
Titel

„Efficacy of dual-task telerehabilitation to prevent worsening in activities of daily living in people with Parkinson’s disease at high risk for dementia: A proof-of-concept study“

„Wirksamkeit der Dual-Task-Telerehabilitation zum Erhalt der Aktivitäten des täglichen Lebens bei Personen mit Morbus Parkinson und hohem Demenzrisiko“

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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
ADL	Activities of Daily Living
Bayer ADL	Bayer Activities of Daily Living Scale
BDNF	Brain-derived neurotrophic factor
CT	Cognitive Training
CMT	Control Motor Training
CONSORT	Consolidated Standards of Reporting Trials
DCT	Dual Cognitive Training
FAQ	Pfeffer Functional Activities Questionnaire
GDS	Geriatric Depression Scale
HRQL	Health related quality of life
MDS-UPDRS-III	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MoCA	Montreal Cognitive Assessment
NFL	Neurofilament light chain protein
PD	Parkinson's Disease
PD-CN	Parkinson's Disease with Normal Cognition
PDD	Parkinson's Disease Dementia
PD-MCI	Parkinson's Disease with Mild Cognitive Impairment
PDQ39	Parkinson's Disease Questionnaire
PwPD	People with Parkinson's Disease
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
UKT	Universitätsklinikum Tübingen
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
SWE	Skala zur Allgemeinen Selbstwirksamkeitserwartung
WIE	Wechsler Intelligenztest für Erwachsene

3. Study summary

3.1. Background

Approximately 60% to 83% of people with Parkinson's Disease (PwPD) develop dementia during the course of their disease [1], leading to devastating consequences for affected persons and caregivers [2]. Therefore, preventing Parkinson's disease dementia (PDD) seems one of the biggest challenges in Parkinson's Disease (PD), but so far effective interventions to delay conversion to PDD are lacking. The stage of mild cognitive impairment (PD-MCI) can be defined as the intermediate stage of cognitive dysfunction between normal cognitive function and dementia [3], affecting around 40-50% of PwPD after 5 years [3-5]. However, PD-MCI is a heterogeneous concept; while only around on third of PwPD with PD-MCI progress to PDD, others remain cognitively stable or even revert to normal cognition [6]. This heterogeneity poses a challenge for clinical care as interventions must start at a point where both objective PDD risk and patients' needs converge. However, as only a small proportion of PwPD with PD-MCI progress to PDD, additional markers are needed to identify those persons at high risk of developing PDD in the near future.

The fundamental feature differentiating PwPD with PDD from those PD-MCI is the loss of the ability to perform activities of daily living (ADLs) [7], which includes basic ADLs such as dressing or bathing to complex instrumental ADLs such as shopping or managing medication [8]. While PwPD maintain their basic ADL skills longer during their disease course, they report problems in more complex ADL skills - even in mild stages of cognitive decline [9]. About 30%-50% of patients with PD-MCI already report first signs of ADL problems [10, 11], and complex ADL impairment worsens during the transition phase from PD-MCI to PDD [12]. Recently, we found that early signs of complex ADL problems related to cognitive impairment (cognitive ADL) increased the risk for the development of PDD within study period [13]: almost half (47.6%) of PwPD with PD-MCI who had cognitive ADL impairment converted to dementia within three years [13]. Therefore, people with PD-MCI and complex ADL problems associated with cognition may be a promising target group for interventions, as they are a high-risk group for serious and rapidly progressive cognitive deterioration.

Most important, self-determination is a basic human need [14] and PwPD with ADL impairment report shame and self-stigma, often leading to withdrawal from activities [15, 16]. Therefore, PwPD wish to maintain their independence in life as long as possible [17]. To date, no pharmacological intervention for both treatment of cognition and ADLs indicative of dementia is available in PwPD with PD-MCI [18-21]. Hence, the value of non-pharmacological interventions for the treatment of cognitive impairment in the prodromal stage of PDD is increasingly recognized [12]. Digital cognitive trainings (CTs) have been shown to improve cognition as assessed by cognitive tests [22], but their positive effect on complex ADLs are only sparsely investigated in PwPD [23-26]. It should also be noted that treatment-induced changes in complex ADLs are rarely considered a primary outcome. Currently, no study has examined the effects of digital CT on prolonging the transition time from PD-MCI to PDD.

Participants often have to travel long distances to attend on-site training. Travelling alone is particularly challenging for PwPD at high risk of PDD conversion, since travelling is a cognitively complex ADL [41], which is expected to be impaired in this high-risk group. Travel difficulties limit access to healthcare, making PwPD dependent on support from relative, increasing the burden on patients and their caregivers. Telerehabilitation has recently been discussed as a feasible and effective treatment solution for overcoming this limitation [11]. The success of unsupervised home-based interventions may be hindered by patients' insecurity to exercise on their own [27, 28]. However, first studies in PwPD have shown acceptance (drop-out rate <15%) and feasibility of home-based digital CTs in PwPD [29], positively impacting cognition [23, 24, 26, 29, 30], but showing only minor improvements in ADLs [24, 26].

Ideally, an economic and low-threshold multidomain intervention combining lifestyle factors such as physical activity, nutrition and cognitive activities should be used to increase one's odds of preventing cognitive decline and future dementia [31]. Many ADLs require motor-cognitive function, as individuals must simultaneously coordinate motor and cognitive actions [32, 33]. For instance, the ADL of cooking involves actions such as monitoring the stove, while keeping track of time, and chopping ingredients. PwPD must often perform each of these, previously habitual actions, intentionally and consciously because of the deterioration in motor automaticity that occurs with basal ganglia impairment [34]. PwPD, in particular those with PD-MCI, show deficits in motor-cognitive function [35], and they also show impaired attentional-control (attention and executive function) [36]. This is problematic because attentional control is needed for compensation of deteriorated motor automaticity [37, 38]. Consequently, impaired attentional control is related to poor performance in ADL tests in PwPD with PD-MCI [36, 39] and with motor tasks in PwPD [40, 41]. Because attentional-control impairments are also linked to an increased risk of falling, PwPD tend to practice especially challenging everyday situations less often [35, 42]. This vicious cycle emphasizes the importance of treatments to improve and maintain motor-cognitive function, and hence ADL function. Dual-task cognitive training, which combine cognitive and motor exercises in trainings shows great potential, as they have been demonstrated to improve motor-cognitive task coordination and to enhance attentional-control [43-45]. First evidence verified that an on-site dual task cognitive training (DCT) enhances ADL function in PwPD [46], and that improvements in executive functions (one component of attentional control) are associated a measurable change in home-based physical activity in PD-MCI [47], implicating a direct consequence on persons everyday behavior due to training [47]. To the best of our knowledge, no home-based digital DCT with the primary aim to enhance cognition and/or complex ADLs in PwPD has been conducted.

