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Increased dynamic flexibility in the medial temporal lobe network following an exercise intervention mediates generalization of prior learning

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ABSTRACT

Recent work has conceptualized the brain as a network comprised of groups of sub-networks or modules. "Flexibility" of brain network(s) indexes the dynamic reconfiguration of comprising modules. Using novel techniques from dynamic network neuroscience applied to high-resolution resting-state functional magnetic resonance imaging (fMRI), the present study investigated the effects of an aerobic exercise intervention on the dynamic rearrangement of modular community structure—a measure of neural flexibility—within the medial temporal lobe (MTL) network. The MTL is one of the earliest brain regions impacted by Alzheimer's disease. It is also a major site of neuroplasticity that is sensitive to the effects of exercise. In a two-group non-randomized, repeated measures and matched control design with 34 healthy older adults, we observed an exercise-related increase in flexibility within the MTL network. Furthermore, MTL network flexibility mediated the beneficial effect aerobic exercise had on mnemonic flexibility, as measured by the ability to generalize past learning to novel task demands. Our results suggest that exercise exerts a rehabilitative and protective effect on MTL function, resulting in dynamically evolving networks of regions that interact in complex communication patterns. These reconfigurations may underlie exercise-induced improvements on cognitive measures of generalization, which are sensitive to subtle changes in the MTL.

1. Introduction

A large body of literature reports that physical exercise helps improve and maintain cognition (Barnes, Yaffe, Satariano, & Tager, 2003; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001) and reduces Alzheimer's disease (AD) risk in healthy older adults (Andel et al., 2008; Larson et al., 2006) via its neuroprotective effects on brain structure and function (Boraxbekk, Salami, Wåhlin, & Nyberg, 2016). Specifically in the medial temporal lobe (MTL), the hippocampus is a major site of neuroplasticity that is sensitive to the effects of physical exercise (Baker et al., 2010; Erickson et al., 2011; Lautenschlager et al., 2008; Ten Brinke et al., 2015).

The MTL is one of the earliest brain regions impacted by AD, and its sub-regions show a selective topography of pathological involvement (Braak & Braak, 1991). The transentorhinal region is among the earliest to be affected by neurodegeneration in the disease course, followed by the hippocampus (Braak & Braak, 1991, 1997). Recent work has also suggested that the hippocampal dentate gyrus (DG) and CA3 subfields are particularly vulnerable to age-related pathological changes (Leal & Yassa, 2018). Increased synchronization, measured by functional connectivity, within the MTL has been associated with cognitive decline in aging (Salami, Pudas, & Nyberg, 2014), mild cognitive impairment (MCI) and AD (Das et al., 2013; Pasquini et al., 2015), and, in non-demented ABCA7 rs115550680 G allele carriers at increased risk of developing AD (Sinha et al., 2019).

There is growing evidence characterizing AD as a disconnection syndrome (Delbeuck, Van der Linden, & Collette, 2003), such that brain dysfunction in AD is better explained by a disruption in distal interactions among different brain networks rather than by local regional deficits. As such, resting state functional connectivity is emerging as a viable biomarker and predictor of future conversion to AD (Greicius, 2008; Pievani, Filippini, Van Den Heuvel, Cappa, & Frisoni, 2014; Yamasaki, Muranaka, Kaseda, Mimori, & Tobimatsu, 2012) and as an indicator of treatment efficacy (Goveas et al., 2011; Li et al., 2012). Measures of functional connectivity obtained within MTL sub-regions may potentially serve as a sensitive measure of early AD-related

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neuroplastic brain changes, and therefore, these intra-MTL measures of connectivity may represent useful biomarkers to measure response to interventions that primarily affect MTL regions. Some interventional studies investigating changes in intrinsic brain connectivity (Bär et al., 2016; Burdette et al., 2010; Tozzi et al., 2016) have found exercise-induced improvements in connectivity between the MTL and other nodes of the default mode network (DMN). However, no prior studies have investigated the effects of an exercise intervention on intra-MTL connectivity.

Here, we aim to address this gap using the emerging field of dynamic network neuroscience (Kopell, Gritton, Whittington, & Kramer, 2014; Medaglia, Lynall, & Bassett, 2015). Previous efforts to characterize resting-state functional connectivity have been based on the assumption that connections remain largely stable throughout a resting-state fMRI scan. However, temporal fluctuations of connectivity may in fact be a fundamental feature of brain networks, particularly in the context of cognitive functioning (Sizemore & Bassett, 2018). We can assess these temporal fluctuations using the multislice community detection tool (Mucha, Richardson, Macon, Porter, & Onnela, 2010), which quantifies network community structure and their reconfiguration over time. “Flexibility,” the index of a brain region’s tendency to communicate with different networks over time, is a key diagnostic measure of network dynamics (Bassett et al., 2011).

Higher network flexibility throughout the brain has been related to higher performance on tasks of cognitive flexibility and working memory in healthy individuals (Jia, Hu, & Deshpande, 2014). High flexibility in the frontotemporal network is associated with enhanced memory performance (Braun et al., 2015), suggesting that high flexibility is favorable in the memory domain. Similarly, low flexibility in the hippocampus and posterior cingulate cortex (PCC) is associated with memory impairments in epilepsy patients (Douw et al., 2015). Chen et al. (2017) suggest that alterations in flexibility of frontal and temporal networks may serve as an early biomarker for diagnosis of AD, specifically in the prodromal stage.

In the present study, we tested the effect of a 20-week aerobic exercise intervention, compared with “treatment as usual” controls, on the dynamical properties of resting-state intra-MTL connectivity, in a group of healthy older adults. As previously described, MTL network dynamics was characterized by flexibility: the amount of reconfiguration in functional connectivity patterns that the regions within the MTL network displayed over time. We expected to observe an exercise-related increase in MTL network flexibility. Additionally, we tested the hypothesis that change in MTL network flexibility will predict improved cognitive performance on an acquired equivalence task (Myers et al., 2003), known to depend on MTL function (Shohamy & Wagner, 2008). This paradigm measures learning from deterministic feedback and the ability to generalize learning to new task contexts, a form of “mnemonic flexibility.” Since the task selectively engages the MTL, its association with MTL network flexibility should elucidate the functional consequences of exercise-induced neuronal network alterations.

