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Neurocognitive Plasticity Is Associated with Cardiorespiratory Fitness Following Physical Exercise in Older Adults with Amnestic Mild Cognitive Impairment

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Abstract.
Background: Aerobic training has been shown to promote structural and functional neurocognitive plasticity in cognitively intact older adults. However, little is known about the neuroplastic potential of aerobic exercise in individuals at risk of Alzheimer's disease (AD) and dementia.
Objective: We aimed to explore the effect of aerobic exercise intervention and cardiorespiratory fitness improvement on brain and cognitive functions in older adults with amnestic mild cognitive impairment (aMCI).
Methods: 27 participants with aMCI were randomized to either aerobic training ($n = 13$) or balance and toning (BAT) control group ($n = 14$) for a 16-week intervention. Pre- and post-assessments included functional MRI experiments of brain activation during associative memory encoding and neural synchronization during complex information processing, cognitive evaluation using neuropsychological tests, and cardiorespiratory fitness assessment.
Results: The aerobic group demonstrated increased frontal activity during memory encoding and increased neural synchronization in higher-order cognitive regions such as the frontal cortex and temporo-parietal junction (TPJ) following the intervention. In contrast, the BAT control group demonstrated decreased brain activity during memory encoding, primarily in occipital, temporal, and parietal areas. Increases in cardiorespiratory fitness were associated with increases in brain activation

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in both the left inferior frontal and precentral gyri. Furthermore, changes in cardiorespiratory fitness were also correlated with changes in performance on several neuropsychological tests.

Conclusion: Aerobic exercise training may result in functional plasticity of high-order cognitive areas, especially, frontal regions, among older adults at risk of AD and dementia. Furthermore, cardiorespiratory fitness may be an important mediating factor of the observed changes in neurocognitive functions.

Keywords: Brain plasticity, cardiorespiratory fitness, cognition, functional MRI, mild cognitive impairment, physical exercise

INTRODUCTION

The effects of physical exercise on the brain have been increasingly investigated over the past two decades. Both interventional and cross sectional studies in animal models and healthy humans show that a physically active lifestyle is related to lower risk of cognitive decline and dementia and improved cognitive function [1–3]. Moreover, physical exercise has been shown to promote neuroplastic changes related to brain structure and function in healthy participants, and these changes were associated with improved cognitive function. Structural changes in the frontal, hippocampal, and temporal grey matter volume following aerobic exercise have been observed [4–6], as well as changes in white matter integrity of the cingulum [7], corpus callosum [8], and fronto-temporal regions [9]. In the context of brain function, several functional magnetic resonance imaging (fMRI) studies demonstrated modifications in brain activity in different areas including the hippocampus [10, 11] and the frontal cortex [12] following intensive exercise intervention, in a variety of cognitive tasks requiring different cognitive processes such as executive control or memory encoding [11]. Interestingly, the brain region that has been found most consistently to demonstrate a positive relationship with aerobic exercise or cardiorespiratory fitness in cognitively-intact adults is the frontal cortex [6, 10, 13, 14]. For example, higher cardiorespiratory fitness was associated with increased working memory-related activity of prefrontal hubs [13] and higher resting state functional connectivity [15] of the fronto-parietal control network. Increased lateral and medial prefrontal activity during associative memory tasks was also demonstrated to be associated with aerobic fitness in healthy older adults [16]. Wagner et al. (2017) [10] reported stronger activation in the brain's motor network as well as in fronto-cingulate brain regions, centrally involved in executive processes. Furthermore, the positive effect of aerobic exercise on prefrontal activation was demonstrated even after a single session of exercise [17–19].

While the majority of these studies used aerobic exercise protocols, several studies have demonstrated benefits in both cognitive performance and markers of brain plasticity in protocols of non-aerobic exercise modalities such as resistance training or balance and coordination exercises [20–23]. The above mentioned neuroplastic changes in brain structure and function following intensive exercise have been mainly described in healthy populations and their relevance to people suffering from neurodegenerative processes remains uncertain and is the focus of substantial research in recent years. Within this context, the current study seeks to broaden understanding of the effects of physical exercise training in individuals who are at risk of neurodegeneration, specifically older adults with amnestic mild cognitive impairment (aMCI).

MCI is a clinical syndrome characterized by neurocognitive deficits more advanced than expected considering the individual's age and education level, alongside preserved overall everyday-life functioning [24, 25]. MCI is considered a major risk factor for development of dementia, and a substantial proportion of these patients deteriorate to dementia within a few years [25]. aMCI is the most common subtype of MCI, and considered the prodromal stage of Alzheimer's disease (AD) [25, 26]. Individuals with aMCI primarily demonstrate deficits in memory processing such as encoding and consolidation of episodic information, which is manifested especially in decreased performance during delayed recall [27–29]. In addition, in a previous work, we demonstrated altered neural patterns during processing of complex ecological auditory information (listening to a plotted story) in participants with aMCI compared to controls [30]. Specifically, we showed in participants with aMCI that while regions involved in early auditory processing of simple information (e.g., A1 +) remained unaffected, synchronized

responses of complex information extended from A1 + to areas not typically involved in this type of cognitive processing (i.e., the pre- and post-central gyri). This was in contrast to healthy controls, in which responses extended from A1 + to higher perceptual and cognitive areas (i.e., temporo-parietal junction and prefrontal cortex).

Current therapeutic approaches to aMCI are symptomatic and of modest efficacy [25, 31]. However, despite the limited pharmacological solutions, the body of knowledge regarding the potential of physical exercise interventions to improve neurocognitive state in these patients is relatively limited. Several studies that examined the effect of exercise interventions in aMCI [32–37] demonstrated improvement in cognitive performance. However, very few interventional studies investigated neural mechanisms by which physical exercise may exert its influence on the neurocognitive capabilities. Several studies which used structural MRI techniques [38–41] demonstrated morphological modifications including increased hippocampal volume [38], preserved whole brain gray matter volume [40] or grey matter in specific brain regions [39], and increased cortical thickness following exercise regimes [41]. The only three studies conducted in recent years that implemented functional imaging found better performance on a functional task conducted in the scanner following aerobic intervention. The improved performance was associated with decreased brain activation. In one study decreased brain activation was found in the left lateral occipital cortex and right superior temporal gyrus, while another study found significant decrease in numerous cortical and subcortical regions [42, 43]. Only one study focused the functional paradigms on the most affected cognitive domain in aMCI, i.e., episodic memory and showed functional changes following resistance training. These changes were observed in the right lingual and occipital fusiform gyri and the right frontal pole [44].

As current knowledge regarding the effect of physical exercise on brain function in people with aMCI is very limited, we aimed to investigate the effect of an aerobic exercise intervention compared to an active control group which performed light balance and toning (BAT) exercises on the following: 1) brain activity during associative memory encoding; 2) synchronized neural responses during complex information processing; 3) cognitive performance. In addition, we aimed to investigate the relationship between changes in cardiorespiratory fitness, and changes in brain function and cognitive performance following the intervention, as previous works have suggested cardiorespiratory fitness to be a potential mediator of the effects of aerobic exercise on the brain in healthy adults [6, 45]. Based on the aforementioned findings, our main hypothesis was that aerobic training would lead to modifications in brain function, which would be primarily manifested in the frontal cortex, and that these changes would be associated with changes in cardiorespiratory fitness. We hypothesized that changes in brain function would be translated to changes in cognitive performance. In addition, we hypothesized that changes in activity patterns may also be evident in the BAT group, although in a less robust or differential pattern compared to the aerobic group.

MATERIALS AND METHODS

Participants

Thirty-four older adults with aMCI were recruited for the study (16 women/18 men). Participants were recruited from the outpatient clinic of the Center for Memory and Attention Disorders at Tel Aviv Sourasky Medical Center (TASMC), after being diagnosed with aMCI by an expert neurologist according to published criteria [26], which included: 1) subjective concern regarding cognitive change reported by the patient or an informant or a clinician; 2) objective evidence of impairment in one or more cognitive domains, including episodic memory; 3) preserved everyday-life functioning; and 4) not demented. Participants were fluent Hebrew speakers, and reported no current or previous neuropsychiatric disorders (other than aMCI) or any other current significant unstable medical illness (e.g., cardiovascular or metabolic). The research was approved by the institutional ethics committee for Human Studies at TASMC, and all participants provided written informed consent to participate in the study. The experiments were undertaken in compliance with the safety guidelines for MRI research. Five participants (3 women/2 men) dropped out during the assessment phase due to inability to complete all procedures or not meeting the inclusion criteria. Two participants decided to terminate their participation during the intervention period (1 woman/1 man). Twenty-seven participants eventually completed their participation and were analyzed in the current study (12 women/15 men) (Fig. 1).