A recent feasibility study presents a solution for this problem [48]. In a small sample of non-demented PwPD, a supervised DCT on a bicycle ergometer showed encouraging results in improving physical and cognitive function. This on-site concept could be adapted as a safe and practical method for incorporating dual-tasking exercises into home-telerehabilitation.

Therefore, we propose a safe and novel leg-strengthening DCT, specifically designed for PwPD with the high-risk profile who may otherwise fall through the net of healthcare.

Cognitive motor rehabilitation has been shown to provide some of the most effective motor improvements in PwPD [34]. Based on previous results, our DCT has the potential to improve objectively measured physical activity, such as leg-strength [47, 49]. This is of utmost importance as, besides cognitive impairment [12], motor symptoms especially problems in gait, also negatively affect ADL function in PD [50-56]. Improving motor-cognitive aspects of ADL impairment and leg-strength may increase PwPDs' ability and self-confidence to engage in different ADL actions. This translates into measurable changes in daily movement patterns.

To date, insight into the pathomechanisms of treatment effects that reflect a person's resilience to dementia is urgently needed. Biomarkers may be promising to evaluate short- and long-term effect of treatments on ADLs. The neurofilament light chain protein (NFL) was recommended to assess the efficacy of neuroprotective interventions in PD [57]. First data suggest that behavioral interventions, such as exercise can lower NFL levels in non-PD cohorts [58]. In PwPD, ADL impairment especially in early stage of deterioration was linked to higher NFL levels [59-61] (see section preliminary work). Apart from NFL, reduced levels of the brain-derived neurotrophic factor (BDNF) are linked to increased dopaminergic neurodegeneration [62] and lower cognition in non-demented PwPD [63-65]. Accordingly, increased BDNF levels in PwPD have been reported after CT [66] and DCT [67].

3.2.Preliminary work

As an import premise of the proposed study, we confirmed that PwPD with PD-MCI and cognitive ADL impairment are at high risk for PDD [13]. Further data of our team indicate that higher cerebrospinal fluid NFL values were associated with complex ADL function in non-demented PwPD [61], supporting the potential of this biomarker to reflect improvement in ADLs. Especially, motor associated ADL in early stages of cognitive impairment were correlated to NFL values. In addition, memory domain impairment did correlate with NFL levels in these PwPD. Therefore, our data are in accordance with previous reports of an association of NFL with markers for motor symptoms (assessed by the Movement Disorder Society Unified Parkinson's Disease Rating Scale, MDS-UPDRS-III [60, 68], global cognitive symptoms [68-71] and morbidity milestones [72].

4. Objectives of the study

The primary focus of the proposed intervention trial is to enhance cognition and ADL function through a telerehabilitation DCT in the long-term. The trial will include a homogeneous group of PwPD with PD-MCI and cognitive ADL impairment assessed by the patient rated cognitive score of the Pfeffer Functional Activities Questionnaire (FAQ).

4.1. Primary Aim

Specifically, this project will define efficacy of a standardized motor-cognitive dual-task telerehabilitation training (DCT) vs. an active control motor training (CMT) in PwPD with PD-MCI to improve ADLs and cognition (especially attentional control).

4.2. Secondary Aim

The efficacy of the DCT vs. an active CMT to improve health related quality of life (HRQL) after intervention will be the secondary outcome. Safety and feasibility of the intervention will be another secondary outcome. Most importantly, we will evaluate if the DCT can prevent further decline in cognition and ADLs and maintain HRQL in the long-term, and identify markers (social-demographic, clinical, biomarkers) predicting positive treatment response.

4.3. Exploratory Aim

Conversion to PDD (exploratory outcome) will be assessed 12 months after baseline assessment. Responsiveness of treatment of participants will also be explored.

5. Outcomes

Table 1 gives an overview of study assessments at each clinical visit.

5.1. Primary Outcome

Primary outcomes for the evaluation of treatment effects will be the informant rated cognition score of the FAQ [73] and the motor-auditory Stroop task [74]. The task involves participants walking while giving spoken responses to the words “high” and “low”. The words are delivered with congruent and incongruent tones

5.2. Secondary Outcome

Secondary outcomes will include (i) composite neuropsychological test performance (z-score), the (ii) total score in the Montreal Cognitive Assessment (MoCA) [75], (iii) the Bayer Activities of Daily Living Scale (Bayer ADL scale, [76]) (supplemented by the frequency of the individual activities), the informant ratings in the (iv) FAQ total and motor score [73], (v) HRQL (Parkinson’s Disease Questionnaire, PDQ-39 [77]), (vi) general self-efficacy scale (GSE) [78], (vii) Chair Stand Test (viii), Timed-up-and-go-test (ix), NFL (x), and BDNF (xi). The composite score of neuropsychological performance will be calculated as mean z-score of tests assigned to the following domains: executive function, attention, memory, language, and visuo-spatial abilities.

5.3. Exploratory Outcome

Conversion to dementia will be a further outcome for the 12-month follow-up, verified by Level II testing (see section 6.1.1 for details). The identification of markers predicting long-term outcome at time of pre-test as another exploratory outcome.

5.4. Hypothesis and research questions

We hypothesize a significant improvement in the informant rated cognitive ADL performance and cognition, especially attentional control (the motor-auditory Stroop task), and in participants assigned to the DCT compared to the CMT after training (short term effects). Impairment of both cognition and ADL lowers HRQL in PwPD [79, 80]. As our DCT is designed to improve ADL and cognition, we anticipate that this training will have a superior effect on improving HRQL than the CMT. We hypothesize that PwPD assigned to the DCT will show better ADL and cognitive performance after 12 months (long-term effects) compared to the CMT. As an exploratory finding, we expect fewer PDD converters in DCT participants than in CMT participants.

6. Study population

PwPD with PD-MCI (see section 6.1.1 for details of cognitive diagnosis) and cognitive ADL impairment will be included.

6.1. Inclusion criteria

- PD diagnosis confirmed by a neurologist
- PD diagnosis at least for one year
- Age between 51-80 years
- German as their mother tongue
- Diagnosis of PD-MCI according to the Level II criteria of the Movement Disorder Society (MDS, see section 6.1.1 for details of the diagnostic process)
- Cognitive ADL impairment as defined by the FAQ quotient (see section 6.1.2 for details)
- An informant who has given consent to provide information about the participant's activities of daily living (ADLs) and who lives in the participant's home.
- Access to a WIFI Network at home
- Unimpaired or corrected vision and hearing
- Appropriate text comprehension and reading ability
- 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

6.1.1. *Diagnosis of cognitive impairment*

Patients will be classified as PD-MCI according to Level-II Movement Disorder Society recommendations if cognitive impairment is present but does not significantly interfere with everyday function [81]. Patients will be classified as PDD according to Movement Disorder

Society Task Force criteria [7] if cognitive impairment is present and severe enough to impair ADL function unrelated to motor or autonomic symptoms and at least one behavioral symptom is present to support diagnosis. Cognitive impairment will be 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 will be classified as PD-CN.