2. Methods

Participants in this study were selected from a larger parent study, which concluded in December 2019, focused on understanding how to best implement culturally appropriate exercise interventions by leveraging and engaging multiple levels of existing community structures in the African American population. This five-year community-based research program investigated the willingness of older African Americans to participate in dance-based aerobic exercise classes that were integrated within local community and faith-based institutions, as well as, the efficacy of interventional efforts in producing both increased physical fitness and improved cognitive health. Recruitment was performed through longstanding partnerships with local churches, senior centers, and, city, county, and state offices for health and aging, as well as, from outreach to public housing and other federally-subsidized, low-income housing sites. Individuals were eligible to participate if they identified as African American and were at least 55 years old. Throughout the duration of this study, subjects were enrolled (on a rolling basis) to 20-week programs of bi-weekly aerobic exercise classes. All participants received an extensive cognitive battery, and, health, fitness, and lifestyle assessments. In addition, they were invited to undergo an fMRI scanning session if they were medically and physically able to do so safely; participation in the neuroimaging component of the study was optional.

With this type of community-based research, specifically in urban African American communities, a randomized controlled trial may not be feasible and can pose as a barrier to research participation given this cohort’s widespread distrust of biomedical research (Corbie-Smith, Thomas, & St George, 2002; Scharff et al., 2010). These suspicions within the African American community, which can deter research participation, predominantly stem from historical and contemporary research and healthcare abuses (Corbie-Smith, Thomas, Williams, & Moody-Ayers, 1999; George, Duran, & Norris, 2014), experienced and perceived institutional and interpersonal racism (George et al., 2014; Shavers, Lynch, & Burmeister, 2001), lack of access to and information about clinical research (Lincoln, Chow, Gaines, & Fitzgerald, 2018), lack of knowledge about the benefits of research (Lambe, Cantwell, Islam, Horvath, & Jefferson, 2011; Shavers et al., 2001), and, concern that African Americans would not necessarily benefit from the advancements in scientific knowledge because of racial discrimination and poverty (Corbie-Smith et al., 1999). As such, we employed a non-randomized controlled design, recruiting “treatment as usual” controls similar in age, education, physical activity level, and physical fitness. Participants in the “treatment as usual” control group underwent all assessments, but had no additional contact with us during intervention period.

Initial screening took place over the phone. People who were diagnosed with or self-reported MCI or dementia, and/or people who were taking medication known to affect cognition, were informed that they did not qualify for participation. Participants exhibiting signs of dementia, evident from the standardized neuropsychological assessments (described in section 2.3), were disqualified from testing with prorated compensation. Consideration of overall memory performance across all relevant assessments was based on race, age, and education. While the Mini-Mental State Examination (MMSE) is used extensively in clinical and research settings to quantitatively assess global cognitive impairment, it is inadvisable to solely rely on the common MCI cutoff of 24 (Kukull et al., 1994; Tombaugh & McIntyre, 1992) because this test can have low specificity in identifying MCI in African Americans as compared to Caucasian populations, even when using adjusted scores (Tsang et al., 2019). Therefore, if someone scored 24 ± 1 on the MMSE, their performance on subsequent assessments was flagged for review to characterize if their cognitive functioning fell within the normal or abnormal range; participants who scored under 23 on the MMSE were disqualified from testing. Raw scores were converted to the age and education-adjusted scaled scores using race-appropriate norms (Ferman et al., 2005; Wechsler, 2008). Using the National Institute on Aging’s recommendation (Albert et al., 2011), any individual who scored at least 1.5 standard deviations below the age and education-based norms on one or more standardized neuropsychological assessment(s) was excluded from the study, so as to retain individuals who were cognitively normal. Other exclusion criteria included: excessive alcohol and/or drug use, psychiatric disorders (including Bipolar Disease and Schizophrenia), seizure disorders (such as Epilepsy), and significant cerebrovascular or cardiovascular diseases. Participants were required to be independently ambulatory (no wheelchair, walker, or cane) and have no other contraindications for exercise; this was confirmed by written physician approval before the start of the study. All participants were fluent English speakers and completed written informed consent prior to participation.

Subjects were not recruited in specific reference to the current research report; rather, we examined a subset that underwent fMRI testing both at baseline and follow-up; this subset included both individuals who participated in the exercise intervention program and controls. All subjects completed a battery of standardized neuropsychological and cognitive tests, as well as, an aerobic fitness and physical health assessment. In addition, participants underwent a resting-state fMRI scanning session. Following the initial testing battery, participants in the exercise intervention group enrolled in a 20-week dance-based aerobic exercise program. As previously mentioned, this was a non-randomized controlled design with a "treatment as usual" control group. At the end of the intervention period, all participants were re-tested on the cognitive and fitness assessments and underwent a follow-up resting-state fMRI scan.

2.1. Participants

34 individuals participated in our present study with a two-group, non-randomized, matched control design. 17 subjects completed the exercise intervention, and, were matched with 17 "treatment as usual" controls based on age and education. While matching controls, we were also cognizant about minimizing baseline differences in physical fitness measures (BMI and aerobic fitness; described in section 2.4) between the two groups. On average participants were 65 years of age, with a mean education level of 14 years. There were 3 males and 31 females. See Table 1 for demographic information by group.

2.2. Exercise intervention

Following the initial assessments, exercise intervention participants enrolled in a 20-week dance-based aerobic exercise program, which met twice a week, for 60 minutes per session. Participants' heart rates were monitored throughout each class session. During the exercise sessions, led by a certified and professional trainer, all participants exercised at a moderate intensity level; all individual sessions were tailored to achieve an intensity of 65–80% of heart rate reserve among our study population. Each session consisted of 10 min of warm-up, 45 min of aerobic exercise in a standard dance-based aerobics format, and 5 min of cool down and stretching. Records of adherence to the program (attended sessions) and any adverse events were kept for each exercise session.

2.3. Standardized neuropsychological assessments

In order to assess cognition, we administered a battery of neuropsychological tests. The neuropsychological battery consisted of the Mini-Mental State Examination (MMSE) (broad assay of cognitive impairment), Rey Auditory Verbal Learning Test (RAVLT) Delayed Recall (verbal memory), North American Adult Reading Test (NAART35) (verbal intellectual ability), and Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span (working memory).

2.4. Aerobic fitness assessment

The Six Minute Walk was used to determine aerobic fitness. Participants were instructed to walk a premeasured length on a flat surface for 6 min, with the goal of covering as much ground as possible (McGavin, Gupta, & McHardy, 1976; McGavin, Artvinli, Naoe, & McHardy, 1978). At the completion of the six minutes, total walking distance was recorded in meters. To approximate participants' maximal oxygen consumption, we utilized the equation determined by Ross, Murthy, Wollak, and Jackson (2010): VO_2 max = [4.948 + (0.023 * Distance)]. This protocol to predict maximal oxygen consumption (VO_2 max) is widely recognized as both a representation of the functional limitations of the cardiovascular system as well as a measure of aerobic fitness (Taylor, Buskirk, & Henschel, 1955). In addition, participants' BMI was computed as a broad measure of physical health.

