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Cognitive Change in Parkinson's Disease

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Summary

In this thesis, we aimed to gain more insight into the cognitive changes that accompany Parkinson's disease (PD). We examined the course of cognitive decline in patients with newly-diagnosed PD using an extensive neuropsychological test battery. We tried to disentangle the relation between executive functioning, memory, and visuospatial skills in PD. Additionally, we also examined specifically the ability to inhibit responses and and to learn from reward-based feedback, and we explored the relation between these two abilities on the one hand and clinical and cognitive status on the other.

The studies that are reported here are embedded in the larger CARPA project (Comorbidity and Aging in Rehabilitation Patients with sequalae of poliomyelitis, osteoarthritis, and PD: the influence on Activities). Between 2002 and 2005, 133 newly-diagnosed PD patients and 69 patients with more advanced PD were recruited to participate in our study. At baseline, newly-diagnosed PD patients had just received the PD diagnosis, while the advanced PD cohort had a longer disease duration of approximately five years.

In *Chapter 1*, we started with a general introduction in PD. Whereas PD was originally described as a purely motor disease, we now know that cognitive changes accompany the disease as well. These changes are generally presumed to arise from impaired striatal-frontocortical dysfunction due to dopamine depletion in the midbrain. However, PD is additionally characterized by extrastriatal pathology, such as Lewy body accumulation in the cortex and other histological changes. As a result, three to eight years after the diagnosis, up to 80% of patients are identified with cognitive impairment. We noted that previous studies on the course of cognitive decline in PD often suffered from methodological issues, such as small and mixed samples of patients, the absence of control groups. Most studies did not include an extensive neuropsychological test battery. Furthermore, we introduce studies that focused on response inhibition and reward-based learning, showing that PD may have a detrimental effect on these abilities. However, these studies first of all await replication. Secondly, these studies would benefit from extension to further factors that may be clinically relevant in modulating these abilities, such as variables related to motor and cognitive impairment. We end the introduction with an outline of the thesis.

In *Chapter 2*, we focused on the cognitive status and course of cognitive decline of newly-diagnosed PD patients after a follow-up of five years. Fifty-nine patients and 40 healthy control subjects were presented with an extensive neuropsychological examination at baseline (that is, the time of diagnosis), and after three and five years. Neuropsychological testing focused on the six major cognitive domains, namely psychomotor speed, attention, language, memory, executive function, and visuospatial skills. Additionally, patients received yearly clinical examinations. We used two methods to determine the rate of cognitive decline: 1) linear mixed models to examine group differences in cognitive performance, and 2) multivariate normative comparisons to identify individual cases of cognitive decline. Overall, the linear mixed models showed performance decreased over time for patients on most

tests, while performance in the control group was relatively stable. This decline in patients did not depend on motor processing speed. The multivariate normative comparisons, a method that identifies individual cases of cognitive decline, revealed that 53% of patients showed significant decline compared to the control group. Prognostic factors of decline were age at onset and poor verbal memory performance at baseline. We also discussed the possible influence of attrition on the outcomes of our study. Most likely, our numbers are an underestimation of the true number of patients who showed cognitive decline.

In *Chapter 3* we assessed the progression of motor impairment, disability, and quality of life in 129 newly-diagnosed PD patients during the first five years of the disease. With the use of linear mixed models, we identified male sex and cognitive dysfunction as the main predictors for increased motor impairment. Furthermore, cognitive dysfunction and more severe motor symptoms that are nonresponsive to levodopa predicted greater disability. A higher age at onset was the only prognostic factor for a decline in quality of life. While patients with more anxiety and depressive symptoms at baseline reported a lower quality of life, the quality of life showed a less steep decline in these patients. These results indicated that the primary determinants of disability in PD are motor symptoms that are not responsive to levodopa.

Recently, new consensus criteria for diagnosing mild cognitive impairment in PD (PD-MCI) have been published. In *Chapter 4* we applied these criteria to our sample of patients to 1) examine the prevalence and progression of PD-MCI in newly-diagnosed patients, and 2) examine the reliability and applicability of these new PD-MCI criteria. We found that at baseline, 35% of 123 newly-diagnosed patients had PD-MCI. After three and after five years, the percentages increased to approximately 50%. Of the 122 patients with at least one clinical follow-up 17% developed PD dementia (PDD), and 26% of patients with PD-MCI at baseline eventually developed PDD. Furthermore, the inter-rater and intra-rater reliabilities of the PD-MCI criteria were good to excellent with kappa values between 0.85 and 0.96. The criteria were easily applicable, showed good to excellent reliabilities, and therefore offer an accurate and easy way to identify patients who are at risk for further cognitive decline and dementia.

