Progression in cognition and associated activities of daily living impairment in Parkinson's disease (PRICOG-PD)

„Verschlechterung der geistigen Leistungsfähigkeit und damit einhergehende Alltagseinschränkungen bei Morbus Parkinson (PRICOG-PD)“

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2. List of abbreviations

ABC-PD	Amyloid-Beta in Cerebrospinal Fluid as a Risk Factor for Cognitive Dysfunction in Parkinson's Disease
AIC	Akaikes information criterion
AD	Alzheimer's Disease
ADDI	Alzheimer's Disease Data Initiative
ADL	Activities of Daily Living
AUC	Area Under the Curve
Bayer ADL	Bayer Activities of Daily Living Scale
CERAD-Plus	Consortium to Establish a Registry for Alzheimer's Disease Plus
CI	Confidence Interval
CSF	Cerebrospinal Fluid
FAQ	Pfeffer Functional Activities Questionnaire
GLMM	General linear mixed model
HR	Hazard Ratios
IADL	Instrumental Activities of Daily Living
IQ-CODE	Informant Questionnaire on Cognitive Decline in the Elderly
LPS 50+	Leistungsprüfsystem für 50- bis 90-Jährige
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
PD	Parkinson's Disease
PD-ABB-Scale	PD Angehörigen Belastungs- und Befindlichkeitsskala
PDD	Parkinson's Disease Dementia
PD-CN	Parkinson's Disease with Normal Cognition
PD-MCI	Parkinson's Disease with Mild Cognitive Impairment
RBD	REM (Rapid Eye Movement) Behavior Disorder
UKT	Universitätsklinikum Tübingen
UPDRS-III	Unified Parkinson's Disease Rating Scale Part III (Motor Part)
ROC	Receiver Operating Characteristic
SWE	Skala zur Allgemeinen Selbstwirksamkeitserwartung
WIE	Wechsler Intelligenztest für Erwachsene
ZCBI	Zarit Caregiver Burden Inventory

3. Study summary

3.1. Background

Presence and severity of non-motor symptoms modulates the rate of Parkinson's Disease (PD) progression with a high impact on patients' quality of life [1-3]. One major clinical milestone in the course of the disease is the conversion to Parkinson's disease dementia (PDD), dramatically increasing the risk for nursing home placement and mortality [4]. Patients with PD have an almost 6-fold increased risk of developing cognitive impairment and PDD compared to age-matched controls [5]. Identification of a high-risk group for converting to PDD (i.e., those PD patients who are in the prodromal dementia phase) is essential to develop and implement early and effective treatments for preventing or delaying dementia. Mild cognitive impairment (PD-MCI) is one of the greatest risk factors for future PDD [6]. A recent meta-analysis found that, on average, 31% of patients with PD-MCI converted to PDD within seven years; however, 24% of patients with PD-MCI reverted back to normal cognitive function [7]. Consequently, the false positive rate for predicting PDD among patients with PD-MCI is high, and better predictive markers to define patients at high risk for PDD development are urgently needed. Therefore, a combination of different markers, including clinical, genetic, and other biomarker data, are proposed to increase ability to predict cognitive worsening and dementia [8-11].

Significant impairments in activities of daily living (ADL) function, in addition to impaired cognition, are the core criterion for diagnosing Parkinson's Disease dementia [12]. Recent studies have shown that even patients with mild cognitive impairment display first signs of ADL dysfunction [13-15], possibly indicating a group at risk for dementia [16]. As the diagnosis of ADL deficits requires these to be solely caused by cognitive deficits, an important step for accurate diagnoses is the measurement of ADL deficits in PD. To confirm the diagnosis of PDD, ADL disabilities should be primarily caused by cognitive, not motor, dysfunction [17, 18]. As PD is primarily a movement disorder, the distinction between motor and non-motor contributions to ADL in PD is an obvious challenge [13]. ADL can be divided into basic (e.g., self-maintenance skills) and instrumental functions (e.g., complex skills). Of these, instrumental ADL (IADL) function is impaired in the earlier stages whereas basic ADL can be preserved for a long time [19]. Based on data of the first follow-up in our non-demented sample (ethic protocol: Baseline 686/2013BO1; Follow-up 284/2018BO1, see below *3.2 Preliminary data*), we were able to show that the presence of both mild cognitive IADL impairment and PD-MCI dramatically increases the risk for PDD: nearly 50% with baseline profile of both markers converted to dementia within three years. In general, our results argue for the importance of differentiating between cognitive and motor aspects of ADL function in PD. Patients with PD-MCI and cognitive IADL impairment may be a valuable target group for clinical trials aiming to slow down development of dementia. However, this assumption needs to be confirmed by future longitudinal data.

In PD, it is unclear whether self- or informant-reports are more useful for judging ADL impairments in the clinical routine, as the loss of functional independence is an important outcome of disease progression. Although IADL is commonly assessed by an informant who can reliably give information regarding patients' level of functioning, cognitive IADL data was collected from both patients and informants in our study. While discrepancies between self- and informant-ratings are greatest in PDD patients [20], between-group comparisons on IADL item, total, and subscore levels did not show differences between raters. However, it is known

that self-reports on the impact of cognitive changes on IADL function are more sensitive in early stages of cognitive decline [21]. Recently, analysis in this cohort showed that agreement between patient- and informant-ratings of IADL function using Pfeffer Functional Activities Questionnaire (FAQ) items were moderate, with only few items reaching substantial agreement [22]. Ratings of patients and informants were associated with patients' cognitive status, but also other characteristics. Therefore, it is currently unclear whether ratings of patients and/or caregiver have a higher prognostic ability to predict decline in cognition and everyday function. We therefore propose a second follow-up of an already existing large PD cohort to longitudinally investigate the association between IADL function rated by either patients themselves or caregivers, cognition, and other clinical and biomarker measures.

3.2. Preliminary data

Methods. The study was conducted as the first follow-up (Title: Cognitive driven ADL impairment as a predictor for PDD; ethic protocol: 284/2018BO1) of "Amyloid-Beta in Cerebrospinal Fluid as a Risk Factor for Cognitive Dysfunction in Parkinson's Disease" (ABC-PD) study (ethic protocol: 686/2013BO1).

