [**sMRI**; see Box 1, Figure 1.3 left panel] studies have shown little or no atrophy in cognitively intact patients [45-48], moderate atrophy in patients with PD-MCI [49-52] and pronounced and widespread atrophy in patients with PDD [53-56]. In addition, a higher level of atrophy at the moment of diagnosis seems to be a predictor for developing PD-MCI or PDD later on in the disease [57, 58]. Post mortem studies, furthermore, have consistently reported negative correlations between the level of global cortical and limbic alpha-synuclein pathology and performance on several cognitive measures [59-61], thereby corroborating the relation between neuropathology, structural changes, and cognition. Also the involvement of concomitant pathology, such as neurofibrillary tau tangles and cortical amyloid beta plaques has been implicated [59]. Although higher cortical amyloid beta at baseline has been associated with a faster rate of cognitive decline [62, 63], the combination of alpha-synuclein, tau pathology, and amyloid beta seems the most robust neuropathological substrate of PDD [57].

Although much progress has been made in the understanding of PD in general, and cognitive impairments in particular, the between-patient heterogeneity in cognitive performance awaits further elucidation. A better understanding of the cognitive variability could potentially help for the future development of disease modifying treatments to sustain preserved brain circuits, restore already failing systems, or to enhance compensatory mechanisms, with, for example, cognitive rehabilitation or modulating neuroplasticity.

TASK-RELATED BRAIN ACTIVITY AND CONNECTIVITY

The brain continuously processes input from internal and external stimuli. This is done by neurons; cells that are specialized in receiving, processing and transmitting signals from and to each other. When the electrical input from other cells exceeds a certain threshold, a cell assembly becomes active and starts firing action potentials, to stimulate, or inhibit, other local or distant neurons. This process can be indirectly measured using functional magnetic resonance imaging [**fMRI**; see Box 1, Figure 1.3 right panel], which detects the hemodynamic response and thus indirectly measures neuronal activation. Neuro-imaging research has consistently shown that certain brain areas, organized in brain networks, become more active during specific tasks. This indicates that the brain is organized in a modular fashion, with specific brain areas being specialized in the processing of specific stimuli or computing specific calculations. The degree of task-related brain activation is

often related to behavioural performance. The causal relationship between brain activation and task performance can be studied using techniques to modulate regional cortical activity, such as transcranial magnetic stimulation (TMS) [64]. Studies combining TMS with fMRI showed that after low-frequency (i.e. inhibitory) repetitive TMS [rTMS; see Box 1, Figure 1.4] on the prefrontal cortex, the area under the coil, and interconnected task-related brain regions, became hypo-active, resulting in decreased behavioural performance [65], and, conversely, memory performance and frontal activation increased after high-frequency (i.e. excitatory) stimulation on the prefrontal cortex in elderly participants with subjective memory complaints [66].