6.1.2. Diagnosis of cognitive ADL impairment

The self-rated Functional Activities Questionnaire (FAQ) [73] is used to define cognitive ADL function. The FAQ consists of 10 items asking about the ability to perform ADL tasks (ranging from “normal or never did but could do now” to “dependent”). The FAQ allows the differentiation between ADL impairment associated with cognition (FAQ cognition) and ADL impairment associated with motor ability (FAQ motor). A quotient of both scores (FAQQ) > 1.008, indicating more cognitive- than motor-driven ADL impairment, is used as cut-off to differentiate between PD-MCI patients with and without cognitive-driven ADL impairment.

6.2.Exclusion criteria

- Diagnosis of PDD
- Intake of anti-dementia drugs
- Deep brain stimulation
- History of brain disease other than PD (e.g. head trauma, stroke, encephalitis) also including muscular diseases (e.g. myasthenia gravis or myopathy)
- Pre-existing condition that limits limb movement (e.g. muscular injuries, knee and hip disorders)
- severe cardiovascular diseases with heart failure
- severe respiratory diseases (e.g. asthma and lung disease)
- severe other accompanying illnesses with impairment of lung function
- renal insufficiency
- acute stage of infectious disease
- acute stage of cancer
- other disease with pronounced physical weakness
- History of brain disease other than PD, e.g., head trauma, stroke, encephalitis
- Alcohol, medication, or drug dependency or abuse (except for nicotine)
- Signs of severe depression indicated by either the 15 item version Geriatric Depression Scale (> 5 points)
- Acute psychosis
- Any disability or issues 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 compound or therapy within 4 weeks prior to baseline visit, and any other limitation of participation based on local regulations

Eligibility for the study will be assessed by a study physician. Eligibility can also be determined by a general practitioner or a licensed specialist.

6.3.Sample size

As described in Section 10.2, the sample size analysis indicates that 42 people (21 in each intervention group) with PD-MCI and cognitive ADL impairment should be recruited. In our recent study [13], out of 216 PwPD, 29 (13.4%) were classified as having PD-MCI with cognitive-driven ADL impairment, which was 32.6% of PD-MCI patients.

6.4.Recruitment

To end-up with 42 PwPD with PD-MCI (21 per treatment group), 312 PwPD need to be screened, estimated based on our prevalence rates for PD-MCI in previous cohorts [36]. Patients are recruited from the Parkinson's outpatient clinic in the Department of Neurodegenerative Diseases and on the Parkinson's ward. Around 1200 PwPD are treated annually in the university hospital of Tübingen. 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. The last follow-up visit was conducted between February 2023 and January 2025 (PRICOG, ethic protocol 702/2022B01). Participants of the study who had consent to be contacted again for study participation offers will be contacted. Patients will be contacted either via phone or in written form.

Based on a previous ethic vote (local ethical number: 199/2011 B01), we are allowed to contact patients via (e)-mail and to ask them in their interest to take part in a novel study if they have given us previous permission for this procedure. In addition, self-help groups will be contacted and informed about the possibility to pre-screen for possible study participation (see attachment Promotional material for participation in the anonymous pre-screening and study for details).

6.4.1. Anonymous Pre-Screening procedure

The anonymous online pre-screening will be conducted using the REDCap online platform [82]. This anonymous online pre-screening procedure will assess eligibility for study inclusion. Patients can access the platform via an invite link or QR code and fill out the questionnaires and provide the necessary information to assess the inclusion and exclusion criteria.

To protect anonymity, no personally identifiable information such as age or gender is collected. Since the REDCap program does not store IP addresses, direct re-identification is not possible. The necessary information for pre-screening for study eligibility and screening for study participation will include the following questions and assessments: age between 51 and 80, German as their mother tongue, profession of the physician who made the PD diagnosis, alcohol consumption, history of alcohol abuse, drug dependency or abuse (except for nicotine), digital short version of the 15-item Geriatric Depression Scale (GDS) and the FAQ. Patients who confirm that they are aged 50 years or over, that German is their mother tongue, that they have been diagnosed with PD by a neurologist, and that they have no history of acute or chronic drug, medication or alcohol abuse or signs of severe depressive symptoms, as indicated by a GDS score of ≤ 5 points and an FAQ score of > 1.008 , will be eligible for further in-house screening. Those who are not eligible to participate in the study will be notified after

the survey has been completed. If there are indications that a reason for exclusion exists, the person will be informed that they are not suitable for current study participation. Once all the data has been entered into the online screening platform, the patient will receive feedback informing them that they fulfil the criteria for the in-house secondary screening. The contact details of the study team will also be provided. Patients who are eligible for secondary screening will have the opportunity to contact the study team via email to arrange a further screening appointment. It is not possible to contact the person who conducted the survey...

6.5. Patient reimbursement

No reimbursement is provided for online pre-screening or in-house pre-screening. Patients are reimbursed with 20€ for the in-house screening visit (limited to 52 subjects) and with 50€ for the pre-test, post-test and the follow-ups at 6 and 12 months.

6.6. Insurance

The study will be covered by clinical trial insurance, which will cover any consequential damage resulting from the study procedures. The insurance also includes travel accident cover. Please see the attached insurance offer.

Insurance Provider: HDI Global SE

Insurance Number Policy: 5701031103013

Insurance Period: 23.12.2025 – 01.10.2027

Name and address of the insurance company: HDI Global SE, HDI-Platz 1, 30659 Hannover Deutschland, E-Mail: info@hdi.global

