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ORIGINAL ARTICLE

Exergame as medicine? Functional brain adaptations linked to cognitive changes in neurocognitive disorders: exploratory randomized controlled trial

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Abstract Tailored multidomain lifestyle modifications are recommended for reducing dementia risk in mild neurocognitive disorder (mNCD). However, evidence of their capacity to modify disease trajectories and restore functional brain abnormalities remains limited. We aimed to explore functional brain adaptations and correlate underlying cognitive improvements in response to a personalized "*exergame as medicine*" program ("*Brain-IT*") for secondary mNCD prevention. Participants were randomized to 12 weeks home-based "*Brain-IT*" (physical-motor-cognitive with integrated biofeedback breathing training; 120 min/week, moderate intensity) + usual care or usual care alone. Resting-state functional connectivity at the seed(hippocampus)-to-voxel level and task-based full-factorial analysis of variance for functional activation (Blood Oxygenation Level Dependent signal responses) and their correlations with episodic memory performance were analyzed. Data from 32 mNCD participants (71.9 ± 8.1 years; 28% females) with mostly biomarker-supported Alzheimer's etiology (57%) were analyzed. Key findings were significantly ($p < 0.0001$) reduced hippocampus hyperactivation during memory encoding (partial $\eta^2 = 0.19$) and compensatory functional activation increases in the right precuneus ($d = 0.76$) and middle cingulate gyrus ($d = 0.26$) that correlated with

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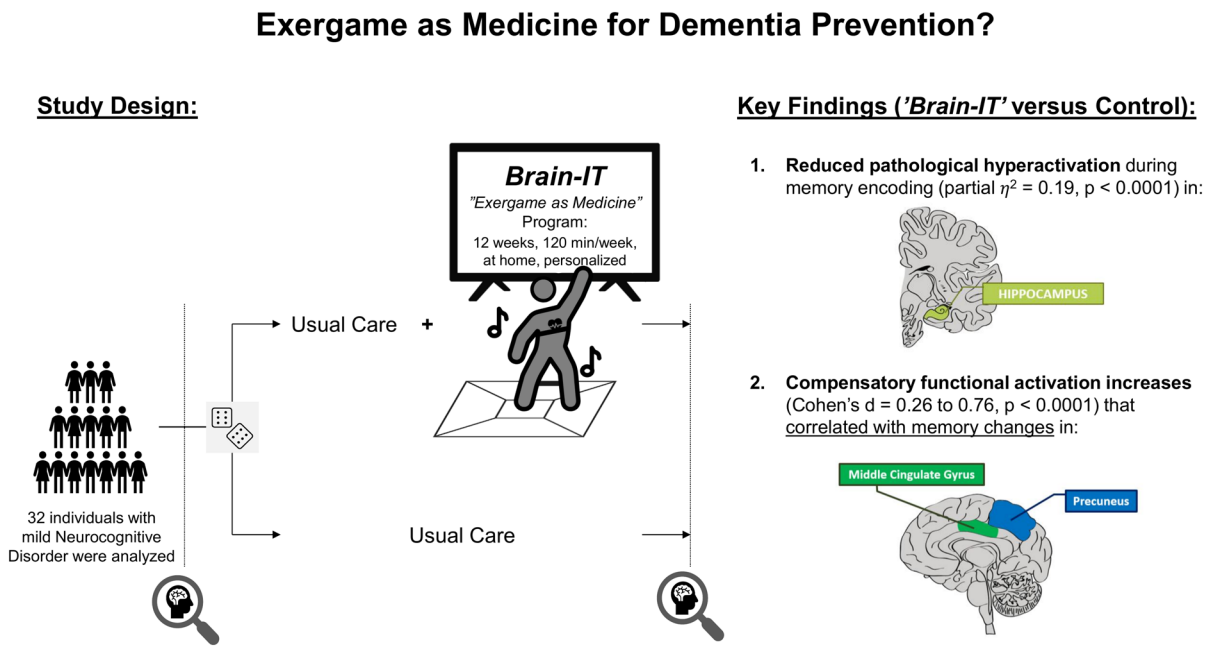
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memory retrieval accuracy changes—all in favor of "*Brain-IT*." These exploratory findings are consistent with a potential short-term brain-protective role of personalized "*exergame as medicine*" therapy in mNCD that require confirmation in hypothesis-driven and adequately powered RCTs. Given the overlooked role of exergames in dementia prevention, hybrid implementation-effectiveness research with long-term follow-up measuring biomarker-related and clinical progression should evaluate whether potential brain-protective effects translate to delaying and/or preventing progression to dementia. Registration: https://clinicaltrials.gov/ct2/show/NCT05387057 (May 18, 2022)

Graphical abstract



Keywords Cognitive impairment · Digital health · Exergaming · Magnetic resonance imaging · Neuroplasticity · Neuroscience

Introduction

Mild neurocognitive disorder (mNCD) is characterized by altered functional connectivity (FC) and task-based activation patterns in brain regions implicated in cognitive functions, including the hippocampus, precuneus, and cingulate [1–3]. Functional mNCD-characteristic brain alterations precede structural atrophy and cognitive decline, predict disease progression, and are considered system-level biomarkers for assessing disease modification [4]. Consequently, to be effective for secondary prevention, therapies should aim at normalizing FC and activation alterations, or at least preserve, compensate for, or slow their progressive worsening [4].

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Tailored multidomain lifestyle modifications targeting multiple dementia risk factors and pathophysiological mechanisms have emerged as a potent strategy for slowing cognitive decline and reducing dementia risk in early disease stages [5, 6]—with rigorous secondary prevention potentially preventing or delaying up to half of all dementia cases [7]. Among these, tailored physical and motor-cognitive exercise therapy represents the predominant non-pharmacological intervention effectively mitigating cognitive decline in mNCD [8, 9], and is endorsed by global consensus recommendations for secondary mNCD prevention [10, 11].

Exercise therapy is proposed to exert disease-modifying effects through several multi-system mechanisms [12–15] that mitigate mNCD-related neuropathological damage [12, 13], promote synaptogenesis, neurogenesis, and angiogenesis [14, 15], and maintain or enhance cognitive reserve [9]. However, evidence on functional brain adaptations underlying exercise-induced cognitive gains in mNCD remains limited. Xu et al. (2024) [16] identified in their recent systematic review seven studies on resting-state and two studies on task-related brain adaptations measured with functional magnetic resonance imaging (fMRI)—each targeting different brain regions and task paradigms. While exercise generally induced FC and activation adaptations across networks associated with cognition, findings on behavioral correlates were mixed: five studies reported that improvements in the hippocampus and cingulate correlated with cognitive gains, whereas two found no significant associations between neuronal and cognitive changes [16].

Following recommendations to address the above-highlighted research gap [16, 17], the present randomized controlled trial (RCT) explored functional brain adaptations and their relationship to cognitive changes following the addition of a personalized "*exercise as medicine*" program to usual care in individuals with mNCD that is enhanced with digital health technologies to improve accessibility, personalization, and user experience [18].

Methods

Prior work

In the past 6 years, we established "*Brain-IT*," a personalized "*exergame as medicine*" program for mNCD [19] that is based on serious exergames—videogames played via physical and motor-cognitive exercises that were co-designed purposefully for secondary mNCD prevention [18]. Thanks to systematically unifying (i) co-development with end-users (individuals with mNCD and healthcare professionals) and (ii) strong theoretical foundation to optimize motor-cognitive learning and user experience [18, 20, 21], "*Brain-IT*" enjoys high user acceptance and has confirmed safety and efficacy [19]—with 55% of participants having shown clinically meaningful cognitive gains [19] that correlated with structural brain improvements [22].

Context

This manuscript is part of a larger RCT evaluating the effectiveness of "*Brain-IT*," with global cognitive performance as the primary outcome. The results for all other planned analyses were published previously [19, 22]. Specifically, we have published our primary, hypotheses-driven analysis in *Alzheimer's & Dementia* in May 2024 showing statistically and clinically significant effects with large effect sizes for global cognitive performance, immediate verbal recall, and delayed verbal recall in favor of the intervention group [19]. Furthermore, we have published our exploratory findings on structural brain changes in *Alzheimer's Research & Therapy* in September 2025, showing that "*Brain-IT*" therapy may positively impact brain structures affected in mNCD, with potential associations suggestive of a causal link to cognitive improvements [22]. This paper builds on these two publications by presenting the results on the remaining planned outcomes. Specifically, this manuscript is dedicated to functional brain adaptations in response to "*Brain-IT*", pre-defined as exploratory tertiary outcomes in the study protocol [23].