The FAQ quotient (cut-off >1), indicating more cognitive than motor-driven IADL impairment, defined cognitive IADL impairment status at baseline ($FAQ_{Q>1}$). The FAQ is a ten item IADL assessment scored on a 4-point Likert scale ranging from normal (score=0) to dependent (score=3) ADL function (max. points 30) [23]. The FAQ quotient was developed by differentiating cognitive and motor aspects of the individual items. Ten linear regressions were conducted defining each FAQ item as the dependent variable, and the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III, motor assessment) as well as the Montreal Cognitive Assessment (MoCA) total score as independent variables, with age, sex, and disease duration entered as covariates [24]. Hazards ratios (HR) were used to compare the impact of different baseline classifications on dementia conversion.

Results. Of 268 patients with PD assessed at baseline, 108 (40.3%) had PD-MCI. After a period of 3.8±0.8 years, 182 (61.2%) patients were re-assessed and 164 analysed (17 excluded due to deep brain stimulation, one patients without classification of cognitive group). At follow-up, 93 (56.7%) patients fulfilled criteria for normal cognitive function (PD-CN), 54 for PD-MCI (32.9%), and 17 (10.4%) had developed dementia. Predictive ratio of baseline cognitive IADL impairment (n=37; 21.3%) for dementia conversion was descriptively higher than for PD-MCI, but highest in patients with both markers [HR=12.01, 95%-confidence interval (CI): 4.47-32.23)]. Nearly half of patients (n=10, 47.6%) with baseline classification of cognitive IADL impairment and PD-MCI converted to dementia. Baseline status of cognitive IADL impairment was associated with higher non-motor burden, worse cognitive performance, and more severe IADL progression over the study period. In a post-hoc Receiver Operating Characteristic (ROC) analysis, the FAQ quotient (cut-off >1.008) was confirmed to best predict conversion to dementia compared to other IADL scores. Only two patients with baseline status of cognitive IADL impairment in our sample scored below the newly identified FAQ quotient cut-off of 1.008 resulting in a total of 35 (21.3%) patients with values above this defined cut-off. The FAQ motor score [AUC(area under the cure)=0.60, 95%-CI: 0.52-0.67, p=0.13], reflecting predominantly motor aspects on IADL function, was not associated with PDD conversion.

4. Objectives of the study

Based on previous analyses in the sample we suggest that monitoring of both cognition and cognitive ADL impairment reflect neurodegeneration associated to PDD development. This study evaluates markers predicting cognitive and ADL long-term outcome in our sample. Additionally, we will investigate whether ratings of patients or informants best predicted decline of cognitive impairment and/or everyday function. Clinical data along with other clinical marker and biomarker status will be investigated.

4.1. Hypothesis and research questions

Based on previous reports and preliminary results, we hypothesize that PD-MCI patients with a more pronounced cognitive-driven ADL impairment ($FAQ_{Q>1.008}$) are at higher risk for worsening in cognition and conversion to PDD than PD-MCI patients with ADL impairment primarily related to motor function ($FAQ_{Q\leq1.008}$).

1. *Prediction of cognitive progression along with progression in IADL function over time*

Aim 1.1: Prediction of conversion rates to PD-MCI (among PD-CN) and PDD (among non-demented patients) according to baseline IADL, cognitive, genetic, and biomarker profiles in blood and CSF

Aim 1.2: Prediction of progression in cognitive scales according to cognitive, IADL, genetic, and biomarker profiles in blood and CSF

Aim 1.3: Prediction of worsening in available ADL scales (patient-/informant-ratings) according to cognitive, IADL, genetic, and biomarker profiles in blood and CSF

2. *Defining the interaction of progression in markers over time*

Aim 2.1: Evaluation of progression in varying cognitive tests assessed along with change in ADL function, non-motor markers and, if available, biomarker status

Aim 2.2: Evaluation of progression in IADL function (patient-/informant-ratings) along with change in cognition, non-motor markers and, if available, biomarker status

5. Study duration

Total duration of the study is 2 years.

6. Study population

6.1. Study population

Between March 30th, 2014 and December 31th, 2017, we recruited a large cohort of 268 PD patients within the frame of the" Amyloid-Beta in cerebrospinal fluid as a risk factor for cognitive dysfunction in Parkinson's Disease" (ABC-PD, ethic protocol 686/2013B01) study. Follow-up visits were conducted between July 2018 and September 2020, all patients of the ABC-PD study were contacted for re-examination.

We propose a second follow-up of the already existing longitudinal cohort described above with a longitudinal assessment including neuropsychological in-depth endophenotyping and CSF biomarker analyses. In total 182 patients will be invited to participate in the second

follow-up assessment. If patients are not able to attend a clinical visit in-house, possibility of assessments at patients' homes shall be offered. Moreover, if patients are not able to give consent for study participation (confirmed by an independent physician), the legal guardian will be contacted to give study consent for participation. Legal guardians are defined as persons with legal care directive or lasting power of attorney. For drop-outs different reasons for drop-out will be coded (e.g. deceases, disabled, disinterested/refuse study participation, unable to reach/unknown address).

Diagnosis of cognitive impairment:
Patients were classified as PD-MCI according to Level-II Movement Disorder Society recommendations if cognitive impairment was present but did not significantly interfere with everyday function [25]. PDD was defined according to Movement Disorder Society Task Force criteria [17] if cognitive impairment was present and severe enough to impair ADL function unrelated to motor or autonomic symptoms and at least one behavioral symptom was present to support diagnosis. Cognitive impairment was defined according to Level-I (impairment of global cognition) for patients with minimal assessments, or Level-II (performance below 1.5 standard deviation of the population mean reported in the test manuals on at least two tests) for patients assessed using a full cognitive battery. Patients not meeting either of the diagnostic criteria were classified as PD-CN. Cognitive status at follow-up was defined as the primary study outcome.

6.2. In- and exclusion criteria for follow-up assessment

The investigator will ensure that all patients considered for the study meet the inclusion and exclusion criteria described in Sections 6.2.1 and 6.2.2.

