Supplementary Files to Publication:

Exergame as Medicine? Functional Brain Adaptations Linked to Cognitive Gains in Neurocognitive Disorders: Exploratory Randomized Controlled Trial

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Supplementary File 1: PETIO Checklist

This manuscript and related publications adhere to the reporting guideline for RCTs of Physical Exercise or Training Interventions in Older Adults (PETIO) [1]. Please find below the complete checklist reporting in which sections or related publications the relevant information is reported.

	Section and criteria	Report in Section
1	**Title and abstract**	
1a	Identification as a randomized trial in the title; if possible, follow the PICO scheme	'Title'
1b	Structured summary of trial design, methods, results, and conclusions	'Abstract'
$1b_1$	*Describe the population (e.g., community dwelling/healthy, diseased etc.) In the case of diseased population, mention the disease.*	'Abstract'
$1b_2$	*All PICO criteria must be reported in the abstract if not specified in the title.*	'Abstract'
1c	Reporting of the age (mean >60 years; age range)	'Abstract'
1d	Reporting the number or percentage of males/females in the total sample.	'Abstract'
1e	Reporting of frequency, intensity, time and type of the exercises according to the F.I.T.T. principles.	'Abstract' (Note: volume (instead of time and frequency) is reported)
2	**Introduction**	
2a	Scientific background and explanation of rationale	'Introduction'
$2a_1$	*Description of the potential theoretical models or mechanisms (including summary of previous studies)*	'Introduction'
$2a_2$	*Summary of previous studies (referring to the FITT principles)*	'Introduction'
2b	Specific objectives or hypotheses	General Objective: 'Introduction' Specific Objectives and Hypotheses: 'Methods - Objectives and Hypotheses'
$2b_1$	*Formulate the research question and hypothesis according to the outcomes of interest and justify if the outcomes match the research question.*	'Methods - Objectives and Hypotheses')
3	**Methods - Trial Design**	
3a	Describe trial design (such as parallel, cluster, factorial) including allocation ratio	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in published study protocol [2]
3b	Describe important changes to methods after trial commencement (such as eligibility criteria), with reasons	'Methods - Important Modifications to the Study Protocol'
4	**Methods - Participants**	
4a	Eligibility criteria for participants	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in published study protocol [2]
$4a_1$	*Including mean age or median of sample age depending on the distribution of your sample, and age range*	'Results - Baseline Data' (see item 15a)
$4a_2$	*Inclusion/exclusion criteria*	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in published study protocol [2]
4b	Table comparing the main characteristics of the different groups of participants	'Results - Baseline Data' (see item 15a)
$4b_1$	*Level of physical activity or functional capacity at baseline (including method of assessment): level of physical activity in METS.h/week (measured with questionnaires or actimeters), functional capacity (assessed with functional tests such as the 6-min walk test) and exercise capacity (such as VO2max or gait speed).*	'Results - Baseline Data' (see item 15a)
$4b_2$	*Percentage of women in each group*	'Results - Baseline Data' (see item 15a)
$4b_3$	*Mean level of education (and SD) of the participants in each group, specify the years or degree*	'Results - Baseline Data' (see item 15a)

4b₄	*Health status: includes the cognitive status of the participants (assessed with MMSE or MoCA, the comorbidities (e.g., depression severity, metabolic disease, diabetes) and pharmacological therapies (e.g., betablockers, antidepressant drugs, sedative drugs).*	'Results - Baseline Data' (see item 15a)
4b₅	*Social support (the help that the participants receive from caregivers.)*	Not assessed.
If the study design includes technology support or usage, describe:		
4b₆	*Experience with technology*	Not assessed.
4b₇	*How the participants got access to the technology*	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in published study protocol [2]
4b₈	*Report on digital literacy*	Not assessed.
4b₉	*Report on any aspects of tailoring the technology*	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in published study protocol [2] and in the full 'Brain-IT' training concept [3]
4c	Settings and locations where the data were collected	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in published study protocol [2]
5	**Methods - Interventions**	
5a	Describe the interventions for each group with sufficient details (if multimodal for every content or modality) to allow replication, including how and when they were actually administered, including description of:	'Methods - Overview of the Trial Design, Participants, and Interventions' and 'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in published study protocol [2] and in the full 'Brain-IT' training concept [3].
5a₁	*Exercise type (single mode or multimodal)*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'
5a₂	*Exercise frequency: the number of sessions per week*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'
5a₃	*Duration of exercise: length of time spent on each exercise session in the intervention (in minutes)*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'
5a₄	*Exercise intensity: the level of difficulty or effort exerted during the exercise in the intervention (and methods used to assess and monitor it): the percentage of HR max/HRreserve/VO2max/VO2peak; Rating of perceived exertion scale/fatigue before and after intervention /report also the scale (i.e. 6-20, 1-10).*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5a₅	*Duration of the whole intervention: For chronic exercise interventions, report the total duration of the intervention. For acute exercise interventions: In pre-post designs, report the time interval between the two exercise bouts (in minutes). In multi-session protocols, report the time between sessions (in days).*	'Methods - Overview of the Trial Design, Participants, and Interventions'
5b	Describe exercise physiology aspects (cardiovascular, metabolic, muscular and other potential adaptations)	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5b₁	*Exercise progression: (increase in the difficulty, duration, and frequency of the exercise program)*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5b₂	*Intensity changes in different exercise types*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5b₃	*Resting times: duration of rest or recovery between sets or exercises during the intervention*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'
5b₄	*Include METs for exercise program/its components: This refers to the estimated energy expenditure during physical activity intervention*	Not assessed, but physiologically controlled physical exercise intensity is described in 'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT'