Table 1
Participant demographics based on group (exercise versus control).

Characteristic	Aerobic Exercise	Control
Sample Size	17	17
Sex (Females)	16	15
Age	65.76 (5.89)	65.12 (5.12)
Education (Years)	14.11 (2.09)	14.17 (1.89)

2.5. Behavioral paradigm: Acquired equivalence task

This task has previously been described in Myers et al. (2003). In brief, during each trial, participants saw both a cartoon face (either a brown-haired man, a blonde-haired woman, a blonde-haired boy, or a brown-haired girl, labeled in Fig. 1 as A1, B1, A2, or B2) and a pair of colored fish (green, red, blue, or purple, labeled in Fig. 1 as X1, Y1, X2, or Y2). Assignment, and mapping of faces to fish were randomized across subjects. Each face shared 1 binary-valued feature with another face: gender (male, female), age (child, adult), and hair color (blonde, brown). The participants were asked to indicate which fish belonged to each face. Correct responses (right vs. left) varied randomly and there was a 1-second pause between trials.

The task had 2 distinct phases: training and test. During training, participants received feedback to guide learning (e.g., the selected fish was circled, and "Correct" or "Incorrect" was displayed for 1 s). Training had 3 stages, though the start of a new stage was not signaled. First, participants learned to pair 2 faces with specific colored fish (e.g., A1-X1, B1-Y1). This stage continued until the participant made 4 consecutive correct responses or for a maximum of 20 trials. Next, participants learned to pair new faces with the same colored fish (e.g., A2-X1, B2-Y1). In the process, participants typically learn that some faces (e.g., A1, A2) are equivalent because they map onto the same outcome (e.g., X1). This stage terminated after 8 consecutive correct responses or a maximum of 40 trials. Finally, participants learned to pair the original faces with a new colored fish (e.g., A1-X2); this stage terminated after 12 consecutive correct responses or a maximum of 60 trials. At each stage, maintenance trials with prior-trained pairs were interleaved with the new pairs.

A test phase followed in which participants no longer received feedback. To measure retention, participants were tested on their recall of the trained fish-face associations in random order (12 trials per block). Intermixed within retention trials were 2 novel fish-face pairings representing generalization (presented once each with the fish in either left–right order). Although these new pairings were never explicitly trained, participants should show successful generalization, defined as predicting the same outcome (fish) for faces that were trained to be equivalent. For example, because A1 was trained to be functionally equivalent to A2 (in that both predict X1), if A1 was also paired with X2, participants should generalize that A2 is also paired with X2. The test included 3 blocks (36 retention and 12 generalization trials); trial order within a block was randomized across subjects.

Generalization trials require the flexible application of associative knowledge, which entails integrative encoding and recombination during retrieval. As such, mnemonic flexibility underlies successful generalization performance, and is known to depend on MTL integrity (Shohamy & Wagner, 2008); individuals with structural changes in the MTL, associated with prodromal AD, show normal learning on the task but are impaired on generalization (Bódi, Csibri, Myers, Gluck, & Kéri, 2009; Myers et al., 2003, 2008).

2.6. MRI data acquisition

Magnetic resonance imaging (MRI) data was acquired on a 3T Siemens TRIO, using a 32-channel Multiband parallel encoding coil, at the Rutgers University Brain Imaging Center (RUBIC) at Rutgers University-Newark. If required, MRI-compatible glasses were used on

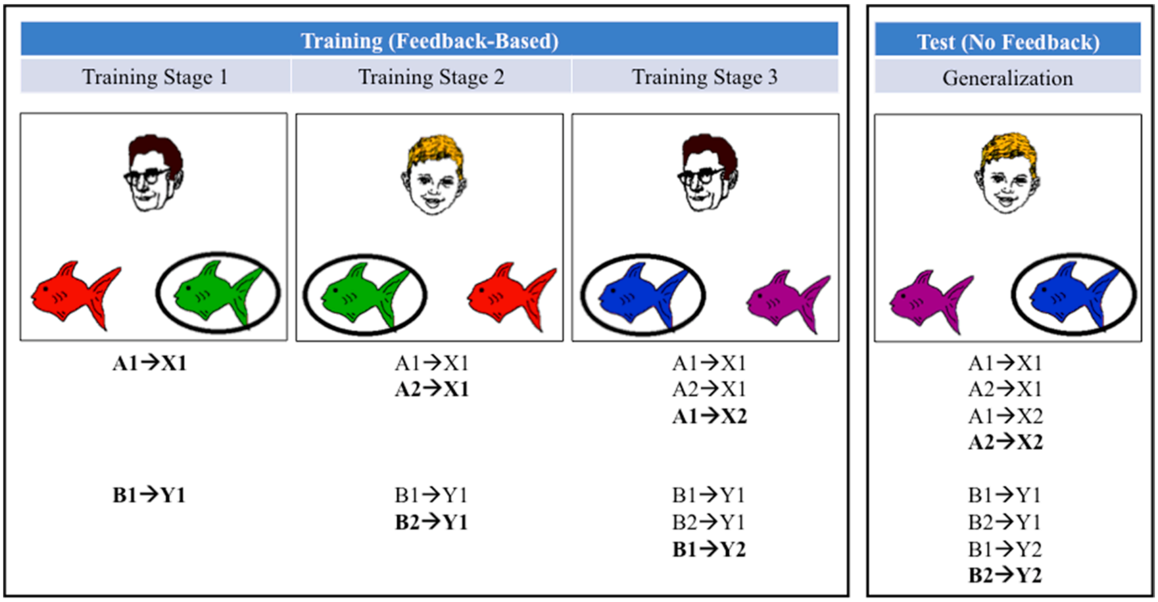

Fig. 1. Sample screen displays of the acquired equivalence task. During training stage 1, participants learn the first 2 associations between difference faces (A1, B1) and fishes (X1, Y1). During training stage 2, different faces (A2, B2) are associated with the same fish, whereas during stage 3, new fishes (X2, Y2) are added. During the test phase, participants are tested on retention of the associations learned in training stages 1–3, and also on generalization to new pairings of faces and fishes (i.e., A2 → X2, B2 → Y2). Retention and generalization pairs were interleaved randomly during the test phase.

the day of scanning. A high-resolution 3D magnetization-prepared rapid gradient echo (MP-RAGE) structural scan was acquired in the sagittal plane for each participant: repetition time (TR) = 1900 ms, echo time (TE) = 2.52 ms, 9° flip angle, 176 slices (no gap), voxel size 1.0 × 1.0 × 1.2 mm, field of view (FOV) = 270 × 254 × 212, with a total acquisition time of 9 min. High-resolution Multiband echo-planar images were collected using a field of view (FOV) of 208 × 208 × 125, a repetition time (TR) of 664 ms, an echo time (TE) of 30 ms, a flip angle of 30°, an isotropic resolution of 1.8 mm, and, a Multiband acceleration factor of 5. Forty-five axial slices were acquired covering the entire brain. Multiband parallel imaging enabled the acquisition of high-resolution functional images, with large sampling rates for full-brain coverage, through the acquisition of multiple slices simultaneously. This resulted in significantly reduced acquisition time, which also limited distortion resulting from magnetic susceptibility. Furthermore, the high temporal efficiency has been shown to provide greater statistical power (Feinberg et al., 2010).