6.2.1. Inclusion criteria

- 50–95 years of age.
- Diagnosis of PD according to the United Kingdom Brain Bank criteria.
- Ability to communicate well with the investigator, to understand and comply with the requirements of the study.
- Provide written informed consent to participate in the study and understand the right to withdraw consent at any time without prejudice to future medical care.

6.2.2. Exclusion criteria

- Any disability that may prevent the subject from completing the informed consent form or other study requirements.
- Other neurodegenerative disease which renders the subject unable to communicate well with the investigator or to understand and comply with the requirements of the study.
- Participation in any clinical investigation of a new investigational compound or therapy within 4 weeks prior to baseline visit, and any other limitation of participation based on local regulations.
- Alcohol, medication, or drug dependency or abuse (except for nicotine).
- History of brain disease other than PD, e.g., head trauma, stroke, encephalitis.

6.3. Recruitment

Participants of the already recruited ABC-PD cross-sectional cohort (ethic protocol: 284/2018BO1) will be asked to participate in the follow-up assessment. Patients who did not agree to participate in a longitudinal study or who have asked not to be contacted after the first cross-sectional assessment will not be contacted again. A drop-out rate of 20% is expected for follow-up retention. Therefore, investigation of 145 patients will be primarily conducted between January 2023 and June 2024. During the executive project phase, around 7 to 9 patients will be assessed per month. Patients will be contacted either via phone or in written form. Reasons for drop-outs will be registered for data analysis.

7. Statistics and Sample size estimation

All following hypotheses will be tested a priori; no post-hoc corrections of p-values will be conducted.

Characterization of study groups: Between-group comparisons at clinical visits will be conducted using Mann-Whitney-U or Welch test (two groups) or Jonckheere-Terpstra test (>2 groups) for numerical variables and X^2 test or Exact Fisher Test for categorical variables. Post-hoc comparisons for IADL and cognitive variables between groups will be corrected for between-group covariates via linear regression models with group status as dummy coded variable. When follow-up cognitive groups are compared (PD-CN vs. PD-MCI vs. PDD), analyses with covariates will be run twice with reference category set as either PD-CN or PD-MCI.

Prediction of cognitive progression along with progression in ADL function over time:
In patients who completed all visits, the predictive values of baseline/follow-up IADL (patients' self-impression vs. informant-rating), stratification (cognitive IADL impairment vs. motor IADL impairment), cognitive status (PD-CN vs. PD-MCI), and both markers combined (PD-MCI + cognitive IADL impairment) will be calculated using multivariate Cox Proportional-Hazard models. Akaikes information criterion (AIC) and concordance index (C-index) [26] will be used as model fit indices. Logistic regression with follow-up cognitive diagnosis (PD-CN vs. PD-MCI or non-demented vs. PDD) as dependent variable will evaluate whether baseline status of cognitive IADL impairment (FAQ quotient >1.008) predicted risk of PDD conversion independent of other clinical variables (e.g., cognitive status), biomarker profile, and covariates. As a post-hoc exploratory analysis to identify which subscore best predicted PDD conversion, ROC curves will be calculated for all FAQ scores (self- and caregiver-assessment). The optimal score/cut-off will be chosen according to the highest Youden Index.
Linear regression will be applied to investigate predictors of neuropsychological scores and IADL measures at follow-up(s).

2. Defining the interaction of progression in markers over time

Generalized linear mixed effects models (GLMMs) will evaluate progression in neuropsychological tests and IADL scores over time. Correlation analyses are planned to investigate association in change of scores over time of different measures.

Sample size calculation:
Between the baseline and first follow-up 17 (10.4%) patients developed PDD within a mean follow-up interval of 3.78 ± 0.84 years (range: 1.67-5.79 years), with higher rates of converters in patients with baseline status of cognitive ADL impairment (29.7%). Estimated follow-up interval between first and second follow-up are expected to be very similar, and a higher rate of patients with cognitive ADL impairment were identified. Moreover, the risk for PDD development is increased in later disease stages [27, 28]. Therefore, a maximum of additional 15 converters are expected.
Monte Carlo simulation-based calculations of observed power (R package simr, version 1.0.6), revealed a minimum sample size of n = 64 (Power = 94.00%; 95%-CI: 83.45-98.75) to detect the three-way interaction in the GLMM evaluation of the progression in the FAQ total score in different study groups (e.g., PD-NC vs. PD-MCI), and of n = 71 (Power = 92.00%; 95%-CI: 80.77-97.78) for the three-way interaction in the GLMM evaluating progression of FAQ motor score.

8. Assessments

The explanation of study requirements and informed consent will be conducted as first procedure.

Table 1: Overview of clinical in-house assessments and assessments which can alternatively be assessed within an additional phone interview.

Assessment of PD patients	Time
Explanation of the study requirements	10 min
Informed written consent	5 min
Neurological assessments:	
Medication intake, concomitant diseases and procedures	10 min
Unified Parkinson's Disease Rating Scale (UPDRS) Parts III-IV, Hoehn & Yahr Stage*	15 min
Cognitive test battery:	
Montreal Cognition Assessment (MoCA)	10 min
Mini Mental State Examination (MMSE)	5 min
Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus, German Version)	25 min
Trail Making Test Parts A and B	10 min
Fragmented Words (Subtest of the Leistungsprüfsystem für 50- bis 90-Jährige, LPS 50+)	5 min
Digit-Symbol Test (Subtest of the Wechsler Intelligenztest für Erwachsene, WIE)	5 min
Similarities (Subtest of the WIE)	5 min
Letter-Number Sequencing (Subtest of the WIE)	5 min
Pill-Questionnaire	5 min
Total time of mandatory in house assessments	**115 min**
Optional: Dementia Apraxia Test (DATE)	5 min
Optional: Kölner Apraxie Screening	8 min
Total maximum time of optional in house assessments	**13 min**
Assessments, which can be alternatively assessed within an additional phone interview	
Demographics & lifestyle	
Age, gender, education, occupation, family history of neurodegenerative diseases, smoking/drinking behavior, height & weight#	5 min
PD Non-Motor Symptom Scale, subscales 1-5 (PD-NMS-S)#	5 min
Unified Multiple System Atrophy Rating Scale (UMSARS) I: History of autonomic symptoms#	2 min
History and self-awareness of cognitive deficits#	5 min
Total maximum time of additional phone interview	**17 min**