		program'; more details in the full 'Brain-IT' training concept [3].
5b$_5$	*If technology was used: describe if and how exposure is controlled in the technology*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5b$_6$	*Describe whether there is any non-exercise component such as diet, mindfulness training, cognitive training, drugs, etc.*	N/A
5e	Describe exercise settings	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5e$_1$	*Whether exercise is performed individually or in a group*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5e$_2$	*Whether exercise is supervised or unsupervised and how exercise was monitored*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5e$_3$	*If technology is used describe how exercise was monitored (e.g., telemonitoring)*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5e$_4$	*Describe any home program component*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5e$_5$	*Whether the exercises are tailored or generic (one-size fits all). If tailored, describe how it was tailored to the individual*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5e$_6$	*Whether there are any simultaneous, consecutive exercise/intervention components (add a short-detailed description.)*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5e$_7$	*Type of exercise equipment*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
If technology is used describe:		
5e$_8$	*The design, specific functions (including a list of examples with description), software, interface, adaptation methods, algorithms*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5e$_9$	*How progression is programmed*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5e$_{10}$	*How the outcome is calculated if available*	Not available
5e$_{11}$	*Specific match between technology of intervention and outcome*	'Methods - Exergame with Integrated Biofeedback Breathing Training – the 'Brain-IT' program'; more details in the full 'Brain-IT' training concept [3].
5f	Describe type of control group in detail, e.g., was the control group active or passive? If active, what type of activity did they perform? If there is an Active control group, describe it according to 5a$_1$ to 5e$_5$ suggestions	'Methods - Overview of the Trial Design, Participants, and Interventions', 'Results - Actual Delivery of the Interventions', and parent RCT [3].
5f$_1$	*Report whether the control group was blinded*	Parent RCT [3] and study protocol [2]
5f$_2$	*Describe if and how exposure is controlled for the control group in the technology*	N/A
5g	Describe motivational control aspects	Parent RCT [3] and study protocol [2]
5g$_1$	*Describe how compliance/adherence to exercise is measured/assessed*	Parent RCT [3] and study protocol [2]

5g₂	*Describe of motivational strategies and behavioral change techniques if used*	Parent RCT [3] and study protocol [2]
5g₃	*If applicable, how do participants get compensated for study participation*	'Methods - Overview of the Trial Design, Participants, and Interventions'
5h	Describe extent to which intervention was not delivered as planned if applicable	'Results - Actual Delivery of the Interventions', and parent RCT [3] for more details.
5i	Control for confounding factors (e.g. participants' beliefs about exercise, additional to the intervention physical activity, new treatments started during the study, and preferences for specific interventions)	Not systematically assessed
5i₁	*If applicable, report beliefs and stereotypes of participants concerning the effects of regular exercise on health*	Not systematically assessed
5i₂	*Physical activity (PA) practiced by the participants beside the intervention. The method to measure PA level (cf. 4b1) should be mentioned (e.g., actimeter, questionnaire)*	Not systematically assessed
5i₃	*If applicable, report participants' preference for a specific intervention (particularly when several interventions are implemented)*	Not systematically assessed
6	**Methods - Outcomes**	
6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	'Methods - Outcomes and Analyses'
6b	Any changes to trial outcomes after the trial commenced, with reasons	'Methods - Important Modifications to the Study Protocol'
7	**Methods - Sample size**	
7a	How sample size was determined	'Methods - Sample Size'
7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A (see 'Methods - Outcomes and Analyses - General Statistical Procedures and Interpretation of Statistics')
8	**Methods - Randomization,** Sequence generation	
8a	Method used to generate the random allocation sequence	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in parent RCT [3] and study protocol [2]
8b	Type of randomization; details of any restriction (such as blocking and block size)	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in parent RCT [3] and study protocol [2]
8c	Use of a minimization process. Example: randomization according to baseline physical and cognitive levels of the participants	N/A
9	**Methods - Randomization,** Allocation concealment mechanism	
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in parent RCT [3] and study protocol [2]
10	**Methods - Randomization,** Implementation	
10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in parent RCT [3] and study protocol [2]
11	**Methods - Randomization,** Masking	
11a	Was a masking or blinding applied, and if yes, who was blinded after assignment to interventions (e.g., participants, care providers, those assessing outcomes), and how	'Methods - Overview of the Trial Design, Participants, and Interventions'; more details in parent RCT [3] and study protocol [2]
11a₁	*If there were any blinding changes, report it*	N/A
11b	If relevant, describe similarity of interventions	Not relevant
12	**Methods - Statistical methods**	
12a	Statistical methods used to compare groups for primary and secondary outcomes	'Methods - Outcomes and Analyses'