2.7. fMRI data analysis

2.7.1. Preprocessing

All neuroimaging data were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) on Linux and Mac OSX platforms. Analyses largely took place in accordance with the standardized afni_proc.py pipeline. Data were despiked (3dDespike), slice timing corrected (3dtshift), coregistered with T1-weighed anatomical images (align_epi_anat.py), motion corrected (3dvolreg), smoothed to 2 mm isotropic (3dmerge) with a Gaussian FWHM kernel, automasked to exclude voxels outside the brain (3dautomask), and bandpass filtered to include 0.06–0.12 Hz frequency band. Trials with motion in excess of 0.3 mm were excluded from the time series using a custom script. Critically, based on processing steps suggested by Power, Barnes, Snyder, Schlaggar, and Petersen (2012), we also regressed signal in white matter and ventricles to account for noise related to motion and scanner artifact. This was accomplished using ANATICOR (Jo, Saad, Simmons, Milbury, & Cox, 2010), which uses local white matter and ventricular signal estimates applied to nearby gray matter voxels. Functional scans were aligned to each subject's skull-stripped MP-RAGE (align_epi_anat.py). Final voxel time courses were estimated using univariate regression (3dDeconvolve), which included nuisance variables for six motion parameters (pitch, roll, and yaw; x, y, and z frame displacement) and linear scanner drift.

We used Advanced Normalization Tools (ANTs) (Avants et al., 2011) to warp each individual participant's structural scan into an in-house high-resolution 0.65 mm isotropic template using a diffeomorphic nonlinear registration algorithm (SyN) (Klein et al., 2009). The transformation parameters were then applied to the coplanar functional data output from the regression described above in order to align them to the custom template.

2.7.2. Construction of dynamic network

Based on our *a priori* hypothesis, dynamic functional connectivity was examined within the MTL, including cortical regions (perirhinal cortex, parahippocampal cortex, and, anterolateral and posteromedial entorhinal cortex) and hippocampal subfields (subiculum, CA1, and DG/CA3). The hippocampus receives input via both lateral and medial entorhinal cortices, which in turn receive input from the perirhinal and parahippocampal cortices, respectively. Studies in rodents (Keene et al., 2016; Knierim, Neunuebel, & Deshmukh, 2014) and in humans (Reagh & Yassa, 2014) have shown a functional dissociation between the lateral and medial entorhinal cortex, with recent evidence suggesting that the human entorhinal cortex seems to more closely follow an anterolateral versus posteromedial functional division (Maass, Berron, Libby, Ranganath, & Düzel, 2015; Schröder, Haak, Jimenez, Beckmann, & Doeller, 2015). As such, in the present study, we considered the anterolateral and posteromedial entorhinal cortices as separate regions of interest (ROIs) within the MTL network. For subsequent analyses, a structural ROI approach was used, selecting all the voxels within an anatomical ROI, based on manual delineations on the custom template. ROIs were segmented based on published protocols (Reagh et al., 2018). Anterolateral and posteromedial entorhinal cortex were segmented based on results from Maass et al. (2015), as also applied by Reagh et al. (2018).

For each ROI, the mean time series was extracted (3dmaskave), consisting of 812 time points. To assess dynamic connectivity between the ROIs, time courses were further subdivided into sub-blocks of 50 time points (~33 s) giving a total of 16 time windows; the first 6 and last

6 time points were discarded. As suggested by Telesford et al. (2016), the length of the time window was chosen to be long enough to allow adequate estimation of correlations over the frequencies that were present in the wavelet band of interest (0.06–0.12 Hz), yet short enough to allow a fine-grained measurement of temporal evolution over the full session.

For each of the 16 sub-blocks, connectivity was quantified as the magnitude squared spectral coherence between each pair of ROIs to later assess modularity over time windows in a manner consistent with previous reports (Bassett et al., 2011; Bassett, Wymbs, et al., 2013). Hence, subject-specific 7 × 7 × 16 connectivity matrices were created for the 7 ROIs and 16 time windows, containing coherence values ranging between 0 and 1. In using the coherence, which has been demonstrated to be useful in the context of fMRI neuroimaging data (Sun, Miller, & D'esposito, 2004), we were able to measure frequency-specific linear relationships between time series.

To examine changes in functional brain network architecture, we used a multilayer network approach in which each layer consists of a network derived from a single time window. Networks in consecutive layers therefore correspond to consecutive time windows. Multilayer networks were constructed for each individual by placing a connection between a node in the connectivity matrix and its respective node in the connectivity matrix of adjacent time windows. Thus, every network node in the multilayer network is connected to itself in the preceding and following time windows to link networks across time. Such a representation creates a time-dependent network, allowing for the partitioning of each network layer into densely interconnected subgroups called communities or modules (Porter, Onnela, & Mucha, 2009), whose identity is robustly tracked across time windows (Bassett, Porter, et al., 2013; Mucha et al., 2010).

2.7.3. Dynamic community detection

The partitioning of each multilayer network into temporally-linked modules was performed using a Louvain-like locally greedy community detection algorithm for optimizing multilayer modularity (Mucha et al., 2010). The multilayer modularity quality function is given by

$$Q_{ml} = \frac{1}{2\mu}\sum_{ijlr}\left\{\left(A_{ijl} - \gamma_l \frac{k_{il}k_{jl}}{2m_l}\right)\delta_{lr} + \delta_{ij}\omega_{jlr}\right\}\delta\left(g_{il}, g_{jr}\right),$$

where Q_{ml} is the multilayer modularity index. The adjacency matrix for each layer l consists of components A_{ijl}. The variable γ_l represents the resolution parameter that defines the weight of intra-layer connections for layer l, whereas ω_{jlr} gives the coupling strength between node j at layers l and r. The variables g_{il} and g_{jr} correspond to the community labels for node i at layer l and node j at layer r, respectively; k_{il} is the connection strength (coherence) of node i in layer l; the total edge weight in the network is $\mu = \frac{1}{2}\sum_{jr}K_{jr}$; the multilayer node strength $K_{jl} = k_{jl} + c_{jl}$; and $c_{jl} = \sum_r \omega_{jlr}$.Finally, the function $\delta\left(g_{il}, g_{jr}\right)$ refers to the Kronecker delta function, which equals 1 if $g_{il} = g_{jr}$, and 0 otherwise. In line with previous reports (Bassett et al., 2011; Bassett, Wymbs, et al., 2013), the connection strengths within layers (intra-layer, γ) and between layers (inter-layer, ω) were set to 1 in the present study.