Legend: *: For patients with an appointment in the outpatient clinic data will be assessed within the frame of the clinical daily routine; #. Information can be assessed within the frame of phone interview

Table 2: Overview of clinical assessments conducted at home by study patients

Patient questionnaires (filled out at home):	
Parkinson's Disease Non-Motor Symptoms Questionnaire (PD-NMS-Q)	3 min
Beck Depression Inventory – II (BDI-II)	5 min
Beck Anxiety Inventory (BAI)	2 min
Pfeffer Functional Activities Questionnaire (FAQ)	2 min
Parkinson's Disease Activities of Daily Living Scale	1 min
Parkinson's Disease Questionnaire (PDQ-39)	5 min
Freezing of Gait Questionnaire (FOG)	1 min
Epworth Sleepiness Scale (ESS)	2 min
REM Sleep behavior questionnaire (RBDS-Q)	2 min
Apathy Evaluation Scale (AES)	3 min
Skala zur Allgemeinen Selbstwirksamkeitserwartung (SWE)	5 min
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Short (QUIP-Kurz)	3 min
Unified Parkinson's Disease Rating Scale (UPDRS) Parts I-II	6 min
International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF)	2 min
Patient Perception of Bladder Condition (PPBC)	1 min
Total time of clinical assessment conducted at home by patients:	**43 min**
Optional: Home-based movement assessment (accelerometry device)	**7 days**

The Kölner Apraxie Test included for validation of the Dementia Apraxia Test (DATE) as well as the Skala zur Allgemeinen Selbstwirksamkeitserwartung (SWE) will be applied as additional study outcome. All other scales and measurement were also included in the first follow-up of the sample (Title: Cognitive driven ADL impairment as a predictor for PDD; ethic protocol: 284/2018BO1). For this scientific study, all investigations will be performed in an ambulatory setting and need the study participants to be available for at least 3 hours, not including the optional blood marker sampling.

If patients agree to the optional CSF and/or blood collection (see also 8.5):

- Blood collection 15 min
- CSF 30 min
- Bed rest after CSF collection 30 min

Total time for biomarker sampling: **<u>75 min</u>**

Invasive biomarker sampling will not be conducted for patients, who are not able to give consent for study participation.

Caregiver assessments:

To validate the patients' self-impression, the following caregiver questionnaires and interview scales will be applied, needing caregivers to be available for at least 38 minutes. Caregiver assessments will only be performed if the respective patient has agreed to the interview.

Table 3: Overview of caregiver assessments

Assessment	Time
Explanation of the study requirements	10 min
Interview-based ratings:	
Informant Questionnaire on Cognitive Decline in the Elderly (IQ-CODE)	6 min
Questionnaires:	
Pfeffer Functional Activities Questionnaire (FAQ)	4 min
Bayer Activities of Daily Living Scale (Bayer ADL)	5 min
PD Angehörigen Belastungs- und Befindlichkeitsskala (PD-ABB-Scale)	8 min
Zarit Caregiver Burden Inventory (ZCBI)	5 min
Total Time of caregiver assessment:	**38 min**

8.1. Retrospective Data

Data collected in the clinical routine, e.g., demographics, medication intake, concomitant diseases and procedures, disease and motor severity, detailed neuropsychological assessments, and detailed non-motor symptom assessments, will be included in the data analysis. If these parameters are collected when participating in other clinical studies, these will also be included.

8.2. Neuropsychological testing

The aim is to diagnose PD-MCI and PDD according to the Level-II recommendations of the Movement Disorder Task Force [17, 18, 25]. Therefore, the following five domains will be quantitatively assessed using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus) battery, three subtests of the Wechsler Intelligence Test for Adults (WIE), and one subtest of the Leistungsprüfsystem für 50- bis 90-Jährige (LPS 50+). At least two tests are assigned to each cognitive domain:

- Executive functions: Lexical and Phonemic Fluency (CERAD-Plus), Trail Making Test Part B (CERAD-Plus)
- Attention/working memory: Digit-Symbol Test (WIE), Letter-Number Sequencing (WIE)
- Language: Boston Naming Test (CERAD-Plus), Similarities (WIE)
- Memory: Word List Learning, Recall, and Discriminability (CERAD-Plus), Praxis Recall (CERAD-Plus)
- Visuospatial abilities: Praxis (CERAD-Plus), Fragmented Words (LPS-50+)

The MMSE included in the CERAD-Plus, as well as the Montreal Cognitive Assessment (MoCA) will serve as global cognitive screening scales. In addition, the DATE will be applied. The DATE by Johnen and colleagues [29] was developed to assess limb and buccofacial apraxia in neurocognitive disorder patients with Alzheimer's disease and frontotemporal dementia. Based on scores in the first follow-up, progression in the DATE performance over time will be investigated. For validation purpose, the Kölner Apraxie Screening [30] will be included as well. Patients' performance in the DATE and KAS will be videotaped for data analysis. Videotaped data will be solely used for scoring of the DATE and KAS, also including registration of patient's body parts and face. After scoring of patient's test performance and finalization of study analysis, videodata will be deleted. Only, information of patients test performances as a result of the videoanalysis will be shared with collaboration partners.
In addition, we will validate a novel scoring algorithm of patients' cube drawing (CERAD-PLUS test battery) proposed as a measure for retrograde procedural memory [31]. Therefore, investigators will be trained for this novel scoring method by the collaborating group of Prof. Rejko Krüger, University of Luxembourg. Patients' performance will be scored by the investigators during test session, therefore, no additional time for patients' examination is expected.

8.3. Home-based movement assessment (Accelerometer)

Physical activity directly influences health-related quality of life in PD [32], with specific aspects of physical activity decreasing with the severity of cognitive impairment [33]. We will therefore conduct a home-based movement assessment in a random subgroup of patients, to examine the influence of physical activity on cognition and other non-motor symptoms in PD. Participants will be asked to wear an accelerometer (MoveMonitor, McRoberts, The Netherlands, FDA registered and CE marked) on their lower back for 7 consecutive days in their home environment. The accelerometer is capable of data uptake for 7-10 days, and assesses various movement parameters (e.g., time spent sitting, lying, walking, and standing, as well as step count).