Table 1. Overview of study assessments per visit

FUNCTION	ASSESSMENT	STUDY VISIT					TIME (min)
		SCREENING	PRE-TEST	POST-TEST	FOLLOW-UP 1 (6 months)	FOLLOW-UP 1 (12 months)	
		T-1	T0	T1	T2	T3	
Demographics, history & medication							
Socio-demographic history	Age	X					1
	Gender	X					1
	Education		X				3
	Occupation		X				4
Cognitive reserve	Lifetime of Experiences Questionnaire		X				10
History of PD	Age at first PD symptom onset		X				1
	Age at diagnosis	X					1
	Family history of PD or dementia		X				4
Medication & diseases	Medication		X	X	X	X	5
	Concomitant diseases	X	X	X	X	X	8
Safety parameter	(Severe) adverse events (SAE/AE)			X			5
Feasibility parameter	Investigator feasibility			X			-
Satisfaction with training	Patients questionnaire			X			5
Activity of daily living function							
Participants' ratings	Pfeffer Functional Activity Questionnaire (FAQ)	X					5
	Pill-Questionnaire	X				X	8
Informant ratings	(modified) Bayer ADL Scale		X	X	X	X	10
	Pfeffer Functional Activity Questionnaire		X	X	X	X	5
Cognitive battery							
Global cognition	Montreal Cognitive Assessment	Form C	Form A	Form B	Form C	Form A	12
Executive function	Lexical fluency (RWT)		Form A	Form B	Form A	Form B	4
	modified Wisconsin Card Sorting Test		X	X	X	X	20
Attention	Motor-auditory Stoop Task		X	X	X	X	6
	Digit-Symbol Test (WIE)		X	X	X	X	6
	Number-Letter Sequences (WIE)		X	X	X	X	8
Language	Boston Naming Test (RBANS)		Form A	Form C	Form D	Form A	5
	Semantic fluency (RWT)		Form A	Form C	Form D	Form A	4
Memory	Word list Learning & Recall (RBANS)		Form A	Form C	Form D	Form A	12
	FigureRecall (RBANS)		Form A	Form B	Form A	Form B	8
Visual-spatial ability	Figure Copy (RBANS)		Form A	Form B	Form A	Form B	8
	Benton Line Orientation		Odd	Even	Odd	Even	10
Motor and non-motor symptoms							
Quality of life	PDQ-39		X	X	X	X	12
Depression	Geriatric Depression Scale (GDS)	X					5
	Beck Depressions Inventory II (BDI-II)		X	X	X	X	8
Self-efficiency	General self-efficacy scale (GSE)		X	X	X	X	5
Motor function	MDS-UPDRS Part III-IV		X	X	X	X	10
	Hoehn & Yahr Scale		X	X	X	X	4
	Chair Stand Test		X	X	X	X	2
	Timed Up and Go Test		X	X	X	X	4
Laboratory							
Blood withdrawal	Neurofilament Light Levels / Brain-Derived Neurotrophic Factor		X	X		X	10
	Proteomics profile		X	X		X	
Total Time (min)		41	208	196	176	194	

Legend. X*. Assessments will be included for the definition of the composite score of neuropsychological test performance (z-score). MDS-UPDRS. Movement Disorder Society Unified Parkinson's disease rating scale; PDQ-39. Parkinson's Disease Questionnaire; RBANS. Repeatable Battery for the Assessment of Neuropsychological Status; RWT. Regensburger Wortflüssigkeitstest WIE. Hamburg Wechsler Intelligence test.

7. Methods

7.1. Study design

We will conduct a single-center randomized, controlled non-pharmacological intervention trial with pre- (T0) and post (T1)-testing, 6-month (T2) as well as 12-month follow-up (T3) in PwPD with PD-MCI and cognitive ADL impairment. A screening visit (T-1) will be conducted to verify eligibility of participants for study inclusion. The study will follow the Consolidated Standards of Reporting Trials (CONSORT) statement for trials of non-pharmacological treatments.

7.2. Randomization and blinding

The investigator who will perform the clinical assessments will be blinded to participants' assignment to treatment arms. Participants will be instructed to not inform the investigator of the kind of treatment received. After recruitment, all participants will be randomly allocated (1:1) to either the DCT or the CMT through a computer program (<http://www.randomizer.org>).

7.3. Study procedure

An anonymous online pre-screening will be conducted to identify patients eligible for in-house screening. Pre-screening is also available for in-house patients who have given consented to participate in the study.

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 copy will be given to the participant and the other copy will be stored at the local study centre in a separate folder (not in the medical records).

In addition to the patients, informants will be contacted and interviewed. Therefore, informed consent will also be obtained from patients' informants using a separate informant informed consent form. The patients will be asked to choose the caregiver who will then be contacted for the informant assessment.

For patients who participated in the online screening, the online pre-screening survey results will be verified. The in-house screening further rule-out study eligibility (see section 7.4.1 for details). Patients will be assigned to one treatment after the verification of Level II diagnosis of PD-MCI (pre-test visit) status and confirmation of all in- und exclusion criteria. If suitability for the study is confirmed by the screening visit, a trial training session with the ergometer training in sitting position will be conducted for at least 35 minutes to familiarise potentially suitable study participants with the training. During the motor skills trial training, the training intensity is determined and the resistance for cycling on the ergometer is set. This resistance of the ergometer is kept constant throughout the entire training period. Only participants who

report no health issues and feel capable of meeting the demands will be considered for further participation.

Randomised patients will start the home training within ten days (see section 7.5 for details). Post-intervention testing (T1) will be scheduled within ten days of the last home training session. In addition, the 6-month (T2) and 12-month follow-up (T3) are planned with an interval of max +/- 3 weeks around the post-testing date.

7.4. Assessments for study visits

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

7.4.1. Screening

Pre-screening is also available for in-house patients who have given consent to participate in the study. For patients who participated in the online screening, the online pre-screening survey results will be verified. The in-house screening (expected to be conducted in 42 participants) further rule-out whether the ADL limitations are so severe that they indicate dementia and if the cognitive ADL impairment is related to worsening in global cognition assessed by the Montreal Cognitive Assessment (MoCA). Patients who meet the inclusion and exclusion criteria for study participation, have a MoCA score of less than 26 points (a Level I diagnosis of PD-MCI), an FAQQ greater than 1.008, and no impairment in activities of daily living (ADLs) indicative of PDD according to the Pill Questionnaire will qualify for pre-testing.

7.4.2. Assessments of study participants

Please see Table 1 for an overview of study clinical scales and questionnaires conducted at each visit.

Table 2. Overview of clinical study assessments per visit

FUNCTION	ASSESSMENT	TIME (min)
Cognitive reserve	Lifetime of Experiences Questionnaire*	10
History of PD	Age at first PD symptom onset*	1
	Age at diagnosis*	1
	Family history of PD or dementia*	4
	Medication	5
Medication & diseases	Concomitant diseases*	8
	(Severe) adverse events (SAE/AE)*	5
Safety parameter	Pill-Questionnaire	8
Participants' ratings	MDS-UPDRS Part III-IV#	10
Motor function	Hoehn & Yahr Scale#	4
	Chair Stand Test	2
	Timed Up and Go Test	4
Max. total time for in-house assessment		38
Max. total time of assessment, which can be assessed which an additional phone interview		29
Total time		67

Legend: #: For patients with an appointment in the outpatient clinic data will be assessed within the frame of the clinical daily routine; MDS-UPDRS. Movement Disorder Society Unified Parkinson's disease rating scale. *. Information can be assessed within the frame of phone interview

7.4.2.1. Clinical assessments

Table 2 present an overview of planned in-house clinical assessments. If individuals are too tired to complete all of the tests, the measurements marked with an asterisk can alternatively

be assessed within an additional phone interview (max. total 29 minutes). In the Timed Up and Go Test, participants rise from a chair, walk three meters, turn, return, and sit down. In the Chair Stand Test, participants perform five sit-to-stand repetitions without arm support. Participants satisfaction will be assessed after each training session needing around 5 Minutes time.