Procedure

Following the initial evaluation, participants were randomized to either experimental group (aerobic training group) or active control group (BAT group) using a random number list generator. This design is in accordance with previous works using low-intensity active control group when examining the effect of physical exercise intervention in healthy older adults and patients with MCI [4, 32, 33, 46]. Participants in both groups carried out their exercise routines for 16 weeks, 3 days/week on a "One-on-One" basis under the supervision of an experienced trainer at the participant's home. One-on-One training was applied in order to ensure high adherence and compliance to the training regime. Importantly, adherence to the intervention was > 90% for each group, indicating that participants in both groups completed almost all training sessions during the intervention period. In addition, participants were asked not to make any additional changes to their usual physical activity/inactivity habits during their participation in the study.

Aerobic training protocol

For the aerobic training, stationary bicycles (NOVO 850, York Fitness Ltd.) were mounted in the participants' homes. According to the recommendations of the American College of Sports Medicine for older adults, exercise intensity was gradually increased over the first 6 weeks of the program until participants were exercising at between 70% to 80% of heart rate reserve (HRR) [47]. This intensity was then maintained for the rest of the intervention duration. HRR was calculated based on the cardiopulmonary exercise testing results as the difference between maximal HR and resting HR. Then, after calculating the percentage of HRR this value was added to the resting HR resulting in the target HR for the workout. Exercise intensity was monitored using a wireless heart rate monitor and by the Borg's Rating of Perceived Exertion (RPE) scale [48].

BAT training protocol

The BAT group carried out a prescribed routine of balance, gross motor coordination, and light toning exercises, while maintaining heart rate below 30% of HRR in order to minimize aerobic stimulation and adaptations.

Session duration in both groups was gradually increased during the first 6 weeks from 20 to 40 min. Each session during the intervention period started with 5 min of warm-up and ended with 5 min of cool-down, with the main part of each session lasting between 10–30 min.

PRE and POST outcome measures

Participants took part in a series of neurocognitive assessments and neuroimaging sessions before and after the intervention, on two separate days. All assessments were conducted within two weeks before or after the intervention.

Assessment of brain function

Associative episodic memory and complex information processing are cognitive abilities that have been shown to be compromised in aMCI, from neural and behavioral perspectives [29, 30, 49]. Therefore, two fMRI paradigms were implemented to assess functional brain patterns during the performance of these two tasks.

A. Associative memory encoding paradigm

Participants performed a block design paradigm of an associative encoding task based on the classic paradigm developed by Sperling et al. [50]. The task was used in previous MCI studies [51, 52]. In the current study, participants were shown unfamiliar pictures of either faces or houses paired with a fictional name. Participants were asked to remember the faces/houses they saw and the name that was shown with each face/house; in addition, they were asked to subjectively decide (by pressing a button) whether the name "fits" the face or the house. This subjective decision has been shown to enhance associative encoding [53]. Participants performed three runs, with each run lasting 5:06 min. Each run consisted of four distinct conditions: 'novel faces' (i.e., presentation of only new and different faces), 'repeated faces' (i.e., presentation of the same specific faces repetitively), 'novel houses' (i.e., presentation of only new and different houses), and 'repeated houses' (i.e., presentation of the same specific houses repetitively). In each run all four conditions were presented twice in a different order, therefore each run consisted of 8 blocks. Overall, each run contained 32 stimuli of faces or houses. Each block lasted 21 s. Each picture (i.e., face/house) was presented to the participants for 480 ms. Blocks were separated from each other by a fixation stimulus (white cross on a black background). Participants were instructed to look at the fixation stimuli in order to focus their visual attention. The paradigm is schematically illustrated in Fig. 2. Prior to the fMRI session, a practice session was

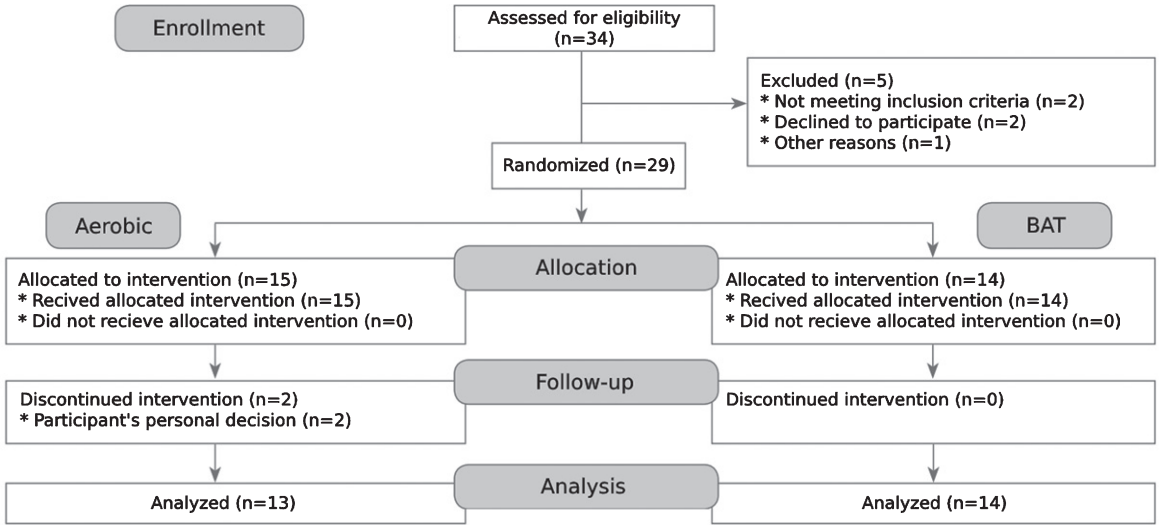

Fig. 1. Flow diagram of the study process.

conducted outside the scanner, on a laboratory computer.

Following the acquisition phase in the scanner, two two-alternative forced choice recognition tests were conducted outside the scanner, on a lab computer. During the first task (Recognition 1 test), participants were shown 56 images of faces/houses and were asked to decide whether they have or have not seen them during the scanning session. In the second task (Recognition 2 test), participants were shown 24 images of faces/houses that they did see during the scan and were asked to choose between two options which name was paired with each face/house.

B. Complex information processing paradigm

During the fMRI sessions, participants were asked to listen to a real-life plotted story. During the pre-exercise intervention scanning session, participants listened to a 12-min story, while on the post-intervention session they listened to an 8-min story. The stories were told in Hebrew by professional storytellers and recorded especially for the study, with no visual stimulus presented. In the paradigm, narration began after a 13 s period of silence. Attentive listening to the story was confirmed by informing the patients that after the scan, they would be asked about the story content. An inter-subject correlation analysis (see below) was used to identify and compare neural responses during the story within and between the groups. By comparing neural responses evoked by the stories, we were able to characterize the informational capacity of brain areas involved in processing of complex information.

MRI acquisition

MRI scanning was performed at TASMC on a 3 T Siemens system (MAGNETOM Prisma, Germany). High resolution, anatomical T1-weighted images (voxel size = $1 \times 1 \times 1$ mm) were acquired with a magnetization prepared rapid acquisition gradient-echo protocol with 176 contiguous slices using the following parameters: field of view (FOV) = 256 mm; matrix size = 256×192; repetition time (TR) = 1740 ms; echo time (TE) = 2.74 ms, inversion time (TI) = 976 ms, flip angle (FA) = 8°. These anatomical volumes were used for co-registration with functional images. Blood oxygenation level dependent (BOLD) functional MRI was acquired with T2*-weighted imaging using the following parameters. For the memory encoding paradigm: TR = 3000 ms; 99 TRs in each run; TE = 35 ms; FA = 90°, FOV = 220 mm; matrix size = 96×96; 44 slices, voxel size = $2.3 \times 2.3 \times 3$ mm, no gap. For the information processing paradigm: TR = 1500 ms (492 TRs in the PRE and 320 TRs in the POST assessments); TE = 30 ms; FA = 75°; FOV = 22×22 cm^2; matrix size = 64×64; 27 slices of 3 mm thickness, 1 mm gap. The slices were positioned nearly horizontal to cover the entire temporal lobe and the parts of the frontal lobe that are involved in hearing and language processing, as well as nearly all of the occipital and parietal lobes.