Optimization of multilayer modularity yielded a community assignment for every node and every time window, indicating the module allegiance. To measure changes in the composition of communities across time, we computed the flexibility of each node as the extent to which it changed module allegiance throughout the set of time windows represented by the multilayer network (Bassett et al., 2011). Flexibility was therefore quantified as the number of times a node displayed a change in community assignment, normalized by the total possible number of changes; this was computed for each of our 7 ROIs. The flexibility of the MTL network as a whole was then computed as the mean flexibility over all nodes.

2.8. Statistical analysis

To evaluate exercise-related changes in physical fitness (BMI & VO_2 max), cognitive (standardized neuropsychological assessments & acquired equivalence task) and neural (MTL network flexibility) function, we used a quasi-experimental study design known as a difference-in-differences (DID) analysis (Wooldridge, 2016). This method allows for comparison of the two groups (aerobic exercise versus control) over time (baseline versus post-intervention), and, when used in a regression framework, can control for unobserved individual differences (Craig et al., 2012). To estimate the effect of aerobic exercise intervention, we used a linear regression model of the form:

$$Y = \beta_0 + \beta_1[Group] + \beta_2[Time] + \beta_3[\boldsymbol{Group*Time}] + \beta_4[Age] + \beta_5[Education] + \varepsilon,$$

where Y was the outcome, β_0 was the baseline average, β_1 was the difference between groups at baseline, and β_2 was the difference in control group's score over time. The coefficient of interest was β_3, which represents the change in outcome for the aerobic exercise group relative to controls, i.e., the difference in the amount of change in outcome over time between the two groups. Age and education were included as covariates.

2.9. Power analysis

We used a power estimation method for non-randomized DID designs, developed by Hu and Hoover (2018). This method uses a generalized least squares (GLS) power estimation framework, incorporating the correlation structure of repeated measures, that results in simple GLS variance formulas of the intervention effect. Based on this estimation method, our sample size of 34 would provide 80% power to detect at least a medium effect size of $d = 0.6$. We therefore considered our study sufficiently powered to support the evaluation of our hypotheses.

3. Results

3.1. Physical fitness

Table 2 presents the baseline and post-intervention data, as well as, coefficients from the DID model. For both BMI and VO_2 max, there were no significant baseline differences between the aerobic exercise and control groups. Participants in the exercise group showed a 7.6% increase in VO_2 max while the controls showed an increase of 3.3%; however, this difference was not statistically significant ($\beta_3 = 0.233$, $p = 0.840$). Additionally, we found no evidence of a significant change in BMI in the exercise group versus those in the control group ($\beta_3 = -0.007$, $p = 0.998$). Therefore, we did not observe any significant exercise-related improvements in either physical health or aerobic fitness at the end of the 20-week intervention.

3.2. Cognitive function

3.2.1. Standardized neuropsychological assessments

Across groups, participants did not differ at baseline or show any significant change in performance after the intervention period on the standardized neuropsychological assessments (Table 2).

3.2.2. Acquired equivalence

The acquired equivalence task had two distinct phases, training and test. On the training phase, all participants reached criterion by completing each stage in fewer than the maximum allowed trials, indicating that they successfully learned the task. Fig. 2A shows the total errors in the training phase for each group at baseline and post-intervention. Both groups learned the task equally well at baseline ($\beta_1 = 4.27$, $p = 0.501$) and there was not a significant difference in

Table 2
BMI, aerobic fitness, and neuropsychological tests scores at baseline and after the 20-week intervention period.

Measures	Aerobic Exercise		Control		Difference-in-differences coefficients		
	Baseline	Post-Intervention	Baseline	Post-Intervention	Group (β_1)	Time (β_2)	Group * Time (β_3)
BMI	30.61 (5.57)	30.56 (5.54)	28.9 (7.66)	28.87 (7.71)	1.70 (−2.89 to 6.30) p = 0.461	−0.037 (−4.63 to 4.55) p = 0.987	−0.007 (−6.59 to 6.57) p = 0.998
VO_2	15.02 (2.96)	15.62 (1.68)	14.86 (2.21)	15.22 (2.4)	0.165 (−1.45 to 1.78) p = 0.839	0.358 (−1.26 to 1.97) p = 0.659	0.233 (−2.05 to 2.51) p = 0.840
MMSE	27.59 (2.6)	27.53 (1.62)	28.12 (1.41)	27.88 (1.05)	−0.529 (−1.74 to 0.682) p = 0.386	−0.235 (−1.45 to 0.976) p = 0.699	0.176 (−1.54 to 1.89) p = 0.838
Digit Span	21.71 (4.58)	22.06 (5.62)	21.12 (6.71)	23.24 (3.78)	0.588 (−3.04 to 4.21) p = 0.747	2.118 (−1.51 to 5.74) p = 0.247	−1.77 (−6.73 to 3.21) p = 0.480
NAART	39.53 (9.58)	40.29 (9.54)	37.0 (11.32)	36.94 (11.85)	2.53 (−4.75 to 9.81) p = 0.490	−0.059 (−7.34 to 7.22) p = 0.987	0.824 (−8.99 to 10.61) p = 0.867
RAVLT-Delayed Recall	7.18 (4.05)	8.12 (3.52)	7.06 (3.49)	8.29 (3.16)	0.118 (−2.34 to 2.56) p = 0.924	1.24 (−1.21 to 3.68) p = 0.317	−0.294 (−3.76 to 3.17) p = 0.866

Note. Group: 1 = aerobic exercise, 0 = control; Time: 1 = post-intervention, 0 = baseline. The Group*Time interaction represents the difference in the amount of change in outcome over time between the two groups (difference-in-differences).

