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Parkinson's Disease and Dementia: A Longitudinal Study (DEMPARK)

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Key Words

Parkinson's disease · Dementia · MCI, cognitive impairment · Cohort study

Abstract

Background: Parkinson's disease (PD) is a progressive neurodegenerative motor disorder. However, non-motor complications frequently alter the course of the disease. A particularly disabling non-motor symptom is dementia. ***Methods/Design:*** The study is designed as a multicentre prospective, observational cohort study of about 700 PD patients aged 45–80 years with or without dementia and PD-mild cognitive impairment (MCI). The patients will be recruited in eight specialized movement disorder clinics and will be followed for 36 months. Information about the patients' functional status will be assessed at baseline and 6-/12-month intervals. In addition, 120 patients with dementia with Lewy bodies (DLB) will be included. Well-established standardized questionnaires/tests will be applied for detailed neuropsychological assessment. In addition, patients will be asked to participate in modules including volumetric MRI, genetic parameters, and neuropsychology to detect risk factors, early diagnostic biomarkers and predictors for dementia in PD. ***Results:*** The study included 604 PD patients by March 2011; 56.3% were classified as having PD alone, with 30.6% of patients suffering from PD-MCI and 13.1% from PD with dementia. The mean age of the cohort was 68.6 ± 7.9 years, with a mean disease duration of 6.8 ± 5.4 years. There was a preponderance of patients in the earlier Hoehn and Yahr stages. ***Conclusion:*** The main aim of the study is to characterize the natural progression of cognitive impairment in PD and to identify factors which contribute to the evolution and/or progression of the cognitive impairment. To accomplish this aim we established a large cohort of PD patients without cognitive dysfunction, PD patients with MCI, and PD patients with dementia, to characterize these patients in a standardized manner, using imaging (serial

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structural MRI), genetic and proteomic methods in order to improve our understanding of the course of the PD process and the development of cognitive dysfunction and dementia in this disease. The inclusion of the DLB patients will start in the second quarter of 2011 in the BMBF-funded follow-up project LANDSCAPE.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders with an incidence that rises with age and a lifetime risk of developing the disease of 1.5% [1]. For Europe, the crude incidence rates reported in various studies and populations range from 5/100,000 to 26/100,000 [2].

PD is characterized clinically by rigidity, tremor, bradykinesia and impaired postural reflexes. In addition to these motor features, non-motor symptoms such as psychiatric disorders, autonomic disturbances and sleep disorders frequently complicate the course of the disease. A particularly disabling non-motor complication of PD with a strong impact not only on the patients but also on their families and caregivers is dementia. Aarsland et al. [3] stated the prevalence of dementia in PD (PD-D) to be 0.5% in subjects older than 65 years for the general population, accounting for 3.6% of all dementia cases. There is increasing evidence that PD-D is a more common non-motor complication than previously thought: about 30% of PD patients suffer from cognitive impairment and dementia [3–6]. A recent 12-year follow-up of a longitudinal cohort study in Norway found the life expectancy of a 70-year-old man with PD but no dementia to be 8 years, of which 5 years are expected to be dementia-free and 3 years are expected to be with dementia; for a female PD patient, the life expectancy is 11 years, of which about 7 are expected to be without, and approximately 4 years are expected to be with dementia. If a PD patient at the age of 70 had already developed dementia, the life expectancy was found to be reduced to about 4 years in the male, and to 5.7 years in the female patient [7].

The natural history of PD-D, however, starting from a mild executive dysfunction [8] to a more generalized cognitive impairment and dementia, has not yet been fully explored in longitudinal designs with sufficiently large samples. Furthermore, current clinical criteria distinguish dementia with Lewy bodies (DLB) and PD-D exclusively by the temporal requirement that parkinsonism precedes dementia by more than 12 months in PD-D, while DLB is assumed if dementia occurs before or concurrently with motor symptoms of PD [9]. However, it is not clear to what extent the two different PD types differ in their course and outcome and to what degree they differ in associated risk factors. The prevalence of DLB is assumed to be high, although reliable estimates are currently lacking. In the population of all demented patients, DLB is estimated to represent between 0 and 30.5% of cases [3]. In a group of PD patients with an age at disease onset of about 70 years, the prevalence of dementia 8 years later was reported to be more than 75% [10].

The Dementia and Parkinson's Disease (DEMPARK) consortium will focus on the topic of PD and PD-D to monitor the progress of PD and the development of cognitive dysfunction in a large cohort of PD patients over 36 months, recruited in eight specialized German centres. The overall main aim is to characterize the natural progression of cognitive impairment in PD and to identify factors which contribute to the evolution and/or progression of the cognitive impairment.

By applying a specifically composed neuropsychological test battery, PD patients will be allocated to three subgroups: (1) PD patients without cognitive impairment (PD); the diagnosis 'idiopathic PD' will be made according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [11]. (2) PD patients with mild cognitive impairment (PD-MCI); the MCI criteria of Petersen [12] with all subclasses will be applied. (3) PD patients with dementia (PD-D). The consensus guidelines by Emre et al. [13] will be applied.