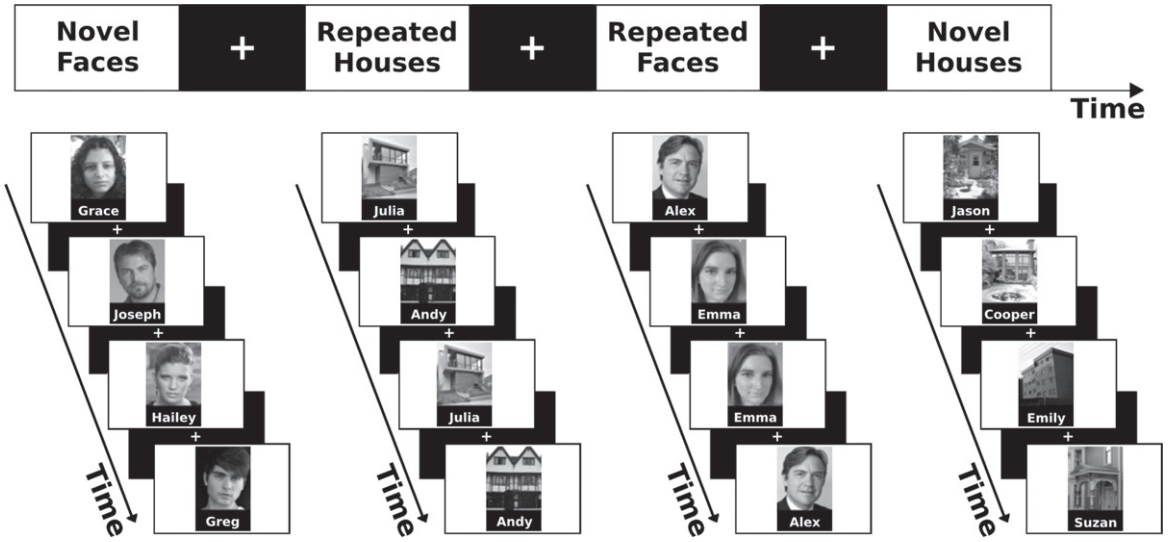

Fig. 2. Associative memory encoding fMRI paradigm of face/house-name pairs. The session consisted of three runs, each comprising 8 stimuli blocks of the 4 conditions (two blocks for each condition): novel faces, novel houses, repeated faces, repeated houses. Participants were asked to memorize the stimuli and names they see, and subjectively decide whether the name "fits" the face/house. Please note that black-and-white pictures here are used for the presentational purposes only; they were colorful in the experiment.

In order to minimize head movements, participants' heads were stabilized with foam padding. MRI-compatible headphones (OPTOACTIVE^{tm}) were used to considerably attenuate the scanner noise and communicate with the participants during the session. Designated software (Presentation®, Neurobehavioral Systems) was used for visual stimuli presentation.

Cardiorespiratory fitness assessment

Cardiorespiratory fitness was evaluated using a graded maximal cardiopulmonary exercise test performed on a cycle ergometer, at the Non-Invasive Cardiology Outpatient Clinic at TASMC. Tests were supervised by a cardiologist and an exercise physiologist while continuously monitoring for cardiopulmonary parameters, including oxygen consumption (VO_2), heart rate, blood pressure, and respiratory exchange ratio (RER). An automated computerized ramp protocol was used to increase exercise intensity by 10 watt every minute while participants were asked to maintain a constant velocity of 60 revolutions per minute. The highest average VO_2 value (VO_2peak) recorded during a 12 s interval (two watts increment) was considered as the cardiorespiratory fitness value obtained from the procedure. Tests were terminated by participants' report of subjective exhaustion. No adverse events were reported for any of the participants. The cardiorespiratory evaluation served two purposes: 1) assessment of the aerobic fitness level of participants prior to and following the intervention; 2) tailoring an individualized training regime for each participant based on his/her physiological parameters.

Cognitive assessment

A neuropsychological battery assessing different cognitive domains (e.g., memory, executive functions, visuo-spatial, language, and attention) was performed before and after the exercise intervention. The assessment included the following standardized tests: the Montreal Cognitive Assessment (MoCA) for general cognitive screening [54]; the Rey auditory verbal learning test (RAVLT) for immediate and delayed verbal learning and memory [55, 56]; the Rey-Osterrieth complex figure for the assessment of visuo-spatial abilities and memory [57]; the Wechsler logical memory test; the color version of the trail making test (CTT) [56, 58]; the verbal fluency test (semantic and phonemic) [56, 58]; and the digit span test [59].

In addition, background characteristics included questionnaires regarding participants' mental state including the Geriatric Depression Scale (GDS) [60], the Spielberger anxiety state and trait tests [61], and the Clinical Dementia Rating (CDR) [62] test, for evaluation of severity of memory impairment. The Physical Activity Scale for the Elderly (PASE)

[63] was also administered to evaluate differences in current everyday physical activity habits between the groups. The PASE has been previously used in research assessing the effect of exercise intervention on cognitive function in MCI [33].

Data analysis

Functional MRI

fMRI data were analyzed with the BrainVoyager QX 2.8 software package (Brain Innovation, Maastricht, The Netherlands). Preprocessing of the functional scans included slice time and motion correction, linear trend removal, high-pass filtering (cut-off: 0.01 Hz), spatial smoothing using a 6 mm full-width at half-maximum kernel and cropping of the first 5 TRs in each run. Data analysis was performed separately for each participant. The functional images were co-registered with the anatomical images using a two-step, semi-automatic procedure. First, an initial alignment by BrainVoyager was performed, followed by an advanced manual alignment. Finally, the data were incorporated into the three-dimensional data sets through trilinear interpolation. The complete functional dataset was transformed to a common 3D Talairach space [64]. Runs in which head motions were greater than 2 mm were excluded from the analyses. Eventually, only two runs from the *pre* data (one from each group) were excluded. All analyses were conducted using a whole-brain approach.

Memory encoding paradigm

Three-dimensional statistical parametric maps were calculated separately for each participant's first-level analysis using a general linear model (GLM) in which all stimuli condition blocks were convolved with the canonical hemodynamic response function (HRF) to form positive regressors. In addition, six movement parameters (three translations, three rotations) were included in the model as covariates of no interest to adjust for residual movement related signal. A second level ANCOVA random-effects whole brain analysis was applied to examine brain areas that demonstrated within-group changes in activation in the novel encoding > fixation contrast ($p < 0.01$, FDR-corrected, cluster size ≥ 5 functional voxels). Next, between-group differences in activation change in the three frontal regions identified in the aerobic group were assessed using a 2-tailed *t*-test. This specific region-of-interest (ROI) analysis was conducted following our hypothesis that aerobic intervention would yield increased frontal activity following the training period compared to the non-aerobic control group.

Information processing paradigm

Change in topology of information processing was analyzed using inter-subject correlation (inter-SC) analysis: this approach explores to what extent similar brain regions of different participants show synchronization of neural responses to natural stimuli. This synchronization is exhibited by significant correlation between participants' neural responses (inter-SC), indicating response reliability. Inter-SC maps were constructed voxel-by-voxel in Talairach space for each group by comparing the fMRI response time-courses across participants. First, the Pearson product-moment correlation was computed between a voxel's fMRI time-course in one individual and the average of that voxel's fMRI time-courses in the remaining participants. Next, the average correlation was calculated at every voxel. Statistical significance of the inter-SC analyses was assessed using a phase-randomization procedure. Phase-randomization was performed by applying a fast Fourier transform to the signal, randomizing the phase of each Fourier component, and then inverting the Fourier transformation. Thus, the power spectrum was preserved but the correlation between any pair of such phase-randomized time-courses had an expected value of 0. Phase-randomized time-courses were generated for every measured fMRI time-course from every voxel in each participant. A correlation value was then computed (as detailed above) for every voxel. This process was repeated 5000 times to generate a null distribution of the correlation values, separately for each voxel. Statistical significance was assessed by comparing empirical correlation values (without phase randomization) to these null distributions. The Benjamini–Hochberg–Yekutieli false-discovery procedure, which controls the false discovery rate (FDR) under assumptions of dependence, was used to correct for multiple comparisons [65–67]. The differences in neural response reliability between groups were assessed using a 2-tailed *t*-test.

Cardiorespiratory fitness

Changes in cardiorespiratory fitness were evaluated both within-group using paired *t*-test and between-group by comparing the pre-post differences between the groups using independent samples *t*-test. In addition, to explore the potential contribution of changes in cardiorespiratory fitness to changes in brain activity and cognitive function following the

intervention, we applied one-tailed Pearson correlation analyses under the hypothesis that increased fitness would be associated with increased brain activity and enhanced cognitive performance. When correlating changes in fitness with changes in cognitive performance on each test, partial correlation analyses were conducted by controlling for baseline performance in the relevant test. Fitness-brain function association was investigated by correlating changes in fitness and activation changes in three frontal clusters found to increase their activity level following the aerobic intervention. Correlation analyses were computed across the entire sample as changes in fitness were identified in both groups.

Neuropsychological assessment

All tests were scored and standardized using appropriate, age- and sex-based norms, except the MoCA test score, which was standardized using the average and standard deviation (22.1 ± 3.1) suggested for MCI by Nasreddine et al. on the MoCA website [68]. For the CTT, delta CTT represents the difference (in seconds) between the time taken to complete CTT2 and CTT1. Paired student's *t*-test was applied separately for each group to establish within-group differences in cognitive performance on all tests following the intervention. Between-group differences were investigated by comparing the post-pre difference in each test between the groups using independent samples *t*-test. For the RAVLT, the 1st, 5th, and 8th repetitions were chosen for the analysis as they represent baseline performance, learning and delayed memory, respectively. Statistical analyses were performed using SPSS software v20.

RESULTS

Participants' characteristics at pre-intervention evaluation

Table 1 summarizes baseline sample characteristics (pre-intervention evaluation) including demographics, clinical characteristics, and cognitive assessment scores. Participants in both groups did not differ in any of the demographic and other background characteristics (CDR, PASE, GDS, and anxiety state and trait questionnaires). The only statistically significant difference between the groups at baseline was demonstrated in the MoCA test, in which the BAT group demonstrated higher scores ($p = 0.02$). Both groups demonstrated MoCA scores higher than age- and sex-based norms. Both groups demonstrated delayed-recall verbal memory performance worse than 1 standard deviation below age- and sex-based norms reflected on the 8th repetition of the RAVLT, emphasizing objective delayed memory decline.

