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A pilot study of combined endurance and resistance exercise rehabilitation for verbal memory and functional connectivity improvement in epilepsy

Jane B. Allendorfer [a,g,*], Gabrielle A. Brokamp [a], Rodolphe Nenert [a], Jerzy P. Szaflarski [a,d,f], Charity J. Morgan [b], S. Craig Tuggle [e,g], Lawrence Ver Hoef [a,f,h], Roy C. Martin [a], Basia A. Szaflarski [a], Manmeet Kaur [a], Adrienne C. Lahti [c], Marcas M. Bamman [e,g,h]

[a] Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA
[b] Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA
[c] Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL, USA
[d] Department of Neurobiology, University of Alabama at Birmingham, Birmingham, AL, USA
[e] Department of Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL, USA
[f] UAB Epilepsy Center, University of Alabama at Birmingham, Birmingham, AL, USA
[g] UAB Center for Exercise Medicine, University of Alabama at Birmingham, Birmingham, AL, USA
[h] Birmingham VA Medical Center, Birmingham, AL, USA

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ABSTRACT

Memory impairment is common in persons with epilepsy (PWE), and exercise may be a strategy for its improvement. In this pilot study, we hypothesized that exercise rehabilitation would improve physical fitness and verbal memory and induce changes in brain networks involved in memory processes. We examined the effects of combined endurance and resistance exercise rehabilitation on memory and resting state functional connectivity (rsFC). Participants were randomized to exercise (PWE-E) or control (PWE-noE). The exercise intervention consisted of 18 supervised sessions on nonconsecutive days over 6 weeks. Before and after the intervention period, both groups completed self-report assessments (Short Form-36 (SF-36), Baecke Questionnaire (BQ) of habitual physical activity, and Profile of Mood States (POMS)), cognitive testing (California Verbal Learning Test-II (CVLT-II)), and magnetic resonance imaging (MRI); PWE-E also completed exercise performance tests. After completing the study, PWE-noE were offered cross-over to the exercise arm. There were no differences in baseline demographic, clinical, or assessment variables between 8 PWE-noE and 9 PWE-E. Persons with epilepsy that participated in exercise intervention increased maximum voluntary strength (all strength tests $p < 0.05$) and exhibited nonsignificant improvement in cardiorespiratory fitness ($p = 0.15$). Groups did not show significant changes in quality of life (QOL) or habitual physical activity between visits. However, there was an effect of visit on POMS total mood disturbance (TMD) measure showing improvement from baseline to visit 2 ($p = 0.023$). There were significant group by visit interactions on CVLT-II learning score ($p = 0.044$) and total recognition discriminability (d′) ($p = 0.007$). Persons with epilepsy that participated in exercise intervention had significant reductions in paracingulate rsFC with the anterior cingulate and increases in rsFC for the cerebellum, thalamus, posterior cingulate cortex (PCC), and left and right inferior parietal lobule (IPL) (corrected $p < 0.05$). Change in CVLT-II learning score was associated with rsFC changes for the paracingulate cortex ($r_S = -0.67$; $p = 0.0033$), left IPL ($r_S = 0.70$; $p = 0.0019$), and right IPL ($r_S = 0.71$; $p = 0.0015$) while change in d′ was associated with change in cerebellum rsFC to angular/

Abbreviations: 1RM, one-repetition maximum; ANOVA, analysis of variance; ASDs, antiseizure drugs; BQ, Baecke Questionnaire; CVLT-II, California Verbal Learning Test-II; d′, total recognition discriminability; fMRI, functional magnetic resonance imaging; GXT, maximal graded exercise test; HRR, heart rate reserve; IEDs, interictal epileptiform discharges; IGE, idiopathic generalized epilepsy; IPL, inferior parietal lobule; LLA, leisure and locomotion activities (from BQ); MCS, mental component score (from SF-36); MNI, Montreal Neurological Institute; MoCA, Montreal Cognitive Assessment; OPA, occupational physical activity during work (from BQ); PAR-Q, Physical Activity Readiness Questionnaire; PEL, physical exercise during leisure time (from BQ); PCA, principal component analysis; PCC, posterior cingulate cortex; PCS, physical component score (from SF-36); POMS, Profile of Mood States; PWE, persons with epilepsy; PWE-E, persons with epilepsy that participated in exercise intervention; PWE-noE, persons with epilepsy that participated as no-exercise controls; QOL, quality of life; ROIs, regions of interest; rsFC, resting state functional connectivity; rs-fMRI, resting state functional magnetic resonance imaging; SF-36, Short Form-36; SIPN, seizure initiation and propagation network; STG/SMG, superior temporal/supramarginal gyrus; TMD, total mood disturbance (from POMS); TRE, treatment-resistant epilepsy; UAB, University of Alabama at Birmingham; UABEC, University of Alabama at Birmingham Epilepsy Center; UCEM, University of Alabama at Birmingham Center for Exercise Medicine; VO_2, oxygen uptake; VO_2max, maximum attained oxygen uptake.

* Corresponding author at: Department of Neurology, University of Alabama at Birmingham (UAB) Epilepsy Center, 312 Civitan International Research Center, 1719 6th Avenue South, Birmingham, AL 35294, USA.
E-mail address: jallendorfer@uabmc.edu (J.B. Allendorfer).

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middle occipital gyrus ($r_S = 0.68$; $p = 0.0025$). Our conclusion is that exercise rehabilitation may facilitate verbal memory improvement and brain network functional connectivity changes in PWE and that improved memory performance is associated with changes in rsFC. A larger randomized controlled trial of exercise rehabilitation for cognitive improvement in PWE is warranted.

1. Introduction

Epilepsy constitutes a major health problem, affecting over 3 million people in the U.S. It is associated with increased risk of death and seizure-related injuries, medication side effects, and stigma; persons with epilepsy (PWE) are less likely to be able to drive or live independently [1–4]. Factors contributing to poor health-related quality of life (QOL) in PWE include psychological stress, sleep problems, depression, seizure frequency, and cognitive dysfunction [5–10]. Up to half of PWE suffer from cognitive impairment in one or more domains including memory, learning, attention, and/or executive functioning [11–16]. Memory impairment is a common cognitive problem in PWE [17–20]. The presence of cognitive deficits in PWE, particularly in memory, significantly contributes to their challenges in participating in school, work, and other daily activities [2,6]. The epilepsy, medical, and scientific community recognize that understanding and ameliorating the negative impact of epilepsy on cognitive function is an important research focus [21].

Formal exercise training and increased levels of physical activity are deemed beneficial for cognition and may alleviate cognitive deficits in PWE [22–24]. Randomized controlled trials have shown endurance exercise training to improve executive function and/or memory performance, particularly in older adults [25–28] but also in young and middle-aged adults [29,30]. Randomized controlled trials have also shown resistance exercise training to improve spatial memory [26] and executive function and attention [31,32]. In epilepsy, intensive exercise training has been shown to improve physical and emotional/mood states of adults with treatment-resistant epilepsy (TRE), with no negative impact on seizure frequency or impact on concentrations of antiseizure drugs (ASDs) [33]. In women with TRE, combined aerobic dancing and strength exercise training decreased seizure frequency and improved their psychosocial functioning and overall QOL [34]. Further, a randomized controlled trial in PWE showed improvement in QOL and reduction in total mood disturbance (TMD) from baseline to week 12 in the exercise training group (combined endurance, resistance, and flexibility training), with no changes in the nonexercise group [35]. This study also showed no negative effects on seizure frequency or ASD concentrations with exercise training [35]. To date, investigations into the effects of exercise rehabilitation on cognitive function in PWE are limited, with one study showing improvements in attention and executive functioning from baseline to week 5 of a supervised exercise program in children with epilepsy [23]. Thus, exercise may have untapped potential for improving cognition and memory in PWE.