The DEMPARK consortium aims to build a large cohort of patients with PD, PD-MCI and PD-D ($n \geq 700$ patients), which will represent the largest ever studied national cohort of PD patients without and with dementia. All patients in the cohort will be subjected to serial standardized neurological and neuropsychological testing (at baseline, and at two follow-ups after 6 and 12 months, respectively) and will thus provide a well-characterized cohort of patients. Recently, the study was extended to follow the PD cohort for two more years (24 and 36 months after enrolment) and to include also patients with DLB($n = 120$), which will start to recruit patients in this indication in the second quarter of 2011. The study will be renamed with the eponym 'LANDSCAPE' (*Lan*gzeitbeobachtung *d*ementieller *S*ymptome und *c*ognitiver Parameter sowie *A*nwendbarkeit neuer prognostischer Marker bei der *P*arkinson-*E*rkrankung) and is part of the Competence Network Degenerative Dementias, funded by the German Ministry for Education and Research (BMBF).

Besides the cohort study, patients will be asked to participate in add-on modules to the study (i.e. MRI at baseline and after 12 months; a genetic module with collection of blood DNA (at baseline) and blood RNA samples (at baseline and after 6 and 12 months), as well as neuropsychological testing for cognitive plasticity (at baseline and at 12 months).

The collection of a large number of blood samples (serum, plasma, blood DNA, and blood RNA) of well-characterized patients will provide a unique source for the search for risk factors, predictors and early differentiating markers for early detection of developing dementia in PD as well as for defining the role of Alzheimer's disease and Lewy body pathology in dementia in PD.

Methods

Design of the Study

The study is a multicentre, prospective, observational cohort study of PD patients. Patients will be consecutively recruited in eight specialized movement disorder centres distributed across Germany (Aachen, Bonn, Dresden, Frankfurt/Main, Kassel, Kiel, Marburg and Tübingen). All patients who are willing to participate and who fulfil the inclusion criteria will be included in the study. Each study centre will recruit consecutively 80–100 PD patients with or without dementia within 12 months. In addition, 120 patients with DLB will be recruited. In patients not willing to participate, an anonymous minimal data set (gender, age, Hoehn and Yahr [14] stage and, if available, a Mini-Mental State Examination (MMSE) score [15] not older than 3 months) will be collected to avoid systematic inclusion errors.

The study centres began screening and enrolment of PD patients during the 3 months from November 2009 to January 2010.

Sample Size

Based upon the main outcomes of this project (see below) and the conversion rates of cognitive decline in PD patients as reported by Aarsland et al. [3], we estimated that a sample size of n = 500 would be sufficient for the investigation. This was confirmed by conservative power analyses ($\alpha = 0.05$, two-sided; power >99.9%). As we expect 10% of patients to be ineligible due to exclusion criteria and 15% of patients to drop out over time, 700 patients must be included initially to provide 500 completers after 12 months (i.e. each study centre will recruit 80–100 PD patients with or without dementia during this period). Based on the prevalence and conversion rates of MCI and PD-D, the sample will be stratified into 250 patients without cognitive impairment, 200 patients with MCI, and 250 patients with dementia [12]. In addition, we included the recruitment of 120 patients with DLB.

Regarding the expected conversion rates, we estimated based on our own and data from the literature an expected 18-month incidence and 3-year incidence among baseline unaffected and MCI, respectively, for cognitive impairment/dementia. Thus, we expect conservatively a total number of patients converted to dementia of 69 patients at the first follow-up and 108 at the 3-year follow-up.

Inclusion Criteria

To be eligible for enrolment in the DEMPARK study, participants must be between 45 and 80 years of age, must meet criteria for the diagnosis 'idiopathic PD' according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [11] or the diagnosis 'idiopathic PD with MCI' according to the criteria given by Petersen [16] or the diagnosis 'idiopathic PD with dementia' according to the consensus guidelines developed by Emre et al. [13] and operationalized by Dubois et al. [17].

MCI criteria by Petersen [16] require: (1) a subjective complaint of cognitive decline by the patient, preferably corroborated by a reliable source; (2) minimal impact of the decline on day-to-day functioning and the absence of dementia (both primarily based on clinical interview and history), and (3) 'objective' evidence of cognitive abnormalities that cannot be simply attributed to age. In this study we included all subclasses including amnestic MCI single domain, amnestic MCI multiple domain, non-amnestic MCI single domain, and non-amnestic MCI multiple domain. For the diagnosis of PD-D, the following characteristics are required [13]: (1) core features, (2) associated features, (3) features which do not exclude PD-D, but make the diagnosis uncertain, and (4) features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible. Accordingly, patients with probable PD-D and possible PD-D were included.

For the extension of the DEMPARK study, the so-called LANDSCAPE study, an additional cohort of patients was included with the diagnosis DLB according to the criteria by McKeith et al. [9]. To be classed as having cognitive impairment (PD-D, DLB), the patient must score an MMSE of ≤28 to 17 points, and a Parkinson Neuropsychometric Dementia Assessment (PANDA) ≤17 points in the initial screening. PANDA has been developed as a screening tool for cognitive and affective complications in PD [18]. In short, the PANDA assesses functions that are typically affected in PD on five subscales: word pair associate learning with immediate (task 1) and delayed recall (task 5), alternating verbal fluency task (task 2), visuospatial task (task 3) and working memory and attention task (task 4) – for a maximum score of 30 points. If test results are ≥18 points, this reflects a normal cognitive function level, 15–17 points suggest 'mild cognitive dysfunctions' and any score below 15 indicates 'severe cognitive impairment', indicative of dementia.