The effect of the exercise intervention on brain function during associative memory encoding

Both groups demonstrated changes in brain activity during associative encoding of novel face/house-name pairs compared to fixation following the intervention period ($p < 0.01$, FDR-corrected), albeit with different patterns. While the aerobic group showed increased activity in several brain areas, primarily in higher order frontal regions (Fig. 3A, Table 2), the BAT group demonstrated decreased brain activation in occipital, temporal, and parietal areas (Fig. 3B, Table 2).

When specifically examining activity changes in the frontal clusters, we found increased activity in the aerobic group compared to the non-aerobic control group in all three ROIs: left inferior frontal gyrus – activity (β value) difference's mean $\pm$ SD $0.43 \pm .35$ versus $-0.20 \pm .32$, $t(24) = 4.08$, $p = 0.000$; left precentral gyrus – $0.40 \pm .29$ versus -0.08 ± 0.37, $t(24) = 3.66$, $p = 0.001$; left middle frontal gyrus – 0.43 ± 0.57 versus 0.09 ± 0.51, $t(24) = 2.12$, $p = 0.044$ (Fig. 4).

The effect of the exercise intervention on information processing

We hypothesized that specific brain areas might demonstrate enhanced change in activity profile when natural stimulation is applied. Our goal was to examine changes in the level of synchronization in response time-courses of participants as a function of training and to map these functional changes, while participants listened to narrated stories in the scanner (Figs. 5 and 6). To this end, we calculated the inter-SC values across the entire stimuli within each group before and after training. The voxel-by-voxel inter-SC maps across whole cortex within each group (aerobic and non-aerobic) revealed the brain areas that responded reliably to the stories within a given group (see Methods). Specifically, before the training, the maps observed in both groups, aerobic (Fig. 5A, light green) and non-aerobic (Fig. 6A, light blue), were very similar to each other. The reli-

Table 1
Socio-demographic characteristics of participants (A), clinical characteristics for participants with MCI in both experimental groups (B)

A. Socio-demographic characteristics of participants			
	Aerobic group (N = 13)	BAT group (N = 14)	Between-group (p)
Age (y)	70.84 ± 5.53	71.92 ± 6.40	0.64
Sex (male/female)	8/5	7/7	0.55
Education (y)	14.07 ± 3.77	14.5 ± 2.73	0.74
B. Clinical characteristics of participants with MCI			
CDR	0.46 ± 0.32	0.42 ± 0.26	0.77
GDS	7.50 ± 5.09	6.9 ± 4.04	0.78
Anxiety trait	33.50 ± 6.16	34.08 ± 6.76	0.84
Anxiety state	28.62 ± 8.56	29.50 ± 7.98	0.81
PASE	124.48 ± 79.86	91.67 ± 50.11	0.21
VO_2 peak (ml/kg/min)	20.74 ± 3.73	20.50 ± 3.56	0.86
MoCA (z-score)	0.51 ± 0.87	1.25 ± 0.72	**0.02***
RAVLT 1 (z-score)	–1.03 ± 1.44	–0.66 ± 1.11	0.45
RAVLT 5 (z-score)	–0.75 ± 1.21	–0.37 ± 1.20	0.41
RAVLT 8 (z-score)	–1.10 ± 1.08	–1.08 ± 1.30	0.96
ROCF copy (z-score)	1.01 ± 0.87	1.34 ± 0.38	0.22
ROCF recall (z-score)	0.43 ± 0.99	0.85 ± 1.24	0.34
LM immediate (z-score)	–0.10 ± 1.17	0.66 ± 0.96	0.07
LM recall (z-score)	0.10 ± 1.67	0.42 ± 1.29	0.57
Digit span (z-score)	–0.30 ± 0.77	–0.04 ± 0.76	0.38
VF phonemic (z-score)	–0.03 ± 1.67	0.36 ± 1.33	0.50
VF semantic (z-score)	–0.50 ± 0.96	–0.65 ± 1.29	0.73
CTT 1 (z-score)	–1.55 ± 1.85	–0.50 ± 1.07	0.08
CTT 2 (z-score)	–1.35 ± 2.0	–0.57 ± 1.19	0.22
Delta CTT (seconds)	68.47 ± 43.20	57.93 ± 26.45	0.49
Recognition 1 (raw score)	34.08 ± 8.27	34.64 ± 11.41	0.88
Recognition 2 (raw score)	14.00 ± 2.04	13.57 ± 2.56	0.64

y, years; CDR, Clinical Dementia Rating; GDS, Geriatric Depression Scale; PASE, physical activity scale for the elderly; VO_2, oxygen consumption; MoCA, Montreal Cognitive Assessment; RAVLT, Rey auditory verbal learning test; ROCF, Rey Osterrieth complex figure; LM, logical memory; VF, verbal fluency; CTT, color trail test.

able responses were found mainly in the parietal and temporal areas involved in auditory processing (i.e., primary auditory areas) and some aspects of content comprehension and/or linguistic processing [69–73]—superior temporal gyrus (STG), middle temporal gyrus (MTG), inferior parietal lobule, lingual gyrus, and precuneus. After the training, the differences across the post-training maps became more profound between the two groups. While in the aerobic group (Fig. 5A, dark green) enhanced post-training response synchronization appeared in the supramarginal gyrus (SMG), temporo-parietal junction (TPJ), inferior frontal gyrus (IFG), middle frontal gyrus (MFG), insular cortices, anterior cingulate, precuneus and cuneus, in the non-aerobic group the main differences were found in the temporal pole (TP) and inferior parietal sulcus (IPS). Note that not all these differences were significant between the pre- and post-training states. Figures 5B and 6B present areas which exhibited significant difference (two-tailed t-test) when comparing results in the aerobic and non-aerobic groups before and after training. Regions demonstrating significantly higher inter-SCs after the training are colored in yellow. Importantly, some regions—bilateral inferior parietal lobule (IPL)–exhibited significantly higher inter-SCs before the training in both groups (colored in orange). Table 3 provides the Talairach coordinates and cluster information for these regions.

The effect of the exercise intervention on cognitive function

Within-group analysis of pre-post intervention demonstrated no significant change in any of the cognitive battery tests or both post-scan recognition tests in the aerobic group ($p > 0.05$). In the BAT group a significant increase in the 8th repetition of the RAVLT ($p = 0.03$), was found, but also decreased performance in the post-scan recognition 1 test ($p = 0.04$). Between-group analysis revealed that the pre-post intervention difference in the performance on the CTT1 test was significantly different between the groups, where the aerobic group demonstrated bet-