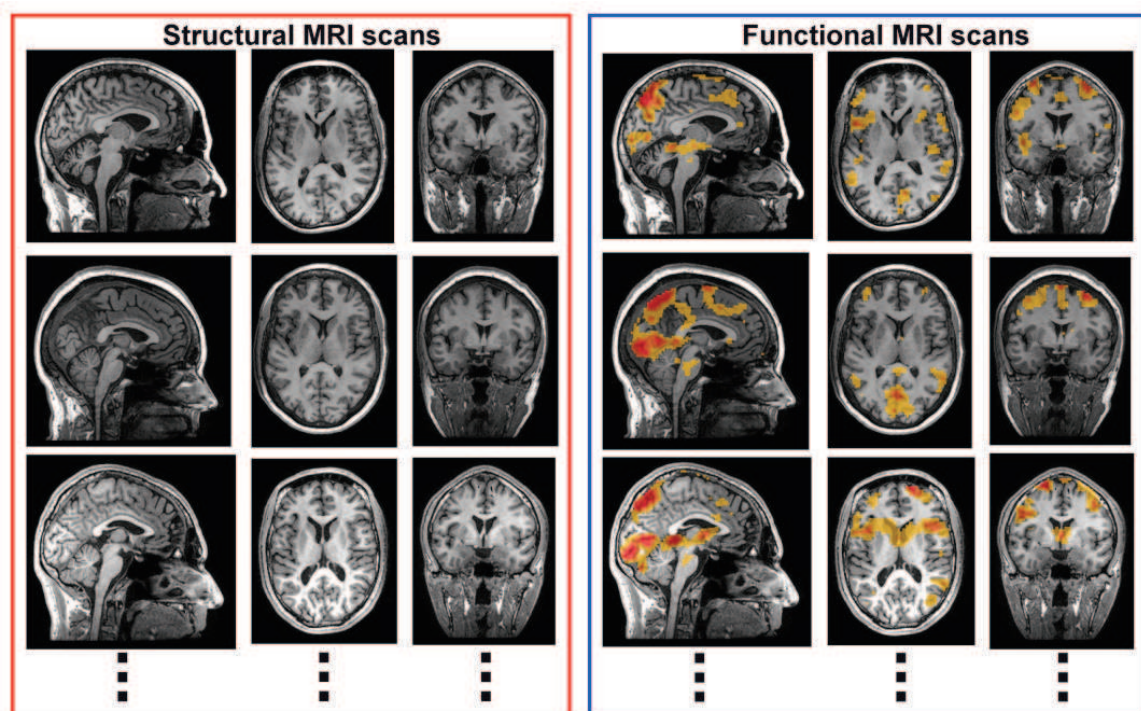


Figure 1.3 Illustration of structural MRI scans (left panel) and activity maps obtained from functional MRI scans (right panel) of three participants in a mid-sagittal (left), axial (middle), and coronal (right) view.

Left panel: It is not difficult to see that individual brains are similar with respect to global anatomy, but differ at a more detailed level. We compared differences in local brain anatomy between healthy participants and patients with Parkinson’s disease using both a voxel-based and a surface-based approach to gain more insight into the relation between disease and cognition in PD.

Right panel: We also assessed brain activity during several cognitive tasks in an MRI scanner. We first assessed which brain areas were most strongly activated during the task (the more red in the picture, the more active it was), and subsequently investigated whether patients and controls differed in the degree of activation of these specific regions.

However, over the years there has been a growing awareness that the processed information of individual brain areas also needs to be integrated, and that task performance never depends on the activity of a single brain region. Therefore, much focus has been placed on the functional connectivity between different brain areas, i.e. how do brain areas communicate during a task or in rest, in both healthy subjects and in disease. Some authors have stated that “*behavioural manifestations of neurological [...] disease are not solely the result of abnormality in one isolated brain region but represent alterations in brain networks and connectivity*” [67], thereby emphasizing the importance of intra- and inter-regional connectivity.

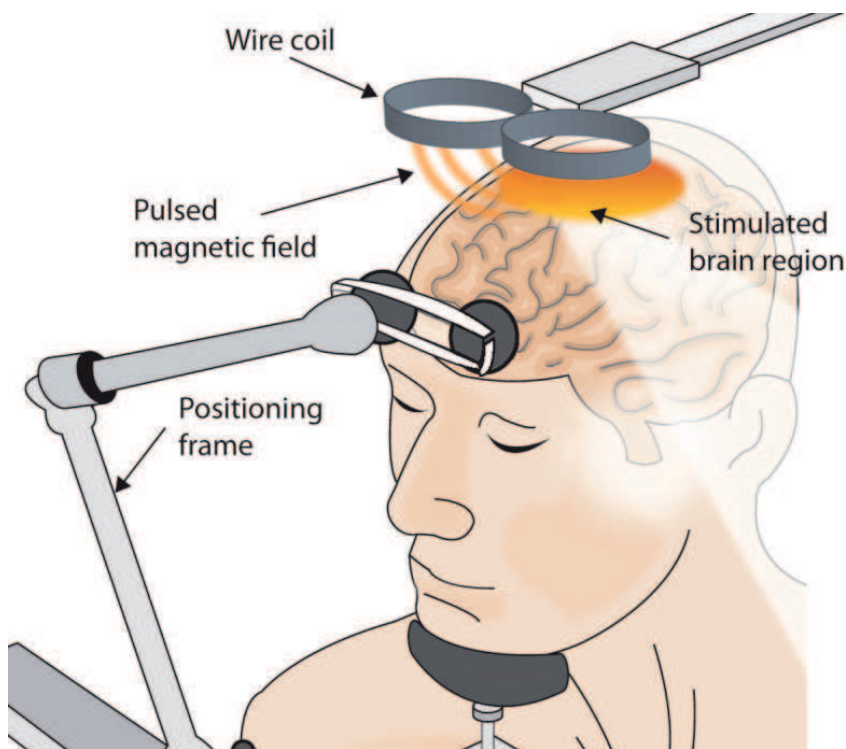


Figure 1.4 Schematic representation of the experimental set-up to apply repetitive transcranial magnetic stimulation (rTMS). We placed the figure-of-eight coil on an a priori defined site within the left dorso-lateral prefrontal cortex (experimental condition) or at the vertex (control condition) and stimulated this area for 20 minutes for low-frequency rTMS. By doing so, we tried to decrease the activity of the area that was under the coil.