8.4. Caregiver IADL assessments

Caregiver assessments have a crucial role determining a diagnosis of PDD, by examining whether patients are able to care for themselves and carry out their daily activities. The Bayer Activities of Daily Living Scale (Bayer ADL) consists of 25 questions answered by the caregiver that evaluate the patient's ability to perform ADL. The Informant Questionnaire on Cognitive Decline in the Elderly (IQ-CODE), a brief screening tool for dementia, compares patients' current abilities to how they were two years ago. In addition, caregiver burden will be assessed using two questionnaires, the Parkinson's Disease Angehörigen Belastungs- und Befindlichkeitsskala (PD-ABB-Scale) and the ZARIT Caregiver Burden Inventory (ZCBI). This provides a useful marker for cognitive ADL progression, as well as helps to distinguish cognitive decline from normal aging. The caregiver assessment of ADL using the FAQ allows us to compare patient and caregiver evaluations of ADL impairments.

8.5. Biomaterial collection

8.5.1. CSF and blood collection

Blood and CSF samples will be collected in the morning, on an empty stomach. If patients do not agree for a lumbar puncture, fasting for blood sampling is not necessary for biomarker analysis.

Blood collection: For patients with no CSF withdrawal about 40 ml venous blood will be collected for data analysis and storage of blood in the neurobank of the Hertie-Institut für klinische Hirnforschung (ethic proposal: 199/2011BO1). This amount does not represent any health hazard. For study related analysis of serum neurofilament light chain 10 ml of venous blood (1 Serum tube) will be collected. If the patient agrees for withdrawal of CSF additional 12,5 ml venous blood (2 serum tube, 1 NaF (glucose) 2,5 ml, total amount of venous blood 52,5 ml) will be taken for safety analysis in the Zentrallabor of the UKT.

Through venipuncture, the following samples will remain in the Hertie-Institut für klinische Hirnforschung (ethic proposal: 199/2011BO1):

- 20 ml of venous blood in 2 large EDTA tubes
- 10 ml of venous blood in 1 Serum tube

Blood in the Neurobiobank will be stored and used for targeted biomarker search, for explorative proteomic and metabolomics approaches, as well as for the determination of genetic markers in those without DNA analysis by using the NeuroChip (e.g. APOE Genotype, MAPT, COMT, and GBA).

CSF collection: The lumbar puncture at level L3/L4 or L4/L5 of the spine will be performed by a qualified clinician. The applicants have extensive experience with this procedure (see, e.g., ethic proposals 46/2010 and 404/2010). Subjects will be closely monitored during and after the procedure. Patients need to rest for 30 min after CSF collection and will be informed that occurrence of side effects of this procedure might be interfere with their driving abilities. Up to 15 ml of CSF will be collected unless there is evidence of clinically significant coagulopathy or thrombocytopenia that would interfere with the safe conduct of the procedure. This amount does not represent any health hazard. The first 2 ml of CSF will be processed at the Zentrallabor to conduct standard analyses on cell count, protein, and glucose levels, while another aliquot of 400 µL Liquor will be sent to the Neurochemisches Labor to conduct analyses of neurodegenerative markers such as Abeta1-42 and Abeta1-40.

8.5.2. Tissue collection

Not applicable.

8.5.3. Analysis of biomaterial

A structured and integrated exploration of biomaterial in combination with the analysis of the extensive quantitative dataset obtained in this study bears the chance for a better molecular, biochemical, and eventually functional understanding of one of the most debilitating symptoms associated with PD, i.e., cognitive deterioration.
For all patients, DNA, CSF, and plasma were sampled at baseline. Available data will be included into data analysis. This includes genetic information received from DNA analysis by using the NeuroChip, especially information on genetic variants associated with dementia and PD, as well as CSF levels of Abeta1-42, phosphor- and total Tau determined within the frame of the ABC-PD study. In collaboration with the company ADX, represented by Hugo Vanderstichele and Erik Stroops, the following baseline CSF biomarkers were provided for further analysis of 200 patients: Abeta1-42, Abeta1-40, Abeta1-38, phosphor Tau 181, NF heavy, neurogranin, BASE-1, and alpha-synuclein.
At time of follow-up, a maximum of 50 PD patients is expected to give a third CSF sampling. Levels of CSF biomarkers indicating cognitive worsening [8, 9, 34-37] will be measured using the solid phase enzyme essays from Fujirebio Germany GmbH: Abeta1-42, Abeta1-40, phosphor- and total Tau. In addition, blood (serum) neurofilament light chain will be analysed in cooperation with Prof. Dr. med. Björn Falkenburger of the Universitätsklinikum Dresden.

8.5.4. Storage of biomaterial

All samples will be stored at -80°C until use. To maximize confidentiality, all biomarker samples and information associated with the samples will be coded to prevent the exposure of the subjects' information and identity. This coding process allows location and destruction of a sample at the subject's request. In addition, sample information is stored in one secured

electronic database, while biomarker data is stored in an independently secured database on a different computer. No one except the investigators of the UKT will have access to the database to deduce the identity of the patient.

9. Risks and possible adverse reactions, end of the study

9.1. Comprehensive non-motor symptom assessment

No relevant risks.

9.2. Neuropsychological testing

No relevant risks.

9.3. Home-based movement assessment (Accelerometer)

No relevant risks.

9.4. Caregiver ADL Assessments

No relevant risks.