Epilepsy is considered a network disease. Several studies have demonstrated that multiple brain regions are simultaneously involved when experiencing focal or generalized epilepsy. We collectively refer to this network of brain regions as the seizure initiation and propagation network (SIPN). The SIPN includes the cerebellum, hippocampus, thalamus, default mode network regions including posterior cingulate cortex (PCC) and inferior parietal lobule (IPL), and paracingulate cortex [36–40]. The effect of exercise on SIPN brain regions in PWE is unknown. Noninvasive investigations can be performed using functional magnetic resonance imaging (fMRI) to assess resting state functional connectivity (rsFC) of SIPN brain regions. Altered functional connectivity of the anterior cingulate cortex has been found to be associated with working memory deficits in persons with cryptogenic epilepsy [17]. Just as improving seizure control has been described as a strategy for improving cognitive function in PWE [24,41], modifying functional connectivity of SIPN brain regions involved in seizure control may yield similar improvements.

Exercise can induce changes in brain functional connectivity, with one intervention trial in healthy older adults showing that endurance training increased functional connectivity between temporal, frontal, and posterior brain regions [42]. A preliminary study in persons with multiple sclerosis showed that endurance training increased both rsFC of the hippocampus and verbal memory performance [43]. Another pilot study in persons with multiple sclerosis showed that resistance exercise training also increased caudate functional connectivity, and that greater training-induced increases in caudate-parietal region functional connectivity were associated with greater decreases in cognitive fatigue [44]. Taken together, these studies suggest that the effects of exercise on brain functional connectivity may be related to improved cognitive functioning. While there is no current evidence to suggest clear advantage of utilizing one mode of exercise over the other, both may improve cognition and change functional connectivity; previous studies in PWE showed beneficial effects from combined endurance and resistance exercise training [34,35]. Thus, in this pilot study, we examined the effects of supervised, combined endurance and resistance exercise rehabilitation on verbal memory function in PWE and tested whether corresponding changes in rsFC of SIPN brain regions were related to changes in memory performance. The working hypothesis was that PWE would show exercise-induced improvements in verbal memory performance and that exercise-related changes in functional connectivity of SIPN brain regions would be associated with memory improvements.

2. Material and methods

2.1. Participants

Persons with electroencephalography (EEG)-confirmed diagnosis of epilepsy between 18 and 55 years old were recruited from the University of Alabama at Birmingham Epilepsy Center (UABEC). Prior to study enrollment, individuals were screened for subjective memory complaint and for the ability to undergo a 3-Tesla MRI scan. Other inclusion criteria included experiencing no more than 4 seizures per month on average in the past 3 months, being relatively healthy with no comorbid medical conditions, no suicidal ideation in the past 3 months, fluent in English language, and not concurrently participating in a different intervention study. We identified potential study participants through reviewing electronic medical records for PWE being treated at the UABEC and referrals from the Center's physicians. Persons with epilepsy were approached either in person (i.e., at their clinic visit) or on the telephone to see if they might be interested in participating in an exercise research study. Of the 55 individuals who were successfully contacted, nine said they were not interested. Forty-six individuals who expressed interest were asked the following question: "Do you feel that you have problems with your memory, whether it is a result of your epilepsy or due to your antiseizure medications?" Forty-one individuals answered 'yes', and five answered 'no'. Individuals who answered 'no' were thanked for their time and told they did not meet study criteria. Individuals who answered 'yes' were asked if they would be willing to receive additional information about the study and if they had time to answer additional screening questions. One individual asked to be called back, but we were unsuccessful in contacting

them again. Forty PWE were eventually screened. In female participants, prior to MRI, pregnancy was ruled out with a urine pregnancy test. The Wilcoxon rank sum test and Fisher's exact test were performed, when appropriate, to assess baseline group differences. Post hoc review of medical records was conducted to obtain additional granularity of the epilepsy and mood treatment for each participant. This study was approved by the University of Alabama at Birmingham (UAB) Institutional Review Board, and participants provided written informed consent before study participation. Study procedures were carried out in accordance with the Declaration of Helsinki ethics principles.

2.2. Study design

Sixteen PWE who met study criteria were enrolled and sequentially assigned to either exercise training (PWE-E) or no intervention (PWE-noE), with the option to switch group assignment depending on availability (Fig. 1A). Persons with epilepsy that participated as no-exercise controls could transition to exercise training after completing the control period to ensure that all eligible participants had equal opportunity for the intervention. Study procedures included a baseline testing visit, followed by 6 weeks of either exercise training or no intervention, and then a second testing visit (Fig. 1B). Persons with epilepsy that participated in exercise intervention were screened using the Physical Activity Readiness Questionnaire (PAR-Q; Canadian Society for Exercise Physiology) and required to pass a physical examination by an epilepsy specialist (JPS or LVH) at baseline prior to engaging in exercise training. The baseline visit for PWE-E also included recording of demographic and clinical variables, exercise testing, assessments, and MRI (described below). Within 1 week, PWE-E began the exercise intervention 3 times/week for 6 weeks on nonconsecutive days (18 sessions total). Session days with scheduling conflicts or those that occurred on holidays were rescheduled, but participants could not have more than 7 days between exercise sessions. Within 1 week of completing the intervention, PWE-E again underwent exercise testing, assessments, and