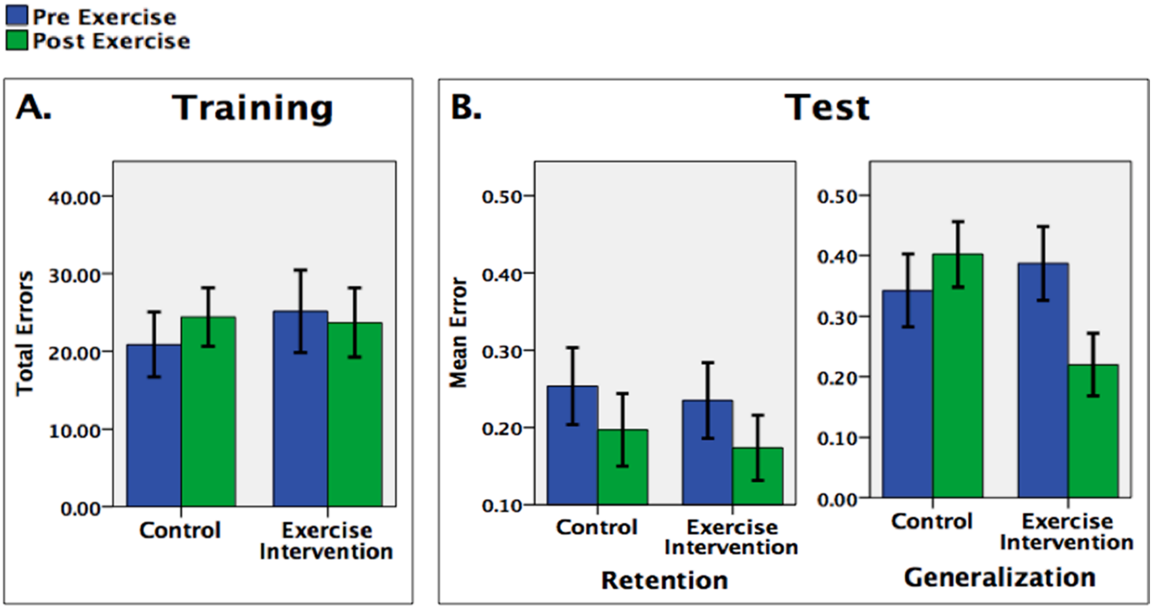

Fig. 2. Performance on the acquired equivalence task, at baseline and post-intervention, for training (A) and test (B) phase. Across groups, no changes were observed for either training (A) or retention (B, left) during the intervention period. On the generalization trials, participants in the aerobic exercise group made significantly fewer generalization errors, while controls exhibited no change in generalization performance.

improvement for task acquisition following the intervention period between the two groups ($\beta_3 = -4.98$, $p = 0.579$). We therefore did not control for learning when analyzing performance on the test phase.

The test phase involved retention (previously trained discriminations) and generalization (new discriminations) trials. As shown in Fig. 2B (left), retention scores (mean error) did not differ between groups at baseline ($\beta_1 = -0.019$, $p = 0.781$) and we found no evidence that the exercise intervention was associated with improvements in retention performance ($\beta_3 = -0.005$, $p = 0.961$).

Fig. 2B (right) shows performance on the generalization trials (mean errors). Participants in the exercise intervention group had a significantly greater decline in generalization errors from baseline compared to the controls ($\beta_3 = -0.227$, $p = 0.018$). Since pre-intervention generalization performance did not differ between groups ($\beta_1 = 0.041$, $p = 0.610$), and the control group showed no change in generalization errors between baseline and post-intervention follow-up ($\beta_2 = 0.06$, $p = 0.455$), we can infer that participants in the aerobic exercise group showed exercise-related improvements in generalization.

3.3. Neural function

To examine exercise-related changes in dynamic functional connectivity within the MTL network, we quantified network evolution throughout each session by computing time dependent network flexibility. The time-dependent flexibility of a region was defined as the probability that the brain region changed its allegiance to putative functional modules between any two consecutive time windows, and the time-dependent flexibility of the MTL network was defined as the average regional flexibility over all ROIs included in the network. Thus, a MTL network flexibility score was computed for each participant both at baseline and at post-intervention follow-up; these scores were submitted into a difference-in-differences analysis.

As shown in Fig. 3, while the groups did not differ at baseline ($\beta_1 = -0.014$, $p = 0.512$), the exercise intervention was associated with a

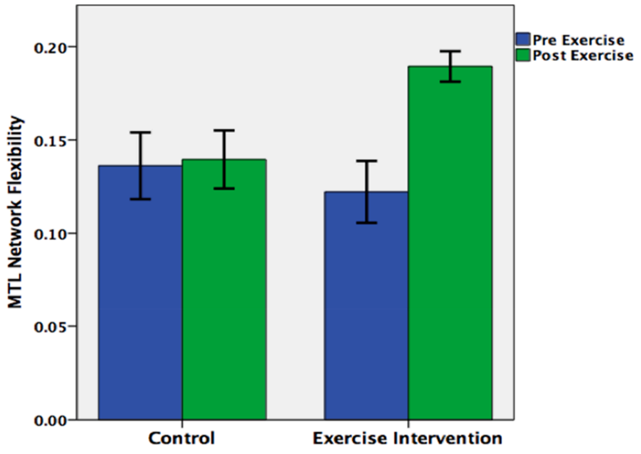

Fig. 3. Resting-state dynamic flexibility in the medial temporal lobe (MTL) network. The exercise group showed an increase in neural flexibility within the MTL network, while there was no difference in flexibility between baseline and post-intervention follow-up for the controls.

significant increase in MTL network flexibility relative to the control condition ($\beta_3 = 0.063$, $p = 0.038$), which did not present any change in MTL flexibility between baseline and post-intervention follow-up ($\beta_2 = 0.003$, $p = 0.875$).

To investigate the potential link between cognitive and neural function, we computed correlations between change scores for MTL network flexibility and generalization error. As shown in Fig. 4, the increase in MTL network flexibility was negatively correlated with increase in generalization errors for the aerobic exercise group ($r(17) = -0.683$; $p = 0.003$) but not for controls, albeit trending in the same direction ($r(17) = -0.328$; $p = 0.199$). The difference between these correlations was not statistically significant, $Z = -1.31$, $p = 0.19$. When collapsed across groups, the negative association between MTL network flexibility and generalization errors remained significant ($r(34) = -0.545$; $p = 0.001$). Thus, increase in MTL flexibility was associated with commensurate improvements in generalization based on previously learned information.