Objectives and hypotheses

We aimed to explore functional brain adaptations in response to the addition of "*Brain-IT*" to usual care for secondary mNCD prevention, while secondarily examining their behavioral correlations with previously reported cognitive improvements. As these objectives were exploratory in nature, no specific hypotheses were prespecified in the study protocol [23].

Protocol, registration, and reporting

The study protocol for this prospectively registered RCT (ClinicalTrials.gov; NCT05387057; registered: May 18, 2022) was published previously [23]. This article with related publications adheres to the reporting guideline for RCTs of Physical Exercise or Training Interventions in Older Adults (PETIO) [24] (Supplementary File 1).

Explanation and choice of comparators

We chose to compare the addition of the "*Brain-IT*" to usual care versus usual care alone as a comparator [23]. This decision is based on the alignment of recommended treatment and management of individuals with mNCD in Switzerland with available global clinical practice guidelines and consensus statements [25] and aligns with the UK Medical Research Council Guidance [26].

Overview of the trial design, participants, and interventions

A two-arm, prospective, parallel-group, assessor-blinded RCT with a 1:1 allocation ratio was conducted between May 2022 and February 2024. The study setup was multicentric (Zurich and St. Gallen) and national (Switzerland). Individuals with mNCD were recruited between May 2022 and October 2023 in collaboration with (memory) clinics. Key eligibility criteria (for a full list, see the study protocol [23]) included the following:

- Clinical diagnosis of "*mild neurocognitive disorder*";
- Absence of clinically relevant (acute and/or symptomatic) neurological disorders (i.e., stroke, multiple sclerosis, Parkinson's disease, epilepsy, brain tumors, or traumatic nervous system disorders); and
- Being physically and cognitively capable of performing intervention and assessment procedures.

To ensure allocation concealment, individual group allocation was done only after completing the pre-intervention measurements in Castor EDC (Ciwit BV) using a variable block randomization model (i.e., block sizes = 4, 6, 8) with a 1:1 allocation ratio stratified by sex and study center.

The control group proceeded with usual care, as provided by the (memory) clinics where the patients were recruited. Participants in the intervention group were prescribed "*Brain-IT*" therapy in addition to usual care. No monetary compensation was granted to participants, but detailed feedback on individual performance and the study's general outcomes was provided.

Exergame with integrated biofeedback breathing training—the "Brain-IT" program

The "*Brain-IT*" concept [19] provides algorithmic decision trees for delivering a holistic "*exergame as medicine*" program targeting multiple relevant mechanisms of action to alleviate mNCD pathology. This is achieved by the following:

I. Implementing a new multimodal intervention type, i.e., complex reactive stepping tasks to solve domain-specific motor-cognitive challenges, with integrated biofeedback-guided resonance breathing training as a neuromodulatory intervention to activate the Vagus nerve and, thereby, enhance self-regulatory abilities and augment cognitive gains via central autonomous network regulation [19, 20];
II. Personalizing the training focus and exergame content based on clinical and neuropsychological assessments to target the neurocognitive domains of (1) learning and memory, (2) executive function, (3) complex attention, and (4) visuospatial skills; and
III. Individually progressing the exercises based on the physiological response (40–60% of individual heart rate reserve) and exergame performance data following established motor-cognitive learning and neurorehabilitation principles (details see [19]).

Participants were prescribed ≥ 120 min/week of "*Brain-IT*" training, achieved by ≥ 5 sessions/week for ≥ 24 min/session. All sessions took place individually at the participants' homes and consisted of 9 games, between which self-selected short (< 2 min) breaks were allowed. Nineteen to 24 training sessions were supervised in person by a designated exercise instructor who ensured adherence to "*Brain-IT*" and related safety protocols [19].

All interactions with the exergame were automatically recorded. The cloud-based software allows telemonitoring protocol adherence and performance progression. All deviations from the "*Brain-IT*" concept [19], which was planned and reported following the Consensus on Exercise Reporting Template [27], were reported. Importantly, while the "*Brain-IT*" training concept standardizes the training characteristics (e.g., training frequency, intensity, and duration), as well as the structure and content of training, it also provides specific instructions on how to adapt and implement it with other technologies to ensure our concept is reproducible and broadly applicable thanks to transferability across equivalent exergame platforms [19]. In this project, we implemented "*Brain-IT*" with: "*Senso Flex*" systems (Dividat AG, Schindellegi, Switzerland; hardware: prototype version 2, software: version 22.4.0–360-gf9df00d5b), Polar M430 heart rate monitors, Polar H10 sensors, and Kubios HRV Premium (Kubios Oy, Kuopio, Finland, version 3.4) [19].

Sample size

The parent RCT's sample size was justified to obtain a sufficiently precise estimate of the treatment effect for the primary outcome (i.e., global cognitive performance) [23]. This sub-study's sample size was based on the number of participants for whom we had complete and evaluable fMRI scan data.

Outcomes and analyses

General statistical procedures and interpretation of statistics

Data are reported as mean ± standard deviation for data fulfilling all the assumptions that would subsequently justify parametric statistical analyses. If these assumptions were not met, medians (interquartile ranges) were reported. The normal distribution of the data was checked via the Shapiro–Wilk test and visually confirmed via QQ plots. The level of significance was set to $\alpha = 0.05$. Statistical analysis was performed after data collection was completed. No interim or subgroup analyses were performed. A modified intention-to-treat analysis was performed to analyze intervention-related effects; i.e., data from all randomized participants who completed pre- and post-intervention measurements, regardless of protocol adherence, were analyzed.

Study population and intervention adherence

Age, sex, body mass index, years of education, physical activity behavior [23], and intervention delivery (adherence to "*Brain-IT*" and details on all usual care interventions) were assessed. Clinical diagnosis, comorbidities, and mNCD etiology were obtained from collaborating recruitment partners. Between-group differences were tested via an independent *t*-test or the Mann–Whitney *U* test when the data were not normally distributed, and Fisher's exact test for categorical variables in R (The R Foundation; version 4.3.1).

fMRI data acquisition

MRI data was recorded using a 3.0 Tesla Philips Ingenia scanner (Philips Medical Systems, Netherlands) with a 32-channel head coil at University Hospital Zurich. All participants who had no contraindications to MRI were measured. Contraindications include MRI-incompatible metallic parts in the body, metallic or electronic implants (e.g., heart or brain pacemakers and cochlear implants), or strong claustrophobia. All measurements were conducted using the same scanner with identical equipment, setup, and measurement parameters.

Measurements were completed within 2 weeks prior to starting (pre) and after completing (post) the intervention at approximately the same time of day (± 2 h) for each participant. All measurements were led by P.M. with the support of a trained research assistant.

Data was collected according to the harmonized Canadian Dementia Imaging Protocol [28] for comparability with other studies. The following imaging sequences were acquired:

1. Resting-state fMRI using a T^*_2-weighted fast field single echo planar imaging sequence, with a resolution of $3.5 \times 3.5 \times 3.5$ mm^3, field of view: 240×240 mm^2, flip angle: 70°, repetition time: 2110 ms, echo time: 30 ms, slices: 40 (ascending order), volumes: 300; and
2. Task fMRI with the same imaging parameters, except for the number of volumes (250).

Participants were asked to fixate on a cross displayed on the screen during resting-state fMRI data acquisition and respond to written instructions by button press to verify that they remained awake during the measurement.