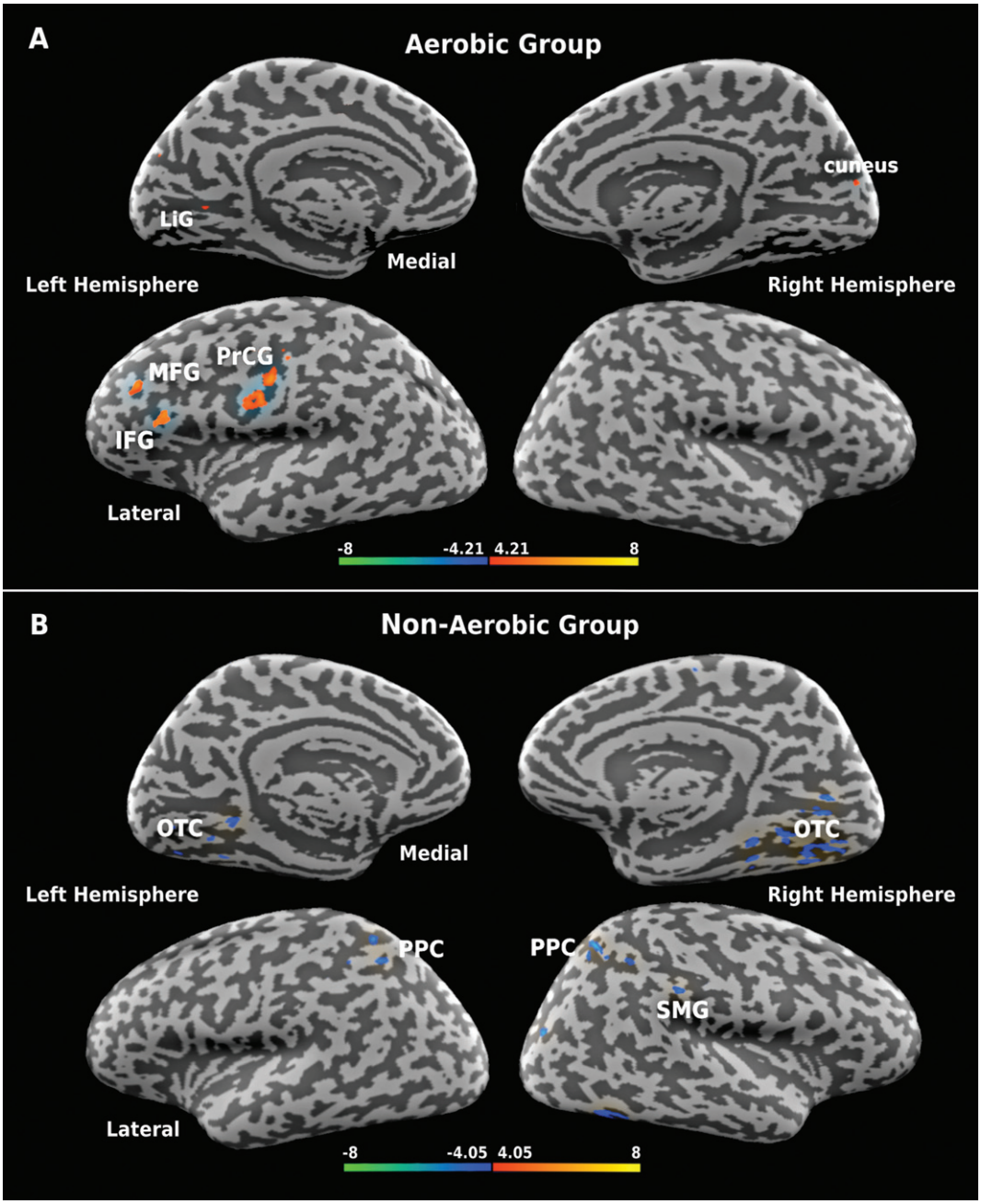

Fig. 3. Changes in brain activity patterns during encoding of novel associations in the aerobic (A) and BAT (B) groups ($p < 0.01$, FDR corrected, cluster size ≥ 5 functional voxels). LH, left hemisphere; RH, right hemisphere; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; LiG, lingual gyrus; OCT, occipitotemporal cortex; PPC, posterior parietal cortex; PrCG, precentral gyrus; SMG, supramarginal gyrus.

ter outcome compared to the BAT group ($p = 0.04$). Supplementary Table 1 summarizes both within- and between-group differences in the cognitive evaluation. Supplementary Tables 2 and 3 summarize the changes in the raw cognitive scores for the aerobic and BAT groups, respectively.

Change in cardiorespiratory fitness following the exercise intervention and association with neurocognitive outcomes

Following the intervention, VO_2peak significantly increased in the aerobic group from 20.92 ± 3.84

Table 2
Changes in brain activation during encoding of novel associations following the exercise intervention in the study groups

Brain region	BA	*x*	*y*	*z*	Cluster size*	*t*-value
Aerobic group						
Frontal						
L Inferior frontal gyrus	45	–43	23	14	18	5.71
L Precentral gyrus	6	–46	–7	13	62	5.30
L Middle frontal gyrus	9	–44	35	27	7	4.57
Occipital						
L Lingual gyrus	19	–29	–62	4	10	5.42
R Cuneus	19	6	–80	27	5	4.72
Sub-cortical						
R Cerebellum		3	–80	–10	10	5.05
		15	–51	6	6	4.68
BAT group						
Frontal						
L Cingulate gyrus	24	0	–1	39	6	–4.49
Parietal						
L Superior parietal lobule	7	–24	–55	47	29	–5.72
	7	–36	–49	47	14	–5.30
R Superior parietal lobule	7	31	–57	46	26	–5.18
R Supramarginal gyrus	40	53	–25	29	10	–5.18
Temporal						
L Fusiform gyrus	37	–37	–58	–6	6	–4.74
R Parahippocampal gyrus	36	24	–37	–5	17	–5.01
Occipito-temporal						
L Occipitotemporal cortex	19	–12	–44	0	19	–5.11
R Occipitotemporal cortex	18	34	–66	–1	158	–5.75
	19	21	–52	–3	19	–4.77
Sub-cortical						
L Cerebellum		–13	–40	–23	5	–5.03

BA, Brodmann area; L, left; R, right; coordinates are in Talairach space; *cluster size is presented in functional space voxels.

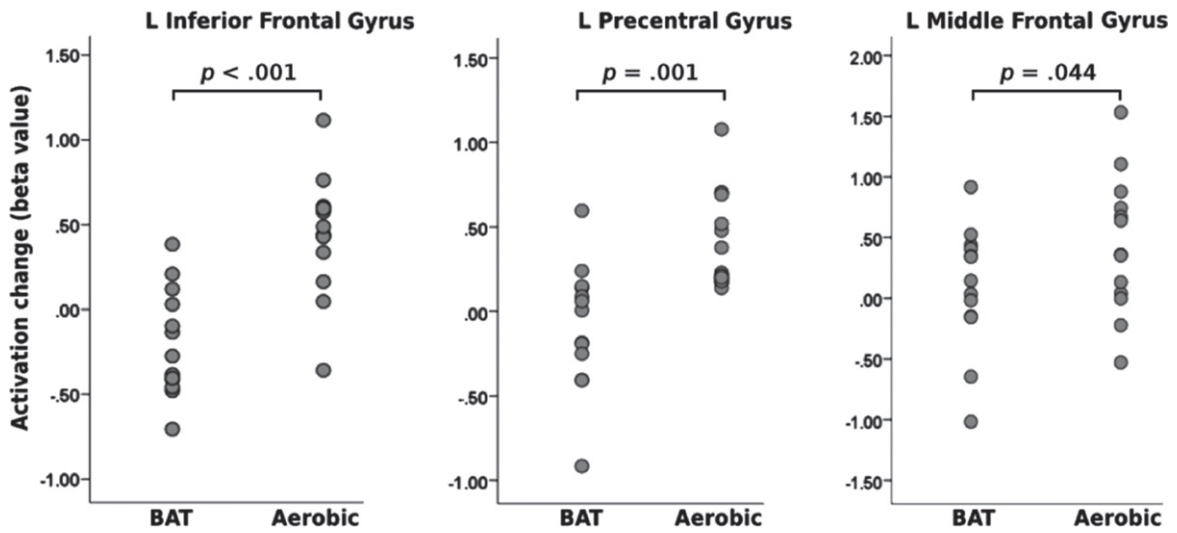

Fig. 4. The change in frontal cluster activation following the exercise intervention in the aerobic group and balance and toning control group. BAT, balance and toning; L, left.

to 25.09 ± 4.82 ml/kg/min ($+21.62\%$, $p = 0.01$), but not in the BAT group (from 20.51 ± 3.57 to 21.10 ± 3.35 ml/kg/min,$+4.15\%$, $p = 0.52$). A between-group analysis confirmed that this change was statistically different between the groups ($p = 0.03$). In addition, statistically significant