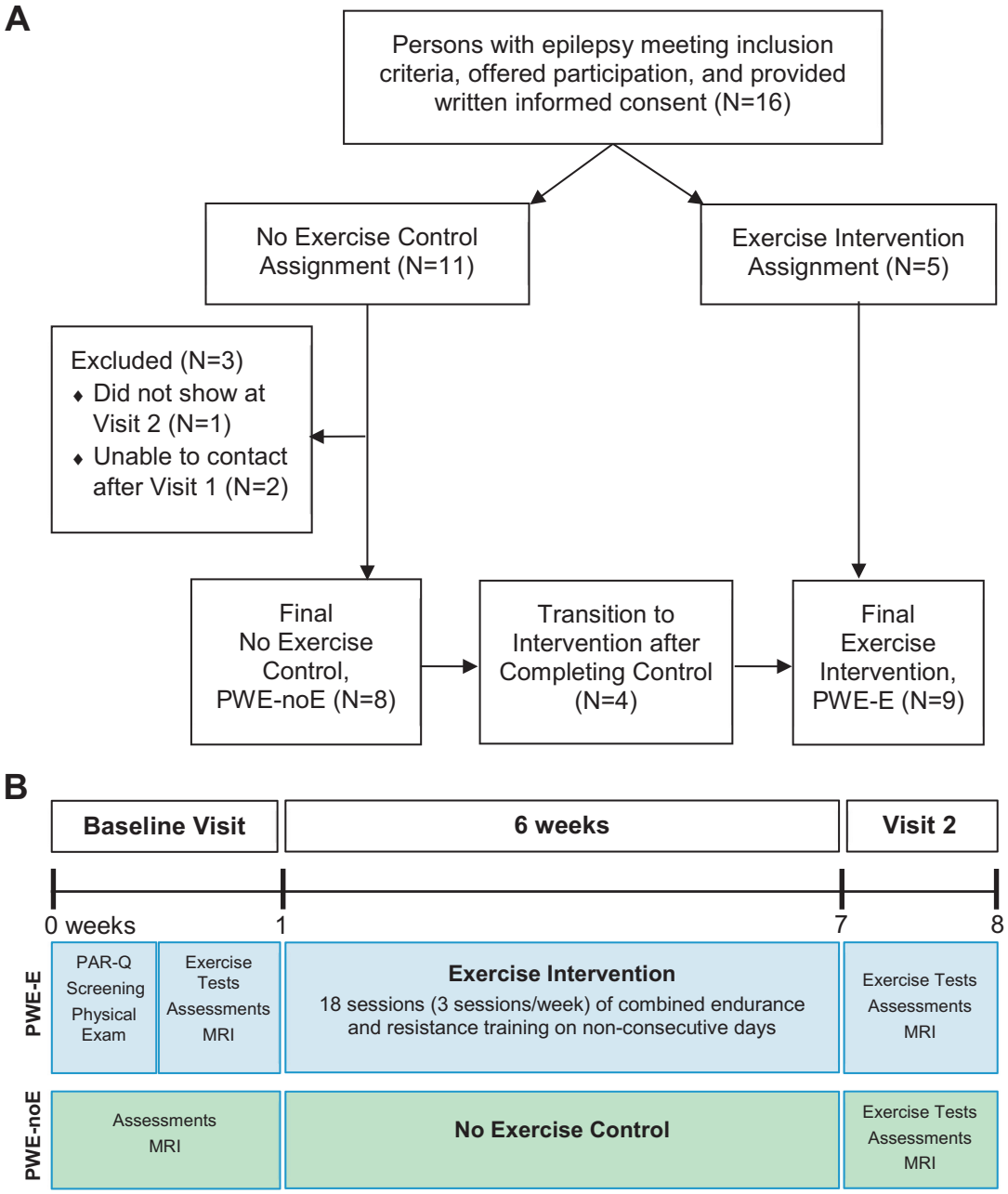

Fig. 1. CONSORT flow diagram for participants with epilepsy in the study (A) and schematic of study procedures (B).

MRI. The baseline visit for PWE-noE consisted of assessments and MRI. After at least 6 weeks of no intervention, PWE-noE returned for visit 2 assessments and MRI, as well as exercise testing. Persons with epilepsy that participated as no-exercise controls performed exercise testing only at visit 2 in order to not influence their perceived health status by them knowing their physical fitness status and potentially changing their level of voluntary exercise [45].

2.3. Exercise tests

All exercise training and testing occurred in the UAB Center for Exercise Medicine's (UCEM) Exercise Clinical Trials Facility. Participants underwent a nondiagnostic maximal graded exercise test (GXT) on a cycle ergometer to determine maximal oxygen consumption rate (VO_2max) and peak exercise heart rate in order to calculate percent heart rate reserve (HRR) and to determine intensity for endurance training. The GXT was performed using a standardized ramp protocol on a Via Sprint 150 P calibrated cycle ergometer, with work rate starting at 25 W and increasing in increments of 25 W every 2 min at 60 rpm. Oxygen uptake (VO_2) and carbon dioxide production were measured using a CareFusion indirect calorimetry system. A hallmark measure of cardiorespiratory fitness, VO_2max was defined as the maximum attained oxygen uptake (i.e., no increase in VO_2 with increasing work rate). Heart rate and the respiratory exchange ratio were monitored continuously, and at each test stage, blood pressure and perceived effort (via a standard 0.5–10 rating of perceived exertion scale) were also monitored. Following the GXT and a rest/recovery period of 15–30 min, participants performed one-repetition maximum (1RM) strength tests on leg press, knee extension, and chest press. For those who reached the maximum weight of an exercise machine for a movement, the number of repetitions at the maximum weight was used for the 1RM estimation [46]. The Wilcoxon rank sum test was performed to assess group differences between PWE-noE visit 2 and PWE-E baseline for VO_2max and 1RM weights. Paired t-tests assessed baseline to visit 2 changes in VO_2max and 1RM weights for PWE-E.

2.4. Exercise intervention

During the intervention period, participants completed 18 supervised sessions of combined endurance and resistance training, 3 sessions each week, approximately 1 h per session, on nonconsecutive days over 6 consecutive weeks. Prior to each session, resting heart rate, blood pressure, and weight were collected, and participants were equipped with a heart rate monitor for the duration of the session. Certified trainers supervised all exercise sessions one-on-one. A second study staff member was also present at the training sessions for participants who were not seizure-free for at least 6 months.

Certified trainers instructed participants in the proper methods of exercise, and warm-up sets preceded each resistance exercise. Endurance training began with 15 min of cycling on a stationary cycle ergometer at 65–85% of HRR and progressed up to 30 min by session 7. Throughout the remaining sessions, intensity was increased to maintain 65–85% of HRR. The volume and intensity for whole-body resistance training progressed over the first four sessions from 1 set to 3 sets of 8–12 repetitions to volitional fatigue for 8 movements to load the major muscle groups (e.g., biceps curl, triceps pushdown, leg press, calf press, chest press, knee extension, lateral pull-down, and seated cable row), with alternating upper-body and lower-body movements during the session. To ensure continuous progression, loads were increased when the participant achieved 12 or more repetitions on 2 or more sets of a given movement. To ensure safety and head/face protection in the unlikely event of a seizure, participants who were not seizure-free for at least 6 months prior to the onset of intervention were required to wear safety headgear (i.e., helmet with a facemask) while engaging in resistance training; the helmet was optional during endurance training on the recumbent cycle ergometer, which secures the subject back and arm rests.

2.5. Assessments

Baseline assessments were performed prior to MRI or exercise testing. Cognitive functioning was assessed with the Montreal Cognitive Assessment (MoCA) [47], which has been found to be sensitive to cognitive impairments in PWE who scored in normal range for cognition on the Mini-Mental State Examination [48]. The Wilcoxon rank sum test was performed to compare assessment scores between groups, with $p < 0.05$ considered significant.

The following assessments were performed at baseline and visit 2. Quality of life was measured with the Short Form-36 (SF-36), which addresses dimensions of physical functioning, limitations due to physical health, limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health, and has been used to facilitate comparisons across control and patient groups, including seizure disorders [8,49]. A physical component score (PCS) and mental component score (MCS) were calculated for the SF-36, with higher scores indicating better QOL [49,50]. Habitual physical activity was assessed using the Baecke Questionnaire (BQ), a validated measure that addresses different domains of real-world physical activity (occupational, leisure time, and locomotion), with separate scores for occupational physical activity during work (OPA), physical exercise during leisure time (PEL), and leisure and locomotion activities (LLA), the sum of which provides a total score, and a higher score reflecting greater level of activity [51–53]. Mood state was assessed with the Profile of Mood States (POMS), which provides a TMD score based on the mood scale scores for tension/anxiety, anger/hostility, depression/dejection, fatigue/inertia, confusion/bewilderment, and vigor/activity, with higher TMD scores reflecting greater mood severity [54]. The POMS provides a global measure of transient mood state (i.e., assessing mood from the past week including today) and has been widely used in epilepsy research [10,35,55–57]. Repeated measures analysis of variance (ANOVA) examined the effects of group, visit, and their interaction for each assessment score, with $p < 0.05$ considered significant. For measures with significant ANOVA results, paired t-tests (2-tailed) were performed post hoc to better characterize baseline to visit 2 changes.