We used a validated face-occupation matching task [29, 30] adapted for mNCD [31]. The task was run in PsychoPy (version 3.2.4); see [23] for details, including a task illustration. It included 6 rounds, each containing the following:

(1) An **encoding** phase: 30 face-occupation pairs (5 in each round) were shown in randomized order with neutral expressions and participants were asked to indicate whether the occupation suited (button press with right index finger) or did not suit (button press with right middle finger) the presented face;
(2) A **retention** phase: 30 silhouettes (5 in each round) were presented in randomized order; participants were asked to indicate whether each silhouette corresponds to a woman (button press with right index finger) or a man (button press with right middle finger); and
(3) A **retrieval** phase for each of the encoded face-occupation pairs, including a:

   a. *Cued recall* task: participants were asked to decide which of two educational degrees (i.e., academic degree [button press with right index finger] or apprenticeship [button press with right middle finger]) the previously encoded occupation of the person matched;
   b. *recognition* task: participants were asked to decide between the correct and a distractor occupation via a button press (right index finger and right middle finger, respectively).

One of four alternative task conditions (i.e., other face-occupation pairs) was allocated using random.org for each participant and measurement, with two different conditions in pre- and post-intervention measurements.

Behavioral analysis

To quantify accuracy, we first classified trials as per each trial's possible answer combinations:

- Both correct (BC): both cued recall and recognition response were correct;
- Cued correct (CC): only cued recall response correct;
- Direct correct (DC): only recognition response correct; and
- Incorrect (INC): both responses are incorrect.

This categorization was applied to the respective task conditions—encoding, cued recall, recognition, and control (retention)—yielding a 4×4 condition matrix. Based on Sperling et al.'s (2003) results, which suggest a distinctive effect of high-confidence compared to incorrect and low-confidence trials [30], we tested the independence of BC, which we assumed are of high confidence compared to all other answer types. The behavioral data was modelled using a generalized linear model with random slopes for subjects within sessions (binomial distribution and logit link function) with a Type III Wald Chi-square (χ^2) ANOVA. We furthermore included age (mean-centered), sex, and etiology, consistent with the approach in our previous study [22] and the other analyses in this study. Because directional improvements in learning and memory were hypothesized a priori [23]—anticipated to manifest as an accuracy increase in the episodic memory tasks following "*Brain-IT*"—a one-tailed test was used, in alignment with the strong and consistent improvements previously reported in this neurocognitive domain [19].

fMRI preprocessing

Preprocessing of fMRI data was performed using CONN (RRID:SCR_009550; release 22.v2407) and SPM (RRID:SCR_007037; release 12.7771), with identical settings for resting-state and task measurements. Functional and anatomical data were preprocessed using a modular preprocessing pipeline [32]

including realignment with correction of susceptibility distortion interactions, slice timing correction, direct segmentation and MNI-space normalization, and smoothing. Functional data was realigned using SPM realign & unwarp procedure [33], where all scans were co-registered to a reference image (first scan of the first session) using a least squares approach and a 6 parameter (rigid body) transformation [34]. Scans were resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of the functional data was corrected following SPM slice-timing correction procedure [35], using temporal interpolation to resample each slice Blood Oxygen Level Dependent (BOLD) time series to a common mid-acquisition time.

Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and cerebrospinal fluid tissue, and resampled to 2 mm isotropic voxels following a direct normalization procedure [36] using a unified segmentation and normalization algorithm [37] with the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 7 mm full width half maximum and denoised using CompCor [38] by including the regression of potential confounding effects characterized by white matter and cerebrospinal fluid timeseries (5 noise components each), linear and quadratic motion parameters and their first order derivatives (24 factors) [39].

Resting-state FC analysis

The analyses on resting-state FC were performed in CONN.

Denoising: We used artifact detection tools [40] based on outlier rejection with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations [36], and a reference BOLD image was computed for each participant by averaging all scans excluding outliers of resting-state data. We included session and task effects and their first order derivatives (4 factors), and linear trends (2 factors) within each functional run for the resting-state data, followed by bandpass frequency filtering of the BOLD timeseries [41] between 0.001 and 0.01 Hz.

First-level analysis: Connectivity maps were initially estimated to characterize FC patterns originating from a bilateral hippocampal seed generated using the AAL3 atlas [42]. FC strength was represented by Fisher-transformed bivariate correlation coefficients from a weighted generalized linear model (GLM) [32], defined separately for each seed, modelling the association between their BOLD signal timeseries. Individual scans were weighted by a boxcar signal characterizing individual task or experimental conditions convolved with an SPM canonical hemodynamic response function and rectified.

Group-level analyses: For each voxel, a separate GLM [32] was estimated, with first-level connectivity measures at this voxel as dependent variables (one independent sample per participant and rs-fMRI condition), and groups as independent variables. Multivariate parametric statistics with random effects across participants and sample covariance estimation across multiple measurements were used. Inferences were performed at individual cluster levels (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory [43]. Results were thresholded using a combination of a cluster-forming $p_{\mathrm{UNC}} < 0.001$ (uncorrected) voxel-level threshold, and a $p_{\mathrm{FWE}} < 0.05$ (familywise error corrected) cluster-size threshold. We calculated main effects of Group and Time as well as interaction effects, followed by two-tailed post hoc *t*-tests adjusted for sex, age, and mNCD etiology.

Task fMRI: Data analysis and statistical procedures

Data analysis for task fMRI was performed using SPM.

First-level analysis: Voxel-wise parameter estimates were calculated during the first-level analysis using a GLM. The design matrix included an autoregressive model of serial correlations and high-pass filter with a cut-off of 128 s. The onsets of each task block were convolved with the SPM synthetic hemodynamic response function.

Group-level analyses: The main model was a full-factorial analysis of variance with the factors Group, Time, and Task (encoding, control, cued recall, recognition). We included age, sex, and clinical etiology as covariates, analogously to our previous structural MRI study [22]. For significant main effects, we computed bidirectional one-tailed *t*-tests comparing Group, Time, and Task. *F*-test results were thresholded at $p_{FWE} < 0.05$. Post-hoc test are reported with a threshold of $p_{UNC} < 0.001$ to allow for a more holistic representation of interaction effects while maintaining spatial sensitivity. All results were additionally thresholded using cluster correction of $p < 0.05$ ($k \geq 33$ voxels) to strictly correct for multiple comparisons across the brain, adhering to a validated approach [44].

Functional brain activity correlates underlying cognitive performance improvements: As we anticipated an accuracy increase in the fMRI task following "*Brain-IT*", we created an expanded model to analyze the interaction of BC (quantified as the ratio of occurrence of both correct to the total number of trials) with the brain activation in the task phases. To minimize the spurious effect of multiple testing, we decided to only test the interaction of BC with intercept Group × Time, since it is the most informative.

Important modifications to the study protocol

Recruitment was extended by 6 weeks to only stop recruitment once we had complete data on the primary outcome for the targeted minimum sample size. As defined in the published study protocol [23], we performed resting-state fMRI analysis at both ROI-to-ROI and seed-to-voxel level. However, while the ROI-to-ROI approach returned the presence FC improvements in ROIs relevant for cognition as defined in the protocol paper [23] using a Group × Time interaction analysis ($p_{UNC} < 0.001$, Supplementary File 3, these did not withstand family-wise error corrections ($p_{FWE} < 0.05$) due to insufficient statistical power. We therefore decided to embrace the exploratory approach and report on a bilateral Hippocampus seed to whole brain voxel analysis. Importantly, this methodological decision only concerns the decision which data to include in the manuscript, whereas all analyses were performed as defined in the published study protocol [23] and were therefore not influenced by the observed data.

Results

Participant flow

Figure 1 summarizes the participant's flow. Datasets from 32 participants (71.9 ± 8.1 years; 28% females) were available for analysis, 18 in the "*Brain-IT*" group and 14 in the usual care group.

Baseline data

Table 1 summarizes the demographic characteristics. Eighty-seven percent of participants had a biomarker-supported characterization of mNCD etiology, mostly Alzheimer's etiology (62%, based on the Aβ42/40 ratio in cerebrospinal fluid). There were no statistically significant between-group differences.

Actual delivery of the interventions

The "*Brain-IT*" group performed 71.5 ± 26.2 exergame sessions with a training volume of 1689 ± 579 min over the 12-week intervention period. No intervention-related serious adverse events occurred. All participants in the intervention group and 94% of participants in the Usual Care group reported that they took medication. Between 0 to 25% of participants received structured nonpharmacological interventions, such as physical or occupational therapy, medical training therapy, or (computerized) cognitive training. There were no significant between-group differences in the types and changes during study participation of pharmacological or nonpharmacological usual care interventions received. More details were reported in the parent study [19].