12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	'Methods - Outcomes and Analyses'
12c	Type of analysis used: intention-to-treat, complete-case, per-protocol	'Methods - Outcomes and Analyses'
12c$_1$	*If the intention-to-treat analysis was used, which imputation technique was carried out to replace missing data, if per-protocol analysis, what protocol was not followed*	'Methods - Outcomes and Analyses'
13	**Methods - Results**	
13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	'Results - Participant Flow'
13b	For each group, losses and exclusions after randomization, together with reasons	'Results - Participant Flow'
13c	For each group, percentage of compliance/adherence to the intervention	'Results - Actual Delivery of the Interventions'
13c$_1$	*Describe if adverse events like injuries occur, number, dropouts, and reasons for dropouts, this also has to be reported if technology was used*	'Results - Actual Delivery of the Interventions' and 'Results - Participant Flow'
14	**Methods - Recruitment**	
14a	Dates defining the periods of recruitment and follow-up	'Methods - Overview of the Trial Design, Participants, and Interventions'
14b	Why the trial ended or was stopped	'Methods - Important Modifications to the Study Protocol'; more details in Parent RCT [3]
15	**Results - Baseline data**	
15a	A table showing baseline demographic and clinical characteristics for each group as well as significant differences between the groups (cf. 6)	'Results - Baseline Data'
15a$_1$	*Mean age or median and age range per group need to be reported*	'Results - Baseline Data'
16	**Results - Numbers analyzed**	
	For each group, number of participants (denominator) included in each analysis and whether the analysis was by originally assigned groups	'Results - Participant Flow'
17	**Results - Outcomes and estimation**	
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A to the type of data (neuroimaging) presented
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A to the type of data (neuroimaging) presented
18	**Results - Ancillary analyses**	
19	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
19	**Results - Harms**	
19a	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	'Results - Actual Delivery of the Interventions'
19a$_1$	*Describe if adverse events like injuries occurred, number of dropouts, and reasons for dropouts*	'Results - Participant Flow' and 'Results - Actual Delivery of the Interventions'
19a$_2$	*If technology was used: report on adverse events like injuries, number and reasons for dropouts according to the technology*	'Results - Participant Flow' and 'Results - Actual Delivery of the Interventions'
20	**Discussion - Limitations**	
20a	Trial limitations, addressing sources of potential bias (e.g., heterogeneity of characteristics, differences in baseline characteristics, changes in blinding), imprecision, and, if relevant, multiplicity of analyses;	'Discussion - Strengths and Limitations'
20b	Unexpected changes regarding the whole study protocol	N/A
20c	Whether and how the results answer the RQ	'Discussion - Potential Restorative Effect on Hippocampal Episodic Memory Retrieval' and 'Discussion 'Modified Role of the Cingulate Cortex'

20d	Discuss imprecision, relevant analyses differences in changes in different groups	'Discussion - Strengths and Limitations'
20e	If surrogate markers answer RQ	N/A
20e	All aspects of 5i	N/A
21	**Discussion - Generalizability**	
21a	Generalizability (external validity, applicability) of the trial findings	'Discussion - Potential Restorative Effect on Hippocampal Episodic Memory Retrieval' and 'Discussion 'Modified Role of the Cingulate Cortex'
21b	Report and discuss the effect sizes	'Discussion - Potential Restorative Effect on Hippocampal Episodic Memory Retrieval' and 'Discussion 'Modified Role of the Cingulate Cortex'
22	**Discussion - Interpretation**	
22a	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	'Discussion - Potential Restorative Effect on Hippocampal Episodic Memory Retrieval' and 'Discussion 'Modified Role of the Cingulate Cortex'
22b	Discuss all possible confounders that might change the demonstration effect	'Discussion - Strengths and Limitations'
23	**Open Science - Registration**	
23	Registration number and name of trial registry	'Methods - Protocol, Registration, and Reporting'
24	**Open Science - Protocol**	
24	Where the full trial protocol and the statistical plan can be accessed, if available	'Methods - Protocol, Registration, and Reporting'
25	**Open Science - Data sharing**	
25	Where and how the data, statistical code and any other materials can be accessed	'Declarations - Data Availability'
26	**Open Science - Funding**	
26	Sources of funding and other support (such as supply of drugs), role of funders, support by training/software development companies	'Declarations - Funding'

