Exploring the Effects of Exercise on Memory and Cognition in Parkinson´s Disease (EMCo)

- Study Protocol & Statistical Analysis Plan -

Principal Investigators:
Prof. Dr. Simon Steib
Institute for Sports und Sports Sciences
Heidelberg University
E-Mail: simon.steib@issw.uni-heidelberg.de

Dr. Philipp Wanner
Institute for Sports und Sports Sciences
Heidelberg University
E-Mail: philipp.wanner@issw.uni-heidelberg.de

Sub-investigators:
Charlotte Hohloch
Institute for Sports und Sports Sciences
Heidelberg University
E-Mail: charlotte.hohloch@issw.uni-heidelberg.de

Collaborators (alphabetical order):
Dr. med. Andreas Becker
Abteilung für Neurologie
SRH Kurpfalzkrankenhaus Heidelberg

PD Dr. med. Julian Conrad
Abteilung Neurodegeneration
Universitätsklinikum Mannheim

Prof. Dr. med. Brigit Friedmann-Bette
Sportmedizin
Universitätsklinikum Heidelberg

PD Dr. med. Heike Jacobi
Neurologie und Poliklinik
Universitätsklinikum Heidelberg

Prof. Dr. med. Rebecca Schüle-Freyer
Sektion Neurodegeneration
Universitätsklinikum Heidelberg

Prof. Dr. med. Jochen Weishaupt
Abteilung Neurodegeneration
Universitätsklinikum Mannheim

Supporting Biometrician:
Dr. Marietta Kirchner
Institut für medizinische Biometrie
Universitätsklinikum Heidelberg

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1 Aims and hypotheses

The study aims to assess the effects of cardiovascular (aerobic) training on memory formation and cognitive function in people with Parkinson's disease (pwPD). Participants will be randomly allocated to one of two groups either performing cardiovascular training (experimental group) or stretching (control group) for twelve weeks, three times a week. We examine whether moderate-intense cardiovascular training (MICT) improves procedural memory formation (primary outcome) compared to stretching and mobility training. Secondary outcomes include episodic memory formation, cognitive function, cardiorespiratory fitness, sleep quality, and brain-derived neurotrophic factor (BDNF) blood concentration levels.

1.1 Primary aims

Our primary research question is to investigate the effects of cardiovascular training on non-declarative (procedural) memory formation. A first study in pwPD demonstrated an improved encoding of motor sequences after a twelve-week cardiovascular training in a pre-post design (Duchesne et al., 2015). Further randomized controlled trials in populations with different neurological conditions reported enhanced encoding (Quaney et al., 2009) and consolidation (Lo et al., 2023) of motor sequences. We, therefore, expect that cardiovascular training improves all aspects of procedural memory formation. To assess the effects of cardiovascular training on non-declarative (procedural) memory formation, we will calculate a global motor learning score (i.e., change from start of encoding to 24h recall test) for explicit and implicit components of motor sequence learning and analyze the change (delta) in the global motor learning scores from pre- to post-intervention assessments. This procedure results in two primary outcome variables: (i) explicit global motor learning score and (ii) implicit global motor learning score. The primary questions (Q) are:

Q1: Does twelve weeks of cardiovascular training improve the explicit components of non-declarative (procedural) memory formation in pwPD?
We expect that a twelve-week cardiovascular training program improves the global motor learning score (i.e., performance changes from start of encoding to a 24 h recall test) for explicit components of motor sequence learning.
Q2: Does twelve weeks of cardiovascular training improve the implicit components of non-declarative (procedural) memory formation in pwPD?
We expect that a twelve-week cardiovascular training program improves the global motor learning score (i.e., performance changes from start of encoding to a 24 h recall test) for implicit components of motor sequence learning.

1.2 Secondary aims

To disentangle the effects of cardiovascular training on the different processes of non-declarative (procedural) memory formation, we will investigate the encoding and consolidation of the motor sequence learning task in secondary analyses. We will calculate the encoding and consolidation performance for the explicit and implicit components resulting in four outcome variables. We expect a global effect of cardiovascular exercise on procedural memory formation, and thus an improvement in all variables.