The California Verbal Learning Test, 2nd Edition (CVLT-II) was used to assess verbal learning and memory at baseline and at the second visit [58]. We used two CVLT-II versions (Standard Form and Alternate Form), which have been shown to have good 1-month test/retest reliability and small practice effects, especially when using both forms, and, thus, making it amenable for longitudinal study designs [59]. During the testing session, participants listened to a list of 16 words (List A) and asked to freely recall the list immediately afterwards. They performed 5 learning trials for List A then were administered a Trial B (second list of 16 words), followed by a short-delay free recall and semantic cued recall for List A. After a 20-minute delay period, they performed a long-delay free recall (LDFR) of List A, then a long-delay cued recall trial, and finally, the long delay recognition trial. Performance was based on standard trials 1–5 total score for learning (Learning score; T-score), long-delay free recall score (LDFR score), and total recognition discriminability (d′), which compares hits versus total false positives. These measures were used since verbal recall and recognition are affected in PWE, especially in temporal lobe epilepsy [60–62]. Normed standardized scores (corrected for age, sex, and years of education) from the CVLT-II manual were used for analyses of the Learning scores (T-score). Since z-scores for the LDFR and d′ scores were in intervals of 0.5 standard deviation (SD), raw scores were used for analysis to provide a range while z-scores were used to classify performance for each individual. For CVLT-II performance, below 1st percentile is considered severely impaired, 1st to 2nd percentiles are considered moderately impaired, 3rd to 9th percentile are considered mildly impaired, 10th to

24th percentiles are considered low average, 25th to 75th percentiles are considered average, 76th to 91st percentiles are considered high average, 92nd to 98th percentiles are considered superior, and 99th percentile and above are considered very superior. Repeated measures ANOVA examined the effects of group, visit, and their interaction for each measure, with $p < 0.05$ considered significant. For measures with significant ANOVA results, paired t-tests (2-tailed) were performed post hoc to better characterize baseline to visit 2 changes.

2.6. Neuroimaging

Neuroimaging was performed using a 3.0T Siemens Prisma scanner using a 20-channel head coil. A 3-plane localizer scan was first acquired to visualize the brain. We then acquired 132 resting state fMRI (rs-fMRI) volumes with the participant's eyes open while viewing a black screen during gradient-echo echo-planar imaging T2*-weighted imaging (TR/TE 3000/23 ms, field of view (FOV): 24.0 × 24.0 × 11.5 cm, matrix: 128 × 128, flip angle: 84°, 2.5 mm isotropic). For the rs-fMRI scan, participants were instructed to keep their eyes open, although blinking was okay, and to let their mind wander and not think about anything in particular. The rs-fMRI scan was followed by a high-resolution T1-weighted anatomical brain scan (TR/TE 2400/2.22 ms, FOV: 25.6 × 24.0 × 19.2 cm, matrix: 256 × 256, flip angle: 8°, 0.8 mm isotropic).

2.7. Resting state fMRI data analysis

Statistical Parametric Mapping (SPM12; Welcome Trust Center for Neuroimaging, London, UK) was used to analyze rs-fMRI data. Standard preprocessing included slice timing correction, brain volume coregistration using rigid-body motion transforms, spatial alignment of anatomical and fMRI scans, and spatial normalization to 2 × 2 × 2 mm^3 voxels into the Montreal Neurological Institute (MNI) standard space using unified segmentation algorithm [63]. For each subject, nuisance regression to remove potential sources of noise was performed using the 6 motion parameters and their first derivatives, followed by a step-wise data scrubbing procedure [64], and contaminated time points were first interpolated prior to bandpass filtering ($0.01 < f < 0.08$ Hz). Then, components of white matter and cerebral spinal fluid were extracted using principal component analysis (PCA), and these were used as regressors in a second nuisance regression [65], followed by 8 mm full-width half-maximum spatial smoothing. The SIPN brain regions were used to define 8 regions of interest (ROIs) to be used as seeds for rsFC analysis: lateral cerebellum, left and right hippocampus, thalamus, PCC, the left and right IPL, and paracingulate cortex (Fig. 4A). The paracingulate cortex ROI was previously described to have widespread increased rsFC with other brain regions with increasing epileptiform activity and was created using a sphere (10 mm radius) with centroid at MNI coordinates $x = 2$, $y = 13.6$, $z = 45.9$ [36]. The remaining anatomical ROIs were taken from the automated anatomical labeling (AAL) atlas [66]. Paired t-tests assessed baseline to visit 2 changes in rsFC for each group. Results were significant at topological FDR-corrected $p < 0.05$ (voxelwise $p = 0.001$).

Significant exercise-related changes in rsFC were assessed for their role in verbal memory improvement. For each participant, mean z-scores were extracted from each region that showed significant changes in rsFC with exercise. Spearman correlations were then performed to evaluate relationships between change in rsFC and significant changes in verbal memory performance.

3. Results

3.1. Demographic, clinical, assessment, and performance data

There were 11 PWE recruited as no-exercise controls (PWE-noE), 8 of whom completed the control procedures and were included in analyses (7 with idiopathic generalized epilepsy (IGE), 1 with left temporal lobe epilepsy). The CONsolidated Standards Of Reporting Trials (CONSORT) flow diagram is provided in Fig. 1A. For the 3 PWE-noE who completed only the baseline visit, one did not show up to visit 2 and could not be successfully rescheduled after multiple attempts, and two could not be contacted again after their baseline visit. Of the 8 PWE-noE participants, 4 transitioned to exercise training intervention after completing the control procedures; thus, their visit 2 data were utilized as baseline data for PWE-E. In total, 9 PWE (7 with IGE, 1 with left temporal lobe epilepsy, 1 with frontal lobe epilepsy) participated in the exercise training intervention (PWE-E) and completed all study procedures (Fig. 1A). At baseline, groups did not significantly differ in age, sex, body mass index, years of education, age at epilepsy onset, illness duration, number of seizure-free participants, number of ASDs, or scores on the MoCA (Table 1). Seizure frequency did not change for the one PWE-noE who was not seizure-free before study participation. In the PWE-E who were not seizure-free before study initiation, seizure frequency did not change for one and decreased for 2 participants.

One PWE-noE patient who transitioned to PWE-E was unable to perform the GXT, and age-/sex-predicted heart rate was used to estimate their HRR. For remaining participants, VO_2max at visit 2 for PWE-noE did not differ from baseline VO_2max for PWE-E ($p = 0.64$) nor did strength on the leg press ($p = 0.70$), knee extension ($p = 0.74$), or chest press ($p = 0.36$). There were improvements in fitness measures with exercise (Fig. 2). Persons with epilepsy that participated in exercise intervention showed a trend toward increased VO_2max (mean difference (SD) of 1.9 (3.3) mL/kg/min) from baseline to visit 2 ($p = 0.15$). One PWE-E patient did not complete strength tests at visit 2; the remaining PWE-E participants showed significant increases in 1RM strength for leg press (mean difference (SD) of 43.5 (47.5) kg; $p = 0.036$), knee extension (mean difference (SD) of 25.5 (21.6) kg; $p = 0.013$), and chest press (mean difference (SD) of 8.8 (3.5) kg; $p = 0.0002$).

Assessment scores at baseline and visit 2 are summarized in Table 2. There were no significant effects for group, visit, or group by visit interactions for any of the SF-36 or BQ measures (all $p > 0.05$). There was a significant effect of visit for the TMD score on the POMS ($p = 0.023$) in which there was a decrease in TMD from baseline to visit 2, but no effects of group or group by visit interactions (all $p > 0.05$). In post hoc analysis of the TMD score, both groups showed numerical decreases from their respective baselines. Persons with epilepsy that participated in exercise intervention showed a nonsignificant decrease (mean difference (SD) of −5.89 (17.77); $p = 0.35$), and PWE-noE showed a trend toward lower scores (mean difference (SD) of −27.38 (34.54); $p = 0.060$) from baseline to visit 2. Post hoc review of medical records showed that none of the participants had any documented treatment for anxiety or depression before or during study participation.

On the CVLT-II, there were no significant effects of group, visit, or group by visit interactions for the LDFR score (all $p > 0.05$). However, there were significant group by visit interactions for the Learning score ($p = 0.044$) and for d′ ($p = 0.0074$) but no main effects for

Table 1
Baseline demographic and clinical variables for the exercise intervention participants (PWE-E) and no-exercise controls (PWE-noE).