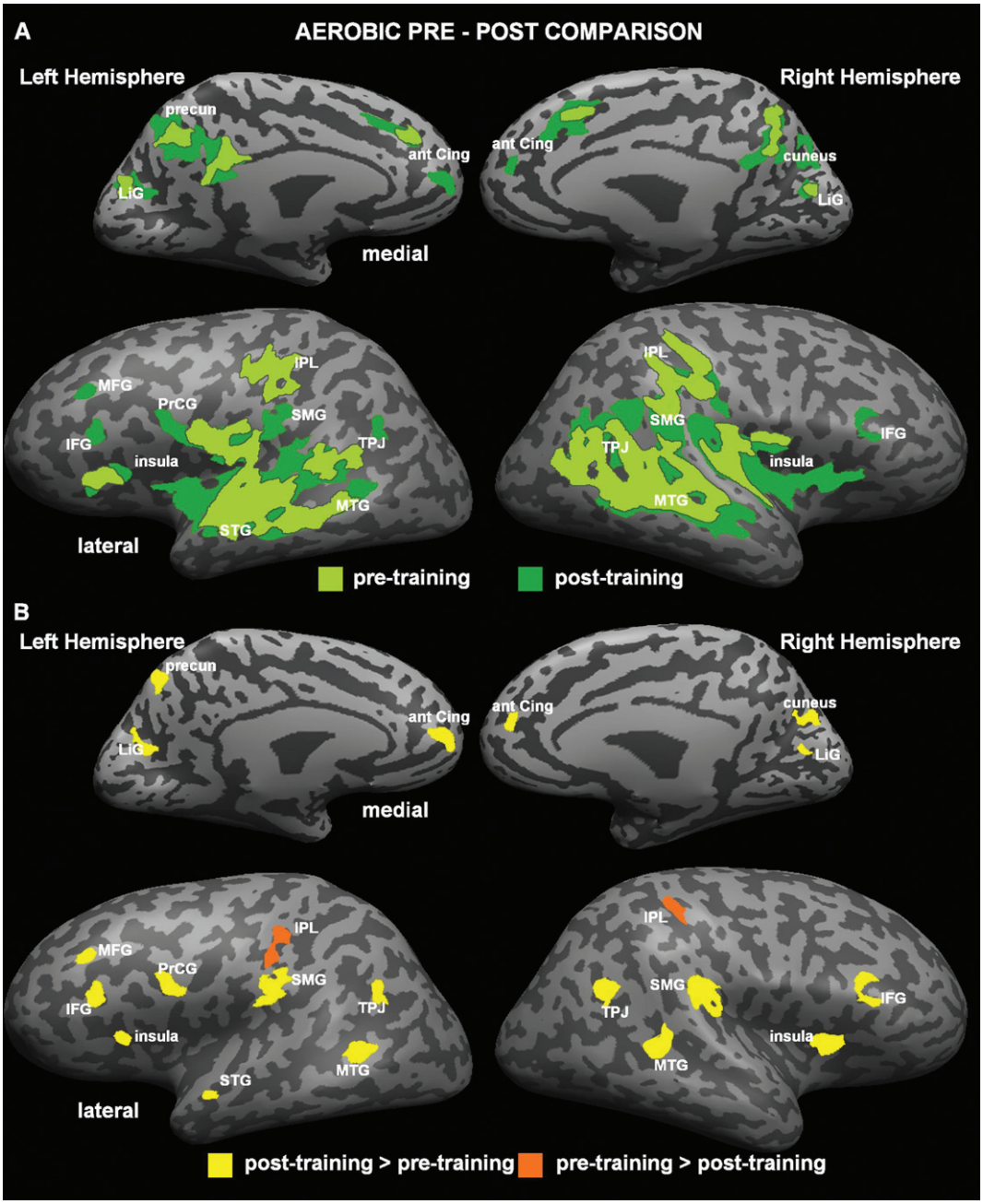

Fig. 5. A) Inter-SC maps during complex information processing in the aerobic group before and after training intervention ($p < 0.05$, FDR corrected). B) Brain regions demonstrating significant differences in correlation values after aerobic training intervention ($p < 0.05$, FDR corrected). Ant Cing, anterior cingulate; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; MTG, middle temporal gyrus; LiG, lingual gyrus; precun, precuneus; PrCG, precentral gyrus; SMG, supramarginal gyrus; STG, superior temporal gyrus; TPJ, temporo-parietal junction.

moderate positive correlations were found between the change in cardiorespiratory fitness and increase in brain activity in both the left inferior frontal ($r = 0.38$, $p = 0.03$) and precentral gyri ($r = 0.37$, $p = 0.03$) clusters that demonstrated increased activity following the intervention in the aerobic group (Fig. 7A, B). Furthermore, moderate positive correlations were also found between the change in fitness

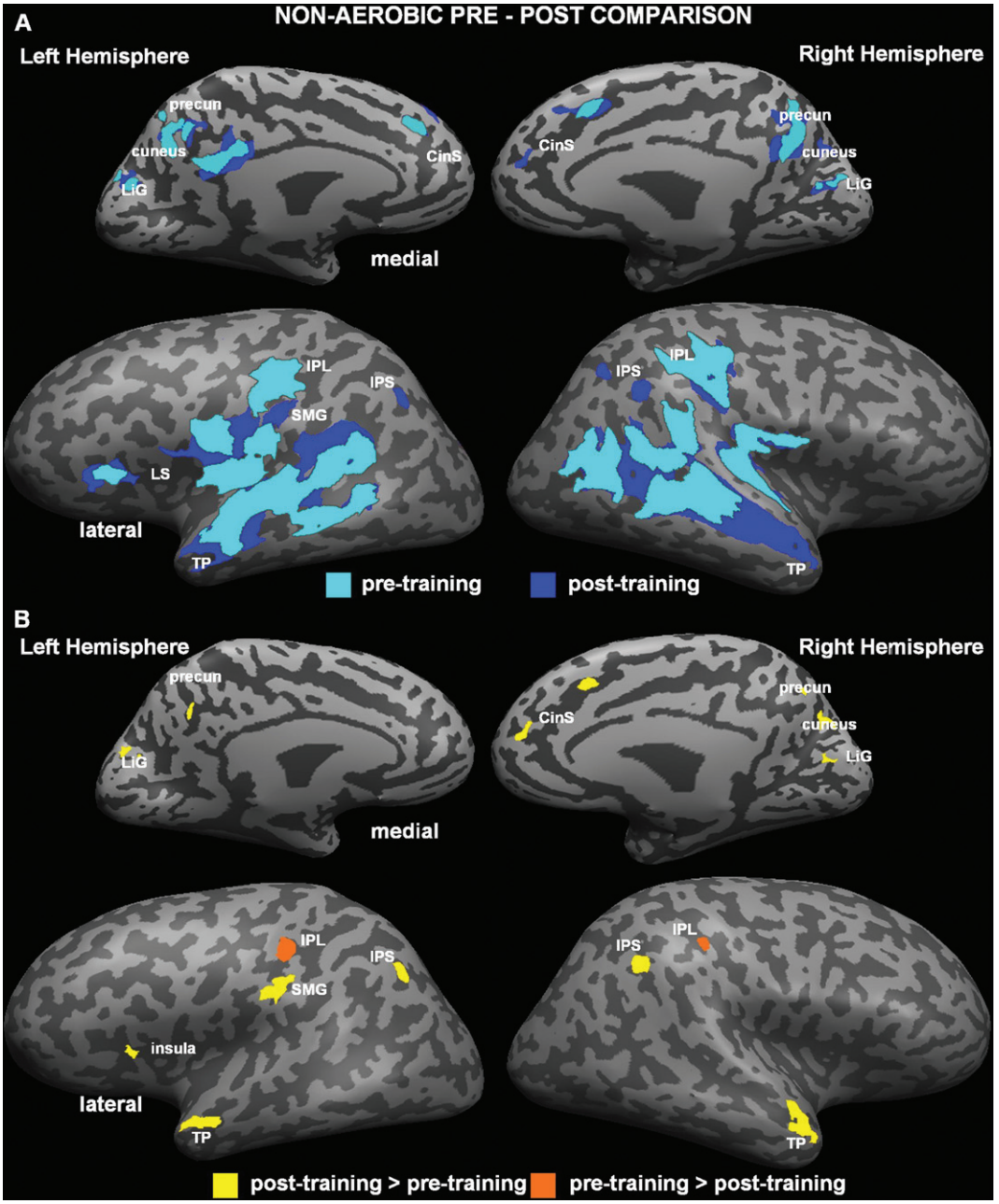

Fig. 6. A) Inter-SC during complex information processing in the non-aerobic group before and after training intervention ($p < 0.05$, FDR corrected). B) Brain regions demonstrating significant differences in correlation values after BAT training intervention ($p < 0.05$, FDR corrected). CinS, cingulate sulcus; IPL, inferior parietal lobule; IPS, intraparietal sulcus; LiG, lingual gyrus; LS, lateral sulcus; precun, precuneus; SMG, supramarginal gyrus; TP, temporal pole.

and the change in RAVLT 1st repetition ($r = 0.44$, $p = 0.01$), and the change in phonemic verbal fluency ($r = 0.41$, $p = 0.02$) across both groups (Fig. 7C, D). A trend was also observed between fitness change and performance in the recognition 1 test ($r = 0.32$, $p = 0.06$).

DISCUSSION

The current study aimed to assess the effect of physical exercise intervention on brain plasticity in patients with aMCI. In addition, we aimed to examine the relationship between changes in cardiorespiratory

Table 3
Changes in inter-SC during complex information processing following the exercise intervention in the study groups

Brain region	BA	*x*	*y*	*z*	Cluster size*
Aerobic group					
Frontal Lobe					
L Middle frontal gyrus (MFG)	9	–36	31	36	226
L Inferior frontal gyrus (IFG)	9/46	–43	27	28	331
R Inferior frontal gyrus (IFG)	9/46	47	33	24	533
L Precentral gyrus (PrCG)	44	–51	9	7	883
Insular Cortex					
L Insula	13	–38	20	5	572
R Insula	13	37	20	4	940
Cingulate Cortex					
L Anterior cingulate	32	–7	37	15	1189
R Anterior cingulate	32	6	36	22	320
Parietal Lobe					
L Inferior parietal lobule (IPL)/PCG	40	–40	–30	32	239
R Inferior parietal lobule (IPL)/PCG	40	38	–34	43	838
L Supramarginal gyrus (SMG)	40	–58	–46	25	947
R Supramarginal gyrus (SMG)	40	55	–48	23	917
Temporal Lobe					
L Temporo-parietal junction (TPJ)	40	–41	–42	21	370
R Temporo-parietal junction (TPJ)	40	49	–55	27	979
L Middle temporal gyrus (MTG)	37	–52	–52	2	1126
R Middle temporal gyrus (MTG)	22	57	–35	4	973
L Superior temporal gyrus (STG)	22	–53	–3	–4	300
Occipital Lobe					
L Precuneus	7	–4	–67	43	952
R Cuneus	18	19	–75	24	910
L Lingual gyrus	18/19	–17	–64	3	370
R Lingual gyrus	18	8	–69	7	306
BAT group					
Insular Cortex					
L Insula	13	–43	7	12	572
Cingulate Cortex					
R Anterior cingulate	32	8	38	25	205
Parietal Lobe					
L Inferior parietal lobule (IPL)/PCG	40	–41	–31	33	275
R Inferior parietal lobule (IPL)/PCG	40	46	–30	41	321
L Supramarginal gyrus (SMG)	40	–57	–45	21	580
L Inferior parietal sulcus (IPS) - posterior	40	–45	–55	44	174
R Inferior parietal sulcus (IPS) - anterior	40	51	–45	45	352
L Precuneus	31	–10	–57	32	299
R Precuneus	7	3	–61	36	284
Temporal Lobe					
L Temporal pole/STG	38	–46	6	–22	650
R Temporal pole/STG	38	47	8	–21	935
Occipital Lobe					
R Cuneus	18	21	–75	22	395
L Lingual gyrus	18	–5	–75	6	337
R Lingual gyrus	18	7	–69	6	202