Exclusion Criteria

Patients will be excluded for the following reasons: diagnosis of or evidence for atypical Parkinson syndromes (e.g. Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), Cortical-Basal Degeneration (CBD); other causes of dementia based on clinical grounds (e.g. Alzheimer's disease, vascular dementia, frontotemporal dementia, Creutzfeldt-Jakob disease, Huntington's Disease); PD patients with severe cognitive impairment that impedes consent; medical and ethical reasons in relation to the morphological and neurobiological examinations; pregnant patients.

Clinical Assessment

Patient-based exposures to be assessed in the DEMPARK study fall into two major categories: cohort study and/or add-on modules (genetic, imaging or neuropsychological testing).

The patients will be followed up at 6-month intervals for 12 months followed by further annual follow-ups for a total period

of 3 years; the types of assessment as well as the time(s) of assessment are shown in table 1.

Patient-based exposures assessed at the time of study enrolment (=baseline) comprise three major sections. Section A documents patient demographics such as age, gender, marital status, and grade of education. Section B documents PD diagnosis, incorporating the Clinical Global Impression scale [19] of PD severity, and parts I (Mentation, Behaviour, and Mood), III (Motor Examination), and IV (Complications) of the Unified Parkinson's Disease Rating Scale [20], severity of illness (Hoehn and Yahr [14] stage), and comorbidities as well as medications taken over the 3 months before enrolment. Information about the duration of PD symptoms, the date of initial diagnosis, and the start of initial PD drug therapy as well as a family history with respect to PD will also be recorded. Section C consists of scales and ratings for the neuropsychological assessment of the patients. The selection of the cognitive outcome measures was done by a group of neuropsychologists and clinicians with experience in the evaluation of cognitive impairment in basal ganglia disorders and followed closely current recommendations [13, 17, 21]: the CERAD plus test battery [22] with nine subtests (learning of word lists, recall, and recognition, letter fluency and semantic verbal fluency, Boston Naming Test, construction, recall of drawn figures, Trail Making Test parts A and B) that assess verbal short- and long-term as well as nonverbal long-term memory, executive functions, language, visuoconstructive abilities, and orientation. The subtests digit span forward and reverse from the revised Wechsler Memory Scale [23] will be used to assess working memory. Executive functions will be further tested by Stroop colour word test [27] and the Modified Card Sorting Test [24], and visuospatial performance with subtests 7 and 9 (spatial rotation, spatial imagination) of the German intelligence test battery 'Leistungsprüfsystem' (LPS 50+) [25]. Attention will be assessed with the Brief Test of Attention [26] and the Stroop colour word test [27]. The short form of the geriatric depression scale [28], a 15-item self-evaluation questionnaire, will be used to assess depression. Apathy will be evaluated using the apathy evaluation scale, which treats it as a psychological dimension defined as 'a state characterized by simultaneous diminution in the overt behavioural, cognitive, and emotional concomitants of goal-directed behaviour' [29]. Health-related quality of life will be assessed using the EQ-5D [30], which has five sections relating to mobility, self-care, usual activities, pain/discomfort and anxiety/depression as well as a visual analogue scale for patients to indicate their own perception of their state of health. The Parkinson's Disease Questionnaire (PDQ-39) [31] will be used as a PD-specific measure of health-related quality of life, consisting of 39 questions, which cover eight aspects of quality of life (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort).

Table 1. Assessments in the DEMPARK study

Exposure/ instrument	Time(s) of assessment
Demographics, baseline diagnosis, medical history	
Questionnaire	BL
Medications	
Questionnaire	BL, FU1, FU2
Health status	
Patient examination	BL, FU2
Neurological status	
Patient examination	BL, FU2
Comorbidities	
Charlson Comorbidity Index	BL, FU2
Severity of illness	
Hoehn and Yahr Scale [14]	screening
Clinical assessment	
UPDRS (I, III, IV) [20]	BL, FU1, FU2
Clinical Global Impression [19]	BL, FU2
Neuropsychological test battery	
MMSE [15, 57]	screening, FU2
PANDA [18, 58]	screening, FU1, FU2
CERAD-Plus [22]	BL, FU2
Brief Test of Attention [26]	BL, FU2
Wechsler Memory Scale-R [23]	BL, FU2
Modified Card Sorting Test [24]	BL, FU2
Stroop Test [27]	BL, FU2
LPS 50+ [25]	BL, FU2
Depression	
Geriatric Depression Scale, short form [28]	BL, FU2
Apathy	
Apathy Evaluation Scale [29]	BL, FU2
Quality of life/health status	
EQ-5D [30]	BL, FU2
PDQ-39 [31]	BL, FU2
Blood sampling	
Blood sampling for serum and plasma	BL, FU1, FU2
Imaging module	
cMRI	BL, FU2
Genetic module	
Blood sampling for DNA	BL
Blood sampling for RNA	BL, FU1, FU2
Cognitive plasticity module	BL

BL = Baseline; FU1 = first follow-up 1 (6 months after enrolment); FU2 = second follow-up (12 months after enrolment).