Variable	PWE-E (n = 9)	PWE-noE (n = 8)	p-Value
Age	28.0 (8.0)	28.0 (9.5)	0.77
Sex, female	3 (33.3)	5 (62.5)	0.35
Body mass index	22.5 (13.0)	26.5 (14.2)	0.56
Education, years	14.0 (4.0)	16.5 (2.5)	0.16
Age at epilepsy onset	15.0 (14.0)	16.0 (6.5)	0.60
Illness duration, years	15.0 (6.5)	13.0 (11.0)	0.70
Seizure-free in the past 6 months	6 (66.7)	7 (87.5)	0.58
Number of current ASDs	1.0 (2.0)	1.5 (2.0)	0.83
Number of ASDs ever tried	3.0 (4.0)	3.0 (3.5)	0.96
Montreal Cognitive Assessment	27.0 (4.0)	25.5 (5.5)	0.81

Data reported as median (interquartile range) except for sex and the number of patients seizure-free in the past 6 months, which are reported as frequency (percentage). Antiseizure drugs = ASDs.

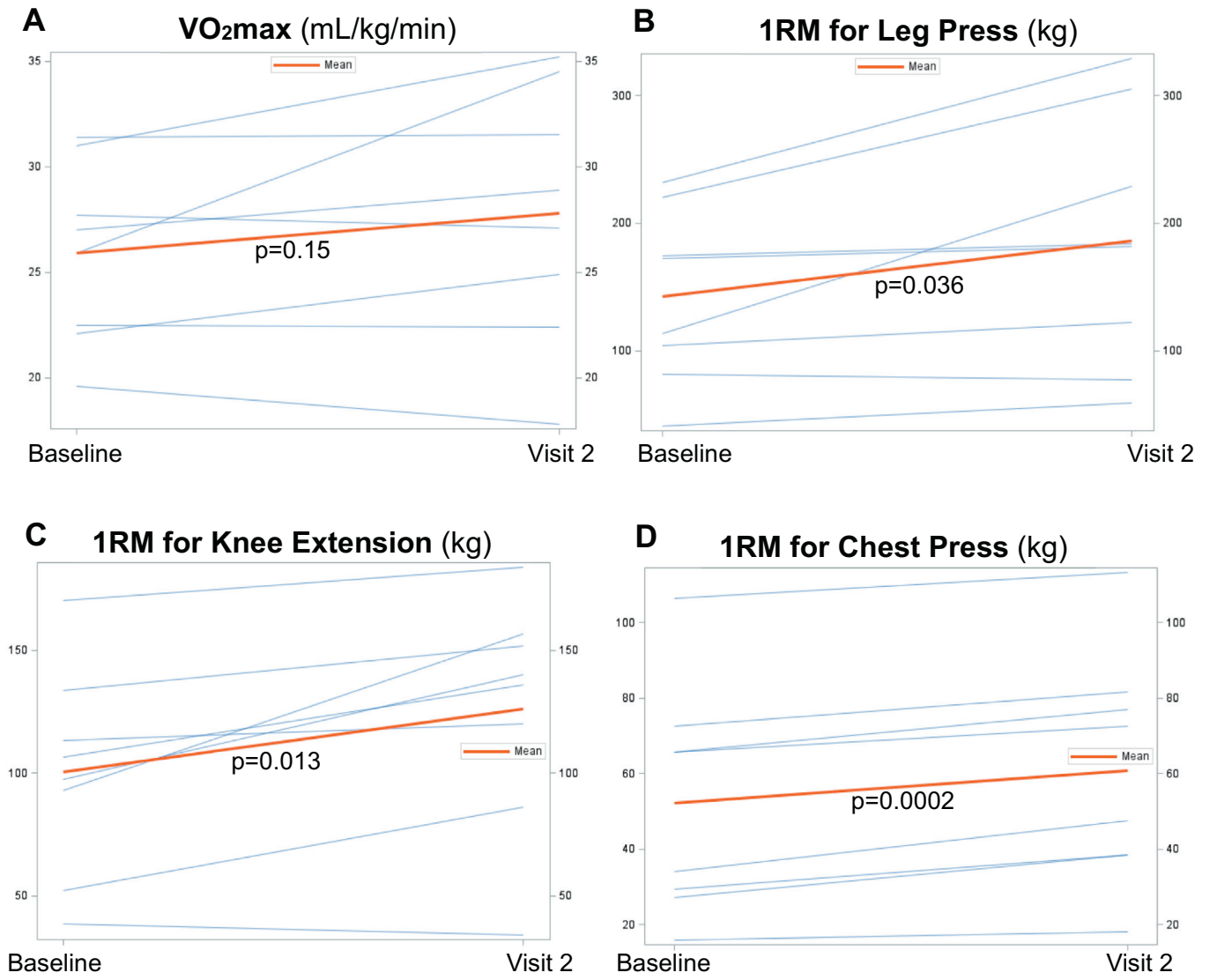

Fig. 2. Exercise test results for the exercise intervention participants (PWE-E) illustrating individual and group mean data. There was a nonsignificant increase in VO_2max (A), while the one-repetition maximum (1RM) weight for leg press (B), knee extension (C), and chest press (D) all significantly increased.

group or visit (all $p > 0.05$) (Fig. 3). Using the F-statistic, the effect size (Cohen's d) for detecting significant group by visit interactions for the Learning score ($F(1) = 4.82$) was $d = 1.07$ and for d′ ($F(1) = 9.56$) was $d = 1.50$, both of which are considered large effects (i.e., $d > 0.80$). Therefore, we would need a sample of 16 patients per group in order to have at least 80% power to detect a significant group by visit interaction at an alpha level of 0.05 (2-tailed) for the Learning score. Since we observed a larger effect for d′, we would need a smaller sample of 8 patients per group in order to have at least 80% power to detect a significant interaction at an alpha level of 0.05 (2-tailed).

In post hoc analysis of the Learning score, both groups showed numerical changes from their respective baselines. Persons with epilepsy

Table 2
Assessment results at baseline and visit 2 for the exercise intervention participants (PWE-E) and no-exercise controls (PWE-noE).

Assessment	Variable	PWE-E (n = 9)		PWE-noE (n = 8)	
		Baseline	Visit 2	Baseline	Visit 2
SF-36	Physical component score	53.2 (5.4)	51.5 (5.3)	55.4 (5.1)	56.7 (3.6)
	Mental component score	49.8 (7.8)	54.2 (12.0)	43.4 (10.6)	44.6 (10.9)
BQ	Occupational physical activity	1.7 (1.4)	1.7 (1.4)	1.8 (1.0)	2.1 (0.8)
	Physical exercise in leisure	2.5 (1.2)	2.4 (1.0)	2.0 (1.0)	2.1 (0.8)
	Leisure and locomotion activities	2.4 (0.5)	2.3 (0.6)	2.2 (0.4)	2.3 (0.4)
	Total score	6.6 (2.3)	6.3 (2.3)	6.0 (1.3)	6.5 (1.1)
POMS	Total mood disturbance score	17.7 (32.4)	11.8 (22.1)	47.8 (35.5)	20.4 (31.8)
CVLT-II	Standard trials 1–5 total Learning score	46.0 (12.4)	53.8 (13.3)	49.9 (10.7)	47.5 (13.1)
	Long-delay free recall score	11.1 (2.0)	11.8 (3.3)	12.3 (2.5)	12.8 (2.4)
	Recognition discriminability, d′	2.9 (0.8)	3.4 (0.6)	3.4 (0.7)	3.1 (0.9)

Data reported as mean (SD). SF-36 — Short Form 36; BQ — Baecke Questionnaire; POMS — Profile of Mood States; CVLT-II — California Verbal Learning Test-II.