BA, Brodmann area; L, left; R, right; coordinates are in Talairach space; *cluster size is presented in anatomical space voxels.

fitness and neurocognitive functions following the intervention. The main findings of the study show that aerobic exercise intervention results in increased activation in several brain regions, mainly frontal areas. In contrast, the BAT group demonstrated decreased activity in other distinct areas with no increased activation observed in any brain region following the intervention. Neural synchronization of complex information processing was found to extend to higher order cognitive areas such as the TPJ, and frontal cortex, but this was observed only in the aerobic exercise group. Furthermore, changes in cardiorespiratory fitness were significantly correlated with changes in frontal activity. Neither group showed significant change in cognitive tests scores, however, changes in some of the cognitive tests scores were

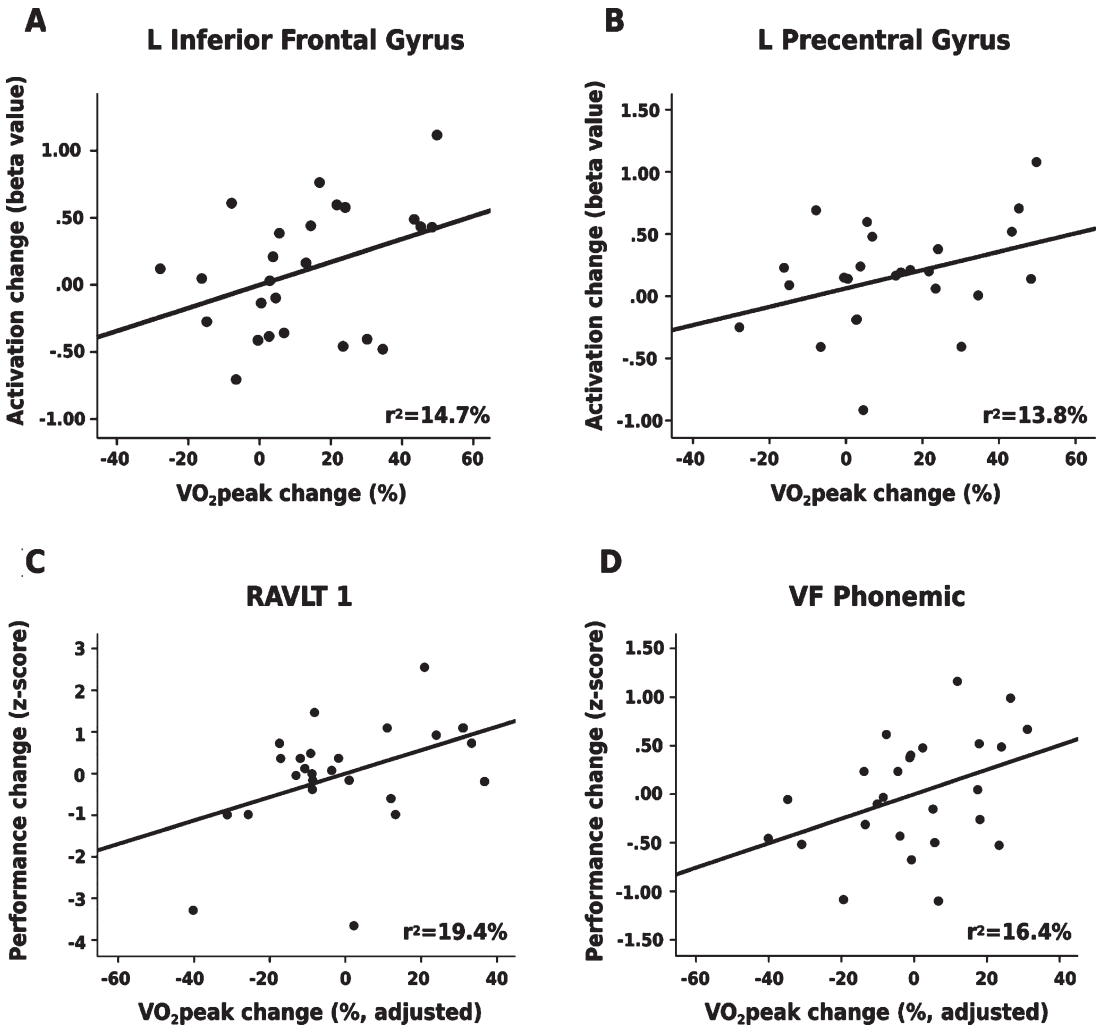

Fig. 7. Relationship between changes in cardiorespiratory fitness and neurocognitive measures: brain activity changes in the inferior frontal gyrus (A) and the precentral gyrus (B), and changes in RAVLT1 (C) and phonemic verbal fluency (D) performance. L, left; RAVLT, Rey auditory verbal learning test; VF, verbal fluency.

positively correlated with the change in cardiorespiratory fitness, supporting the potential mediating effect of cardiorespiratory fitness in processes of brain plasticity.

Our study is the first to examine the effect of aerobic exercise and cardiorespiratory fitness on neural substrates of episodic memory and information processing in aMCI. Our findings in this group of patients complement previous works in cognitively-intact adults demonstrating a relationship between aerobic exercise, cardiorespiratory fitness, and frontal brain function, especially in areas related to executive and cognitive control [6, 13–15]. For example, in two studies conducted by Colcombe et al. [12] and Wagner et al. [10], increased frontal activation was demonstrated in healthy older adults after 6 months' aerobic exercise [12], and in younger adults following 6 weeks of aerobic exercise [10]. Colcombe et al. [12] found increased brain activation in frontal and parietal regions while performing a modified version of the Ericksen flanker paradigm (an executive task of selective attention and response inhibition), while Wagner et al. [10] who used a memory task paradigm, demonstrated increased activation in several brain regions including the motor circuitry, prefrontal regions, and left anterior hippocampus. Increased cardiorespiratory fitness was also shown to be linked to the function of executive-control related prefrontal areas [13, 15]. In contrast, decreases in brain activation were reported in two pre-

vious studies assessing the effect of aerobic exercise intervention in patients with MCI [42, 43]. Smith et al. (2013) [42] showed that following aerobic intervention, brain activation during a semantic memory task decreased significantly in participants with MCI in several cortical and sub-cortical regions including left pre-central gyrus, bilateral precuneus, left middle temporal gyrus, right superior parietal lobule, right superior temporal gyrus, left lateral occipital gyrus, and left cerebellum. Similarly, Hsu et al. [43] found that after 6 months of aerobic exercise, patients with mild vascular cognitive impairment showed reduced activation in left lateral occipital cortex and right superior temporal gyrus while performing a similar executive task as conducted by Colcombe et al. (i.e., Eriksen flanker task) [12]. In addition to the increased activity found in the current study in the left middle frontal gyrus, a central hub of the fronto-parietal control network, the aerobic group also demonstrated increased activity in the left inferior and precentral gyri. These areas had previously been shown to be a part of several brain regions in which increased activity was predictive of successful associative memory performance in healthy adults [74].

Interestingly, in addition to the functional changes observed following aerobic training, the BAT group also demonstrated changes in brain activity, however, differing in pattern and regions. We found that low intensity BAT training that included light balance, coordination, and toning exercises resulted in decreased brain activity in areas related to higher order visual processing, spanning the occipital, parietal, and temporal lobes [75]. Voelcker-Rehage et al. (2010) [76] found higher balance and coordination abilities to be associated with decreased activity in lateral occipital areas. Our findings also show decreased brain activity in these areas following the BAT intervention, although we did not measure changes in balance and coordination following the intervention. Voelcker-Rehage et al. also found activity in the posterior parietal cortex (PPC), which is involved in visuo-spatial processing [77], to be associated with motor fitness [76] and to increase after a coordination training intervention [78], as opposed to our results. In contrast, Kwon et al. (2012) [79] and Gobel et al. [80] found reduction in PPC activation after a period of motor skills training. The decreased activity found in the PPC and other higher order visual areas in our and other works following physical training based on motor skills, may indicate an adaptive pattern of more efficient processing, as was also suggested by previous works [42, 43]; however, this hypothesis needs further investigation. Furthermore, it is important to note that these changes in neural patterns were not associated with improved cognitive performance in our study.