Add-On Modules of the DEMPARK Study

Genetic Module

It is hypothesized that synucleinopathies including PD and PD-D are caused by the dysregulation of intracellular α-synuclein that leads, via still unknown mechanisms of protofibril formation and aggregation, to cell type-specific neuronal dysfunction and cell death. PD itself is heterogeneous in its aetiology, and there is evidence that different genetic risk factors for PD may be associated with a different risk for dementia in PD. For example, patients with autosomal dominantly inherited PD due to point mutations in *SNCA*, the gene encoding α-synuclein, have a high prevalence of dementia [32, 33], as have patients with triplications of the *SNCA* locus [34]. Likewise, patients with mutations in the gene for glucocerebrosidase, the gene causing Gaucher's disease and predisposing to PD [35], appear to have a higher prevalence of dementia, whereas patients with LRRK2-associated PD seem to have a somewhat lower risk for cognitive impairment, compared to PD in general [36]. It is likely that genetic factors also have a

profound influence on whether and when a patient with PD develops dementia. Knowledge of these factors will be important for identifying specific subgroups at risk when disease-modifying treatments become available. Therefore, this subproject aims to investigate candidate genes for their association with dementia in this prospectively characterized cohort and to perform a genome-wide association study with the endophenotype of dementia as well as with other endophenotypes characterized in this study, and thus to identify novel risk genes.

The aim of this project is therefore to identify the genetic determinants of the development of dementia in patients with PD. Blood samples for DNA isolation will be taken at baseline from patients who participate in the genetic add-on module, as well as blood samples for RNA isolation at baseline and both follow-ups (table 1).

Imaging Module

It is hypothesized that PD patients who develop dementia represent a subgroup within the PD spectrum that is characterized by the early occurrence of neuropsychological and morphological or functional brain abnormalities. Therefore, we will perform a longitudinal MRI study to identify imaging alterations and their correlations with neuropsychological features and other biomarkers. Finally, we aim to determine the predictive value of MRI changes for the development and progression of dementia in the PD cohort. The MRI investigations will be conducted at 3 T field strength and refer to different aspects of brain morphology and functioning: global and local brain atrophy and grey matter loss (T_1 MPRAGE, T_1 and T_2* relaxometry), total load and strategic localization of vascular white matter hyperintensities (PD/T_2 TSE sequences), disintegration of white matter fibres (DWI and DTI) and dysfunction of the so-called resting state network activity of the brain (fMRI). In a common and standardized MRI data acquisition approach, T_1 MPRAGE and PD/T_2 TSE sequences will be acquired in each of the study centres with direct access to a 3-tesla MRI scanner (Frankfurt/Main, Bonn, Dresden, Marburg). In addition, each imaging centre has designed additional local projects dealing with new MRI techniques or special research questions, which will be added to the standard multicentre MRI sequences.

All participants in the imaging module will receive two MRI scans, one at baseline (within 14 days after enrolment) and one after a 1-year follow-up period (table 1). After image transfer to one centre (Frankfurt/Main), data will be analysed by blind-ed investigators according to region of interest and voxel-based methods.

Cognitive Plasticity Module

'Cognitive plasticity' is a concept that is open to direct testing. It refers to the learning potential and the potential of cognitive performance after directed interventions [37]. Specific neuropsychological paradigms have been developed to operationalize cognitive plasticity. In contrast to common 'static' tests, which result in an absolute measure of cognitive performance (e.g. 'remembers a mean of 5 out of 10 words in a word list learning paradigm'), these 'dynamic tests' or 'testing the limits' instruments assess the dynamics of the individual learning curve during the task in which interventions for cognitive enhancement, for example in the form of feedback, reinforcement, or explanation of strategies, are integrated. By analysing pre- and post-test measures, the current performance can be differentiated from latent reserves for cognitive enhancement on an individual basis [38, 39]. It has been shown that learning potential (also called cognitive plasticity) is a tool that can be used to discriminate healthy, MCI and AD subjects [39]; the learning potential of people with cognitive impairment is diminished compared to cognitively healthy persons.

In the participants of the neuropsychological add-on module, cognitive plasticity will be assessed at baseline with German versions of published dynamic tests [39] for three cognitive domains that are typically impaired in PD patients, i.e. verbal memory, nonverbal memory, and executive functions [8, 13] (table 1). In all three dynamic tests applied, pre- and post-test trials will be administered, with an interval in between in which strategies to enhance cognitive performance will be explained to the participant with some practice trials. Post- minus pre-test differences will be used as indicators of cognitive plasticity. The aim of this study module is to examine whether cognitive plasticity might be a predictor for the development of dementia in PD patients.

Data Security and Data Quality

The interviews/patient examinations will be performed by trained scientists and study nurses at the study centres using printed forms for data collection. Filled survey sheets will be stored in a locker in the study centres. Data will be entered in the local centres via an Internet-based remote data entry system (Secutrial 3.3) [40, 42]. The data will be transferred via 128 bit SSL encryption. The data will be stored in a central ORACLE database on the server farm of the Central Information Office of the Competence Network on Parkinson's Disease, located in a specially secured hosting centre for sensitive data in Fürth, Germany. Access to the internal database and web server is controlled by two consecutive firewalls and an intrusion detection system. The duties of the hosting system such as daily checks of the access logs, security updates, daily backups and storing backup families in a bank deposit have been determined in a service level agreement contract. An alphanumerical pseudonym (a random combination of three letters and three digits) will be automatically created when the identification data of a patient are entered, and a printed copy with a pseudonym and the identification data for each patient will be archived in the individual centres. The identification data will neither be electronically transferred nor stored. The members of the DEMPARK/LANDSCAPE consortium will be given access to the electronic data entry system according to a detailed concept of roles and rights upon application. An audit trail will ensure an automatic protocol for all data entries, changes and deletions. Quality assurance will be performed according to the current guidelines of the Telematic Platform for Medical Research (Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V.; for details see http://www.tmf-ev.de/Home.aspx).