9.5. Biomaterial (Blood and CSF) collection

Venipuncture is usually well-tolerated and rarely associated with complications. However, at the site of injection it may cause symptoms such as local pain, small bruises, induration, and dizziness a. In rare cases infection, phlebitis (thrombophlebitis), a thrombosis, or it can wash away the smallest blood clots (embolisms) and small scars on the site of injection. Circulatory reactions (so-called vagovasal reactions) can also occur. In very rare cases abnormal sensations around the puncture due to unintentional nerve injury (median nerve in some cases with long-lasting sensory and motor deficits).
Lumbar puncture is a routine assessment in neurological hospitals. The risk of injury of nerves, bones or other viscera is possible in theory but is extremely unlikely because of atraumatic injection needles.
Side effects of lumbar puncture:

- Frequent side effects (1 of 2-3 cases):
    - The needle prick can hurt locally at the site of injection
    - Small bruises at the site of injection without further complication or functional deficits
- Occasional side effects (< 10 von 100 cases):
    - Contact between the side of the lumbar puncture needle and a spinal nerve root can result in anomalous sensations (paresthesia) for a short time period (seconds)
    - Circulatory reactions (so-called vagovasal reactions) with occurrence of dizziness. Patients body position will be stabilized (lateral position) if symptoms occur. Lumbar puncture will be interrupted if circulatory symptoms did not meliorate and vanish in the lateral body position.

- Rare side effects (< 3 von 100 cases):
    - Post spinal headache, nausea, vomiting, increased sensitivity to light and dorsal pain, lasting for hours or days after the lumbar puncture. In rare cases those symptoms can last for several days or weeks.
    - Local infection at the side of injection.
    - As a consequence of the circulatory reactions a syncope (period without consciousness, circulatory collapse) can occur.
- Very rare cases (single cases reported in the literature). Those side effects occur in very rare cases, but can't be excluded as a consequence of the lumbar puncture:
    - Strong post-lumbar puncture headache in upright and sitting position, which requires an additional puncture in the region of the spine and an epidural blood patch. During this procedure injection autologous blood (10-20 ml) into the epidural space at the site of the dural puncture closing the puncture due to coagulation. This injection can be performed ambulatory or ad the ward, normally within 1-2 hours after the lumbar puncture in very rare cases.
    - (Bacterial) Meningitis after lumbar puncture, subdural hematoma or brain oedema can occur. Normally symptoms restitute after some time, without long lasting functional deficits. The risk for those side effects is increased in patients with genetic or acquired coagulation disorders.
    - Temporary deficits of single of cerebra nerves including temporary functional deficits like hearing loss or problems in vision.
    - Pulmonal deficits causing problems in breathing and severe circulatory reactions causing life threatening events shortly after the lumbar puncture. Often specific primary diseases promote these side effects.
    - Spinal cord inflammation
    - Provocation of seizure disorders (z.B. migraine, epilepsy).

So far, severe side effects has never occurred during the conduction of several study related lumbar punctures performed every year at the Department of Neurodegenerative diseases at the UKT ever since atraumatic needles have been available. Ever since the introduction of atraumatic needles, the frequency of post-puncture headache in people older than 50 years has decreased substantially and is now below 2% [38].

10. End of the study

Execution phase & recruitment: June 2024
Data analysis expected: December 2024
Anticipated study end: December 2024

11.Data protection

11.1. Data collection

Data collection and use of personally identifiable information in this study complies with the General Data Protection Regulation (EU) 2016/679. Participants will be given the appropriate information on dealing with data collected in the study and asked to sign a separate informed consent form concerning data protection.

11.1.1. Which data are collected; is it possible to identify the donor?

Data of every subject – name, age, disease duration, as well as all assessed parameters and results of the biomarker assessments – are collected in separate folders and will be stored in a lockable office of the Principal investigator or his/her representative. As a database platform, the REDCap electronic data capture tool will be used [39]. The database will be secured with password protection, individually assigned to each team member with database access. Pseudonymized data will be saved in the database inside the firewall of the medical faculty, using a 4-digit number not associated with any demographics of the study participant. Thus, the identification of a participant using only the code number is not possible and confidentiality will be ensured by use of these identification codes. The informatics manager and PI will only receive coded information that has been entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information.

11.1.2. Shall patients be informed about novel scientific findings?

If participants meanwhile wish to be informed about their individual CSF Abeta1-42 results (as per indication on the ABC-PD cross-sectional patient consent form, ethic protocol: 686/2013B01), this will take place during a one-on-one consultation with the PI/representative. If the patient agrees, he/she will be informed about the cognitive outcome. Beyond these specific parameters, it is not planned to keep the participants informed about the individual study results.

11.1.3. Period of data storage

Data will be stored for 10 years.

11.1.4. Erasure of personal data

Participants have the right to gain information about stored data, to correct false data, to demand the erasure of personal data, and to demand the anonymization of their data. The PI of the study, Prof. PD Dr. Inga Liepelt-Scarfone (phone: +497071-2980424, fax: +497071-294490, e-mail: inga.liepelt@uni-tuebingen.de), and PD Dr. Kathrin Brockmann (phone: +497071-2980171; fax: +497071-2925195, e-mail: kathrin.brockmann@uni-tuebingen.de) are responsible for the adherence of all law regulations.
Contact information: Hertie Institute for Clinical Brain Research, Department of Neurodegeneration, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany.

11.2. Transfer of data to collaboration partners

If the patient agreed for this procedure, pre-processed blood samples will be transferred to Prof. Dr. med Björn Falkenburger, Fetscherstraße 74, 01307 Dresden, for further analysis of serum neurofilament light chain. Samples are coded with a pseudonym (Lab-ID 2). If more than one sample is transferred coded with two different identifiers (Lab-ID 2) for one sample, additionally the patient pseudonym will be transferred and the information which samples belong to the same person.

In cooperation with the IB Hochschule für Gesundheit und Soziales Standort Stuttgart, Paulinenstr. 45, 70178 Stuttgart, we are planning to share data with students of this private University for data analysis reported either as a Bachelor or Master thesis. Only anonymized data will be transferred.
In addition, we will ask the participants to give consent for shipment of plasma samples and clinical study data for proteomics analysis. Currently, Janssen Research & Development is forming a consortium including different collaboration partners for harmonization of proteomics analysis and building of large cohorts to analyse samples and clinical data in the spectrum of normal age and neurodegenerative diseases ("Alzheimer's Disease and Related Dementias (ADRD) Proteomics Consortium"). Different PIs of cohort are represented in the steering committee of this consortium, regulating access to proteomics and clinical data. The consortium is not regulated by a pharmaceutical company and independent from industrial interests. Data will be stored in the cloud hosted by the Alzheimer's Disease Data Initiative (ADDI) located in the United States (Aridhia). Aridhia completed the ISO 27001 certification in June 2019, maintaining this certification through multiple audits. ISO 27701 certification was achieved in June 2022. The Azure-hosted Aridhia DRE is also HITRUST CSF certified and holds several UK certifications (for details please see https://knowledgebase.aridhia.io/aridhia-security-and-compliance/https://knowledgebase.aridhia.io/aridhia-security-and-compliance/).