Resting-state functional connectivity

A large Group × Time interaction effect in the left middle cingulate gyrus (MCG; $T_{(26)} = -4.52$, Cohen's $d = -1.74$, peak $p_{UNC} = 0.0001$, cluster size of 51, MNI coordinates: −16, −20, 38) was observed (Figure see Supplementary File 2). Analysis of variance (Type III) with the raw connectivity values

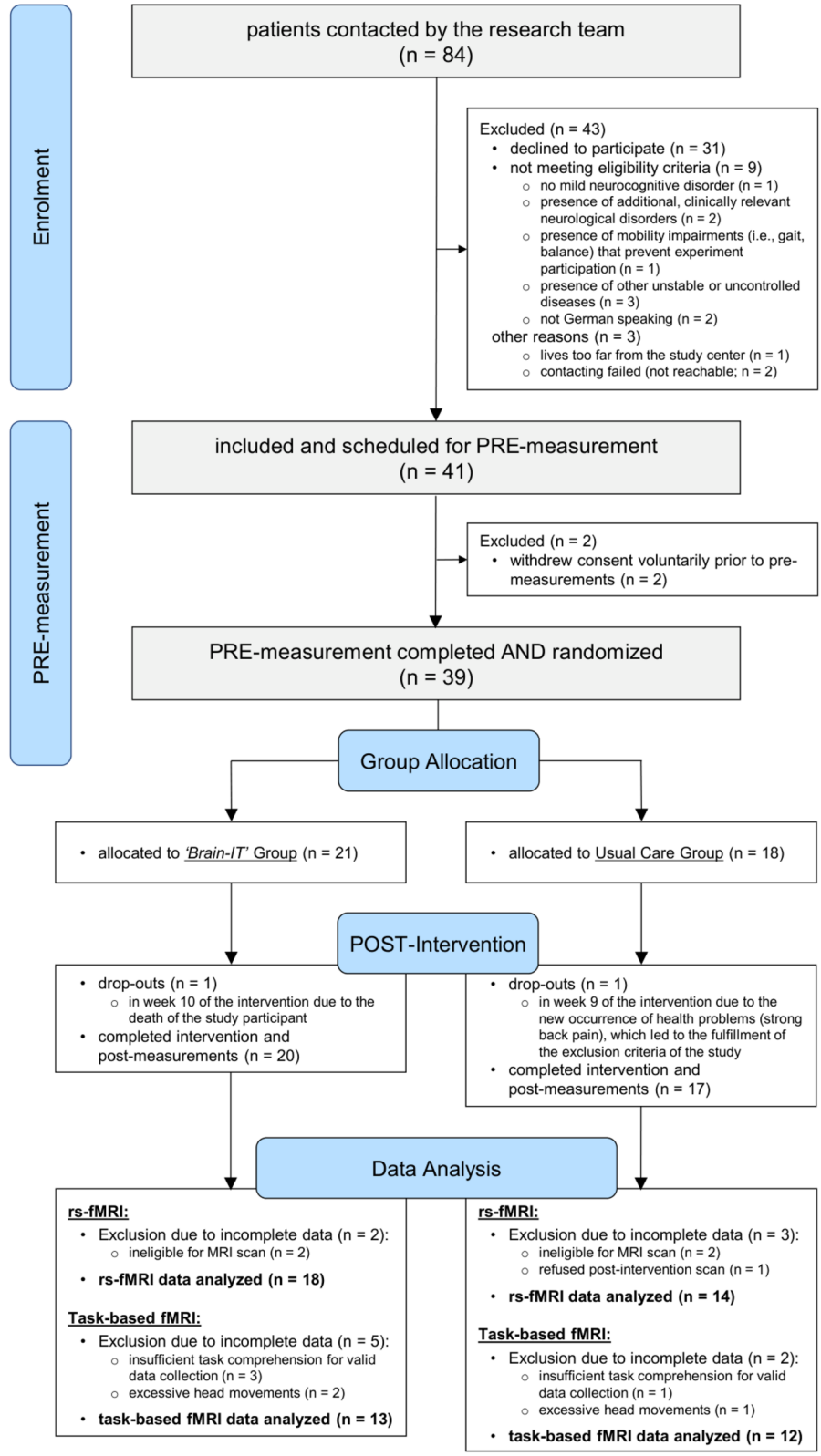


Fig. 1 Summary of the participants' flow throughout the study. Abbreviations: fMRI, functional magnetic resonance imaging; rs, resting-state

Table 1 Demographic characteristics of the study population

	Group: "*Brain-IT*" ($n=18$)	Group: usual care ($n=14$)	Between-group difference		
			Test statistics[(1)]	p value[(2)]	|Effect size|[(3)]
Age [years]	73.7 ± 6.7	69.5 ± 9.3	$t=1.39$	0.18	$r=0.28$
Sex [% females]	33	21	N/A	0.70	OR = 1.51
Body mass index [kg·m^{-2}]	24.5 ± 2.6	23.1 ± 3.0	$t=1.39$	0.18	$r=0.26$
Years of education [years]	16.0 ± 3.8	15.2 ± 3.8	t = 0.58	0.56	$r=0.11$
IPAQ-SF [MET·week^{-1}]	2343 (1899)	1559 (1459)	$W=171$	0.09	$\rho=0.29$
Etiology of mNCD:					
mNCD due to Alzheimer's disease	$n=9$ (50%)	$n=7$ (50%)	N/A	1.00	OR = 1.00
Mild frontotemporal NCD	$n=3$ (17%)	$n=0$ (0%)	N/A	0.24	OR = ∞
Mild vascular NCD	$n=3$ (17%)	$n=5$ (36%)	N/A	0.25	OR = 0.37
mNCD with Lewy Bodies	$n=0$ (0%)	$n=1$ (7%)	N/A	0.44	OR = 0.00
Unclear/not yet determined	$n=3$ (17%)	$n=1$ (7%)	N/A	0.44	OR = 0.00

Data are reported as the mean ± standard deviation for continuous parametric data and median (interquartile range) for continuous nonparametric data

(1)*t*-statistics for the between-group differences tested with an independent *t*-test or Mann–Whitney *U* test in case the data are not normally distributed

(2)*p* values for the between-group differences tested with an independent *t*-test or Mann–Whitney *U* test in case the data are not normally distributed, or Fisher's exact test for categorical variables

(3)Effect size estimates for the between-group differences tested with an independent *t*-test (=> effect size Pearson *r*) or Mann–Whitney *U* test (=> effect size Spearman rho (ρ)) in case the data are not normally distributed, or Fisher's exact test for categorical variables (=> odds ratio)

Abbreviations: mild neurocognitive disorder; *IPAQ-SF*, International Physical Activity Questionnaire Short Form-short form (IPAQ-SF); *IQR*, interquartile rage; *MET*, metabolic equivalent of task; *n*, sample size; *OR*, odds ratio; *Qmci*, Quick Mild Cognitive Impairment Screen; *SD*, standard deviation

confirmed that only the Group × Time interaction was significant ($F_{(1,119)}=22.87$, Cohen's $d=0.16$, $p_{UNC}=5.01e^{-6}$)—not the difference in seed from left to right hippocampus ($F_{(1,119)}=3.33$ Cohen's $d=0.03$. $p_{UNC}=0.07$). Post hoc *t* tests pooling bilateral hippocampi confirmed that these effects stem from a FC decrease in the MCG ($T_{(62)}=3.58$, Cohen's $d=0.91$, $p_{UNC}=0.0007$) in the "*Brain-IT*" group, whereas the Usual Care group showed stronger FC ($T_{(60)}=3.74$ Cohen's $d=0.96$, $p_{UNC}=0.0004$) in the post-assessment—both with large effect sizes.

Task fMRI

In the main model (Table 2A, Fig. 2B), we observed a Group × Time interaction (Fig. 2A) for a cluster located in the right hippocampus ($F_{(1,181)}=42.60$ and $p_{FWE}<0.0001$). No significant main effects for Time, but main effects for Group [in the left precuneus ($F_{(1,181)}=31.55$), left angular gyrus ($F_{(1,181)}=46.69$), and three distinct clusters in the right exterior cerebellum] and of Task [in the lingual gyri (left: $F_{(3,181)}=46.97$, right: $F_{(3,181)}=46.85$) and left supramarginal gyrus ($F_{(3,181)}=12.63$] were observed—all at $p_{FWE}\leq 0.002$.