In *Chapter 5*, we explored the relation between motor symptom severity, memory, and visuospatial skills. Although the common view holds that executive impairment disrupts memory and visuospatial functioning, there is debate as to whether executive dysfunction can fully explain impairments in these other domains. For example, the decline in memory on a visual association test (see *Chapter 2*) most likely does not directly depend on frontostriatal cortical systems which are presumed to be responsible for executive impairment. Therefore, we applied structural equations modeling to our neuropsychological data to examine the association between executive functions, memory, and visuospatial skills. We tested three models: 1) the executive primacy model which assumes that memory and visuospatial impairments are secondary to executive dysfunction, 2) the combined model which resembles the executive primacy model, but adds the direct influence of disease severity on memory and visuospatial functioning, and 3) the independence model which assumes that executive functioning, memory, and visuospatial skills are independently affected by disease

severity. We tested these three models at two time-points: at time of diagnosis and after five years. At both time-points, the executive primacy model was preferred over the combined and independence models. These results favor the traditional view that holds that executive impairment lies at the core of cognitive impairment in PD.

Chapters 6 and *7* focused on more specific abilities, namely response inhibition and reward-based feedback learning. Both abilities rely greatly on proper frontostriatal functioning, and therefore dopamine depletion in the striatum may result in their impaired performance. In *Chapter 6*, where we focused on response inhibition, we made a distinction between two theoretically separable modes of cognitive control: 1) reactive control, which refers to the detection and resolution of conflict between a response impulse and the actual response that is needed, and 2) proactive control, which refers to the anticipation and prevention of this response conflict. To examine response inhibition in PD, we presented 33 patients and 27 healthy controls with the Simon task. In the Simon task, participants had to respond to stimuli based on the stimulus color, while ignoring the stimulus location. Colored circles were presented either to the left or to the right of the center of the computer screen. In case of a compatible trial, the location of the stimulus and the location of the response were similar, while incompatible trials were trials where the location of the stimulus did not match the location of the correct response. The Simon effect refers to the difference in RT between a compatible and incompatible trial. PD patients showed the typical response-conflict effects, but did not differ from controls in either proactive or reactive control. Among PD patients, however, proactive control co-varied with cognitive deficits, whereas reactive control was associated with motor symptom severity. Thus, we observed an important interaction among our sample of PD patients: whereas individual differences in markers of reactive control co-varied with individual differences in motor symptom severity but not cognitive dysfunction, markers of proactive control showed co-variance with cognitive dysfunction but not motor symptom severity.

In *Chapter 7*, we focused on reward-based learning, an ability that also greatly depends on sufficient levels of dopamine in the striatum. We presented the same 33 patients and 27 controls of *Chapter 6* with a probabilistic feedback learning task where they had to learn which picture corresponded with a left or right button press. All subjects completed three blocks that varied in their level of probability; these were 100/0, 90/10, and 80/20. In the 80/20 condition for instance, the probability of a positive outcome was 0.8 (in 20% of the trials the participant would receive incorrect feedback after selecting the correct response). We examined reward-based feedback learning with the Q-learning model. The Q-learning model distinguishes between outcome evaluation and reward prediction. Outcome evaluation refers to the reward prediction error (RPE), which represents the difference between the expected outcome of an action and the actual outcome of the action. In early learning stages RPE values will be high, whereas in later stages RPE values will decrease as a result of learning. Reward prediction in the Q-learning model is computed as the stimulus-action dependent reward prediction (SADRP). The SADRP is updated according to RPE values. In early learning stages, SADRP values will be low because an individual cannot adequately predict the reward; however, during learning SADRP values will increase. Furthermore, we

aimed to examine the association between task performance, and clinical and cognitive status.

Our results indicated that patients were worse at predicting rewards (lower SADRP values) than controls, while no differences were seen in outcome evaluation (RPE values) or the total monetary rewards earned. Patients with good cognitive performance showed better reward-based learning (better reward prediction and outcome evaluation, and greater rewards earned) in the non-probabilistic condition, and earned more rewards in the most difficult probability condition. Thus, PD may negatively affect the ability of learning to predict which outcomes yield rewards, but does not influence outcome evaluation. Furthermore, extensive neuropsychological profiling may contribute to explaining, at least some, of the individual variation in reward-based learning in PD.

These results were integrated and discussed in *Chapter 8*. Our findings provide evidence for the recently postulated dual-syndrome hypothesis. This hypothesis states that PD can broadly be divided into two syndromes: 1) a syndrome characterized by fronto-striatal dysfunction with a slower disease progression, and 2) a syndrome with distinctive early visuospatial and memory deficits that are indicative of the involvement of temporal and other posterior cortical areas, which has a faster progressive course. Our observations of 1) a decline on memory tests that reflect more posterior and medial temporal lobe dysfunction, 2) memory impairment predicting further cognitive decline, and 3) the primary determinants of disability in PD being motor symptoms that are not responsive to levodopa, are all in favor of this dual-syndrome hypothesis. This shows that although dopamine depletion is characteristic of PD, the consequences of the disease are far more complicated and diverse. There is a need for more prospective studies that include a large neuropsychological test battery. Studies should include multiple valid and reliable tests that not only focus on executive functioning and attention, but also on the domains of memory, visuospatial skills, and psychomotor speed.