Ethical Approval

The study will be conducted in compliance with the Helsinki Declaration [43]. The study protocol was approved by the Ethics Committee of Philipps University Marburg (approval No. 178/07) in March 2009 and subsequently by the local ethics committees of the participating centres.

Informed Consent

Patients can only be included in the study or add-on modules after giving their written informed consent. Separate consent is required for each module (cohort study, genetic module, cognitive plasticity module, and imaging module).

Table 2. Baseline characteristics of patients enrolled in the study (as of April 2011)

Total patient number	604
PD	56.3%
PD-MCI	30.6%
PD-D	13.1%
Male	68.2%
Female	31.8%
Age at baseline, years	68.6 ± 7.9 (range: 44–83)
≤65 years	33%
66–75 years	53%
≥76 years	14%
Disease duration, years	6.8 ± 5.4 (range: 1–38)
Hoehn and Yahr stage	
I	16%
II	48%
III	27%
IV	8%
V	1%
Family status	
Married/living with partner	83.3%
Divorced	4.6%
Single	3.9%
Widowed	6.9%

Statistical Analysis

This will include prevalence and incidence estimates, crude and multiple logistic regression of outcomes on predictors, nonparametric regression analysis for visualizing patterns of outcomes on predictors, analysis of time-dependent associations of outcomes on predictors by Latent Growth Mixture models, all statistical inference account for design aspects (clustering within settings, stratification criteria).

The statistical analyses will be conducted stepwise and in accordance with the strategy of the program, as follows:

(1) Descriptive statistics (for example age-related weighted prevalence and incidence accounting for strata and clustering within settings) in the first stage.

(2) Nonparametric regression models (local polynomial regression for dimensional variables, generalized additive models for categorical variables) for analysing and visualizing the functional form of associations of outcomes on predictors.

(3) Cross-sectional associations using crude and multiple logistic regressions (odds ratio and 95% confidence intervals for categorical) and univariate and multivariate regressions for dimensional variables.

(4) (Sub-)group comparison (e.g. by age group, PD severity) will be conducted – depending on the type of data – with either t tests (two-way comparisons of continuous variables) or F tests (for categorical or polythetic variables).

(5) Upon availability of time-related information (either retrospective or prospective in follow-up) we plan to use more sophisticated structural equation models to explore the effect of predictor variables on the course of cognitive impairment by using latent growth mixture models, which are favoured against the more traditional ANOVA and MANOVA approach.

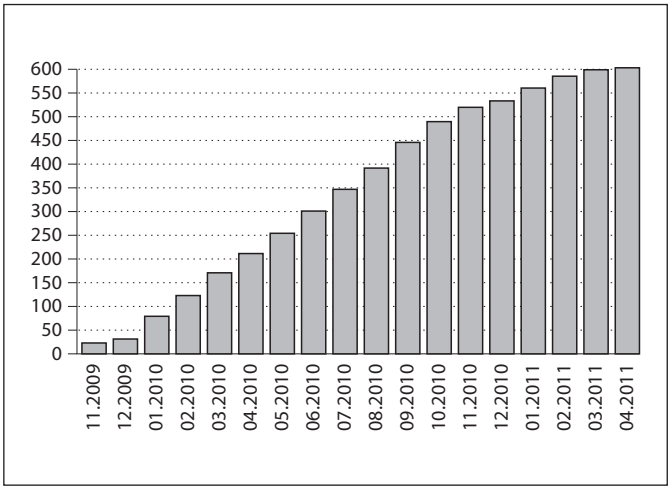

Fig. 1. Recruitment of PD patients for the DEMPARK cohort.

All final statistical modelling and analyses will be conducted controlling for confounders and the effect of clustering within the settings. Descriptive statistics and parametric regression models will be conducted by STATA (Stata Corp., 2006), and latent growth mixture models by applying the STATA procedure GLAMM [44] and MPLUS [45]. Non-parametric estimates of patterns of associations between outcomes and predictors will be analysed by user-written algorithms in STATA and MATLAB (Mathworks Inc., 2006).

Results

A detailed list of the applied instruments and assessments in this study is compiled in table 1. As of March 2011, the study enrolled 604 patients with PD, PD-MCI and PD-D (table 2). The enrolment was efficient and quick and nearly all centres were able to recruit the predetermined number of patients (fig. 1). The mean age of the cohort was 68.6 years with 31.8% of the patients being female. Mean disease duration was 6.8 years (range: 1–38). The Hoehn and Yahr stage with the early stages was overrepresented with 16% of the patients being in stage I, 48% in stage II, 27% in stage III, 8 and 1% in stages IV and V, respectively. The majority of patients had no memory impairments (PD: 56.3%) followed by 30.6% of the patients having PD-MCI and 13.1% of the patients having PD-D. The number of patients recruited for the different modules were: module Genetics: 79%; module Imaging: 19%; module Cognitive Plasticity: 24%. The recruitment of patients with DLB will be started in the second quarter of 2011.

Discussion

Recent epidemiological studies of PD patients suggest that dementia is much more common in PD than previously thought, ranging from estimates of a 10-year prevalence of approximately 40% [5] up to an 8-year prevalence of almost 80% [10]. Cognitive dysfunction may be present in more than 20% of newly diagnosed PD patients [46]. The available epidemiological data identified only a weak correlation of dementia with the akinetic-rigid syndrome; brain morphological changes predicting the development of dementia have not yet been identified, despite scientific efforts especially in the field of metabolic brain networks [47–49].