Table 3. Overview of clinical assessments conducted at home by study patients

FUNCTION	ASSESSMENT	TIME (min)
Participants' ratings	Pfeffer Functional Activity Questionnaire (FAQ)	5
Quality of life	PDQ-39	12
Depression	Geriatric Depression Scale (GDS)+ (Screening visit)	5
	Beck Depression Inventory II+	8
Self-efficiency	General self-efficacy scale (GSE)	5

Legend: +. Only one of the assessment is used in one study visit. PDQ-39. Parkinson's Disease Questionnaire.

The questionnaires described in Table 3 will be given to the study participants, who can then complete them at home. The patient will only complete the FAQ at the screening visit, when the GDS will also be applied. The questionnaire will take a maximum of 25 minutes to complete during one study visit.

7.4.2.2. Biomarker assessment

Fasting before blood sampling is not necessary for biomarker analysis.

Biomarker assessment will contain the following assessment:

- Blood collection 10 min
- Total time for biomarker sampling: 10 min**

Through venipuncture, the following samples will remain in the Hertie Institute for Clinical Brain Research (ethic proposal: 199/2011BO1) until sample analysis (see section 13.4):

- 14 ml of venous blood in 2 à 7 ml Serum tube

7.4.2.3. Retrospective assessments

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 observational clinical studies, these will also be included.

7.4.2.4. Neuropsychological assessments

The aim is to diagnose PD-MCI and PDD according to the Level-II recommendations of the Movement Disorder Task Force [7, 81, 83]. Therefore, the following five domains (see Table 1) will be quantitatively assessed using three subtests of the Wechsler Intelligence Test for Adults (WIE), the Regensburger Word Fluency Test, the modified Wisconsin Card Sorting Test, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS):

At least two tests are assigned to each cognitive domain:

- Executive functions: Lexical fluency (Regensburger Word Fluency Test), modified Wisconsin Card Sorting Test
- Attention: Digit-Symbol Test (WIE), Letter-Number Sequencing (WIE)

-
- Language: Boston Naming Test (RBANS), semantic fluency (Regensburger Word Fluency Test)
 - Memory: Delayed Recall (RBANS), Figure Delayed Recall (RBANS)
 - Visuospatial abilities: Copy (RBANS), Benton Line Orientation

The Montreal Cognitive Assessment (MoCA) will serve as global cognitive screening scale. Additionally, the German version of the Motor-auditory Stoop Task [74] will be designed. The task involves participants walking while giving spoken responses to the words “high” and “low”. The words are delivered with congruent and incongruent tones. To avoid learning effects parallel version of tests (MoCA, Regensburger Word Fluency Test, RBANS) will be included if available (see Table 1).

7.4.3. Informant ADL assessments

As independent impression the modified Bayer ADL Scale (10 min) and the informant rated version of the FAQ informant questionnaires (5 minutes) will be applied, needing informants to be available for at least 15 minutes.

7.4.4. Assessments of satisfaction with training

During the intervention period, participants’ motivation will be addressed, as well as the importance of exercising at home irrespective of training group. These aspects have been reported by professionals as important contributors to compliance with home-based exercise [27]. Satisfaction surveys will be administered after each session.

7.5. Intervention

For 8 weeks, both DCT and CTM group will train 3 times a week for 30 minutes. Both groups will leg-cycle on a bicycle ergometer (e.g., Mini-Ellipsentrainer, aktiv shop GmbH) in a seated position. The DCT group will perform the cycling along with CT, while the CMT will only perform the cycling exercise. After randomization, which will be conducted at day of pre-test, participants will be trained on the use of the ergometer in the clinic. During the trial training within the screening, the training intensity is individually determined and the resistance for cycling on the ergometer is set. This resistance of the ergometer is kept constant throughout the entire training period.

Adherence and feasibility will be ensured as follows. Ongoing technical assistance will be provided, videoconferences will be conducted prior training (1-2 days) to anticipate technical problems. To further increase training safety, participants will sit in a comfortable chair during the lower limb ergometer training. The seating position will be supervised. After the first training session, another video call will be conducted to enquire about difficulties and to answer questions. Booster sessions will be provided whenever desired.

Those assigned to dual task CT will be taught how to handle the tablet computer and to use the HeadApp/NEUROvitalis Digital CT (<https://www.prolog-shop.de>). Each session of the CT will consist of three exercises á 10 minutes covering attention, working memory and executive function. The program will automatically adapt the difficulty level to participants’ performance. A training schedule for each session will be preprogrammed, remotely accessible and modifiable if needed. At sessions 8 and session 16, the training schedule will be altered by changing the cognitive tasks for each cognitive function.

7.6. Timeline of study assessments and procedures

An Overview of the timeline of different study phases is presented in Figure 1.

Study Phase	Tasks & Milestones	2025		2026					2027		
		Sep-Nov	Dec	Jan-Feb	Mar-May	Jun-Aug	Sep-Nov	Dec	Jan-Feb	Mar-May	Jun-Aug
Planning	contract signed and returned										
	IRB approval & trial registration										
	Design of dual task cognitive training										
	Design of clinical trial report form & database programming										
	Training of staff										
Execution	Recruitment of eligible patients/screening visit										
	Baseline tests/ pre-tests										
	Biomarker collection and processing										
	Conduction of intervention										
	Post-tests with assessment of short-term effects										
	6 moths follow-up testing for assessment of mid-term effects										
	12 months follow-up testing for assessment of long-term effects										
	Data entry										
Analysis	Analysis of biomaterial										
	Statistical analysis of short- and mid-term effects and preparation of manuscripts										
	Statistical analysis of long-term effects and preparation of manuscripts										

Figure 1. Overview of timelines and milestones during the study funding period

7.7. Study duration

The end of the funding period is 31.08.2027. Based on the project investigator's experience of working on similar projects, we anticipate that the final analysis and submission for publication will take another year.