Q3: Does twelve weeks of cardiovascular training improve the encoding and consolidation of non-declarative (procedural) memory in pwPD?
We expect that a twelve-week cardiovascular training program improves the encoding of explicit components of motor sequences.
We expect that a twelve-week cardiovascular training program improves the encoding of implicit components of motor sequences.
We expect that a twelve-week cardiovascular training program improves the consolidation of explicit components of motor sequences.
We expect that a twelve-week cardiovascular training program improves the consolidation of implicit components of motor sequences.

In a next step, we will investigate the effects of cardiovascular training on (i) declarative (episodic) memory and (ii) cognitive function (Kim et al., 2023). We expect that if the exercise-induced effects on brain function are global, declarative memory and cognitive function should also be enhanced. For declarative (episodic) memory, similar to non-declarative (procedural) memory we will first analyze the global episodic learning score (i.e., performance change from start of encoding to recall test) followed by a separate analysis of encoding and consolidation. For global cognitive function we will first analyze a composite score including the domains (i) short-term memory, (ii) working memory, (iii) inhibition, and (vi) cognitive flexibility followed by a separate analysis of each domain.

Q4: Does twelve weeks of cardiovascular training improve declarative (episodic) memory in pwPD?
We expect that a twelve-week cardiovascular training program improves the global episodic learning score (i.e., performance changes from start of encoding to a 24 h recall test).
Q5: Does twelve weeks of cardiovascular training improve the encoding and consolidation declarative (episodic) memory in pwPD?
We expect that a twelve-week cardiovascular training program improves the encoding of episodic memory.
We expect that a twelve-week cardiovascular training program improves the consolidation of episodic memory.

Q6: Does twelve weeks of cardiovascular training improve cognitive function in pwPD?
We expect that a twelve-week cardiovascular training program improves global cognitive function in pwPD.
We expect that a twelve-week cardiovascular training program improves short-term memory, working memory, inhibition, and cognitive flexibility in pwPD.

We will then examine the effects on (i) cardiorespiratory fitness (Schootemeijer et al., 2020), (ii) sleep (Cristini et al., 2021), and (iii) BDNF blood concentration (Kaagman et al., 2024) to explore potential mechanisms of the exercise-induced effects on memory and cognition (see exploratory analyses) (Loprinzi et al., 2021).

Q7: Does twelve weeks of cardiovascular training improve cardiovascular fitness in pwPD?
We expect that a twelve-week cardiovascular training program improves peak oxygen consumption (VO_{2peak}).
Q8: Does twelve weeks of cardiovascular training improve sleep in pwPD?
We expect that a twelve-week cardiovascular training program improves objectively measured sleep efficiency.
We expect that a twelve-week cardiovascular training program improves subjective disease-related sleep disturbances.
Q9: Does twelve weeks of cardiovascular training improve brain-derived neurotrophic factor (BDNF) blood concentration level in pwPD?
We expect that a twelve-week cardiovascular training program increases resting serum BDNF blood concentration levels.

In exploratory analyses, we will lastly investigate potential determinants of the exercise-induced effects on memory formation and cognition (Loprinzi et al., 2021). We will explore the associations between changes in memory formation and (i) cognitive function (especially working memory), (ii) cardiorespiratory fitness, (iii) sleep, and (iv) BDNF levels, respectively. We will further test whether changes in cognitive function are associated with changes in (i) cardiorespiratory fitness, (ii) sleep, and (iii) BDNF levels, respectively. We expect that changes in these variables will be associated with changes in memory formation and cognition. The following questions are analyzed in exploratory analyses:

Q10: Are exercise-induced changes in non-declarative (procedural) memory formation associated with changes in (i) cognitive function (especially working memory), (ii) cardiorespiratory fitness, (iii) sleep, and (iv) BDNF blood concentration in pwPD?
Q11: Are exercise-induced changes in declarative (episodic) memory formation associated with changes in (i) cognitive function (especially working memory), (ii) cardiorespiratory fitness, (iii) sleep, and (iv) BDNF blood concentration in pwPD?
Q12: Are exercise-induced changes in cognitive function associated with changes in (i) cardiorespiratory fitness, (ii) sleep, and (iii) BDNF blood concentration in pwPD?