3.4. Mediation analysis

We examined whether the effect of an exercise intervention on generalization is mediated by MTL network flexibility. A multiple mediator model (Preacher & Hayes, 2008) was tested with change in MTL flexibility as the mediator and change in generalization errors as the dependent variable; age and education were entered in the model as covariates. The mediation model is shown in Fig. 5, with the indirect effect estimates and 95% CIs in Table 3. There was a significant indirect effect of MTL network flexibility on the relationship between exercise intervention and generalization scores (total indirect effect = −0.11, CI = −0.28, −0.02). Furthermore, the direction of the paths indicated that the exercise intervention was associated with increased MTL network flexibility ($\beta = 0.06$, $p = 0.031$), which was subsequently associated with a decrease in generalization errors ($\beta = -1.69$, $p = 0.003$).

4. Discussion

In the present study, we observed exercise-related improvements in behavioral generalization, mediated by increases in MTL network flexibility. Following a 20-week aerobic exercise intervention, the exercise group showed an increase in neural flexibility within the MTL network, together with an increase in mnemonic flexibility, measured by improvements in generalization on the behavioral paradigm. For the matched controls, no behavioral or neural network changes were observed at the end of the no contact period. For the aerobic exercise group, an increase in MTL network flexibility was positively correlated with improvements in generalization. Our results are consistent with the hypothesis that aerobic exercise increases neuroplasticity in the MTL and therefore improves mnemonic flexibility.

Following the intervention period, the exercise group made significantly fewer generalization errors, while the control group showed an increase in generalization errors on the behavioral paradigm. This exercise-related improvement in generalization does not reflect enhanced learning; both groups learned the task equally well at baseline and did not show a significant change in learning during the intervention period. Improved generalization was also not due to better retention of the trained pairs that support flexible transfer because memory retention of the initial learning did not differ across group or session. Hence, exercise selectively increased the ability to flexibly apply and recombine information from past learning. Notably, no group differences were observed on common standardized measures of cognitive function and episodic memory performance, either at baseline or at follow-up, indicating that participants remained cognitively healthy over the course of the study. Thus, the acquired equivalence behavioral paradigm, which measures mnemonic flexibility, may be a sensitive tool for assessing the efficacy of aerobic exercise-based interventions in

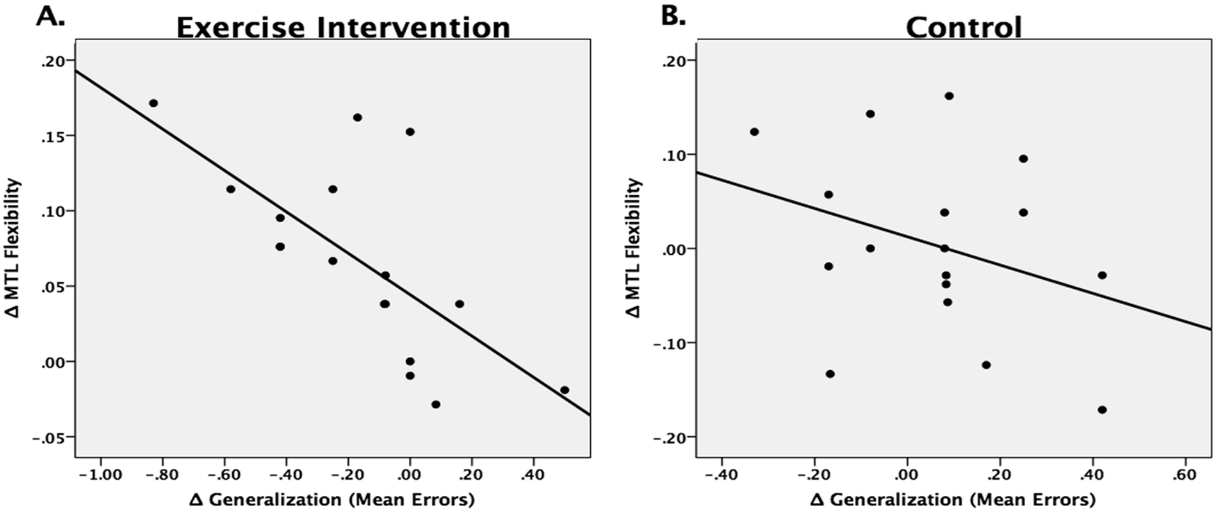

Fig. 4. Correlations between change in MTL network flexibility and generalization errors during the intervention period. For the exercise group (A), increase in MTL network flexibility was significantly correlated with improvements in generalization performance. This association was not significant for controls (B).

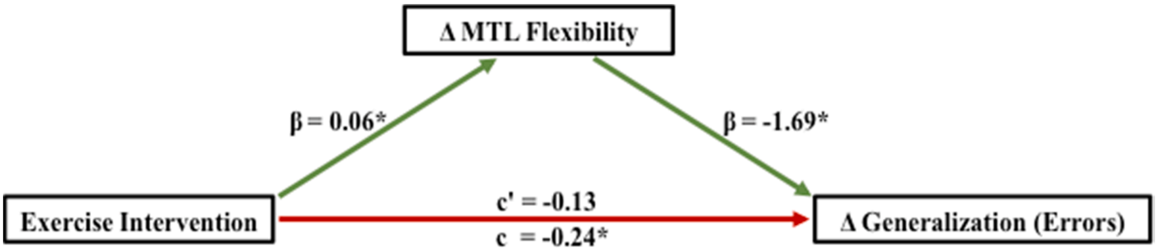

Fig. 5. An illustration of the mediation model. β values indicate the coefficient of the arrow's partial effect. Green arrows indicate significant effects and an asterisk (*) is appended to significant coefficients. c' (c-prime) represents the direct effect and c represents the total effect of aerobic exercise intervention on generalization errors. Indirect effect coefficients indicate that exercise was associated with increased MTL network flexibility, in turn, resulting in cognitive improvements.

Table 3
Mediation of the effect of exercise intervention on generalization (errors) through MTL network flexibility.

	Product of Coefficients			Bootstrapping 95% CI		Coefficients	
	Point Estimate	SE	Z	Lower	Upper	Exercise → Δ MTL Flexibility	Δ MTL Flexibility → Δ Generalization Errors
Δ MTL Flexibility	−0.11*	0.06	−1.81	−0.28	−0.02	0.06*	−1.69*

Note. Asterisk (*) is appended to significant coefficients

remedying the subtle cognitive deficits seen in the earliest phases of preclinical AD in otherwise cognitively healthy individuals, before the more severe and more commonly reported deficits in episodic memory arise.