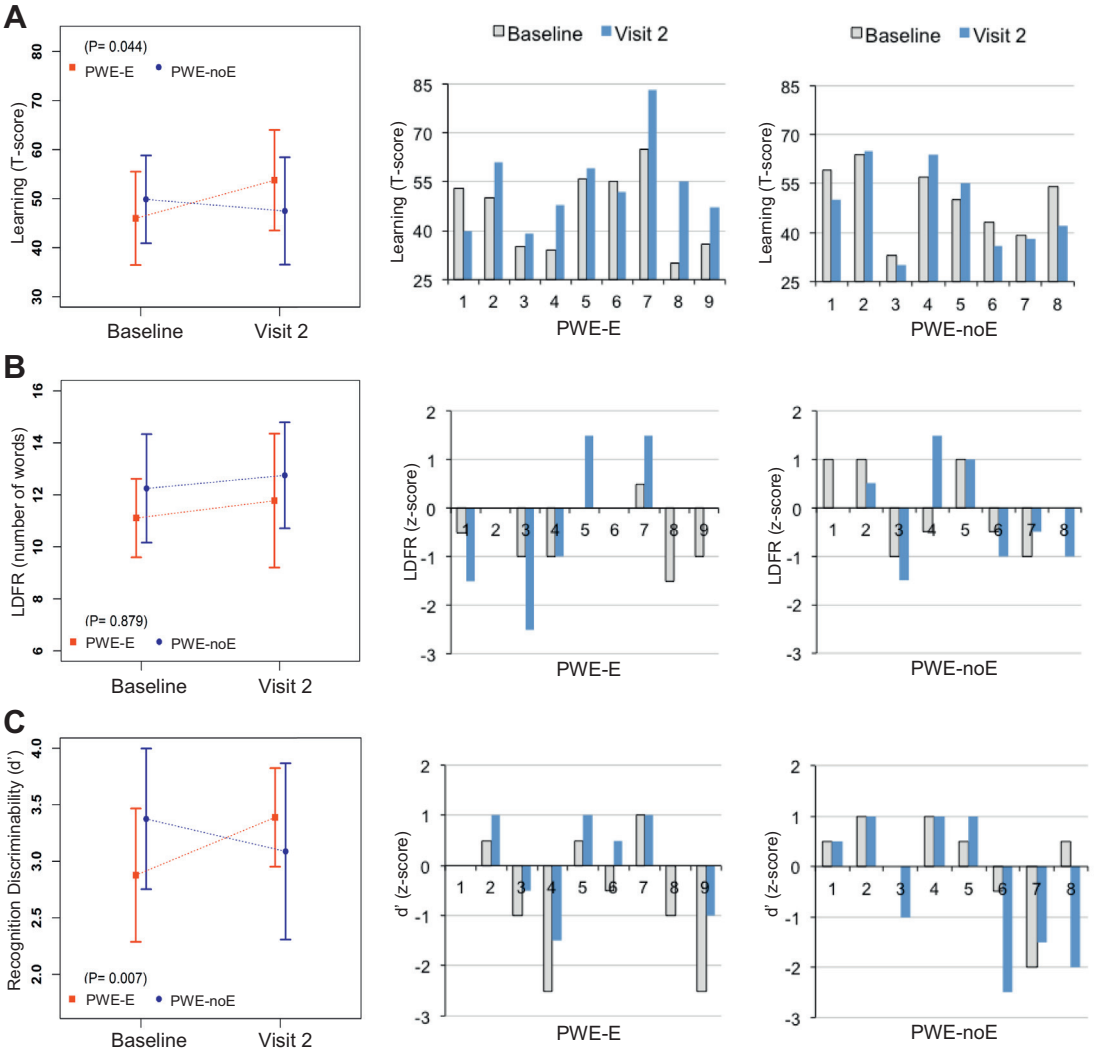

Fig. 3. Changes in verbal learning and memory on the CVLT-II. Repeated measures ANOVA shows (A) a significant group by visit interaction for the Learning score (T-score), (B) no effect for long-delay free recall (LDFR), and (C) a significant group by visit interaction for recognition discriminability, d′. Graphs on the left show mean (SD) for each measure at each visit. Standard scores are shown for each participant in the PWE-E (middle) and PWE-noE (right) groups at each visit. Interpretation of T-score ranges (performance classification) is as follows: 30–37 (mildly impaired); 37–42 (low average); 43–57 (average); 57–63 (high average); 63–71 (superior); 72 and above (very superior). Similarly, interpretation for z-scores (performance classification) is as follows: −2.5 and below (severely impaired); −2.0 (moderately impaired); −1.5 (mildly impaired); −1.0 (low average); −0.5, 0.0, and 0.5 (average); 1.0 (high average); 1.5 and 2.0 (superior).

that participated in exercise intervention showed a trend toward higher scores (mean difference (SD) of 7.78 (11.43); $p = 0.076$) while PWE-noE showed a nonsignificant decrease (mean difference (SD) of −2.38 (6.70); $p = 0.35$) from baseline to visit 2. Similarly, in post hoc analysis of d′, PWE-E showed a significant increase (mean difference (SD) of 0.51 (0.40); $p = 0.0051$) while PWE-noE showed a nonsignificant decrease (mean difference (SD) of −0.23 (0.65); $p = 0.25$) from baseline to visit 2. The PWE-E's Learning performance ranged from "mildly impaired to superior" at baseline and ranged from "low average to very superior" at visit 2 while PWE-noE ranged from "mildly impaired to superior" for both visits (Fig. 3A, middle-right). The PWE-E's performance for LDFR ranged from "mildly impaired to average" at baseline and ranged from "severely impaired to superior" at visit 2 while PWE-noE ranged from "low average to high average" at baseline and ranged from "mildly impaired to superior" at visit 2 (Fig. 3B, middle-right). The PWE-E's performance for d′ ranged from "severely impaired to high average" at baseline and ranged from "mildly impaired to high average" at visit 2 while PWE-noE ranged from "moderately impaired to high average" at baseline and ranged from "severely impaired to high average" at visit 2 (Fig. 3C, middle-right).

3.2. Functional connectivity and verbal memory function

Compared with baseline, at visit 2, PWE-noE showed decreased rsFC between the left hippocampus and both the left superior parietal lobule and cerebellum; PWE-E showed decreased rsFC between the left hippocampus and left superior temporal/supramarginal gyrus (STG/SMG) and decreased paracingulate cortex rsFC to the bilateral anterior cingulate (Fig. 4B). Compared with baseline, at visit 2, PWE-noE showed increased rsFC between the cerebellum and right orbitofrontal cortex while PWE-E showed increased rsFC for the cerebellum to both the left superior frontal gyrus and the angular/middle occipital gyrus (Fig. 4C). Persons with epilepsy that participated in exercise intervention also showed increased rsFC for the thalamus, PCC, and the right and left IPL seeds (Fig. 4C).