Aridhia achieves compliance with General Data Protection Regulation through the implementation of ISO 27701 policies and processes which ensure that:

- Information is processed on a lawful and transparent basis.
- Strong data security is achieved through design.
- Information security governance and accountability within Aridhia is clear.
- Individuals' privacy rights are respected.

Within the DRE, security controls include:

- All user access is via HTTPS URL protected by a rooted certificate issued by DigCert SHA2 Secure Server CA, utilising sha256RSA signature algorithm with sha256 signature hashing algorithm. Will only utilise TLS 1.2 protocols or above.
- Encryption in transit: All internal network traffic is protected by HTTPS, TLS 1.2, or above protocols.
- Encryption at rest: By default, Microsoft Azure encrypts data using FIPS 140-2 compliant 256 AES encryption for storage accounts and virtual machine disks.
- Two-factor authentication is required to access DRE services.
- The secure workspace boundary is created through a virtual network configuration and enforced through a permissions model.
- An Intrusion Detection System and Intrusion Protection System is implemented with security alerts automatically raised to Aridhia's Service Desk Team.
- Data upload and data extraction is only permitted through an approval process.
- All uploads go through a malware scanning process.
- Full audit reporting of events.

Operational Processes: The DRE is a managed service, where Aridhia performs the following operations:

- OS patching (scheduled and ad hoc in the event of emergency updates).
- Nightly back-ups of the environment.
- All support teams have separate privileged admin accounts and these require 2FA. All support team actions are logged.
- Regular audits of the privileged accounts.
- All Aridhia employees who have access to the operational environment go through a criminal record check.
- Mandatory security training at inductions and periodic refresher training for all employees.
- All changes to the platform are subject to change control.
- Incident management and CSIRT processes.
- Monthly audit of key ISO27001 controls.
- Quarterly BCP/DR exercises.
- Data is backed up to the Azure region agreed with the customer, either the local Azure region or a remote region within the same territory, as per customer's statutory and legal obligations.
- Back-ups are tested on a bi-monthly basis to ensure the data is recoverable.
- All environments are monitored, with security, back-up failures, and capacity alerts being automatically logged with the Operations and Service Desk teams.
- The Aridhia DRE has a Recovery Point Objective of 24 hours and a Recovery Time Objective of 72 hours.

For data analysis we will ask the patients and informants for written informed consent for transfer of plasma samples and clinical data to the proteomics database of the Proteomics Consortium. If applicable, we will also ask to give consent for transfer of samples and data of previous study visits. Only pseudonymized data will be transferred. If data/biosamples of more than one clinical visit is provided to the Proteomics Consortium, an identifier allowing to identify which data belong to the same persons will be coded. It is not possible for members of the consortium to download data on local workstations or storage media. Additionally, patients' consent will be asked for a data transfer of the investigator scored results of the cube analysis along with clinical data needed for validation of the novel scoring system. Data will be transferred to Prof. Dr. Rejko Krüger, Luxembourg Institute of Health, Transversal Translational Medicine (TTM) Initiative, 1A-B, rue Thomas Edison, 1445 Strassen, Luxemburg. Only pseudonymized data will be transferred.

11.3. Information and informed consent

Prior to the respective assessments, every prospective participant will be informed in oral and written form about the general goal of the study and how the assessments will be performed. In particular, the informed consent form will contain comprehensive information about contents, objectives, duration, procedures, voluntariness, and possible risks of the study participation. Any kind of questions will be considered and answered. In case of agreement to study participation, the participant has to sign two copies of the informed consent form. One form will be given to the participant and the other form will be stored at the local study centre in a separate folder (not in the medical records).
In addition to the PD patients, caregivers will be contacted and interviewed. Therefore, informed consent will also be obtained from patients' caregivers using a separate caregiver

informed consent form. The patients will be asked to choose the caregiver who will then be contacted for the caregiver assessment.

12.Insurance

A road accident insurance (SV SparkassenVersicherung AG Hessen-Nassau-Thüringen, Wiesbaden) including insurance for accidence during study visit will be offered (limited to 145 patients and 90 companions/caregivers).

Insurance Nr.: 50100561414
Date: 01.03.2023 - 31.12.2024
Maximal insurance costs for patient and cargiver:
100.000 EUR disability case
50.000 EUR death
10.000 EUR salvage costs
5.000 EUR cosmetic surgeries

13.Information text and text of the informed consent

See attachments:

- Patient information sheet and informed consent form
- Patient data privacy statement
- Caregiver information sheet and informed consent form
- Caregiver data privacy statement
- Legal guardian information sheet and informed consent form
- Legal guardian data privacy statement
- Questionnaires for informants
- Offer and conditions of road accidence insurance (including accidence insurance during study visit)

14.Reference list

1. Fereshtehnejad, S.M., et al., *New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression: A Prospective Cohort Comparison With Other Phenotypes.* JAMA Neurol, 2015. **72**(8): p. 863-73.
2. Fereshtehnejad, S.M., et al., *Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression.* Brain, 2017. **140**(7): p. 1959-1976.
3. van Uem, J., et al., *Health-related quality of life in patients with Parkinson's disease-A systematic review based on the ICF model.* Neurosci Biobehav Rev, 2015.
4. Bjornestad, A., et al., *Clinical milestones in Parkinson's disease: A 7-year population-based incident cohort study.* Parkinsonism Relat Disord, 2017. **42**: p. 28-33.
5. Aarsland, D., et al., *Parkinson disease-associated cognitive impairment.* Nat Rev Dis Primers, 2021. **7**(1): p. 47.
6. Aarsland, D., et al., *Cognitive decline in Parkinson disease.* Nat Rev Neurol, 2017. **13**(4): p. 217-231.
7. Saredakis, D., et al., *Conversion to MCI and dementia in Parkinson's disease: a systematic review and meta-analysis.* Parkinsonism Relat Disord, 2019. **65**: p. 20-31.