A proposed mechanism underlying functional connectivity between brain areas is by neural oscillations [68]. Upon firing at a similar frequency, individual neurons can become phase-locked and subsequently turn into a synchronized assembly or network [69-71]. This synchronized activity can be observed as rhythmic neural activity using non-invasive techniques, such as magneto-encephalography (MEG). These oscillations can occur at different frequencies, depending on the post-synaptic potentials (often interpreted as firing rate) of the neuronal assembly. The

signal is sub-divided into different bands, based on the frequency of the oscillations. Resting-state studies employing MEG in PD patients have demonstrated a general slowing of local synchrony (i.e. in power) in early-stage PD patients [72]. A recent longitudinal study showed that the neural rhythm progressively slows with increasing disease duration, which was related to the development of cognitive impairments and, to a lesser extent, with increasing motor complications [73]. This is in accordance with cross-sectional studies showing a pronounced reduction in power in PDD [74, 75]. In addition, global integration, measured as the synchronization of activity between distributed brain regions (i.e. functional connectivity), is also changed already at the early stages of the disease [76] and deteriorates further over time [77]. It thus seems that with disease progression, local and global synchrony in rest declines and that this desynchronization can be used as a biomarker to predict the development of cognitive deficits and PDD [78, 79]. ON-OFF studies in PD patients receiving deep brain stimulation (DBS) have further substantiated the role of oscillations in relation to PD by showing that certain frequency bands normalized after taking dopaminergic medication, which was related to the degree of motor improvement [80]. Dopaminergic medication also normalized performance on a motor task, which was associated with normalized connectivity between task-related brain areas [81]. These studies suggest that PD-related pathology in general, and striatal dopamine depletion in particular, leads to a desynchronization in oscillations within and between cell assemblies, which seems to be related to the observed cognitive deficits, and can be partly restored by dopamine replacement therapy.

To summarize, a part of the patients with PD suffers already at the early stages of disease from cognitive impairments, most pronounced in the domain of executive functions. These deficits are related to a hypo-activation of mainly fronto-striatal areas, and with a decrease in local power and global integration during rest, which are, in turn, associated with pathological oscillations due to striatal dopamine depletion. As the disease progresses, the integrative abilities of cortical assemblies further declines, and disease-related structural changes, probably induced by the progression of the neuropathology, further deteriorate cognitive abilities.

Although previous studies have greatly enhanced our understanding of cognitive dysfunction in PD, many issues still require further elucidation. First, an important limitation of previous studies on cognition in PD is the use of dopamine replacement therapy. While measuring patients in an OFF medication phase (i.e. patients have not taken their medication 12 – 18 h prior to the investigation) greatly reduces medication effects, residual effects on both behavioural performance and neuronal activation, may persist due to the long half-life of the medication [82, 83]. Also, withdrawal from medication can cause physical (e.g. rigidity, hypokinesia, and

pain) and / or emotional distress (e.g. panic attacks, apathy, and cognitive rigidity) in the patients [84, 85], influencing cognitive task performance. Both consequences can potentially occlude specific PD-related changes in brain function.

Second, whereas several studies have studied task-related brain activity patterns in relation to executive functioning in PD, the role of task-related functional connectivity is still poorly understood. Since previous studies showed changes in functional connectivity during rest, it would be interesting to see how functional connectivity changes during task performance. Also the relation between activity and functional connectivity during task performance has never been investigated in unmedicated PD patients. A better understanding of how connectivity and activity relate to each other might provide insight into the aetiology of cognitive disturbances in PD (e.g. whether a decrease in functional connectivity is related to an increase in activity).

Third, previous MRI studies on executive task performance in PD patients often only employed a single task, thus hindering a comparison between tests on performance, activity and functional connectivity. It is still unclear as to why some patients show normal performance on certain tasks, while displaying impairments on others. A between-task comparison within the same cohort of patients might provide valuable insights into the underlying neural mechanisms that relate to the cognitive heterogeneity between PD patients.

Fourth, the role of structural differences between patients and controls in relation to cognition has been investigated, but often using small sample sizes while insufficiently controlling for potential confounding factors, such as age, gender, or education. Most studies in PD focused on between-group changes in grey matter (GM) volume using voxel-based morphometry (VBM), and only a handful investigated the relation between GM and task performance on neuropsychological tasks. VBM is a well-validated voxel-wise approach to study regional GM volume differences between groups or correlations between specific characteristics and regional GM volume. GM volume, however, is the product of cortical surface area and cortical thickness and therefore an a-specific measure. A surface-based approach, which investigates surface area and cortical thickness separately, would thus provide more insight into whether these measures are separately affected in PD.