Since we observed significant improvements in CVLT-II Learning score and d′ with exercise, we investigated if exercise-induced changes in rsFC were associated with changes in either measure of verbal memory (significant at $p < 0.00625$ after Bonferroni correction for multiple comparisons). There were significant associations between changes in Learning score and changes in rsFC of the paracingulate cortex ($r_S = -0.67$; $p = 0.0033$) and left ($r_S = 0.70$; $p = 0.0019$) and right IPL ($r_S = 0.71$; $p =$

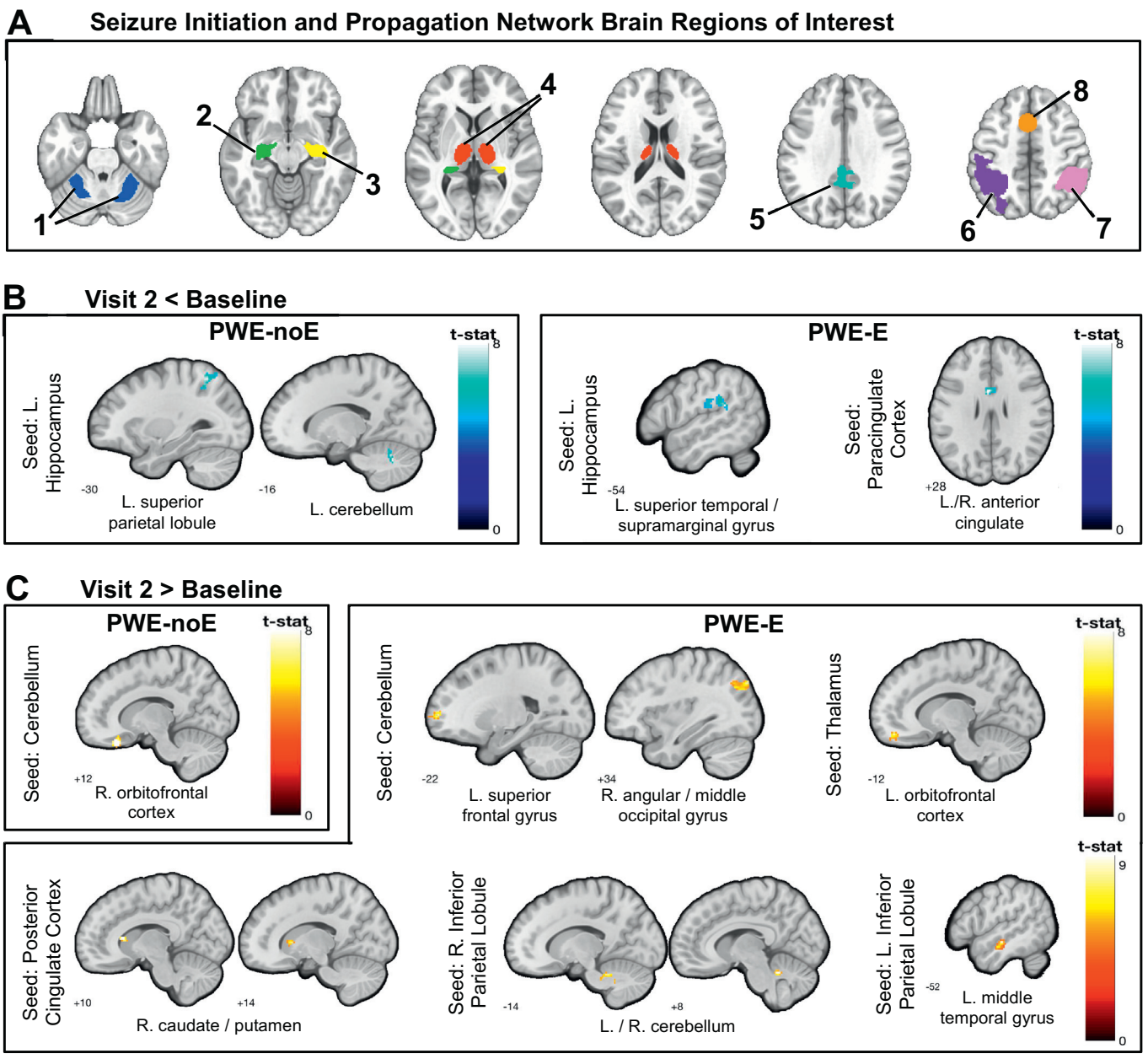

Fig. 4. Seed regions used in resting state functional connectivity (rsFC) analysis and resulting differences between baseline and visit 2 for each group. (A) Regions of interest involved in the seizure initiation and propagation network, 7 of which were defined anatomically (1 — cerebellum; 2, 3 — left and right hippocampus; 4 — thalamus; 5 — posterior cingulate cortex; 6, 7 — left and right inferior parietal lobule) and one being a spherical region of interest (8 — paracingulate cortex) were used as seed regions for resting state functional connectivity. (B) Reductions and (C) increases in rsFC from baseline to visit 2 for the no-exercise control group (PWE-noE) and participants who completed the exercise intervention (PWE-E). Differences are significant at corrected $p < 0.05$. L. = left; R. = right.

0.0015), as well as between change in d′ and change in cerebellum rsFC ($r_S = 0.68$; $p = 0.0025$) (Fig. 5).

4. Discussion

Improvements in fitness, mood, and cognition are well-established benefits of exercise training. Yet, studies investigating exercise in PWE are scarce, and potential epilepsy-specific benefits have received limited attention. Given the prevalence of memory deficits in PWE, and the potential for exercise-induced memory improvement, we piloted a novel and structured supervised exercise program to assess its effects on verbal memory function and brain network functional connectivity. We hypothesized that PWE-E would show exercise-related improvements in verbal memory performance and that exercise-related changes in functional connectivity of SIPN brain regions would be associated with memory improvements. Our results show that not only did exercise training positively affect physical fitness in PWE, it also improved aspects of verbal memory function. We also provide to our knowledge the first evidence in PWE that exercise induces changes in rsFC of SIPN brain regions and that these changes in functional connectivity are associated with memory improvement.

4.1. Feasibility of an intensive exercise intervention in PWE

The combined endurance and resistance training was well tolerated, as all participants completed the 18 sessions with no adverse events. Combined training is known to induce benefits of each mode when performed alone [67,68]. Without evidence in PWE to suggest one mode over the other, and with previous trials having utilized combined training [34,35], we chose to test both tolerability and efficacy of combined

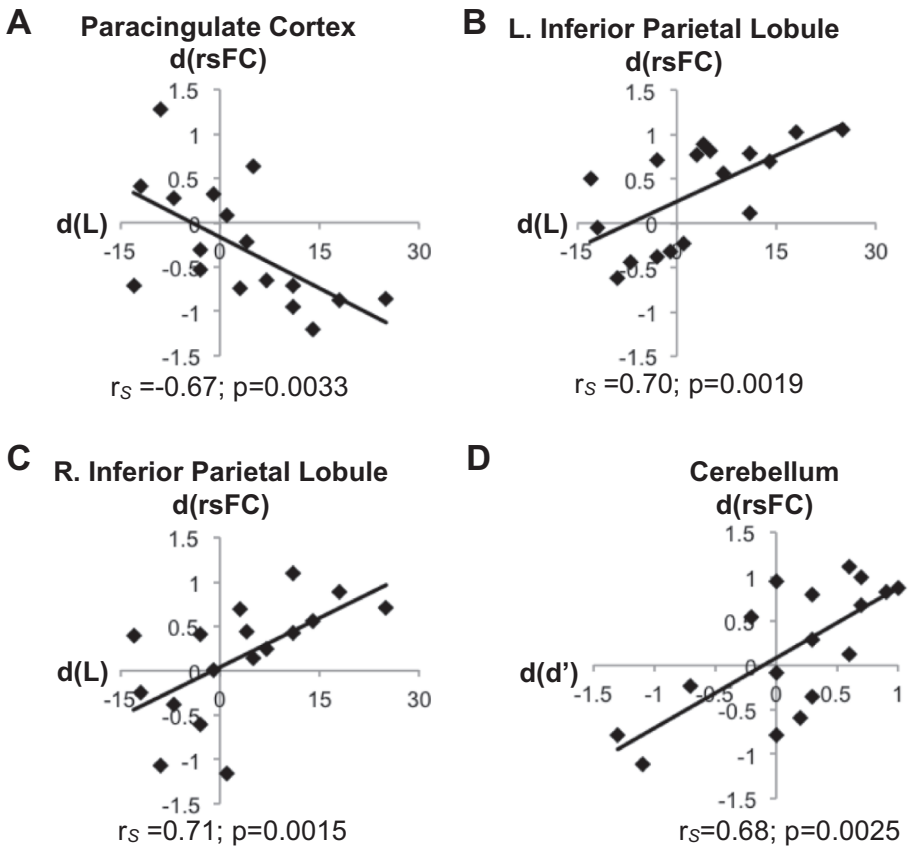

Fig. 5. Relationships between change in verbal memory performance and change in resting state functional connectivity (rsFC). Change in CVLT-II Learning score (d(L); x-axis) was significantly associated with change in rsFC (d(rsFC); y-axis) for the paracingulate cortex to anterior cingulate (A), for the left inferior parietal lobule to left middle temporal gyrus (B), and for the right inferior parietal lobule to cerebellum (C). Change in CVLT-II recognition discriminability (d(d′); x-axis), was only significantly associated with change in rsFC (d (rsFC); y-axis) for the cerebellum to the right angular/middle occipital gyrus (D). All associations are significant at $p < 0.00625$ after Bonferroni correction. L. = left, R. = right.