Post hoc *t*-test of the main model (Table 2B, Fig. 2C) showed that the cluster in the right hippocampus found in the Group × Time interaction is also apparent in the pre-intervention measurement in "*Brain-IT*" > Usual care ($T_{(1,181)}=3.94$ and $p_{UNC}<0.0001$) as well as in the Group × Time interaction effect for Usual care > "*Brain-IT*" and Post > Pre ($T_{(1,181)}=4.17$ and $p_{UNC}<0.0001$), as shown in Fig. 2A. Group effects shown in the cluster in the left precuneus coincided with significant homologous clusters found in the encode ($T_{(1,181)}=3.88$ and $p_{UNC}<0.0001$) and recall phases (Cued: ($F_{(1,181)}=4.29$ and $p_{UNC}<0.0001$, Direct: $T_{(1,181)}=4.04$ and $p_{UNC}<0.0001$) for "*Brain-IT*" > Usual care in the post-assessment.

Table 2 Results on task functional magnetic imaging analysis

	Comparison		Area	*H*	*k*	p_{FWE}	df	TlF	p_{unc}	$d \mid \eta^2_p$	MNI		
											x	*y*	*z*
A	GLM without behavior (*F* test)												
A.1	Main effect of group		Exterior cerebellum	Right	33	6.66E−08	1.181	56.44	2.57E−12	0.24	36	−72	−26
			Angular gyrus	Left	48	2.61E−06	1.181	46.69	1.22E−10	0.21	−46	−56	12
			Precuneus	Left	33	1.05E−03	1.181	31.55	7.22E−08	0.15	−10	−66	30
A.2	Main effect of Task		Lingual gyrus	Left	418	0.00E+00	3,181	46.97	4.44E−16	0.44	20	−78	−14
			Lingual gyrus	Right	401	0.00E+00	3,181	46.85	4.44E−16	0.44	12	−86	−10
			Supramarginal gyrus	Left	36	2.41E−03	3,181	12.63	1.55E−07	0.17	−62	−30	20
A.3	Interaction: Group × Time		Hippocampus	Right	35	1.27E−05	1.181	42.60	6.53E−10	0.19	28	−18	−24
B	GLM without behavior (*t*-test)												
B.1	"Brain-*IT*" > Usual Care in post	Encode	Middle occipital gyrus	Right	63	3.64E−01	181	3.94	5.86E−05	0.56	30	−62	28
			Precuneus	Left	49	4.26E−01	181	3.88	7.37E−05	0.55	−6	−68	30
		Cued recall	Middle occipital gyrus	Right	98	7.30E−02	181	4.43	7.98E−06	0.63	36	−68	24
			Precuneus	Left	125	1.21E−01	181	4.29	1.44E−05	0.61	−12	−64	36
		Direct recall	Precuneus	Left	58	2.73E−01	181	4.04	3.95E−05	0.57	−10	−62	36
B.2	"*Brain-IT*" > Usual Care in pre	Encode	Posterior insula	Right	34	4.00E−02	181	4.59	4.06E−06	0.65	38	−14	−6
			Parahippocampal gyrus	Left	34	2.92E−01	181	4.02	4.33E−05	0.57	−16	−26	−20
			Hippocampus	Right	50	3.59E−01	181	3.94	5.74E−05	0.56	30	−20	−22
			Middle temporal gyrus	Left	38	3.99E−01	181	3.90	6.70E−05	0.55	−46	−56	8
B.3	**"*Brain-IT*" < Usual Care and post > pre**	Encode	Hippocampus	Right	56	1.82E−01	181	4.17	2.36E−05	0.59	22	−18	−24
C	**GLM with behavior (*t*-test)**												
C.1	**"*Brain-IT*" > Usual Care and post > pre**	Summed tasks **positive** interaction with both correct (controlling for retention)	Middle occipital gyrus	Right	163	3.59E−04	181	5.70	2.40E−08	0.81	30	−74	36
			Angular gyrus	Left	95	8.65E−04	181	5.51	6.17E−08	0.78	−40	−72	22
			Precuneus	Right	45	1.64E−03	181	5.37	1.23E−07	0.76	6	−54	36
			Middle cingulate gyrus	Right	136	5.83E−03	181	5.07	4.86E−07	0.72	12	−12	50
			Precentral gyrus	Left	37	2.56E−02	181	4.71	2.46E−06	0.67	−36	−10	60
			Supplementary motor cortex	Both	49	1.54E−01	181	4.22	1.92E−05	0.60	−2	0	56
			Precuneus	Left	96	2.07E−01	181	4.13	2.77E−05	0.58	−4	−60	26

Table 2 (continued)

Comparison		Area	*H*	*k*	p_{FWE}	df	T|F	p_{unc}	$d \mid \eta^2_p$	MNI		
										x	*y*	*z*
C.2 **"*Brain-IT*" > Usual Carel and post > pre**	Summed tasks **negative** interaction with both correct controlling for retention)	Superior frontal gyrus	Left	137	2.59E−03	180	5.26	2.02E−07	0.74	−22	2	60
		Precuneus	Left	433	1.16E−02	180	4.91	1.03E−06	0.69	−6	−56	66
		Anterior cinculate gyrus	Left	37	2.52E−02	180	4.71	2.42E−06	0.67	−18	30	24
		Fusiform gyrus	Right	34	6.24E−02	180	4.48	6.71E−06	0.63	42	−56	−26

Shown are the results from the second level SPM analysis of the analyzed general linear models (GLM), reporting *F* values for contrast that showed significant Family-Wise Error (p_{FWE}) corrected voxel ($a = 0.05$) with a minimum cluster size (*k*) of 33 (cluster threshold $a = 0.05$) as well as contrast that presented with significant uncorrected (p_{unc}) voxel ($a = 0.001$) with the same cluster correction in the post hoc one-tailed *T*-tests. Region assignments were performed using the Neuromorphometric atlas provided in the SPM toolbox. Reported are also the MNI space (*x*, *y*, *z*) coordinates of the cluster peaks as well as the effect sizes—partial eta squared (η_p^2) for the *F*-tests and Cohen's *d* (*d*) for the *T*-tests

The upper table (A and B) refers to the model that included all four task phases (encoding, retention, cued recall, and direct recall) separated by Time (pre, post) and Group ("*Brain-IT*" and Usual Care) controlling for age, sex, and mNCD etiology

The lower table (C) uses an expanded model including the same covariates as the previous model with the addition of ratio of occurrence of both correct (cued recall and direct recall answered correctly) to the total number of trials. This table shows the results of the exploratory analysis of the effect of the summed task phases (encoding, cued recall and direct recall controlling for activity in the retention interval) with both correct in the interaction Group x Time showing both the positive (C.1) and negative (C.2) effects

Abbreviations: *d*, Cohen's *d* effect sized; *df*, degrees of freedom; *η2p*, partial η2 effect sizes; *H*, hemisphere; *k*, number of voxels; *PFWE*, familywise error corrected *P*-value; *Punc*, uncorrected *P*-value; *T\|F*, test-statistic (i.e., *T*-values for *t*-tests and *F*-values for *F* tests)