2 Study design

2.1 General procedure

In a randomized controlled trial, pwPD with mild to moderate disease stage (i.e., Hoehn & Yahr ≤3) will either perform moderate-intensity cardiovascular training (experimental group) or stretching training (control group) for twelve weeks (three times per week, totaling 36 training sessions; duration per training session 30 to 55 min). For group allocation, we will use block randomization stratified by biological sex (male / female) and age (<62 / ≥ 62), since these two factors may influence procedural memory (Smith et al., 2005) and the effects of exercise on cognition (Kramer & Colcombe, 2018). The outcome variables will be assessed at baseline (pre-assessment, within two weeks before the intervention) and after the intervention (post-assessment, within two weeks after the intervention has terminated).

2.2 Intervention

Both, cardiovascular training (experimental group) as well as stretching training (control group), will be performed in supervised sessions and in small groups of 2-5 persons at the study site.

Experimental group (Duchesne et al., 2015; Sacheli et al., 2019): Cardiovascular training is performed on a cycle ergometer at 60% of peak power output (Wmax) for 30 min (i.e., 5 min warm-up, 20 min at 60% Wmax, 5 min cool-down) three times a week for twelve weeks. The exercise program will be increased by 5 min (max. 55 min) and 5% of intensity (in Watt) every two weeks. If participants report a too low (i.e., Borg scale ≤ 11) or too high (i.e., Borg scale ≥ 16) subjective rate of perceived exertion (RPE; Borg scale 6-20) intensity will be increased or decreased until the target levels are met (i.e., Borg scale 12-15). During training, heart rate, intensity (in Watt) and RPE will be monitored. Participants missing training sessions will be offered an additional week to perform up to three training sessions.

Control group (Duchesne et al., 2015; Sacheli et al., 2019): Stretching training consists of lying, seated, and standing flexibility exercises (according to the recommendations of the American Parkinson´s Disease Foundation and the Parkinson Society Canada) for 30 min (i.e., 5 min warm-up, 20 min main part, 5 min cool-down) three times a week for twelve weeks. The exercise program will be increased by 5 min (i.e., adding additional repetitions and exercises; max. 55 min). Intensity of stretching exercises will be assessed by subjective rate of perceived muscle tension on a visual analog scale (VAS) from 0 to 10. We aim for a moderate muscle tension defined as 5 to 7 on the VAS. During training VAS, heart rate, and RPE will be

monitored. Participants missing training sessions will be offered an additional week to perform up to three training sessions.

2.3 Study sample

Inclusion criteria:

- Diagnosed Parkinson's disease (Postuma et al., 2015)
- Disease stage ≤3 on the Hoehn & Yahr scale
- Age ranging from 50 – 80 years
- Naive to the memory tasks (primary outcome)
- Ability to stand and walk at least 10 meters independently

Exclusion Criteria:

- Atypical Parkinsonism
- Significant level of cognitive impairment (i.e., Montreal Cognitive Assessment <21) (Dalrymple-Alford et al., 2010)
- Deep brain stimulation or brain pacemaker
- Diagnosed psychiatric illness
- Known clinically relevant neurological, internal or orthopedic conditions besides Parkinsonism that would interfere with the exercise paradigm
- Exceeding the recommended level of cardiovascular exercise for older adults (i.e., cardiovascular exercise done ≥150 min per week of moderate-intensity or ≥75 min per week of vigorous-intensity)

2.4 Sample size justification

Following the recommendations by Lakens (2022), the sample size is based on the available resources and the potential gain in information. Due to resource constraints the maximum sample that can be collected is n = 60 participants (n = 30 per group). We used this sample size to perform a sensitivity power analysis (G*Power, version 3.1.9.7) for the primary analysis (see 4). The analysis of covariance (ANCOVA) includes the respective primary outcome (i.e., explicit global motor learning score and implicit global motor learning score) as dependent variable, group (i.e., experimental vs. control group) as between-subject factor, and the baseline value of the primary outcome variable and the stratification criteria (i.e., age and biological sex) as covariates. With an alpha level of 2.5% (adjusted for two primary outcomes) the study has 80% power to detect an effect of at least $f = 0.41$, which is considered a large effect according to Cohen (1988). With an anticipated drop-out rate of ~15-20% resulting in a total sample size of n = 50 the study has a power of 80% to detect an effect of at least $f = 0.45$ (due to imputation of missing values, a power increase can be expected). Therefore, the study

has sufficient power to detect an effect size reported in comparable studies investigating the effects of cardiovascular training on procedural memory formation in people with neurological conditions (Lo et al., 2023; Quaney et al., 2009). Furthermore, this will be the study with the largest sample of people with neurological conditions to date assessing the effects of cardiovascular training on non-declarative (procedural) memory.