Neural topology of complex information processing

In the aerobic group, extended topology to higher order cognitive areas was observed. In previous studies [30, 81] we showed that in both healthy young and older adults who performed a similar task of listening to a story, synchronized responses were found in areas that extended along the STG, TPJ, dorsolateral prefrontal cortex, inferior frontal sulcus, temporal pole, precuneus, and mPFC. In contrast, synchronized responses in participants with aMCI were found [30] in the pre- and post-central gyri, suggesting a functional shift of higher order auditory-presented information processing, possibly reflecting a functional response to concurrent or impending neuronal or synaptic loss. The current study showed that aerobic exercise was followed by functional changes in the topology of complex information processing. In particular, synchronized responses shown in the TPJ and frontal regions following aerobic training in our study have also been demonstrated in healthy adults [30]. This functional shift, observed only in the aerobic group, support previous findings emphasizing the possibility of neuroplastic changes following aerobic exercise training [9, 46, 82].

Strikingly, although the two different training modalities elicited functional changes in distinct brain areas, each training intervention was followed by functional changes with similar regional pattern in both fMRI paradigms. While aerobic training elicited functional changes in the same frontal areas in both paradigms (inferior and middle frontal gyri, and precentral gyrus), the non-aerobic exercise was followed by changes in the posterior parietal cortex (e.g., intraparietal sulcus). These region-specific functional patterns observed across different cognitive stimuli strengthen our findings and further support the general neuroplastic potential of physical exercise. Furthermore, it also emphasizes the potential effect of distinct types of exercise on different functional regions or neural networks. For example, as discussed earlier, aerobic exercise and fitness have been previously associated with the function of executive-control frontal regions [6, 13]. Motor learning-based training, on the other hand, has been repeatedly associated with functional modifications in the posterior

parietal cortex [76, 78, 80], which has been linked to visuo-spatial attention, and planning and execution of movements [83]—primary cognitive processes when learning and performing non-aerobic balance and coordination exercises.

Overall, our findings suggest that different modalities of physical exercise, in this case cardiorespiratory/metabolic and motor skill-based, may have a differential effect on distinct functional regions and networks associated with different cognitive processing, not only in cognitively intact individuals but also among cognitively impaired older adults. Furthermore, these findings are supported by a novel measure of brain function we implemented to examine brain plasticity, i.e., neural synchronization across participants during the processing of naturalistic multidimensional cognitive stimulus.

Change in brain activation following aerobic exercise intervention: possible mechanisms

The possible neural mechanisms underlying increased and decreased brain activation after aerobic training are different. While reduction in brain activity is generally associated with an increase in neural efficiency [42, 43], Colcombe at al. [12] suggested that the increase in activation is related to increases in the number of synapses in the frontal and parietal gray matter, resulting in greater recruitment of these brain regions when performing a demanding cognitive task. Both Colcombe et al. and Wagner et al. [10, 12] proposed that increased activation may be mediated by improved cardiorespiratory fitness leading to improved perfusion and blood supply, which in turn enable changes in neural recruitment. In addition, previous studies suggested that cardiorespiratory fitness may mediate brain plasticity by increasing the levels of neurotrophic factors, e.g., vascular endothelial neurotrophic factor, insulin-like growth factor-1, and brain-derived neurotrophic factor, which are associated with angiogenesis, synaptogenesis and neurogenesis [1, 84]; reducing inflammation, and improving insulin sensitivity [85]. Correlations between cardiorespiratory fitness and change in scores of cognitive tests were also found in the current study, supporting the potential mediating effect of cardiorespiratory fitness in processes of brain plasticity. Regardless of exercise intervention, increase in brain activation, particularly in frontal regions while performing a demanding cognitive or motor task, was previously found in older adults compared to young adults, and in patients with MCI compared to healthy older adults [86–89]. This was suggested to reflect compensatory processes that prevent age-related decline of brain function and permit successful performance of the task. Supporting this possibility are further works conducted in both healthy older adults and individuals with MCI which demonstrated patterns of increased frontal activation during cognitive processing. In a previous meta-analysis comparing activation patterns, older adults were shown to recruit the left lateral prefrontal cortex to a greater extent than younger adults, when cognitive performance was equivalent between the two age groups, and to generally show increased prefrontal activity independent of cognitive scores [90]. Increased prefrontal activation has also been demonstrated to be associated with the extent of cognitive decline in patients with aMCI. Clement and Belleville (2012) have shown that individuals at earlier stages of aMCI demonstrated increased bilateral prefrontal activation compared to healthy controls in a more cognitively demanding memory task (i.e., associative recognition) compared to a less demanding task (item recognition) [91]. In contrast, more severely affected patients with aMCI demonstrated increased left prefrontal activity during the less demanding task (i.e., item recognition), while no hyperactivation was found during the associative task. This in turn suggests that patients with aMCI may demonstrate a shift in the over-recruitment of prefrontal areas as cognitive decline progresses, which may indicate a compensatory phenomenon aimed at coping with even less demanding cognitive tasks. Furthermore, Gigi et al. (2010) found patients with aMCI to demonstrate increased bilateral prefrontal activity during a semantic memory task compared to healthy controls, while demonstrating equal cognitive performance [92]. This study also found that patients with AD exhibit lower activity compared to both aMCI and controls, further suggesting that increased brain activity in persons with MCI may demonstrate a compensatory neural pattern in the less severe phases of cognitive decline. Considering that participants in the aerobic group in the current study demonstrated preserved performance in the post-scan Recognition 1 test, while a decline in performance was shown among participants in the BAT group on the same task, it could be hypothesized that the increased frontal activity seen in the aerobic group may indeed reflect compensatory processes. Overall, the results of the

current study support the idea that increased prefrontal activation may be a result of increased cardiorespiratory fitness, which enables a compensatory neural strategy when performing demanding cognitive tasks.

Discrepancies between imaging and behavioral changes

Despite the significant results of increased activation in frontal regions, and functional changes in patterns of information processing, behavioral results among participants in the aerobic group showed minor changes in cognitive test scores. This was also shown in the study conducted by Smith et al. (2013), in which significant improvement was found in only one test (RAVLT 1st trial) of the entire cognitive battery. Some other interventional studies, however, assessing the effect of exercise interventions on cognition in patients with MCI using neuropsychological assessments without imaging outcomes, did show improvement in more than one cognitive test in the executive or memory domains [32–34, 37]. Although there were no significant widespread changes in cognitive functions within and between groups following the intervention, we did find positive correlation between change in cardiorespiratory fitness and two cognitive test scores (RAVLT 1 and phonemic verbal fluency) across participants in both groups. Furthermore, a legitimate question should be raised regarding the effect of exercise dose, and whether a larger dose of exercise would have yielded an improvement in cognitive tests scores at the post-intervention evaluation. Two systematic reviews and a meta-analysis that were recently published [93, 94] studied the issue of dose-response relationship between exercise and cognitive function in both older adults and individuals with cognitive decline. Gomes-Osman et al. (2018) [93] found that 52 training hours or more are associated with improved cognitive function in older adults with and without cognitive decline. However, this review did not evaluate other outcomes such as neural plasticity markers. In contrast, Sanders et al. (2019) [94] did not find an association between program duration and intensity, and change in cognitive function. Furthermore, they found that longer program duration was not predictive of larger changes in cognitive function and concluded that although changes in fitness may predict neuroplastic modifications these may not always translate to cognitive improvements. Participants in our study completed 45–48 sessions of exercise, which is somewhat less than the 52 sessions suggested by Gomes-Osman et al. [93]. However, in line with the findings of Sanders et al. (2019), our results showed that changes in brain activity were not translated to major changes in cognitive performance, as we expected. Accordingly, it could be hypothesized that in patients with aMCI, or other progressive neurodegenerative conditions, the possibility for significant broad cognitive improvement is limited, but preservation of cognitive function and enhancement of compensatory processes are achievable. Taken together we suggest that although cognitive function was not improved, it was possibly preserved, as no significant decline was shown in any domain, and that this preservation may be mediated, at least in part, by the increase in cardiorespiratory fitness.

Study limitations

The main limitation of this study is the modest sample size, resulting from the complex nature of interventional studies that use neuroimaging paradigms, and the study population itself. In addition, we speculate whether addition of ecological cognitive tests which assess changes in daily function and questionnaires of participants' spouses, in addition to the traditional neuropsychological tests that we used, could shed more light on the behavioral modifications occurring following exercise interventions. This should be further investigated in future studies, as well as conducting interventional studies using fMRI paradigms, which would aid in supporting our results, and determine the effectiveness of exercise interventions on functional brain plasticity in neurodegenerative conditions.

CONCLUSIONS

Our study provides further evidence that distinct modalities of physical exercise intervention may result in functional plasticity of differential brain areas related to distinct neurocognitive networks. Furthermore, we provide evidence that these changes may be observed not only in healthy individuals but also in cognitively impaired older adults at risk of AD and dementia. In addition, we demonstrate that improvements in cardiorespiratory fitness may mediate changes in neurocognitive functions, both at the neurobiological and the behavioral levels in these patients. While changes in brain activation were only mildly translated to cognitive improvement, the results suggest that aerobic exercise intervention can

lead to preserved cognitive function in patients with aMCI, possibly by enhancing compensatory neural processes.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-201429.

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