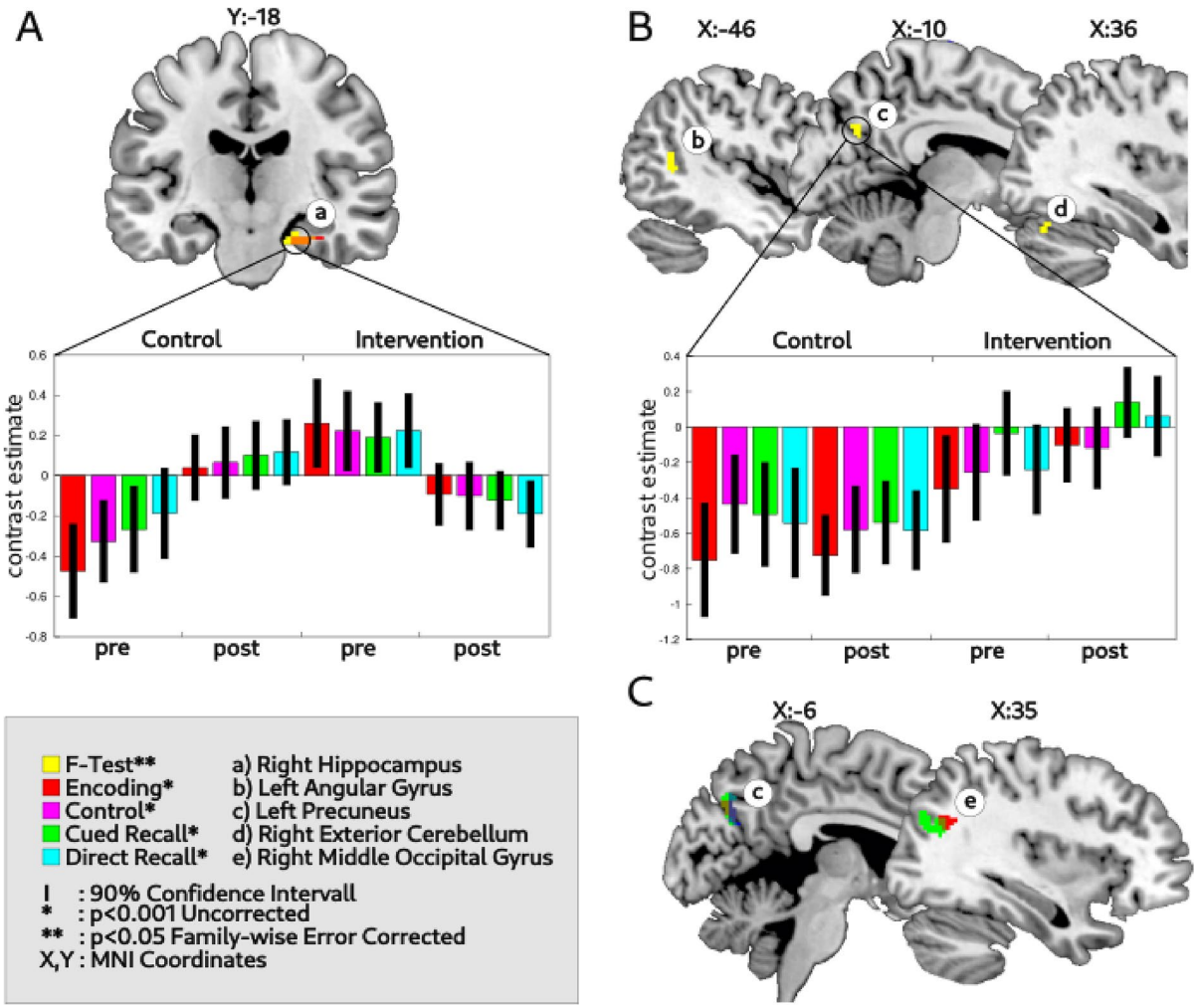


Fig. 2 Task fMRI main model The plot illustrates the significant (Family-Wise Error corrected voxel ($a = 0.05$) for the *F*-test and uncorrected voxel ($a = 0.001$) for the other contrasts) the second level SPM analysis, including all four task phases (encoding, cued recall, and direct recall) separated by time (pre, post) and group ("*Brain-IT*" and Usual Care) controlling for age, sex, and mNCD etiology. Shown are relevant brain slices as well as the contrast estimates (with 95% confidence interval) for peak value voxels for the main effect of group (**A**) the group x time interaction (**B**). Panel A includes the overlay of the one tailed *t* test for the interaction of "*Brain-IT*" < Usual Care & Post > Pre (uncorrected $a = 0.001$). **C** The group difference ("*Brain-IT*" > Usual Care) in post (Table 2). To better illustrate overlapping regions, the colors assigned to the different task phases are added using the additive overlay. This is especially apparent in the left precuneus (c) where the significant voxel of all encoding and recall phases overlaps. Region assignments were performed using the Neuromorphometric atlas provided in the SPM toolbox

Cognitive performance changes

In the fMRI task, trials where the participant failed to answer within the response window (3.75 s) were considered misses (7% of the trials across all participants and conditions). No significant dependence was detected across task types, measurement time, and group allocation. Therefore, we categorized these responses as incorrect, to reduce the complexity of the comparisons.

Descriptively, we observed a higher occurrence of BC in the "*Brain-IT*" group (68%) compared to Usual Care (52%) at post-assessment. However, the adjusted Group × Time interaction model yielded an odds ratio of 1.18 ([0.71–1.95], $X^2_{df(1)} = 0.42$), which failed to reach statistical significance. None of the

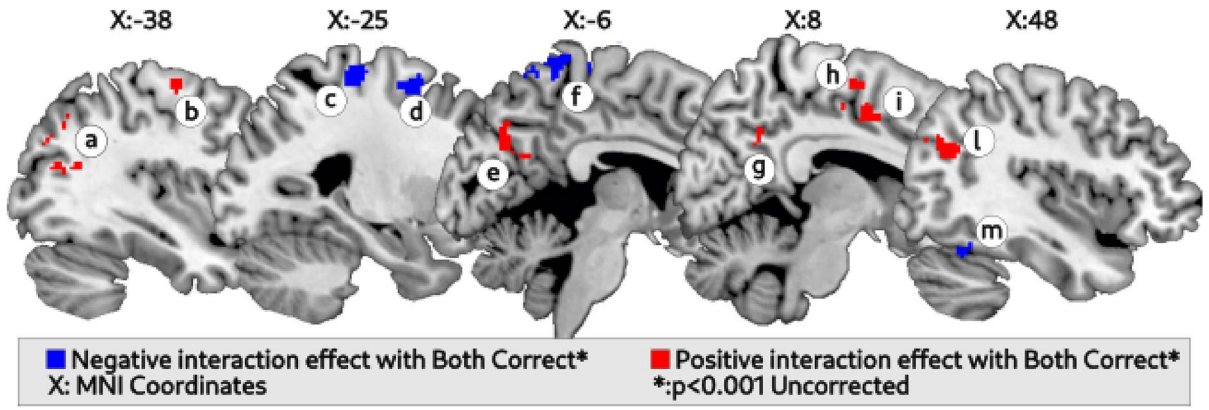


Fig. 3 Task fMRI interaction with both correct (extended model) Illustrated are relevant significant (uncorrected $a = 0.001$) voxel clusters of the expanded model, showing both negative (blue) and positive (red) effects of the summed task phases (encoding, cued recall and direct recall; controlling for activity in the retention interval) with the ratio of occurrence of both correct (cued recall and direct recall answered correctly) to the total number of trials in the contrast "*Brain-IT*" > Usual Care & Post > Pre. Detailed results are listed in Table 2 to note is the presence of significant voxel of the negative interaction in the Left Postcentral gyrus c) this is part of a larger cluster (433 voxel) with the peak in dorsal part of the left precuneus (f). We would also like to point out that the cluster illustrated in the Supplementary motor cortex (h) has local maxima in homologous areas of both hemispheres. Region assignments were performed using the Neuromorphometric atlas provided in the SPM toolbox. a) left angular gyrus, b) left precentral gyrus, c) left postcentral gyrus, d) left superior frontal, e–f) left precuneus gyrus g) right precuneus h) bilateral supplementary motor cortex, i) right middle cingulate gyrus, l) right middle occipital gyrus, g) right fusiform gyrus

contrasts in fMRI task performance were statistically significant, except for the BC model, where we found significant effects of sex (adjusted Odds ratio of 0.41 [0.24–0.71], $X^2_{df(1)} = 10.82$, $p = 0.001$) and etiology ($X^2_{df(4)} = 16.83$, $p = 0.002$)).