8. Radiation application

Not applicable

9. Benefit-risk assessment

9.1. Individual benefit of study participation & statement for cost-benefit analysis

Since the effectiveness of the training has not yet been investigated, the positive effects on study participants cannot be anticipated. A comparable study using a DCT on an ergometer has so far only been conducted as an in-house training session in a very small study group [48], with different outcomes than this study. First evidence has shown that telerehabilitation improves cognition in PwPD [23, 24, 26, 29, 30], and online Occupational Therapy program can positively affect motor skills, cognitive function, and ADL function in PD patients [84]. Patients often have to travel long distances to attend on-site training. Travelling alone is particularly challenging for our target group, since travelling is a cognitively complex ADL [41], which is expected to be impaired in PwPD with PD-MCI and cognitive ADL impairment. These travel difficulties limit access to healthcare, making PwPD dependent on support from relative, increasing the burden on patients and their informants. Because our training is a home-training, requiring no travelling, our training facilitates access to healthcare. Improving motor-

cognitive aspects of ADL impairment and leg-strength may increase PwPDs' ability and self-confidence to engage in different ADL actions. This translates into changes in daily movement patterns. Hence, implementing the DCT at home can help participants in maintaining and improving autonomy in daily life.

In summary, based on the current evidence, we believe that the benefits of participating in the study outweigh any potential disadvantages.

9.2. Risks and possible adverse events

The potential risks and side effects of participating in the study are described below. In general, no negative effects on individuals are known from the use of paper and pencil tests. However, there is a risk that individuals with limited resilience may become fatigued during the clinical visit. Therefore, care was taken in advance to ensure that only the minimum of essential information will be collected, and some of the questions could also be asked during a telephone interview.

9.2.1. Clinical assessments

The Timed Up and Go and Chair Stand pose minimal to low risk when conducted with appropriate supervision and standardized safety protocols. In people with gait instability or/and orthostatic dysfunction, the risks potential risks include falling during transfer or/and walking. Additionally, risks include vertigo, or fainting. For people with gait instability, the test is performed by two investigators to prevent falls and stabilise the patient. Those who experience severe difficulties and a fall tendency during the task will not be given the opportunity to complete it. The other assessments pose no relevant risk.

9.2.2. Biomarker sampling

The amount of blood intended to be taken (2x 7 ml serum blood) is harmless to health. 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. 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).

9.2.3. Neuropsychological testing

No relevant risk.

9.2.4. Informant ADL Assessments

No relevant risk.

9.2.5. Assessments of training motivation and satisfaction with training

No relevant risk.

9.2.6. Intervention

During the lower limb ergometer training, participants will sit in a comfortable chair. Therefore, risk for falls is minimized. Informants will be instructed to supervise participants seating position according to the instructor's recommendation. Regarding the DCT, the computer tablet is stabilized on the arm by a specialist holder. This holder allows the participants to perform cognitive tasks in a comfortable sitting position. Therefore, we

expected minimal safety risks for our study participants. However, it is possible for participants to overexert themselves during training, especially if the training is repeated on several consecutive days. The individual resistance level of the machine will be determined on-site during a supervised trial session and should not result in any visible strain after 30 minutes. The determined resistance level will be kept constant throughout the training period. In principle, it is possible that test subjects might not release the foot strap of the ergometer and therefore injure themselves. To minimize the risk of injury, we recommend wearing sturdy (sports) shoes during the training.

9.3. Criteria for study termination

9.3.1. Criteria for terminating study participation of individual study participants

Participants can withdraw from the study at any time, for any reason or no reason. No written statement is required. A verbal statement is sufficient. Participants will be excluded from the study if they develop any of the conditions listed in the exclusion criteria before completing the post-test. If any of these conditions develop after the post-test but before the follow-up examinations, the respective participant will not be asked to undergo further testing.

9.3.2. Criteria for termination of the whole study

The study will be terminated if it is not possible to recruit at least 20% of the calculated sample size of study participants, even if a sufficient number ($> n = 60$) of PwPD with PD-MCI and cognitive ADL impairment are identified and contacted for study participation. This would suggest that there is no need for our training. Another reason for terminating the study is if more than 75% of people PwPD randomised to the intervention group drop out. This would mean that it would not be feasible to conduct our telerehabilitation for study participants.

Table 4. Overview of primary and secondary study outcomes and predictors

FUNCTION	ASSESSMENT	OUTCOME		
		PRIMARY	SECONDARY	PREDICTOR
Socio-demographic history	Age			X
	Gender			X
	Education			X
	Occupation			X
Cognitive reserve	Lifetime of Experiences Questionnaire			X
History of PD	Age at first PD symptom onset			X
	Age at diagnosis			X
	Family history of PD or dementia			X
Medication & diseases	Medication			X
	Concomitant diseases			
Safety parameter	(Severe) adverse events (SAE/AE)			X
Feasibility parameter	Investigator feasibility		X	
Satisfaction with training	Patient's questionnaire		X	
Informant ratings	(modified) Bayer ADL Scale		X	
	Pfeffer Functional Activity Questionnaire	X		
Global cognition	Montreal Cognitive Assessment		X	
Executive function	Lexical fluency (RWT)		X*	X*
	modified Wisconsin Card Sorting Test		X*	X*
Attention	Motor-auditory Stoop Task	X		
	Digit-Symbol Test (WIE)		X*	X*
	Number-Letter Sequencing (WIE)		X*	X*
Language	Boston Naming Test (RBANS)		X*	X*
	Semantic fluency (RWT)		X*	X*
Memory	Word list learning & Recall (RBANS)		X*	X*
	Figure Recall (RBANS)		X*	X*
Visual-spatial ability	Copy (RBANS9)		X*	X*
	Benton Line Orientation		X*	X*
Quality of life	PDQ-39		X	
Depression	Beck Depressions Inventory II (BDI-II)			X
Self-efficiency	General self-efficacy scale (GSE)		X	X
Motor function	MDS-UPDRS Part III-IV			X
	Hoehn & Yahr Scale			X
	Chair Stand Test			X
	Timed Up and Go Test		X	
Laboratory				
Blood withdrawal	Neurofilament Light Level/ Brain-Derived Neurotrophic Factor		X	
	Proteomics profile			X

Legend. X*. Assessments will be included for the definition of the composite score of neuropsychological test performance (z-score). PDQ-39. Parkinson's Disease Questionnaire; Repeatable Battery for the Assessment of Neuropsychological Status. RWT. Regensburger Wortflüssigkeitstest; WIE. Hamburg Wechsler Intelligence test.

However, an undersample would require adjustments to the analytical procedures (e.g. the calculation of effect sizes) and will be conducted at least on a descriptive level also with this

very small sample size. However, we expect the greatest gain in information after a study discontinuation to come from the publication of the low feasibility and low acceptance of the training in our target patient group. Due to the limited number of studies, we believe that the results of our training study still provide valuable additional knowledge.