Several cohort studies are underway, which, however, differ from the study outlined in this communication. For example, they have a cross-sectional design, did not include a detailed evaluation of cognitive impairment, focus on a certain cognitive domain or are based on a small sample [6, 50–52]. The Longitudinal and Biomarker Study in PD (LABS-PD) is an observational study designed to prospectively measure the evolution of motor and non-motor features of PD and samples promising biomarkers from early to late-stage illness [53]. LABS-PD is organized on the premise that cohorts from completed clinical trials can be re-recruited for long-term follow-up. LABS-PD will contain multiple cohorts and will not be enriched with the question of PD-D and PD-MCI.

The Parkinson's Progression Markers Initiative (PPMI) is an observational research study to identify biomarkers of PD progression (http://www.ppmi-info.org/). This study will use a combination of imaging techniques, collection of blood, urine, and spinal fluid, and clinical tests. PPMI requires the participation of 400 newly diagnosed PD patients not currently taking standard PD medications and 200 individuals who do not have PD. Participants must be at least 30 years of age. They will be enrolled at about 18 PD centres – 14 across the United States and 4 in Europe – over approximately 2 years. The goal of the PPMI study is to identify one or more biomarkers of PD. The study will not focus on cognitive impairment in those patients, thus not including a large battery of cognitive assessments and is not powered for the detection of longitudinal evaluation of cognitive impairment. Another study aims to investigate the progression of disability in PD over a 2-year period with 6-month follow-up periods including 200 PD patients [51]. No evaluation of cognitive impairment is part of this study.

In contrast, the DEMPARK consortium aims to establish a large cohort of patients with PD, PD with MCI, and PD-D ($n \geq 700$ patients) in Germany. The patients in the cohort will be consecutively recruited in eight study centres (neurological clinics), subjected to serial standardized testing (at baseline and two follow-up examinations after 6 and 12 months) and will thus provide a well-characterized cohort of PD, PD-MCI, and PD-D patients. Three add-on modules (to search for genetic determinants to develop dementia, serial structural MRI, and neuropsychological testing of 'cognitive plasticity') will provide further information about the course of cognitive decline in PD within the observation period. The collection of a large number of blood samples (serum, plasma, blood DNA, and blood RNA) of well-characterized patients will be a unique source for the search for risk factors, predictors and early differentiating markers for the early detection of developing cognitive dysfunction and dementia in PD as well as for defining the role of Alzheimer's disease and Lewy body pathology in dementia in PD.

Despite a careful and detailed study design, the study may have some limitations:

(1) A community-based study design would be theoretically preferable. However, it is neither logistically nor financially feasible to conduct a multi-stage community survey to recruit subjects for this relatively rare condition. Instead, we opted for a clinical prospective longitudinal cohort study.

(2) A selection bias towards less disabled patients may occur due to the ambulatory setting of the study, i.e. patients must be able to visit the study centre; institutionalized patients are not included into the study or are excluded upon institutionalization.

(3) A selection bias towards patients in the proximity of the specialized centre participating in the study. Even with eight participating centres, the cohort will probably not be fully representative of all German PD patients.

(4) New criteria for PD-MCI and DLB are currently being developed by the Movement Disorder Task Force [41]. This may change the classification of the patients and may therefore change the outcome of this study.

(5) The collection of data on medication, ancillary therapies, etc. of PD is based in part on a patient-reported questionnaire and service utilization data we used in this study are self-reported. Such study designs naturally suffer from recall bias. Recall bias will particularly occur when infrequent resource use has to be remembered. Additionally, with increased disease severity of the cognitive decline in PD patients, the ability to recall is reduced by the progression of the disease. Recall bias may lead to un-

derestimates of total service use. This is especially important in patients with severe cognitive decline.

In conclusion, this large study will help to discern distinct patterns in the development and progress of dementia in patients with PD and identify variables associated with these patterns. This is especially important as dementia is the main reason for nursing home placement [54] and increased caregiver burden [55]. Early intervention in the identified risk factors may help to delay nursing home placement and will increase the quality of life of the patients and their caregivers but also reduce their burden to society [56]. The more refined definition of cognitive domains affected by PD may help to develop better screening and diagnostic instruments and better therapeutic interventions. Finally, we expect to identify new biomarkers and/or be able to evaluate and validate those in our large cohort for the different diagnoses. Researchers in other countries are welcome to join this effort. For maximal usefulness to patients and to the scientific community, the consortium has agreed to make available the complete dataset of this study for research purposes.

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Disclosure Statement

The authors declare that they have no competing interests in respect to the content of this article.

References

1 de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meché FG, Hofman A: Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology 1995; 45:2143–2146.

2 Twelves D, Perkins KS, Counsell C: Systematic review of incidence studies of Parkinson's disease. Mov Disord 2003;18:19–31.

3 Aarsland D, Zaccai J, Brayne C: A systematic review of prevalence studies of dementia in Parkinson's disease. Mov Disord 2005;20: 1255–1263.

4 Janvin CC, Aarsland D, Larsen JP: Cognitive predictors of dementia in Parkinson's disease: a community-based, 4-year longitudinal study. J Geriatr Psychiatry Neurol 2005;18: 149–154.