Functional brain activity correlates underlying cognitive performance changes

For the expanded model (Table 2C, Fig. 3), we found homologous activation in the left precuneus in the positive interaction of the summed task phases (encoding, cued recall, and recognition; controlling for retention interval activity) with the ratio of occurrence of BC to the total number of trials in the contrast "*Brain-IT*" > Usual Care & Post > Pre ($T_{(1,181)} = 4.13$ and $p_{UNC} < 0.0001$) as well a partial overlap with the activation in the left middle occipital gyrus ($T_{(1,181)} = 5.70$ and $p_{UNC} < 0.0001$). While the negative interaction also showed a significant cluster with peak in the left precuneus ($T_{(1,181)} = 4.91$ and $p_{UNC} < 0.0001$), it is topographically distinct being located much more dorsally and incorporating parts of the Posterior Central Gyrus.

Discussion

This RCT explored resting-state FC and task-related activation adaptations in mNCD introduced by the addition of a co-designed and personalized "*exergame as medicine*" program ("*Brain-IT*") compared to usual care alone, as well as their relation to cognitive performance changes. The personalization of "*Brain-IT*" therapy is mechanisms-focused on maximizing motor-cognitive learning and memory because mNCD-related functional brain alterations depend on clinical severity and appear in regions of early Aβ accumulation that impact learning and memory—particularly the hippocampus, precuneus, and posterior cingulate cortex (PCC) [4, 45]. Key exploratory findings include intervention-related reductions of resting-state FC between the hippocampus and the left MCG and hippocampus activation during memory

encoding, and task-related activation increases in the precuneus and MCG that were associated with episodic memory retrieval accuracy changes (i.e., greater accuracy improvement related to greater functional brain changes).

Reduced hippocampus hyperactivation during memory encoding

While recent meta-analyses showed no statistically significant hippocampus activation changes following non-pharmacological interventions generally [46] or physical exercise specifically [47, 48], we observed a Group × Time interaction effect on task-related functional activation in the right hippocampus post-intervention during encoding (partial $\eta^2 = 0.19$, $p < 0.0001$)—stemming from a reduction in the "*Brain-IT*" group. While the present data do not allow direct comparisons of whether data at pre-measurement confirm mNCD-related hyperactivation in the absence of a healthy control group, we interpret this finding as a potential reduction of hippocampus hyperactivation in the context of the inverted-U-shaped, disease-stage dependent functional activation alterations in NCDs [45] because our study population is well characterized clinically, with biomarker-supported etiological characterization. Specifically, early mNCD is characterized by compensatory task-related functional hyperactivation consistently linked to Aβ accumulation, which emerges to hypoactivation in late mNCD shortly before progressing to dementia due to neocortical tau pathology accumulation—suggesting that such hippocampus hyperactivation may be a transient sign impending clinical worsening [49]. Consequently, both pharmacological and non-pharmacological therapies for early mNCD have targeted reducing hyperactivity in the hippocampus during memory tasks, and success in doing so has been shown to improve memory [50, 51]. Participants in this study were clinically diagnosed and predominantly at an early mNCD stage, whereas clinical worsening that would be indicative of disease progression-related collapse of hippocampus activation was not apparent in the neurophysiological data. In contrary, the "*Brain-IT*" group improved their global cognitive performance to 62.6 ± 13.5 points post-intervention [19]—exceeding the threshold between healthy and NCDs [52]. While an alternative explanation may be a potential regression to the mean in the intervention group, the reduction of hippocampal hyperactivation we observed in this exploratory study is consistent with the structural hippocampal gains that correlated with memory improvements reported earlier in the same sample of study participants [22], indicating a potential brain-protective role underlying cognitive gains of personalized "*exergame as medicine*" therapy in early mNCD that requires confirmation in hypothesis-driven and adequately powered randomized controlled trials.

A meta-analysis of 75 fMRI studies suggests that functional activation alterations also depend on task phase, with memory task-related alterations in the right hippocampus mainly observed during retrieval [1]. Given that our earlier reported improvements in immediate and delayed recall in the "*Brain-IT*" group, the lack of hippocampus activation adaptations during recall might be explained by the findings in the precuneus and MCG.

Improved precuneus recruitment during memory retrieval

The precuneus plays a key role in episodic memory retrieval and in directing attention during movement preparation and execution [46, 53]—coinciding with the training focus of our intervention [19]. In line with this, we observed intervention-related increases in functional activation in the right precuneus that correlated with episodic memory task changes (Cohen's $d = 0.76$, $p < 0.0001$). We interpret this observation to be indicative of successful compensatory upregulation [54].

For compensation, two criteria must be met. One criterion is that enhanced activation is related to a beneficial effect on cognitive performance. The other criterion is that hyperactivation must emerge when neuronal resources to accomplish a given mental operation are diminished. [55] We consider both criteria to be met in our exploratory analysis. First, intervention-related functional activation increases in the precuneus correlated with episodic memory task accuracy changes (i.e., greater accuracy improvement related to greater functional brain changes), and second, atrophy and memory retrieval-related hypoactivation of the precuneus are characteristic of mNCD [3]. Meta-analyses show that these precuneus alterations can be effectively mitigated through non-pharmacological treatments [46] and specifically

physical exercise [47, 48]. The literature coincides with our finding that task-related precuneus activation increases may correlate positively with cognitive task performance improvements [47]. Such potential signs of brain activation changes have been suggested reflective of potential neuroplasticity underlying cognitive performance improvements, which may contribute to the deceleration of disease progression [46, 47].

Modified role of the cingulate gyrus

Our findings regarding the MCG are two-fold.

In the resting-state, we observed a FC decrease in the left MCG in the "*Brain-IT*" group (Cohen's $d = 0.96$, $p = 0.0004$) that diverged from our expectation for a FC increase in more anterior areas due to our earlier reported finding of protective effects on anterior cingulate cortex (ACC) gray matter volume [22]. Based on the findings of a recent meta-analysis reporting elevated FC in the ACC in mNCD [2], we speculate that this observation could be indicative of reduced reliance on compensatory routes, whereby the brain attempts to reroute hippocampal signals through the anterior/middle cingulate (executive centers) to bypass the damaged posterior "*highway*", congruent with the Scaffolding Theory of Aging and Cognition [54]. However, no significant mNCD-specific FC alterations in the MCG appeared in recent meta-analyses [2, 56] while evidence on Cingulate hyper- [2] versus hypo-connectivity [56] appears conflicting and dependent on disease stage—similarly to the inverted U-shaped patterns of NCD-specific functional activation alterations [45]. Therefore, studies with long-term interventions that measure biomarker-related and clinical progression of mNCD—controlling for disease stage—are needed to elucidate whether our preliminary observation reflects a beneficial "*re-normalization*" of former hippocampus-MCG hyperconnectivity or rather a progression of pathological hypoconnectivity.

On the other hand, we found intervention-related functional activation increases in the right MCG (Cohen's $d = 0.26$, $p < 0.0001$). We interpret this observation to be indicative of (i) possible hemispheric compensation in the context of right-biased atrophy in Alzheimer's disease pathology and (ii) a potential behavioral strategy shift promoted by the design of our intervention. Specifically, given that the changes in the right MCG correlated with episodic memory retrieval accuracy changes and resting-state data indicate potential progressive FC alterations in the left MCG, this observation may hint towards a compensatory task-related hemispheric shift (in our case, to the right MCG), as per the HAROLD model [57]. The literature on physical exercise coincides with this observation by showing stable task-related increases in Cingulate activation, albeit predominantly in the left hemisphere [48]. Converging data in mNCD, specifically if due to Alzheimer's disease, suggests rightward-biased asymmetries of neurodegenerative changes [58], which could indicate that the observed functional activation increases in the right MCG in our exploratory analysis may reflect "*re-normalization*" *underlying* the episodic memory task accuracy changes. While hypothesis-driven and adequately powered studies are needed to confirm this potential explanation, such potential effects could be explained by the design of the "*Brain-IT*" training in two ways. First, the multisensory exergame feedback mechanisms mainly reward correct task execution through positive reinforcement, whereas speed of task execution is only indirectly penalized (by missing the response window). Second, the individualized tailoring algorithms heavily focus on precision of task performance as a gating criterion to progress to the next game level. While not statistically significant, these incentives have led to an observable change in strategy in the neuropsychological assessment in many participants, who took more time to favor response accuracy, especially in complex attention and executive functioning tasks [19, 20]. Given that the MCG is activated in humans when the possible responses are conflicting, our finding may therefore be explained by an increased awareness of outcome-related effects during task performance [59] promoted by the design and content of our intervention paired with possible hemispheric compensation.