AIMS, RESEARCH QUESTIONS AND OUTLINE OF THIS THESIS:

The primary aim of this thesis was to gain more insight into the neural underpinnings of the cognitive heterogeneity among early PD patients. We did this by stud-

ying the relation between behavioural performance, task-related neural activity, and task-related functional connectivity during different executive tasks in an MRI scanner. In addition, we used low-frequency (i.e. inhibiting) rTMS at the left dorsal PFC in a sample of healthy controls prior to performance on a set-shifting task and thus tried to gain more insight into the causal relationship between activation of the DLPFC and behavioural performance on a set-shifting task. By doing so, we mimicked the typical neural deficit that is described in PD patients and thus induced a “temporary lesion model” for the set-shifting deficits in PD. Last, we assessed the role of local variation in brain structure in relation to cognition in PD.

To avoid the potential confounding factor of medication on behavioural and imaging outcomes, all task-related studies were performed in a sample of early PD patients (N=25) who were not on dopamine replacement therapy, and subsequently compared them with a group of well-matched healthy controls (N=43). We thus measured the effect of PD on task performance, task-related brain activity, and task-related network function (or functional connectivity) as unbiased as possible.

For the association between brain structure and cognitive status, we studied i) between-group differences in brain structure, and ii) correlations between task performance and brain structure within the PD group. We employed both a voxel-based as a surface-based approach, two complementary analysis techniques, to gain an optimal insight into the role of structural brain correlates of variance in cognitive functioning in PD. The T1-weighted scans and neuropsychological test scores we used for the structural studies were obtained from clinical data of PD patients (N=93) which were collected for diagnostic purposes while visiting the outpatient clinic for movement disorders at the VU University Medical Center (VUMC). The structural scans of the healthy controls (N=46) were ad hoc selected to match the PD cohort with respect to age and gender, and using the same 3 Tesla scanner, from other studies at the VUMC.

This thesis addressed the following research questions:

1. Do unmedicated patients with PD show impaired set-shifting performance, associated with decreased neural activation and decreased task-related functional connectivity?

To answer this research question, we compared task performance and neural activation between PD patients and matched healthy controls in an MRI scanner while performing an in-house developed, simplified feedback-based set-shifting paradigm. Background and results are described in **chapter 2** [86]. In **chapter 3** [87], we describe the task-related functional connectivity analyses between patients and controls while performing this task.

2. *Is it possible to mimic these set-shifting-related behavioural and neural impairments in healthy participants, using low-frequency (i.e. inhibiting) rTMS on the left dorsal PFC?*

In **chapter 4** [88] we provide an answer to the second research question, by assessing the role of the left dorsal PFC in set-shifting, after applying a single-session low-frequency rTMS on the left DLPFC (verum), compared with the vertex (sham), in healthy controls.

3. *Do unmedicated patients with PD show impaired working memory performance, associated with decreased neural activation and task-related functional connectivity?*

In **chapter 5** [89], we measure the behavioural performance, neural activity and neural connectivity of PD patients and healthy controls while performing a working memory task in an MRI scanner.

4. *Do unmedicated patients with PD show impaired response inhibition, associated with decreased task-related brain activation?*

Chapter 6 [90] comprises a study that compared behavioural performance and neural activity between patients and controls during a response inhibition task in an MRI scanner and provides an answer to the fourth research question.

5. *What is the contribution of variation in regional brain structure across PD patients to differences in performance on neuropsychological tasks; and what is the best analysis technique to study this?*

Chapter 7 [91] entails the results from a VBM study in which we correlated task performance on several neuropsychological tasks with regional GM volume within a large cohort of patients with PD.

In **chapter 8** [92] we tried to replicate the results from the volume-based analysis from chapter 7, employing a surface-based approach, and to investigate whether cortical surface area and cortical thickness are differentially affected in PD.

Chapter 9 discusses the main findings of this thesis, proposes a working model on cognitive heterogeneity in PD, and makes recommendations for future research.