10. Biometrics

This section describes the sample size analysis and the statistical procedure used to test the questions and hypotheses.

10.1. Study outcomes

An overview of the parameters used as primary, secondary, and exploratory endpoints is provided in Table 4. For primary and secondary outcomes change in the DCT compared to the CMT (group x time interaction) will be defined. The composite score of neuropsychological performance will be calculated as mean z-score of tests assigned to the following domains: executive function, attention, memory, language, and visuo-spatial abilities.

Feasibility of the investigator includes a comparison of the total number of treatment sessions between groups during the intervention period, the total time of the intervention in minutes, the quotient of the total intervention time per participant by the maximum required treatment time, the number of participants lost to follow-up between randomization and the post-test, and the reason for dropping out of the study.

The number of PwPD with diagnosis of PDD at 12-month follow-up will for each study group will serve as exploratory outcome. Table 4 indicates possible predictors for response to treatment.

10.2. Sample size calculation

The required sample size was calculated using G*Power. Medium effect sizes ($d=0.56$) are estimated based on the non-telerehabilitation dual-task cognitive-motor intervention versus cycling exercises only in a small sample [48]). Additional, efficacy of a previous 12-week home-based digital cognitive training in PD-MCI patients ([29]) also revealed moderate effect sizes ($g = 0.31$). Therefore, an effect size of $f=0.28$ were included in the sample size analysis. With a power of 80% and an alpha level of 5% for an ANOVA repeated measures within-between interaction (drop-out rate of 20% per group) over four time points (correlation among repeated measures $r=0.40$), 21 PwPD per group need to be included.

10.3. Statistical analysis

Statistical analyses will be conducted using R (<https://www.r-project.org/>), IBM SPSS Statistics (Version 29) and Jasp (<https://jasp-stats.org/>).

10.3.1. Between group comparison

Comparisons are made between the groups in the pre-test for PwPD, who were randomly assigned to either the DCT or the CMT, appropriate to the data level. The Mann-Whitney U or Mann-Whitney-U or Welch test will be applied for non-parametric numeric data, and the t-test for independent samples for parametric numeric data. The χ^2 test or Exact Fisher Test will be applied for between-group comparison of for categorical variables. If the intervention

groups differ in their baseline profiles, confounding variables will be included in adjustable analyses of treatment effects.

10.3.2. Efficacy of intervention

The effect of the intervention on primary and secondary outcome parameters (time [pre-test, post-test, follow-up] x group [DCT, CMT] interaction) will be analyzed with ANOVA repeated measures within-between interaction or linear mixed effects models to add between-group covariates. Participants will be added as random effects and random slopes of time will be tested for improved model fit. Bayesian tests will be also calculated (mixed ANOVA for mixed model, t-test for post-hoc comparisons).

If the efficacy analysis of intervention is underpowered due to problems in recruitment effect size analysis will be conducted to rate treatment effects.

10.3.3. Safety, feasibility and satisfaction of intervention

The feasibility of training will be assessed as number of participants undergoing randomization/ number of participants undergoing post assessment as well as the difference between the total maximum recommended training time and the actual training time performed by each participant. Additionally, learning rate will be assessed by the change in the quotient of correct answers to total answers. The elapsed distance in kilometers cycled by participants will also be assessed. Safety will be assessed based on the number of adverse events. Satisfaction with the training will be assessed using a survey after each session. The analysis will include an average of a 6-point Likert scale (1 = “not at all”, 6 = “very satisfied”) over items covering various aspects.

10.3.4. Between group comparison of PDD conversion at 12-months follow-up

Long-term follow-up status of PDD among study groups will be compared with logistic regression models.

10.3.5. Prediction of responsiveness to treatment

Exploratory linear regression models will be used to examine the responsiveness to intervention (change scores) for possible predictors with forward selection to identify variables influencing the responsiveness. To minimize the number of variables into the regression models correlation between each single variable and the change score of interest will be conducted. Only variables with at least a moderate association with the change score ($r \geq 0.30$) will be included in the regression models. The change scores will be calculated for the following study intervals: between pre-test and post-tests, between pre-test and 6-months follow-up and between pre-test and 12-months follow-up.

In addition, the protein profile associated with treatment response will be explored by proteomics analysis.

11.Data management and 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.

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

A list of participants' name, age, and contact data are collected in a separate folder 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 [82]. 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 PIs will only receive coded information that has been entered into the database under those identification numbers. Data stored will include the measurements described in Table 1.

Electronic communication with outside collaborators will involve only unidentifiable information.

11.3. Transfer of data to collaboration partners

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 pseudonymized data will be transferred.

If the patient agreed for this procedure, pre-processed blood samples will be transferred to

- Prof. Dr. Andrea Pilotto,
- Digital Neurology and Biosensors Laboratory & Neurobiorepository and Laboratory of advanced biofluid markers
Spedali Civili of Brescia, Brescia, Italy.

Prof. Dr. Andrea Pilotto will conduct Proteomics analysis to identify proteins associated with a positive treatment response, especially in the long-term. For this analysis further clinical data (e.g. outcome data to define treatment response) will be transferred.

11.4. Image and sound recordings

Not applicable.

11.5. Withdrawal of study participation

Participants can withdraw from the study at any time, for any reason or no reason. No written statement is required. A verbal statement is sufficient. Participants will be excluded from the study if they develop any of the conditions listed in the exclusion criteria before completing the post-test. If any of these conditions develop after the post-test but before the follow-up examinations, the respective participant will not be asked to undergo further testing.

11.6. Period of data storage

Data will be stored for 10 years.

11.7. 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 the Co-PI M.Sc. Merle Bode (phone: +497071-2980424, fax: +497071-294490, e-mail: Merle.Bode@med.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.

12. Telemedical Assessment

12.1. Data Registration

Access to the software program is provided via a tablet. The tablet will be made available to the test subjects for the duration of the training. Recommended is the use of Tablets with Android operating system from version 9 (Pie API 28, screen size from 10 inches) and Tablets with Apple operating system iPadOS 13 (screen size from 9.7 inches).

We will use the HeadApp/NEUROvitalis Professional Online programm, which enables cognitive teletherapy under the supervision of a therapist, without physical contact. HeadApp/NEUROvitalis Professional Online can be installed and used on multiple devices, including PCs and mobile devices. One license covers the training of up to 10 patients exercising simultaneously.

12.2. Software information, certificate, producer

HeadApp / NEUROvitalis is a class I medical device for the therapy of cognitive impairments. HeadApp / NEUROvitalis is software for cognitive rehabilitation therapy / brain performance training. The platform provides numerous therapy programs for those affected by cognitive impairments in the areas of attention, memory, executive functions and language. The software meets all the provisions of the Medical Device Directive MDD (93/42/EEC), which apply to it.