Supplementary File 2: Plot for Resting-State fMRI Analyses

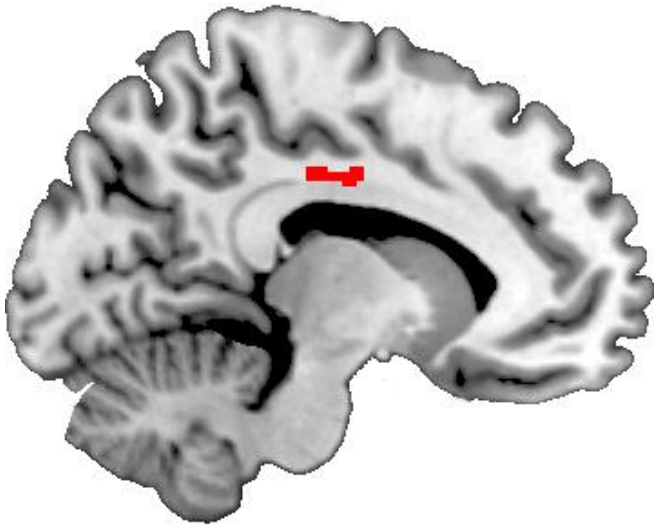

Figure S1: Resting state connectivity: bilateral hippocampus to whole brain. Shown is the cluster in the left middle cingulate gyrus that showed a significant functional connectivity difference ($T_{(26)}$ = -4.52, Cohen's *d* = -1.74, peak p_{UNC} = 0.0001, cluster size of 51, MNI coordinates: -16, -20, 38) in the contrast *'Brain-IT'* < Usual Care & Post > Pre, controlling for sex, age, and mNCD etiology.

Supplementary File 3: ROI-to-ROI Functional Connectivity

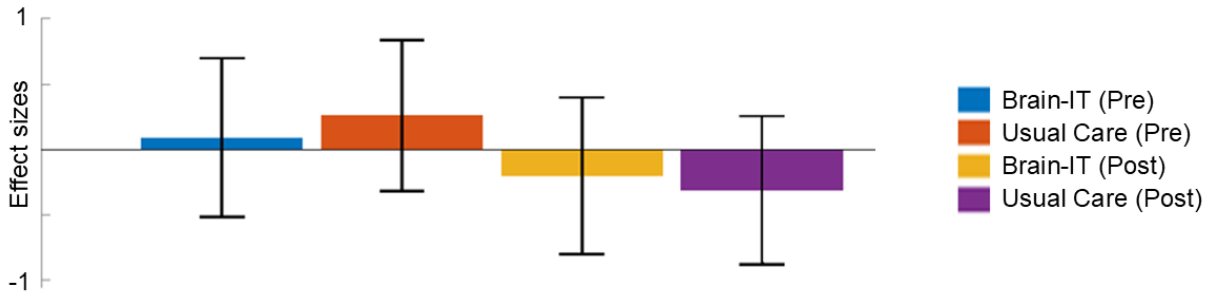

Figure S2: Illustration of the Group x Time interaction of the ROI-to-ROI resting-state functional connectivity analysis (pUNC < 0.001). Bilateral ROIs: medial prefrontal cortex, hippocampus, parahippocampal gyri, angular gyri, precunei, posterior cingulate cortices, supramarginal gyri, postcentral gyri, inferior and superior parietal cortices, temporal cortex (middle, superior, inferior, pole). Effect sizes are shown for the connection left angular gyrus – right inferior parietal cortex.

1 References

1. Wollesen B, Asuako PAG, et al. Reporting randomised trials of physical exercise or training interventions in older adults: the PETIO guideline. European Review of Aging and Physical Activity. 2025;22(1):24. doi: https://doi.org/10.1186/s11556-025-00390-x.

2. Manser P, Michels L, et al. Effectiveness of an Individualized Exergame-Based Motor-Cognitive Training Concept Targeted to Improve Cognitive Functioning in Older Adults With Mild Neurocognitive Disorder: Study Protocol for a Randomized Controlled Trial. JMIR Resarch Protocols. 2023;12:e41173. doi: https://doi.org/10.2196/41173.

3. Manser P, de Bruin ED. “Brain-IT”: Exergame training with biofeedback breathing in neurocognitive disorders. Alzheimer's & dementia. 2024;20(7):4747–4764. doi: https://doi.org/10.1002/alz.13913.