5 Riedel O, Klotsche J, Spottke A, Deuschl G, Forstl H, Henn F, Heuser I, Oertel W, Reichmann H, Riederer P, Trenkwalder C, Dodel R, Wittchen HU: Cognitive impairment in 873 patients with idiopathic Parkinson's disease: results from the German study on epidemiology of Parkinson's disease with dementia (GEPAD). J Neurol 2008;255:255–264.

6 Riedel O, Klotsche J, Spottke A, Deuschl G, Forstl H, Henn F, Heuser I, Oertel W, Reichmann H, Riederer P, Trenkwalder C, Dodel R, Wittchen HU: Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease. J Neurol 2010;257:1073–1082.

7 Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D: Dementia and survival in Parkinson disease: a 12-year population study. Neurology 2008;70:1017–1022.

8 Caviness JN, Driver-Dunckley E, Connor DJ, Sabbagh MN, Hentz JG, Noble B, Evidente VG, Shill HA, Adler CH: Defining mild cognitive impairment in Parkinson's disease. Mov Disord 2007;22:1272–1277.

9 McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872.

10 Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P: Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003; 60:387–392.

11 Hughes AJ, Daniel SE, Kilford L, Lees AJ: Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.

12 Petersen RC: Challenges of epidemiological studies of mild cognitive impairment. Alzheimer Dis Assoc Disord 2004;18:1–2.

13 Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, Goldman J, Goetz C, Korczyn A, Lees A, Levy R, Litvan I, McKeith I, Olanow W, Poewe W, Quinn N, Sampaio C, Tolosa E, Dubois B: Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22: 1689–1707;quiz 1837.

14 Hoehn MM, Yahr MD: Parkinsonism: onset, progression and mortality. Neurology 1967; 17:427–442.

15 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

16 Petersen RC: Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–194.

17 Dubois B, Burn D, Goetz C, Aarsland D, Brown RG, Broe GA, Dickson D, Duyckaerts C, Cummings J, Gauthier S, Korczyn A, Lees A, Levy R, Litvan I, Mizuno Y, McKeith IG, Olanow CW, Poewe W, Sampaio C, Tolosa E, Emre M: Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. Mov Disord 2007;22:2314–2324.

18 Kalbe E, Riedel O, Kohn N, Dodel R, Calabrese P: Sensitivität und Spezifität des 'Parkinson Neuropsychometric Dementia Assessment' (PANDA): Ergebnisse der GEPAD-Studie. Akt Neurol 2007;34:140–146.

19 Guy W: ECDEU Assessment Manual for Psychopharmacology – Revised (DHEW Publ No ADM 76–338). Rockville, MD, U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976, pp 218–222.