3 Outcome Measures

An overview of all primary and secondary outcomes as well as screening and descriptive variables is listed in the table in the appendix. The outcome variables will be assessed at baseline (pre-assessment, within two weeks before the intervention) and after the intervention (post-assessment, within two weeks after the intervention has terminated). For primary and secondary outcomes measures, we will calculate the change (delta) from pre- to post-intervention assessments to evaluate the effects of cardiovascular training.

3.1 Primary outcomes

Domain	Measures	Outcome measure
Non-declarative (procedural) memory: global motor learning score	To evaluate non-declarative (procedural) memory formation, we will use the Visuomotor Serial Targeting Task (VSTT). The VSTT has been widely used to study motor sequence learning in pwPD and other neurological condition (Ghilardi et al., 2003; Ghilardi et al., 2007; Marinelli et al., 2017). The task consists of eight radially arranged circles (targets) around a central circle (center) on a computer screen (distance from center to targets: 4 cm; radius of targets: 1 cm). One of the targets turn red in a fixed interval of 1.5 sec in synchrony with a tone. The participants are instructed to move a cursor using a digitizing tablet (Wacom Intuos Pro Large, Wacom; Wacom; Toyonodai, Kazo-shi, Saitama, Japan) with the dominant hand from the center to the displayed target with a single, uncorrected out movement, reverse sharply inside the target and do a similar back movement to the center. To assess motor sequence learning, the eight targets appear in a repeating order. The participants are instructed to learn the sequence while moving the cursor to the targets and reach the target in synchrony with its appearance (i.e., movement start before appearance) when the location is known (i.e., learned). Encoding consists of six blocks with each block including eight repetitions of the eight-target sequence (i.e., 64 movements per block), whereas the recall test contains three blocks of similar size. For each movement, we will calculate (i) onset time (i.e., time between target display and out movement start), (ii) movement time (i.e., time from out movement start to end), (iii) peak velocity, (iv) directional error at peak velocity (i.e., angular deviation between real and ideal movement trajectory at peak velocity), (v) spatial error to target (i.e., shortest distance of the out movement end to	1) Change in explicit global motor learning score from pre- to post-assessment 2) Change in implicit global motor learning score from pre- to post- assessment

	the target center), (vi) spatial error to ideal movement (i.e., root mean squared error between real and ideal movement trajectory), and (vii) normalized hand-path area (i.e., area enclosed by the out and in movement divided by the squared path length) to analyze practice-related changes in temporal and kinematic movement characteristics. We will use the number of correct anticipatory movements defined as movements with onset times lower than in random trials and directed to the correct target (directional error at peak velocity <22°) to analyze the learning of explicit components of the motor sequence (Ghilardi et al., 2009). To assess the learning of implicit components of the motor sequence, we will use spatial error to target (shortest distance of the movement end point from the center of the target) (Ghilardi et al., 2009). We will calculate a global motor learning score defined as relative change from first block of encoding to first block of 24h recall test for the explicit and implicit component of the task, respectively. To assess the effects on non-declarative (procedural) memory formation, we will analyze the change (delta) in the explicit and implicit global motor learning score from pre- to post-intervention assessment. Hence, two primary outcome measures from the VSTT are considered to answer the primary research questions.	

3.2 Secondary outcomes

An overview of all secondary outcome measures is listed in the table below.