BOX A: THE APPLIED TECHNIQUES

When a participant is placed into a **magnetic resonance imaging (MRI)** scanner, the protons within the human tissue automatically align in a horizontal orientation with the externally induced magnetic field. Then, radiofrequency coils within the MRI scanner bombard the protons with electromagnetic waves at a certain frequency, making them resonate, and changing the horizontal alignment of the

protons. When the radio pulse is switched off, the protons flip back to their original alignment and emit a radiofrequency wave which can be detected. Since different tissue-types emit different radiofrequency waves upon flipping back to their original alignment, this information can be used to reconstruct an image of the location and tissue-types that were present within the magnetic field. This principle underlies **structural MRI (sMRI)**. Although the overall brain anatomy is similar across people, there is considerable inter-individual variability between the exact shape and location of the different brain structures (see Figure 3, left panel). Different computer algorithms and methods can be applied to investigate differences in brain structure. A voxel-based method assesses the tissue-type (i.e. grey matter / white matter / CSF) of every voxel, thereby obtaining a relative estimation of the average tissue-type for each particular voxel for a group of participants. A volume-based technique measures the distance between the cortical grey/white matter boundary and the pial surface, and of the sub-cortical structure and surrounding white matter, thus obtaining an absolute measure of cortical thickness and sub-cortical volume for each participant. These measures can be averaged and later compared between groups. Both techniques thus measure structural brain-related features, but do so in a different matter.

When task performance depends on certain specialized brain regions (e.g. primary motor cortex during a finger-tapping task), the neuronal metabolic activity of that area increases while performing a task that depends on this specialization, and, consequently, the surrounding vasculature supplies oxygenated blood to sustain its activity. Since deoxygenated haemoglobin possesses paramagnetic properties, the increase in metabolic activation can indirectly be detected in an MRI scanner as a change in the blood-oxygenated level dependent (BOLD) response. The BOLD signal is used in **functional MRI**. It is important to emphasize that fMRI is thus an indirect measurement of brain activity, and, although it possesses a high spatial resolution (i.e. the disturbance of the magnetic field can be located within a resolution of several millimetres), the BOLD signal has a low temporal resolution in the order of several seconds.

fMRI can be used to investigate neural activity and connectivity, during a task or in rest. Although resting state studies have provided a wealth of information during the last decade, this thesis focuses on task-related activation and connectivity. A cognitive task exerts pressure upon the task-related network thereby forcing brain areas to work together. Therefore, task-related brain imaging studies provide more insight into the neural network alterations that underlie changes in the cognitive performance than a resting state scan. When assessing **task-related differences in activity** between conditions or groups, contrasts are defined and computed (e.g.

which areas were more active during the visual stimuli, when compared with the tactile stimuli; see Figure 3, right panel). Subsequently, between-group differences in the degree of activation for that contrast can be assessed. **Task-related functional connectivity** assesses the extent of synchronization in activity between different brain areas while performing a task. When neural assemblies show synchronized fluctuations in activity over time in a statistically predictable manner, they are expected to be functionally connected, and thereby working together while performing the task. Both task-related functional activity and connectivity assess different aspects of brain function, although the exact relation between the two measures is still largely unresolved.

Repetitive transcranial magnetic stimulation (rTMS) is a method to selectively increase or decrease neural activation in a specific brain area, and also influences its interconnected brain network areas (see Figure 4). This technique employs a coil (in this study a figure-of-eight shaped coil for optimal spatial accuracy) in which an electrical current is rapidly alternated. This current induces a magnetic field perpendicular to the centre of the coil within the brain that penetrates scalp, skull, meninges, and liquor. By rapidly alternating the electrical current in the coil, the magnetic field inside the brain changes accordingly, and thereby induces an electrical current within the brain tissue through electromagnetic induction. When applying repetitive TMS (rTMS) pulses at a high frequency (> 5 Hz) for a longer period of time (e.g. twenty minutes) on the primary motor cortex (M1), the motor evoked potential (MEP) following a subsequent single pulse of TMS is increased, suggesting that the activity of the area under the coil is increased. Conversely, applying low frequency (< 5 Hz) rTMS at M1 results in a decreased MEP, suggesting that the activity of the area under the coil is decreased. rTMS presumably works similarly in other brain regions, (e.g. the DLPFC) and can thus be used to modulate the excitability of any cortical area.

Single-photon emission computed tomography (SPECT) is an imaging technique that can detect intravenously injected radioactive isotopes and produce a three-dimensional image of the distribution of the compound inside the body. In PD, SPECT studies often employ dopamine transporter (DAT) ligands, such as [123 I]FP-CIT, which bind to the pre-synaptic DAT terminals in the striatum, thereby providing an indirect measure of the available quantities of striatal dopamine. SPECT is often employed for clinical and diagnostic purposes, and a sub-sample of our unmedicated PD patients cohort received a DaT-SPECT scan prior to participating in our study for clinical evaluation. We used this data in a number of chapters to further investigate the relation between striatal dopamine, behavioural task performance, and task-related activity / functional connectivity.

