Cognitive sequelae of Parkinson’s disease: nature, course, risk factors and functional impact
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Parkinson’s disease (PD) is one of the most common neurodegenerative disorders of later life. Although traditionally considered as a movement disorder, it is now increasingly recognized that PD also manifests itself with a wide range of non-motor symptoms. Cognitive dysfunction is among the most prevalent of these non-motor symptoms and may worsen the prognosis and exacerbate the personal and socioeconomic burden of the disease. As health care professionals and researchers have become aware of the clinical importance of cognitive dysfunction in patients with PD, considerable research efforts have been devoted to characterizing the nature and extent of cognitive changes in PD. The cognitive dysfunction in PD may vary from subtle and relatively circumscribed deficits to frank dementia. However, the exact pattern, frequency and the natural evolution of cognitive impairments in PD are still poorly defined. In addition, the impact of specific cognitive deficits on daily activities in PD patients is unclear.

This thesis focuses on: 1) the natural course and risk factors of cognitive decline, and 2) the impact of cognitive impairments on daily functioning in patients with PD. The attendant methodology included two cohorts of patients with PD - one with newly diagnosed disease recruited consecutively from several neurology outpatient clinics, and one with established, more advanced disease identified from medical records of the participating hospitals and from the Dutch Parkinson’s Disease Association. In addition, a control group of demographically matched healthy subjects was also included in the study. All participants received a comprehensive neuropsychological test battery at baseline and at 3-year follow-up. The patients also underwent clinical examination and assessments of functional status annually over the 3-year interval.

Chapter 1 provides a general introduction to PD, followed by a brief overview of literature on cognitive changes associated with this disorder. In addition, methodological shortcomings of previous research on cognitive function in PD are discussed and the aims of the present thesis are presented.

Chapter 2 reports the results of a systematic review of the literature investigating the magnitude of cognitive changes over time that accompany the progression of PD. Twenty-
five longitudinal studies involving 901 initially non-demented PD patients who were assessed serially with neuropsychological tests, met the pre-established criteria and were included in the meta-analysis. The results revealed a relatively small decline in cognitive functions during an average follow-up period of 2.5 years in initially non-demented PD patients. Of the eight cognitive domains assessed, only global cognitive ability (d = 0.40), visuoconstructive skills (d = 0.32), and memory (d = 0.29) showed a statistically significant degree of decline. Changes in performance on measures of attention and processing speed, verbal ability, verbal fluency, mental flexibility/reasoning, and visuoperceptual functions were found to be negligible (d ≤ 0.10). Contrary to expectation, executive function was not the cognitive domain that showed the fastest rate of decline over time. The results further showed that lower educational level is associated with a faster rate of decline across all cognitive domains. In addition, older age was found to be a significant predictor for more rapid decline in global cognitive status and memory. We concluded that our review probably underestimates the true extent of cognitive decline in patients with PD due to several methodological limitations in the current literature, such as short follow-up intervals, lack of control groups, selection bias, and insufficient control of practice effects inherent to repeated cognitive testing.

Chapter 3 describes a baseline study that examined the frequency and nature of cognitive dysfunction in a sample of newly diagnosed PD patients. A cohort of 115 consecutive patients with newly diagnosed PD and 70 healthy controls underwent a comprehensive neuropsychological assessment including tests of psychomotor speed, attention, language, memory, executive and visuospatial functions, as well as measures of affective status. In addition to comparison with healthy controls, neuropsychological performance of PD patients was also compared with available normative data to establish the cognitive profile in a more clinically meaningful manner and with greater external validity. The results showed that 24% of patients exhibited evidence of cognitive dysfunction already at the time of PD diagnosis, which was significantly higher than among healthy control subjects (4%). Deficits were found to be most frequent in the domain of attention and executive function (100%), but they appeared to be also fairly common on measures of psychomotor speed (59%), visuospatial skills (48%), memory (44%), and language (22%). Further analysis
focusing on the magnitude and the discriminant utility of cognitive changes revealed that deficits in the domains of memory, and attention and executive function constitute the core feature of cognitive impairment in the early stages of PD. Later onset of disease was independently associated with the presence of cognitive impairment early in the course of PD.