Domain	Measures	Outcome measure
Non-declarative (procedural) memory: encoding and consolidation	To evaluate the effects on the different processes of non-declarative (procedural) memory formation, we will investigate the encoding and consolidation of the motor sequence for the implicit and explicit components, respectively. Encoding will be defined as relative performance change (delta) from beginning (first block of encoding) to end (last block of encoding) of practice, whereas consolidation will be calculated as relative performance change (delta) from end of practice (last block of encoding) to a 24h recall test (first block of recall). This results in four secondary outcome variables for the VSTT.	1) Change in encoding of the explicit component from pre- to post assessment 2) Change in encoding of the implicit component from pre- to post assessment 3) Change in consolidation of the explicit component from pre- to post assessment 4) Change in consolidation of the implicit component from pre- to post assessment
Declarative (episodic) memory	To evaluate the effects on declarative (episodic) memory, we will use the German version of the Rey Auditory Verbal Learning Test (Helmstaedter et al., 2001). In addition to the standard retrieval after 20 min, we conduct a recall test after 24h to investigate the consolidation following nocturnal sleep and to be comparable to the procedural memory task. Similar to non-declarative (procedural) memory we will first analyze the (i) global episodic learning score (correctly recalled words at 24 h recall test) followed by a separate analysis of (ii) encoding (correctly recalled words after listening five times to the wordlist) and (iii) consolidation (change in correctly recalled words from end of encoding to recall test).	1) Change in global episodic learning from pre- to post assessment 2) Chang in encoding from pre- to post assessment 3) Change in consolidation from pre- to post assessment

Cognitive function	To evaluate the effects on cognitive function, we will assess the domains (i) short-term memory (Digit and Spatial Span Task forward: length of correctly reproduced sequence of digits/locations) (Helmstaedter et al., 2001), (ii) working memory (Digit and Spatial Span Task backward: length of correctly reproduced sequence of digits/locations) (Helmstaedter et al., 2001), (iii) inhibition (Stroop Test interference score: number of correctly named colors in the color-word condition compared to the predicted color-word score) (MacLeod, 1991), and (vi) cognitive flexibility (Trail Making Test A & B trail flexibility score: time to complete test B compared to test A) (Salthouse et al., 2000). We will first calculate a composite score including all domains to analyze global cognitive function followed by a separate analysis of the domains.	1) Change in global cognitive function from pre- to post assessment 2) Change in short-term memory from pre- to post assessment 3) Change in working memory from pre- to post assessment 4) Change in inhibition from pre- to post assessment 5) Change in cognitive flexibility from pre- to post assessment
Cardiorespiratory fitness	To evacuate the effects on cardiorespiratory fitness, we will perform a graded exercise test (GXT) on a cycle ergometer with spiroergometry (peak oxygen consumption). Depending on anticipated peak power output participants will start with 25 W or 50 W. The load will be increased every 3 min by 25 W until exhaustion.	1) Change in cardiorespiratory fitness from pre- to post assessment
Sleep	To evaluate the effects on sleep, we will assess (i) sleep efficiency using wrist-worn actigraphy (ActiGraph GT9X; ActiGraph; Pensacola; USA) for seven nights, and (ii) subjective disease-related sleep disturbance using the Parkinson's Disease Sleep Scale 2 (PDDS-2) total score (Trenkwalder et al., 2011).	1) Change in objective sleep efficiency from pre- to post assessment 2) Change in subjective disease-related sleep disturbance from pre- to post assessment
Brain-derived neurotrophic factor (BDNF)	To evaluate the effects on brain-derived neurotrophic factor (BDNF), we will collect serum blood samples at rest. Samples will be analyzed using ELISA kits.	1) Change in brain-derived neurotrophic factor (BDNF) from pre- to post assessment

3.3 Other measures

An overview of all screening and descriptive variables is listed in the table below.

Domain	Measures
Sociodemographic & physical characteristics	Age, biological sex
	Years of education
	Height, weight, body mass index
	Handedness: Edinburgh Handedness Inventory (Oldfield, 1971)
Medical information & health status	Time since diagnosis
	Severity of disease (Hoehn & Yahr, 1967)
	Motor & non-motor symptoms: Movement Disorder Society Unified Parkinson´s Disease Rating Scale part I & III (Goetz et al., 2008)
	Drugs & levodopa equivalent daily dose (LEDD) (Schade et al., 2020)
	Quality of life: Parkinson´s Disease Questionnaire-39 (Jenkinson et al., 1997)
	Depression. Beck-Depression-Inventory (Beck & Beamesderfer, 1974)
	Anxiety: Beck-Anxiety-Index (Beck et al., 1988)
	Self-reported falls in the past 12 months (Schwenk et al., 2012)
	Other disease besides Parkinsonism or acute injuries
Cognitive status	Montreal Cognitive Assessment (Dalrymple-Alford et al., 2010)
Sleep	Sleep quality: Pittsburgh Sleep Quality Index (Monk et al., 1994)
	Daytime Sleepiness. Epworth Sleepiness Scale (Johns, 1991)
Physical activity	Sensor-based physical activity (ActiGraph GT9X) for 7 days/nights