20 Fahn S: Unified Parkinson's disease rating scale; in Fahn S, Marsden CD, Goldstein M, Calne DB (eds): Recent Developments in Parkinson's Disease Vol. 2. Florham Park, Macmillan Healthcare Information, 1987, pp 153–163.
21 Goetz CG, Emre M, Dubois B: Parkinson's disease dementia: definitions, guidelines, and research perspectives in diagnosis. Ann Neurol 2008;64(suppl 2):S81–S92.
22 Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, Heyman A: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology 1994;44:609–614.
23 Härting CMH, Neufeld H, Calabrese P, Deisinger K, Kessler J (eds): WMS-R, Wechsler Memory Scale, revised version. 2000.
24 Nelson HE: A modified card sorting test sensitive to frontal lobe defects. Cortex 1976;12:313–324.
25 Sturm W, Willmes K, Horn W: Leistungsprüfsystem für 50–90jährige (LPS 50+). Göttingen, Hogrefe, 1993.
26 Schretlen D: Brief Test of Attention (BTA). Florida, Psychological Assessment Resources, 1997.
27 Bäumler G: Farb-Wort-Interferenztest (FWIT) nach J.R. Stroop. Göttingen, Hogrefe, 1985.
28 Burke WJ, Roccaforte WH, Wengel SP: The short form of the geriatric depression scale: a comparison with the 30-item form. J Geriatr Psychiatry Neurol 1991;4:173–178.
29 Marin RS, Biedrzycki RC, Firinciogullari S: Reliability and validity of the apathy evaluation scale. Psychiatry Res 1991;38:143–162.
30 Brooks R: Euroqol: the current state of play. Health Policy (Amsterdam) 1996;37:53–72.
31 Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N: The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 1997;26:353–357.
32 Golbe LI, Di Iorio G, Bonavita V, Miller DC, Duvoisin RC: A large kindred with autosomal dominant Parkinson's disease. Ann Neurol 1990;27:276–282.
33 Zarranz JJ, Alegre J, Gomez-Esteban JC, Lezcano E, Ros R, Ampuero I, Vidal L, Hoenicka J, Rodriguez O, Atares B, Llorens V, Gomez Tortosa E, del Ser T, Munoz DG, de Yebenes JG: The new mutation, e46k, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol 2004;55:164–173.
34 Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K: Alpha-synuclein locus triplication causes Parkinson's disease. Science 2003;302:841.
35 Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, Bar-Shira A, Berg D, Bras J, Brice A, Chen CM, Clark LN, Condroyer C, De Marco EV, Durr A, Eblan MJ, Fahn S, Farrer MJ, Fung HC, Gan-Or Z, Gasser T, Gershoni-Baruch R, Giladi N, Griffith A, Gurevich T, Januario C, Kropp P, Lang AE, Lee-Chen GJ, Lesage S, Marder K, Mata IF, Mirelman A, Mitsui J, Mizuta I, Nicoletti G, Oliveira C, Ottman R, Orr-Urtreger A, Pereira LV, Quattrone A, Rogaeva E, Rolfs A, Rosenbaum H, Rozenberg R, Samii A, Samaddar T, Schulte C, Sharma M, Singleton A, Spitz M, Tan EK, Tayebi N, Toda T, Troiano AR, Tsuji S, Wittstock M, Wolfsberg TG, Wu YR, Zabetian CP, Zhao Y, Ziegler SG: Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. New Engl J Med 2009;361:1651–1661.
36 Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, Brice A, Aasly J, Zabetian CP, Goldwurm S, Ferreira JJ, Tolosa E, Kay DM, Klein C, Williams DR, Marras C, Lang AE, Wszolek ZK, Berciano J, Schapira AH, Lynch T, Bhatia KP, Gasser T, Lees AJ, Wood NW: Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol 2008;7:583–590.
37 Baltes PB: The aging mind: potential and limits. Gerontologist 1993;33:580–594.
38 Baltes MM, Kuhl KP, Gutzmann H, Sowarka D: Potential of cognitive plasticity as a diagnostic instrument: a cross-validation and extension. Psychol Aging 1995;10:167–172.
39 Fernández-Ballesteros R, Zamarrón M, Tàrraga L: Learning potential: a new method for assessing cognitive impairment. Int Psychogeriatr 2005;17:119–128.
40 Eggert K, Wüllner U, Antony G, Gasser T, Janetzky B, Klein C, Schöls L, Oertel W: Data protection in biomaterial banks for Parkinson's disease research: the model of GEPARD (Gene Bank Parkinson's Disease Germany). Mov Disord 2007;22:611–618.
41 Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, Rodriguez-Oroz MC, Troster AI, Weintraub D: Mds task force on mild cognitive impairment in parkinson's disease: critical review of pd-mci. Mov Disord 2011, DOI: 10.1002/mds.23823.
42 Stausberg J, Nonnemacher M, Weiland D, Antony G, Neuhäuser M: Management of data quality – development of a computer-mediated guideline. Stud Health Technol Informatics 2006;124:477–482.
43 World Medical Association declaration of Helsinki: Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925–926.
44 Rabe-Hesketh S, Skrondal A: Parameterization of multivariate random effects models for categorical data. Biometrics 2001;57:1256–1264.
45 Lubke GH, Muthen B: Investigating population heterogeneity with factor mixture models. Psychol Methods 2005;10:21–39.
46 Muslimovic D, Post B, Speelman JD, Schmand B: Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 2005;65:1239–1245.
47 Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D: Metabolic brain networks associated with cognitive function in Parkinson's disease. Neuroimage 2007;34:714–723.
48 Eidelberg D: Metabolic brain networks in neurodegenerative disorders: a functional imaging approach. Trends Neurosci 2009;32:548–557.
49 Hirano S, Eckert T, Flanagan T, Eidelberg D: Metabolic networks for assessment of therapy and diagnosis in Parkinson's disease. Mov Disord 2009;24(suppl 2):S725–S731.
50 Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, Burn D, Barone P, Pagonabarraga J, Allcock L, Santangelo G, Foltynie T, Janvin C, Larsen JP, Barker RA, Emre M: Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. Neurology 2010;75:1062–1069.
51 Dibble LE, Cavanaugh JT, Earhart GM, Ellis TD, Ford MP, Foreman KB: Charting the progression of disability in Parkinson disease: study protocol for a prospective longitudinal cohort study. BMC Neurol 2010;10:110.
52 Lee SJ, Kim JS, Yoo JY, Song IU, Kim BS, Jung SL, Yang DW, Kim YI, Jeong DS, Lee KS: Influence of white matter hyperintensities on the cognition of patients with Parkinson disease. Alzheimer Dis Assoc Disord 2010;24:227–233.
53 Ravina B, Tanner C, Dieuliis D, Eberly S, Flagg E, Galpern WR, Fahn S, Goetz CG, Grate S, Kurlan R, Lang AE, Marek K, Kieburtz K, Oakes D, Elliott R, Shoulson I: A longitudinal program for biomarker development in Parkinson's disease: a feasibility study. Mov Disord 2009;24:2081–2090.
54 Aarsland D, Larsen JP, Tandberg E, Laake K: Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc 2000;48:938–942.
55 Thommessen B, Aarsland D, Braekhus A, Oksengaard AR, Engedal K, Laake K: The psychosocial burden on spouses of the elderly with stroke, dementia and Parkinson's disease. Int J Geriatr Psychiatry 2002;17:78–84.
56 Spottke AE, Reuter M, Machat O, Bornschein B, von Campenhausen S, Berger K, Koehne-Volland R, Rieke J, Simonow A, Brandstaedter D, Siebert U, Oertel WH, Ulm G, Dodel R: Cost of illness and its predictors for Parkinson's disease in Germany. Pharmacoeconomics 2005;23:817–836.
57 Kessler J, Markowitsch HJ: Der Mini Mental Status Test. Weinheim, Beltz, 1990.
58 Kalbe E, Calabrese P, Kohn N, Hilker R, Riedel O, Wittchen HU, Dodel R, Otto J, Ebersbach G, Kessler J: Screening for cognitive deficits in Parkinson's disease with the Parkinson Neuropsychometric Dementia Assessment (PANDA) instrument. Parkinsonism Relat Disord 2008;14:93–101.