Implications for research and clinical practice

Our cumulative, preliminary research findings indicate that the personalized "*Brain-IT*" "*exergame as medicine*" therapy may have a structural (exploratory analysis one) [22] and functional (this exploratory analysis) brain-protective role supportive of a causal contribution underlying clinically meaningful improvements in global cognition and memory

(primary, hypothesis-driven analysis) [19]. Importantly, while these three separate analyses stem from the same RCT and therefore do not create independent replication or additional independent evidence, they provide valuable preliminary evidence that the observed behavioral improvements (i.e., in global cognitive performance and memory) may be causally linked to neural changes on both structural and functional level—all in response to a 2 h/week behavioral intervention that lasted 12 weeks.

Thanks to home-based and remotely monitored therapy tailored to meet "*real-world*" needs of patients and reduce participation barriers [20, 21], "*Brain-IT*" shows high suitability for practical applications.

Despite recommendations and evidence on their efficacy [60, 61], exergame therapies such as "*Brain-IT*" have been overlooked in motor-cognitive neurorehabilitation and prevention [61]—with no published studies that evaluated their implementation or long-term effectiveness in healthcare for mNCD. Therefore, future research should focus on testing the deployment and implementation in clinical practice and evaluating its long-term effectiveness as a secondary prevention intervention. Given the paucity of evidence on long-term disease modification of exercise with hard outcomes (e.g., delay of Dementia onset) [11], a special emphasis should be on measuring biomarker-related and clinical progression criteria for confirming (or rejecting) potential disease modification in different mNCD etiologies along with the intervention's cost-effectiveness in mNCD.

To optimize uptake in clinical practice, the "*Brain-IT*" program would benefit from refinement to improve delivery efficiency. This could be achieved through developing a complementary exergame evaluation module paired with artificial intelligence-powered, human-in-the-loop algorithms. These algorithms should augment clinical decision-making with human data input (e.g., perceived task difficulty), oversight, and control [18] by automatizing processing of, and providing theory-informed suggestions on implementing underlying decision trees for individualized tailoring provided by our validated "*Brain-IT*" concept [19]. Thereby, an effective, practical, and well-accepted balance between automatization and clinical judgement for delivering personalized interventions can be provided—so that therapy can be focused on quality clinician-patient time.

Finally, *"exergame as medicine"* therapies could be further enhanced by using system level readouts like FC and task-related BOLD responses not only for evaluating interventions aimed at stabilizing or restoring cognitive function in mNCD [4], but also to predict intervention adherence and responsiveness—which could further optimize personalization in light of a precision "*exergame as medicine*" approach.

Strengths and limitations

This study had several important strengths and limitations, which were elaborated in detail previously [19].

Key strengths of the overall RCT include (i) the rigorous co-development of the study's intervention that systematically combined patient and public involvement with strong theoretical backing to target relevant mechanisms of action in order to alleviate the pathological state of mNCD, support motor-cognitive learning, and optimize user experience [18, 20, 21], (ii) the generalizability of the findings in relation to the broad selection of study participants including various etiologies of mNCD and relatively broad eligibility criteria [19], and (iii) comprehensive evaluations of neural correlates potentially underlying cognitive improvements [22, 23].

Key limitations of the overall RCT include that our investigation of the addition of the "*Brain-IT*" therapy to usual care was limited by the fact that the (memory) clinics where participants were recruited provided the usual care interventions, making it impossible to standardize contact times. As a result, this study does not demonstrate superiority of "*Brain-IT*" over conventional exercise, nor does it isolate the effects of exergame-based training from the other components of the intervention. However, comparing an intervention against treatment as usual is a recommended practice for effectiveness studies [26] and is supported by the alignment of recommended treatment and management of individuals with mNCD in Switzerland with available global clinical practice guidelines and consensus statements [25].

The neuroimaging analyses presented here have three additional key limitations. *First*, and most importantly, while the primary RCT was powered for clinical outcomes [23], this study was not powered for exploratory neuroimaging analysis. The relatively modest sample size resulted in baseline imbalances across several imaging markers, which may lead to

unstable effect sizes that either limit our ability to detect subtle treatment effects or, conversely, lead to inflated effect sizes. Furthermore, the large number and complexity of our analyses in relation to this modest sample size require hypothesis-driven and adequately powered studies to provide information on the stability and reproducibility of the findings and well as the strength of potential effects. Acknowledging these limitations and given we present the first RCT exploring neural correlates of a console-based exergame-based training in mNCD [17], we focused our interpretation on Group × Time interaction effects to account for these imbalances and guide hypothesis-generation for adequately powered studies to build on and substantiate our initial exploratory findings. *Second*, while the validated fMRI task used was adapted specifically for individuals with mNCD [29–31], 13% of participants had insufficient task comprehension despite extensive instructions and had to be excluded from task fMRI data collection to ensure validity of data. The associated data loss further reduced the sample size available for analysis and indicates that the complexity and speed of the task might still be too high for more advanced mNCD. *Finally*, while the inclusion of multiple mNCD etiologies is a strength for generalizability of findings and their transferability to clinical practice in the context of an intervention that was tailored to these different etiologies [19], the heterogeneity of disease etiology represents an inherent limitation for the analyses presented here. While we adjusted our analyses accordingly, follow-up studies are required to elucidate potential etiology-specific nuances in intervention responsiveness.

Conclusion

This exploratory RCT observed reduced hippocampus hyperactivation during memory encoding and potential compensatory functional activation increases in the right precuneus and MCG that correlated with episodic memory retrieval accuracy changes in mNCD following "*Brain-IT*" therapy. These initial findings should inform the design of hypothesis-driven and adequately powered RCT to provide stronger evidence on the neural correlates and underlying cognitive performance improvements in response to serious exergame-based training. While resting-state findings require long-term follow-up investigations to allow robust interpretation, these initial exploratory findings indicate a potential short-term brain-protective role of personalized "*exergame as medicine*" therapy underlying cognitive improvements in mNCD.

Cumulatively, our preliminary research findings are consistent with potential structural [22] and functional (this study) brain-protective role of personalized "*Brain-IT*" "*exergame as medicine*" therapy supportive of a causal contribution underlying clinically meaningful improvements in global cognition and memory [19]—all in response to a 2 h/week behavioral intervention that lasted 12 weeks. These preliminary and exploratory findings require confirmation in hypothesis-driven and adequately powered RCT.

While exergame therapies have been overlooked in motor-cognitive neurorehabilitation [61], "*Brain-IT*" therapy shows high suitability for practical application thanks to its home-based and remotely monitored application that is tailored to meet "*real-world*" needs of patients and reduce barriers for participation [20, 21]. Therefore, in addition to hypothesis-driven studies to confirm effects on the brain and behavior, hybrid implementation-effectiveness research with long-term follow-up measuring biomarker-related and clinical progression should evaluate whether potential brain-protective effects translate to delaying and/or prevention progression to dementia.

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Author contribution P.M. was responsible for the conception of the study under the supervision of E.dB. and with the support of L.M. and A.S. for the fMRI data collection and analyses. P.M. was responsible for participant recruitment and all the study procedures and data collection under the supervision of E.dB. and support of L.M. in setting up and running fMRI scans. M.R., L.M., and P.M. did the data processing and analysis, with methodological guidance from E.dB. and A.S. Finally, P.M. and M.R. were responsible for drafting the manuscript, while all authors contributed to revisions and approved the submitted version of the manuscript.

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Data availability Datasets on participant characteristics and all non-MRI related outcomes are available in the Zenodo repository (https://doi.org/10.5281/zenodo.10695988). fMRI scan data are not publicly available owing to the sensitive nature of neuroimaging data, but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate All study procedures were performed in accordance with the Declaration of Helsinki, local legislation, and institutional requirements. The study protocol was approved by the Ethics Committees of Zurich and Eastern Switzerland (EK-2022-00386). All participants provided written informed consent to participate in this study.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process The authors attest that there was no use of generative artificial intelligence (AI) technology in the generation of text, figures, or other informational content of this manuscript. A non-generative artificial intelligence (DeepL) specialized to improve and clarify language was used for refinement and correction of the manuscript text.

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