	German Physical Activity Questionnaire 50+ (Huy & Schneider, 2008)
	International Physical Activity Questionnaire (Craig et al., 2003)

4 Data analysis

We will perform all statistical analyses with IBM SPSS Statistics or RStudio. Boxplot, scatter plots or bar charts will be used for an initial inspection of the data. Data will be checked graphically for normality (Rochon et al., 2012) and error outliers will be excluded from the respective analysis (e.g., measurement errors) but included in the other analyses (Leys et al., 2019). The alpha level for statistical significance will be set at $p \leq .05$ unless otherwise stated. We will additionally report effect sizes.

In a first step, we will use summary statistics (mean and standard deviation or median and interquartile range or frequencies depending on the scale of the variable) to provide a comprehensive description of the baseline sociodemographic, physical, and health characteristics.

To investigate the effects of the cardiovascular training program on procedural memory formation including (i.e., primary aim), we will conduct separate analyses of covariance (ANCOVA) for the two primary outcomes (i.e., Q1 & Q2: explicit global motor learning score and implicit global motor learning score) (O'Connell et al., 2017; Wan, 2021). The ANCOVA will contain the respective primary outcome as dependent variable, the group (i.e., experimental vs. control group) as between-subject factor, and the baseline value of the primary outcome variable and the stratification criteria (i.e., age and biological sex) as covariates. The analysis will be performed according to an intention-to-treat principle including all participants randomized after pre-assessment. As sensitivity analysis, a complete-case analysis is used to check the robustness of the results. For missing data, we will perform multiple imputations using multivariate imputation by chained equations (MICE) with predictive mean matching while assuming that data is missing at random. The alpha level for statistical significance in the primary analysis will be corrected using the Bonferroni-Holm method to adjust for multiple primary outcome measures.

The effects of the intervention on the secondary outcome measures (i.e., secondary analyses) will be tested in separate ANCOVA models using the same procedure as the primary analysis. We will first analyze the effects on (i) the encoding and consolidation of the motor sequence learning task to disentangle the effects of cardiovascular training on the different processes of procedural memory formation (Q3), followed by (ii) episodic memory (Q4 & Q5), and (iii) cognitive function (Q6). For cognitive function, we will analyze global cognitive function

(composite score of cognitive tests) in a first step and in a second step the individual test scores. We will then investigate the effects on (iv) cardiorespiratory fitness (Q7), (v) sleep (Q8), and (vi) BDNF blood concentration (Q9). We will familywise adjust the alpha level using Bonferroni-Holm correction for secondary analyses with multiple outcome measures.

To explore the potential influence of subject characteristics on the exercise effects, we will separately include cardiorespiratory fitness, sleep parameters, BDNF blood concentration, cognitive function, disease stage, and symptoms at baseline (pre-assessment) as covariates into the ANCOVA models testing for changes in procedural memory formation (primary analysis), episodic memory formation (secondary analysis), and cognitive function (secondary analysis). Additionally, potential associations between changes in memory formation or cognitive function and subject characteristics at baseline will be explored using Pearson product-moment correlations or Spearman's rank correlation (cardiorespiratory fitness, sleep parameters, BDNF blood concentration, cognitive function, disease stage, and symptoms) and point-biserial correlation (biological sex). Correlations are performed at group level. To further explore if these baseline characteristics moderate exercise-induced changes in memory and cognitive function, we plan to run separate multiple linear regression models including changes in memory formation or cognitive function (Y) and the baseline subject characteristics listed above (i.e., moderation analysis). Interactions with group allocation will be examined to explore potential moderators.

In a last exploratory step, we will examine potential associations between the exercise-induced changes in memory formation or cognitive function and changes in the other secondary outcomes (Q10-Q12). According to the currently proposed contributors to the exercise-memory interaction, we will correlate (i.e., Pearson product-moment correlations or Spearman's rank correlation) the changes from pre- to post-assessment in procedural and episodic memory with the changes in (i) global cognitive function, (ii) working memory, (iii) cardiorespiratory fitness, (vi) sleep parameters, and (v) BDNF blood concentration. For changes in cognitive function, we will explore associations with the changes in (i) cardiorespiratory fitness, (ii) sleep parameters, and (iii) BDNF blood concentration. All correlations are performed at group level. To further explore potential candidates that drive the exercise-memory interaction, the mediating effect of changes in (i) global cognitive function, (ii) working memory, (iii) cardiorespiratory fitness, (vi) sleep parameters, and (v) BDNF blood concentration on changes in procedural or episodic memory formation will be analyzed (Cerin et al., 2006). For changes in cognitive function, mediating effects of changes in (i) cardiorespiratory fitness, (ii) sleep parameters, and (iii) BDNF blood concentration will be analyzed.