8. Backstrom, D.C., et al., *Cerebrospinal Fluid Patterns and the Risk of Future Dementia in Early, Incident Parkinson Disease.* JAMA Neurol, 2015. **72**(10): p. 1175-82.
9. Berlyand, Y., et al., *An Alzheimer's Disease-Derived Biomarker Signature Identifies Parkinson's Disease Patients with Dementia.* PLoS One, 2016. **11**(1): p. e0147319.
10. Backstrom, D., et al., *Prediction and early biomarkers of cognitive decline in Parkinson disease and atypical parkinsonism: a population-based study.* Brain Commun, 2022. **4**(2): p. fcac040.
11. Myers, P.S., et al., *Proteinopathy and Longitudinal Cognitive Decline in Parkinson Disease.* Neurology, 2022. **99**(1): p. e66-e76.
12. Emre, M., et al., *Clinical diagnostic criteria for dementia associated with Parkinson's disease.* Mov Disord, 2007. **22**(12): p. 1689-707; quiz 1837.
13. Cheon, S.M., K.W. Park, and J.W. Kim, *Identification of Daily Activity Impairments in the Diagnosis of Parkinson Disease Dementia.* Cogn Behav Neurol, 2015. **28**(4): p. 220-8.
14. Fellows, R.P. and M. Schmitter-Edgecombe, *Multimethod assessment of everyday functioning and memory abilities in Parkinson's disease.* Neuropsychology, 2019. **33**(2): p. 169-177.
15. Pirogovsky, E., et al., *Instrumental activities of daily living are impaired in Parkinson's disease patients with mild cognitive impairment.* Neuropsychology, 2014. **28**(2): p. 229-37.
16. Beyle, A., et al., *The Multiple Object Test as a performance-based tool to assess the decline of ADL function in Parkinson's disease.* PLoS One, 2018. **13**(8): p. e0200990.
17. Dubois, B., et al., *Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force.* Mov Disord., 2007. **22**(16): p. 2314-2324.
18. Emre, M., et al., *Clinical diagnostic criteria for dementia associated with Parkinson's disease.* Mov Disord., 2007. **22**(12): p. 1689-1707.
19. Rosenthal, E., et al., *Association between cognition and function in patients with Parkinson disease with and without dementia.* Mov Disord, 2010. **25**(9): p. 1170-6.
20. Deck, B.L., et al., *Cognitive Functional Abilities in Parkinson's Disease: Agreement Between Patients and Informants.* Mov Disord Clin Pract, 2019. **6**(6): p. 440-445.
21. Cholerton, B., et al., *Participant and Study Partner Reported Impact of Cognition on Functional Activities in Parkinson's Disease.* Mov Disord Clin Pract, 2020. **7**(1): p. 61-69.
22. Becker, S., et al., *Divergence Between Informant and Self-Ratings of Activities of Daily Living Impairments in Parkinson's Disease.* Front Aging Neurosci, 2022. **14**: p. 838674.
23. Pfeffer, R.I., et al., *Measurement of functional activities in older adults in the community.* J Gerontol, 1982. **37**(3): p. 323-9.
24. Becker, S., et al., *Assessment of cognitive-driven activity of daily living impairment in non-demented Parkinson's patients.* J Neuropsychol, 2018.
25. Litvan, I., et al., *Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines.* Mov Disord, 2012. **27**(3): p. 349-56.
26. Harrell, F.E., et al., *Evaluating the yield of medical tests.* Jama, 1982. **247**(18): p. 2543-2546.
27. Maetzler, W., I. Liepelt, and D. Berg, *Progression of Parkinson's disease in the clinical phase: potential markers.* Lancet Neurol, 2009. **8**(12): p. 1158-71.

28. Aarsland, D. and M.W. Kurz, *The epidemiology of dementia associated with Parkinson disease.* J Neurol Sci, 2010. **289**(1-2): p. 18-22.
29. Johnen, A., et al., *Dementia Apraxia Test (DATE): A brief tool to differentiate behavioral variant frontotemporal dementia from Alzheimer's dementia based on apraxia profiles.* J Alzheimer's Dis, 2016. **49**(3): p. 593-605.
30. Wirth, K., et al., *[A New Diagnostic Tool for Apraxia in Patients with Right-Hemisphere Stroke: The Revised Cologne Apraxia Screening (KAS-R)].* Fortschr Neurol Psychiatr, 2016. **84**(10): p. 633-639.
31. Pauly, L., et al., *Retrograde Procedural Memory in Parkinson's Disease: A Cross-Sectional, Case-Control Study.* J Parkinsons Dis, 2022. **12**(3): p. 1013-1022.
32. van Uem, J.M., et al., *Health-Related Quality of Life in patients with Parkinson's disease--A systematic review based on the ICF model.* Neurosci Biobehav Rev, 2016. **61**: p. 26-34.
33. Cerff, B., et al., *Home-Based Physical Behavior in Late Stage Parkinson Disease Dementia: Differences between Cognitive Subtypes.* Neurodegener Dis, 2017. **17**(4-5): p. 135-144.
34. Siderowf, A., et al., *CSF amyloid {beta} 1-42 predicts cognitive decline in Parkinson disease.* Neurology, 2010. **75**(12): p. 1055-61.
35. Alves, G., et al., *CSF Abeta42 predicts early-onset dementia in Parkinson disease.* Neurology, 2014. **82**(20): p. 1784-90.
36. Zhang, J., et al., *Longitudinal assessment of tau and amyloid beta in cerebrospinal fluid of Parkinson disease.* Acta Neuropathol, 2013. **126**(5): p. 671-82.
37. Brockmann, K., et al., *SNPs in Abeta clearance proteins: Lower CSF Abeta1-42 levels and earlier onset of dementia in PD.* Neurology, 2017. **89**(23): p. 2335-2340.
38. Blennow, K., A. Wallin, and O. Hager, *Low frequency of post-lumbar puncture headache in demented patients.* Acta Neurol Scand, 1993. **88**(3): p. 221-3.
39. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.