Chapter 4 presents the results of a study investigating procedural learning and its possible relationship with functional status in patients with PD. Procedural learning refers to the capacity to acquire motor or cognitive skills gradually through practice, and is typically conceptualized as a form of non-declarative or implicit memory. A sample of 95 patients with PD and 44 demographically matched healthy control subjects were assessed with the Serial Reaction Time Task (SRTT), one of the most frequently employed experimental measures in research on motor procedural learning. The SRTT is a four choice reaction time task in which visual stimuli are presented in six blocks of 100 trials either in a repeating sequence of 10 stimuli or randomly. Learning was inferred from the reduction of response times over five successive blocks of repeating sequence trials and from the increase in response times in the sixth random block. In addition to the SRTT, neuropsychological tests of declarative memory, attention and psychomotor speed, executive and visuospatial functions were administered to all participants, and patients also received quantitative ratings of functional outcome. The results revealed no differences between the PD and control groups in the learning rate across blocks of repeating sequence trials. However, PD patients were significantly less efficient than controls in acquiring sequence-specific knowledge, although this impairment was relatively small (d = 0.38). Analysis of the individual data revealed that the majority of PD patients were able to acquire procedural knowledge of a motor sequence, but they learn it somewhat less efficiently than controls. Patients with more advanced clinical symptoms tended to show worse performance. Separate analyses of a subgroup of 24 non-medicated patients in the early stages of PD revealed no differences in SRTT performance relative to control subjects. Neuropsychological testing showed impairments in attention and executive functions, immediate and delayed explicit memory, and visuospatial skills in the PD group, but none of the cognitive measures were related to procedural learning. Reduced motor sequence learning in PD patients did not influence their functional status.
Chapter 5 describes the results of a cross-sectional study examining determinants of functional disability and quality of life (QoL) in a combined sample of 190 patients with newly diagnosed and more advanced PD. Data on demographic and clinical characteristics, motor impairments, specific cognitive functions, affective symptoms, comorbidity and social support were collected during neurological and neuropsychological examinations. Disability was rated using the Schwab and England Activities of Daily Living Scale (SE-ADL), the AMC Linear Disability Score (ALDS) and the Functional Independence Measure (FIM). QoL was evaluated with a disease-specific instrument, the Parkinson’s Disease Quality of Life questionnaire (PDQL) and a generic measure, the Medical Outcome Study Short Form (SF-36). Multiple linear regression analyses revealed that axial impairment (postural instability and gait difficulty) contributed most to disability. While accounting for other potential contributors, axial symptoms alone explained 31 to 37% of the variance in functional disability. Comorbidity and bradykinesia also contributed to disability, but to a lesser extent. Using QoL as the outcome measure in the multivariate linear regression analysis, self-reported mood symptoms and axial impairment were found to be the two factors most closely associated with poor QoL. Cognitive changes had little impact on disability and QoL once the effect of motor and mood symptoms had been taken into account.

Chapter 6 reports a prospective longitudinal study that aimed to describe the nature, degree and prognostic factors of cognitive decline over a 3-year interval in groups of newly diagnosed and more advanced PD patients compared to demographically matched healthy control subjects. Consecutive patients diagnosed at baseline with PD (n = 89), established PD patients (n = 52) with a mean disease duration of 6.5 years, and healthy control subjects (n = 64) were re-examined 3 years after the initial assessment with an extensive neuropsychological battery. Different analytic methods were employed in an attempt to overcome methodological limitations of previous research in this area. The evolution of cognitive deficits in PD patients at the group level was examined using a standardized-regression based (SRB) method, which takes into account sources of measurement error inherent in test-retest designs, such as practice effects and regression to the mean, as well as demographic variables that may affect test performance (e.g. age, sex, education), and differences in initial level of performance. Additionally, standard scores were derived from avail-
able normative data for each neuropsychological measure to assess cognitive changes over time in a more clinically meaningful manner. Finally, the multivariate normative comparison method was employed to identify individual PD patients exhibiting a significant decline in cognitive performance. This method compares the pattern of change in test performance of each PD patient over the follow-up interval with the control group to identify individual patients who deviate from the norm on several cognitive variables simultaneously, while controlling for false positive rate due to multiple comparisons. The results revealed that patients diagnosed at baseline with PD exhibited a greater degree of decline on 20 of the 27 cognitive measures used than healthy controls during the 3-year follow-up. The most severe and consistent decline occurred on measures of psychomotor speed and attention (> 1 SD). Deterioration in the domains of memory, visuospatial skills, and executive function was smaller in magnitude, but still significantly greater than in controls. The frequency of cognitive deficits (test score ≥ -2 SD relative to norms) in this patient cohort increased during the follow-up period on tests of psychomotor speed, attention, constructive skills, verbal memory, and selective executive abilities. Analysis of cognitive change at an individual level revealed that nearly a half of the patients exhibited cognitive decline that exceeded the 5th percentile in the control group. These patients did not merely show lack of practice effects, but exhibited actual change on several tests, which contributed to the overall cognitive decline. This decline appeared to occur in a diffuse rather than a specific manner, but deterioration in psychomotor speed and attention seemed to be more prominent than in other cognitive areas. Nine percent of newly diagnosed PD patients developed dementia during follow-up. Longitudinal evaluation of patients with more advanced PD revealed a similar trajectory of decline to that observed among newly diagnosed patients. Analysis of cognitive change at the individual level showed that 50% of established patients displayed cognitive decline that exceeded the 5th percentile in the control group and 7% of them developed dementia during follow-up. Axial symptoms at baseline and age at disease onset predicted cognitive decline in the established PD group. We concluded that within few years after diagnosis patients with PD exhibit progressive decline in cognitive function beyond cognitive changes associated with normal aging. This decline occurs diffusely across multiple cognitive domains, but appears to be the most prominent for psychomotor speed and
Summary

attention. Contrary to findings from cross-sectional studies, traditional measures of executive function did not appear to be the first to exhibit decline in our PD sample. Referral bias and selective attrition during the follow-up interval are likely to have underestimated the true extent of cognitive decline and the prevalence of dementia in our group of patients with more advanced PD.

Chapter 7 provides a general discussion concerning the results of this thesis. The main findings of the research presented in this thesis are summarized and put into context. Methodological issues were described and the relevance and implications of the present findings for clinical practice were discussed. Finally, some recommendations for future research were made.