Analogous to behavioral improvements, there was an exercise-related increase in resting-state MTL network flexibility. Functional brain networks constructed from both resting and task-based data, display a modular organization (Sporns & Betzel, 2016), containing local clusters, or communities of densely interconnected nodes (Newman, 2006). Network flexibility measures the dynamic rearrangement of this modular community structure (Bassett et al., 2011), and therefore captures overall network evolvability. Conceptually, dynamic evolution of network architecture on the scale of seconds is consistent with very rapid plasticity (Arnsten, Paspalas, Gamo, Yang, & Wang, 2010; Arnsten, Wang, & Paspalas, 2012). Furthermore, a genetic association analysis revealed neuroplasticity-related biological processes underlying network flexibility (Liu et al., 2019). To our knowledge, the present study is the first to provide evidence of exercise-related changes in MTL network functional plasticity. Our results suggest that MTL network flexibility may capture individual differences in neuroplasticity and can be an effective biomarker that indexes the potential for adaptive reorganization following intervention.

Our mediation analysis established a significant indirect effect of MTL network flexibility on the effect of aerobic exercise on the generalization of learning. Specifically, participation in the exercise intervention was associated with an increase in MTL network flexibility, which was consecutively related to generalization improvements. While this significant indirect effect is consistent with the proposed mediation model, given the present study's non-randomized design, we cannot rule out MTL network flexibility as a potential confounder. However, previous studies exploring associations between aerobic exercise, network modularity, and cognition provide the theoretical framework supporting the hypothesized direction of causal pathways in this model (Gregory, Parker, & Thompson, 2012; Rosenzweig & Barnes, 2003; Tozzi et al., 2016). As such, neural flexibility facilitates the participation of MTL regions in multiple functional communities, thereby optimizing the network's ability to engage in and benefit from exercise training. Recent work has demonstrated that baseline levels of brain network modularity predict greater cognitive improvements after both exercise (Baniqued et al., 2018) and cognitive training (Gallen et al., 2016) in healthy older adults. We build significantly on these results as our findings suggest a model where exercise exerts neurogenerative effects on the dynamic modular rearrangement of the MTL, which in turn, potentiates exercise-induced improvements on MTL-related cognitive function. The exploration of temporally evolving network architecture therefore forms a critical frontier in neuroscience, which may provide insight into the mechanisms underlying the effectiveness of interventions geared toward ameliorating age-related cognitive decline.

There were no measurable exercise-related improvements in aerobic fitness (VO_2 max) or BMI. Although the participants in the exercise group showed a greater increase in aerobic fitness than controls, this difference was not significant. Our participants were older African Americans, primarily women, living in and around Newark, New Jersey. Previous research has shown that African American women are less sensitive to the effects of physical activity and exercise (Hickner, Privette, McIver, & Barakat, 2001; White & Jago, 2012). Specifically, higher levels of daily physical activity were associated with lower levels of obesity in adolescent Caucasian women, while there was no relationship between activity level and obesity rates in female African American adolescents (White & Jago, 2012). Further, African American women burn off fewer fatty acids than Caucasian women in response to aerobic exercise (Hickner et al., 2001). Another recent study in African Americans found significant gender-based differences in exercise-induced alteration in VO_2 max, such that, an exercise intervention produced statistically significant increases in VO_2 max in men, but not in women (Allard et al., 2017). With just three male participants in the present study, our sample was mostly comprised of African American women, a group shown to gain the least physical benefits from exercise. Conversely, despite the absence of changes in physical condition, we observed an exercise-related increase in MTL flexibility that was associated with improvements in behavioral generalization. These findings suggest that the informative nature of dynamic brain network organization can be used to maximize exercise effectiveness, via the modification of training intensity or duration. This is particularly pertinent in populations where traditional measures of training efficacy, such as aerobic fitness or BMI, may not be commensurate with brain health improvements. For example, interventions targeting obesity reduction in the African American community may benefit from the implementation of complementary approaches such as diet management. Future research in a racially diverse and gender-balanced sample is needed to elucidate whether the neural and cognitive benefits of aerobic exercise are akin to improvements in physical condition.

Within the context of recent recommendations for improving methodological standards in behavioral interventions (Green et al., 2019) the primary limitations of this study include non-randomized group assignments and the absence of an active control group. Therefore, the findings need to be interpreted with caution. While random group assignment is the "gold standard" of experimental methods, in studies with smaller sample sizes it can create imbalanced groups with baseline differences, which makes it difficult to interpret intervention-related changes (Green, Strobach, & Schubert, 2014, 2019). As such, even though employing a randomized controlled trial would have been ideal, our matched control design resulted in two groups with no significant baseline differences on participant characteristics or outcome measures.

In exercise intervention trials, having both an active (for example, stretching and toning) and passive control group allows researchers to test proposed mechanisms while accounting for any benefits of increased social contact afforded by the group exercise classes. Further, with an exercise intervention there is no way to blind subjects to the content of their training, but the inclusion of an active control condition that has some degree of face validity as an "active" intervention from the participants' perspective may alleviate expectation effects. In the present study, since the controls were a passive "treatment as usual" group, it is plausible that the difference in the neural and cognitive changes between the two groups can be attributed not only to the specific effect of aerobic exercise but to the effect associated with social interaction in a group class setting, as well as, differential expectancies created by group membership.

Despite these limitations, the current study has established that a dance-based aerobic exercise intervention of this nature can yield positive effects on cognitive and neural outcomes. To enhance the scientific rigor and generalizability of these results, future studies should strengthen methodological practices by having an active comparison group, pre-intervention measures of expectations that can be utilized as a control variable in analyses (Boot, Simons, Stothart, & Stutts, 2013), and methods for group assignment that retain many of the aspects and benefits of true randomization while allowing for some degree of control over group balance (Green et al., 2014). Establishing adequate trust within African American communities through education and outreach with trusted community liaisons will facilitate future acceptance of aforementioned rigorous study designs.

5. Conclusions

In summary, the results of this study show that in cognitively healthy individuals, the MTL remains plastic in old age. Furthermore, 20 weeks of aerobic exercise was related to the enhancement of neural network flexibility, yielding improvements in mnemonic flexibility and function. Our findings suggest that measuring the dynamic brain network can serve as a non-invasive quantification of neuroplasticity, and, may have future clinical applications for detecting neuronal dysfunction in both healthy elderly and those in the prodromal stages of neurodegenerative diseases. Importantly, our data show that brain health may improve following exercise, even in the absence of observable changes in aerobic fitness. Ultimately, these results reinforce the neuroprotective value of aerobic exercise: even if an exercise regimen is undertaken later in life, it may still mitigate cognitive decline.

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CRediT authorship contribution statement

Neha Sinha: Conceptualization, Methodology, Software, Formal analysis, Writing-Original and Revised Drafts. **Chelsie N. Berg:** Investigation, Writing-Original and Revised Drafts, Visualization. **Michael A. Yassa:** Writing - review & editing, Supervision. **Mark A. Gluck:** Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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