5 Appendix

Variable	Measures	T1	INT	T2
	Sociodemographic & physical characteristics			
ST, SC, DV	Age, biological sex	X		
DV	Years of education	X		
DV	Height, weight, body mass index	X		X
DV	Handedness: Edinburgh Handedness Inventory (Oldfield, 1971)	X		X
	Medical information & health status			
DV	Time since diagnosis	X		
SC, DV	Severity of disease (Hoehn & Yahr, 1967)	X		X
DV	Motor & non-motor symptoms: Movement Disorder Society Unified Parkinson´s Disease Rating Scale part I & III (Goetz et al., 2008)	X		X
DV	Drugs & levodopa equivalent daily dose (LEDD) (Schade et al., 2020)	X	X	X
DV	Quality of life: Parkinson´s Disease Questionnaire-39 (Jenkinson et al., 1997)	X		X
DV	Depression. Beck-Depression-Inventory (Beck & Beamesderfer, 1974)	X		X
DV	Anxiety: Beck-Anxiety-Index (Beck et al., 1988)	X		X
DV	Self-reported falls in the past 12 months (Schwenk et al., 2012)	X		
SC, DV	Other disease besides Parkinsonism or acute injuries	X		
	Memory formation			

PO
SO
	Procedural memory: Visuomotor Serial Targeting Task (Ghilardi et al., 2003; Ghilardi et al., 2007; Marinelli et al., 2017)
	- Explicit global motor learning score
	- Implicit global motor learning score
	- Encoding:
	  - explicit component
	  - implicit component
	- Consolidation 24 h:
	  - explicit component
	  - implicit component
		X		X

SO	Episodic memory: German version of the Rey Auditory Verbal Learning Test (Helmstaedter et al., 2001) - Global episodic learning score - Encoding - Consolidation 20 min - Consolidation 24 h*	X		X
	Cognitive function			
SC, DV	Cognitive status: Montreal Cognitive Assessment (Dalrymple-Alford et al., 2010)	X		X
SO	Short-term & working memory: Digit & Spatial Span Test forward & backward (Härting et al., 2001)	X		X
SO	Inhibition: Stroop Test (MacLeod, 1991)	X		X
SO	Cognitive flexibility: Trail Making Test (Salthouse et al., 2000)	X		X
	Cardiovascular examination			
DV, SO	Graded exercise test with spiroergometry (VO_{2peak})	X		X
	Biomarkers			
SO	Brain-derived neurotrophic factor (BDNF) blood concentration level at rest	X		X
	Sleep			
DV, SO	Sensor-based sleep (ActiGraph GT9X) for 7 days/nights	X		X

DV, SO	Disease-related sleep disturbance: Parkinson's Disease Sleep Scale–2 (Trenkwalder et al., 2011)	X		X
DV, SO	Sleep quality: Pittsburgh Sleep Quality Index (Monk et al., 1994)	X	X	X
DV, SO	Daytime Sleepiness. Epworth Sleepiness Scale (Johns, 1991)	X		X
	Physical activity			
DV	Sensor-based physical activity (ActiGraph GT9X) for 7 days/nights	X		X
DV	Self-reported physical activity: German Physical Activity Questionnaire 50+ (Huy & Schneider, 2008) International Physical Activity Questionnaire (Craig et al., 2003)	X	X	X

T1 = pre-assessment (baseline) within 2 weeks before intervention; T2 = post-assessment within 2 weeks after intervention; PO = primary outcome; SO = secondary outcome; SC = screening parameter for inclusion; ST = stratification criterion; DV = descriptive variable

*In addition to the standard retrieval after 20 min, we conduct a recall test after 24 h to investigate the consolidation following nocturnal sleep and to be comparable to the procedural memory task.

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