Producer

HelferApp GmbH
Zur Klus 31
39175 Gommern OT Wahlitz

Tel.: +49 392 00 491 491
E-Mail: info@helferapp.com

12.3. Contraindication and risk for product use

Patients with impaired vision and reading ability, poor hearing and impaired text comprehension and children under 12 years of age should not use HeadApp / NEUROvitalis or only use it under therapeutic supervision.

No residual risks and undesirable side effects are known when using HeadApp / NEUROvitalis. According to IEC 62304, the HeadApp / NEUROvitalis software was classified in safety class A: No injury or damage to health is possible.

The medical device must be used in an environment that avoids distractions and disturbances during exercise.

12.4. Datatransfer, Data storage, Authorized access, Encryption type, deletion

Therapy material is constantly being downloaded from servers on the Internet, and therapy progresses are stored on servers. A constant internet connection is necessary for this. A speed of at least 4 Mbps is necessary to ensure smooth work.

If a mobile data connection is used, an average data consumption of 200 Mbit (0.2 GB) per patient and month can be expected.

HeadApp / NEUROvitalis communicates with various web servers via the HTTPS protocol. The attached document, 'HeadApp Info Data Protection and Server', provides an overview of all the technical and data privacy issues. Figure 2 visualises the data flow.

The HTTPS connection to the servers described in the document must be allowed in the firewall.

Data Flow Diagram (DFD)

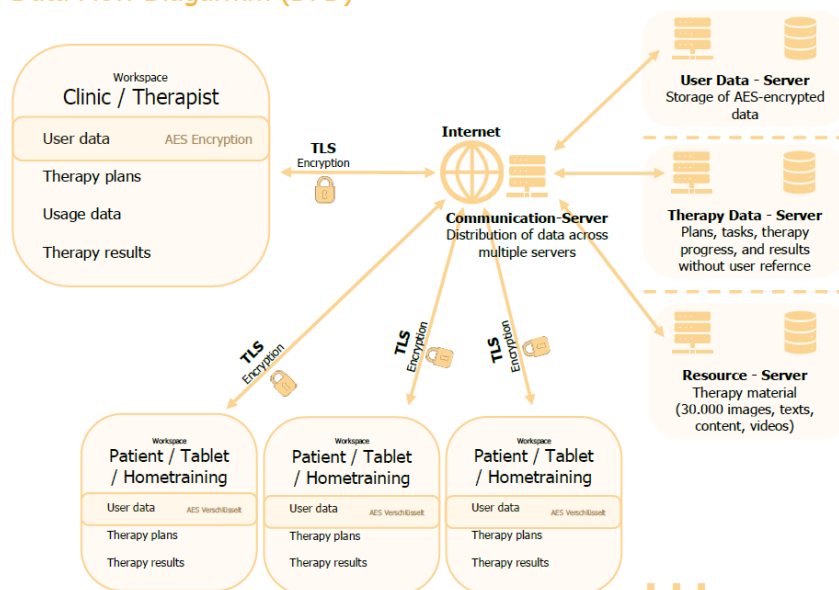


Figure 2. Overview of data flow using the HeadApp/Neurovitalis

All servers are located in Germany/EU and are rented from Amazon Web Services (AWS) and its resellers. AWS guarantees secure data storage in accordance with EU regulations, is certified under the EU–US Data Privacy Framework (DPF), and adheres to the DPF principles. The user data server uses AES-256 encryption to ensure the highest security for stored data. Similarly, data on the therapy data server is encrypted with AES-256 to protect sensitive information from unauthorized access. AES-256 encryption is extremely secure. It is currently the most secure encryption algorithm available and is widely used in government and military applications, as well as by companies in highly regulated industries. The encryption uses a 256-bit key length, which is considered practically unbreakable—even with the most advanced

computational power and algorithms. This provides the same level of security used by banks and other financial institutions to safeguard sensitive customer information. Additionally, TLS encryption version 1.3 is used for secure data transmission, offering the highest currently available security level for Transport Layer Security.

Participants will log in to the training using a pseudonymised code. During the training period of the study, both the study participant and the supervising neuropsychologist will have access to the data. Afterwards, the study participant the supervising neuropsychologist can access the data at all time. Data will be transferred to the study center every three months as csv file. Data will be stored on the HeadApp/Neurovitalis server until the complete dataset has been transferred to the study centre. Once this has been done, the data will be deleted from the company's server.

All members of the study team will then have access to the trainings data. The data on the server will be deleted once it has been transferred.

12.5. Temporary Access Link to the program

Download Programm is available under the following link:

<https://www.headapp.com/en/download-en/?td=o>

Login Data:

- Login (E-Mail): headapp@uni-tuebingen.de
- Passwort: 72076

The following access code is valid until 31.12.2025.

First steps with HeadApp:

- Launch HeadApp in your browser at <https://start.headapp.com> and log in using the above credentials for the Professional version. Alternatively, you can download the app from the App Store or Play Store.
- You can use the login on multiple devices simultaneously.
- After logging in, you will be taken to the patient list. To start training or screening, create a "test patient."

A brief overview and decription of the subtests be found via this link: <https://www.headapp.com/wp-content/uploads/HeadApp-Klappflyer-A3-innen.pdf>.

Additionally, we attached the manual of the HeadApp/Neurovitalis program including an overview of tests.

13.Biomaterial

13.1. Type of Biomaterial and Responsibilities

Serum BDNF and NFL parameters will be analysed in cooperation of the Neurobiobank of the Hertie Institute for Clinical Brain Research and the Neurolaboratory of the Universitätsklinikum Tübingen (UKT). 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. Additionally, some biomaterial will be transferred to our collaborator, Professor Andrea

Pilotto, for proteomics analysis (see Section 11.3 for details). Proteomics data will be analysed as potential predictor for treatment response.

13.2. Storage of biomaterial

All samples will be stored at -80°C until the time of analysis. 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. Samples will be destroyed after analysis of BDNF and NFL values.

13.3. Withdrawal of Consent

The test subject may request the anonymisation or deletion of stored data, as well as the destruction of stored biological samples, at any time and without providing reasons. However, this only applies if the samples and data have not already been released to other researchers or anonymised.

13.4. Biobank Storage

Sample storage in the Hertie Institute for Clinical Brain Research (ethic proposal: 199/2011BO1) is only temporary until sample biomarker analysis.

14. Attachments

See attachments:

- Patient information sheet and informed consent form
- Patient data privacy statement
- Informant information sheet and informed consent form
- Informant data privacy statement
- HeadApp Information on Dataprotection and Server
- Promotional material for participation in the anonymous pre-screening and study
- Insurance offer and insurance conditions

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