training. Our findings are consistent with previous investigations both supporting the feasibility of exercise training in PWE and suggesting that exercise does not worsen and may even decrease seizure frequency [23,33–35,69,70].

4.2. Verbal memory and functional connectivity changes in PWE with exercise

Memory deficits are common in PWE, even in those with well-controlled seizures [14,19,20]. The majority of our study sample was seizure-free (6 of 9 PWE-E and 7 of 8 PWE-noE) and comprised mainly of individuals with IGE (7 per group). If we consider just these participants, studies have shown that adolescents with IGE in whom seizures were well-controlled and who were within the normal range of intellectual abilities, performed worse than age-matched healthy controls on tests of nonverbal and verbal attention, word fluency, CVLT-II learning and memory [71], and on short- and long-term memory on the Rey Auditory Verbal Learning Test [19]. Compared with controls, adults with IGE also performed worse on face recognition, word recognition, complex figure recall, and verbal recall [72]. Therefore, despite normal intelligence and well-controlled seizures, children with IGE are at long-term risk for learning and memory impairments that can persist into adulthood. In the present study, we show that PWE can improve their CVLT-II verbal learning and memory performance, specifically their Learning score and recognition discriminability score, with a structured, prescriptive exercise program (Fig. 3).

Our CVLT-II results are consistent with previous randomized control trials showing memory improvements with exercise training [25,26,29]. We show that exercise facilitates encoding of information as evidenced by the increase in Learning score in PWE-E. We also show that exercise facilitates improvement in how encoded information is retrieved with respect to the increase in d′. Recall and recognition are different mechanisms for retrieving information from memory [73]. Since recognition involves retrieval in the presence of a cue, the depth of information processing is reduced and puts less of a load on memory systems than does recall. It should also be considered that recognition discriminability not only represents the total number of target items recognized, but also takes into account recognition of nontarget items (i.e., false-positive errors). Improvements in recognition discriminability may have significant real-world implications. For example, when one's medications are laid out on a table (i.e., cues are presented), it is important to recognize that the orange pill is the correct medication to be taken (i.e., recognition of target item) while the blue pill is not the correct medication (i.e., recognition of nontarget item).

Both groups showed baseline to visit 2 reductions in left hippocampus rsFC to left parietal regions and increases in cerebellum rsFC to prefrontal cortical regions (Fig. 4B–C). In addition to its role in memory function, the hippocampus is also part of the limbic network of brain regions and is able to modulate stress responses [74,75]. The observed change in rsFC may have been due to the corresponding improvement in mood state from baseline to visit 2, since mood and emotional state have previously been shown to influence hippocampal rsFC [76,77]. The cerebellum has been shown to have functional connections to association cortices [78], as well as involvement in language, working memory, social cognition, and emotion processing [79]. Thus, it is plausible that the corresponding rsFC increase between cerebellum and prefrontal cortex in both groups may be attributed to the mood state changes between visits.

Only PWE-E had reductions in paracingulate rsFC with the anterior cingulate (Fig. 4B), which we interpret as specific to the exercise

intervention. The paracingulate seed region was previously shown to have widespread increased rsFC with brain regions including the anterior cingulate cortex with increasing interictal epileptiform discharges (IEDs, an epilepsy biomarker) on EEG [36]. We did not perform EEG on our participants, but others have shown reduction in the number of IEDs in response to exhaustive physical exercise [69,70,80]. This was beyond the scope of our pilot study and is a direction for future investigations. However, the exercise-induced decrease in paracingulate to anterior cingulate rsFC is of significance, particularly since we show that this decrease in rsFC was significantly associated with improvements in the Learning score (Fig. 5A). Paracingulate cortex activity has been shown to play a role in verbal functions [81,82], as well as spatial tests involving executive and working memory functions [83–85]. In a visual/auditory divided attention task, a similar region in the paracingulate/anterior cingulate gyrus interface was activated during fMRI when discriminating speech sounds for high vs. low load conditions [86]. In that study, the results of psychophysiological interaction analysis suggested a modulatory role of this paracingulate/anterior cingulate gyrus region by allocating less attentional resources to speech processing when cognitive load is high [86]. In relation to our study results, the association of decreased paracingulate to anterior cingulate functional connectivity with improved performance on the Learning score is suggestive of a more efficient allocation of attentional resources to perform the verbal memory task.

We also interpreted the rsFC increases observed only in PWE-E to be specific to the exercise intervention. These included increased rsFC for the cerebellum to angular/middle occipital gyrus, and right IPL to cerebellum. Changes in cerebellum rsFC have been previously shown with combined cognitive and exercise training [87]. Furthermore, exercise trials in Parkinson's disease [88] and stroke [89] have shown increased cerebellar activity during motor fMRI with exercise training. As stated above, cerebellum activity has been shown not only for motor function, but also for tasks focused on language, working memory, social processing, and emotion processing [79]. Our own group found that longitudinal changes in cerebellum activity in persons with poststroke aphasia were related to improved language function [90]. Therefore, it is not surprising that we found an increased cerebellar functional connectivity to visual processing and association regions, and vice versa (i.e., rsFC of IPL to cerebellum), with exercise training. Our findings of significant association between changes in cerebellar rsFC and changes in verbal memory performance further support the role of the cerebellum in cognitive functions [91].

There were also exercise-induced increases in rsFC for the thalamus to orbitofrontal cortex, PCC to caudate/putamen, and left IPL to left middle temporal gyrus. Increased thalamus rsFC has been observed with a single exercise session in healthy young adults [92] and after 12 weeks of a walking exercise intervention in persons with multiple sclerosis [93]. Interestingly, the change in rsFC of the thalamus to left middle frontal gyrus was positively associated with change in cognitive processing speed [93]. A recent study has shown significant reductions in rsFC of several brain networks (i.e., default mode network, executive control network, dorsal attention network, and salience network) in healthy older (average age of 65 years) compared with young (average age of 22 years) adults [94]. However, cardiorespiratory fitness in older adults was positively correlated with rsFC in primarily default mode network regions including the PCC and IPL [94]. This is consistent with our result of increased PCC and IPL rsFC in PWE-E that also showed a trend in increased cardiorespiratory fitness with exercise. Additionally, increased PCC rsFC has been observed in exercise intervention trials in older adults [42] and in persons with mild cognitive impairment [95]. The IPL is also part of somatosensory association cortex (BA 7) involved in various functions including visuomotor coordination and attention [96,97] and showed increased functional connectivity with several regions after combined cognitive and exercise training [87]. Further, persons with posterior parietal lobe damage including the IPL were shown to have working memory impairments, particularly with memory retrieval and recognition [98–100]. Thus, our findings of improved verbal memory performance with increased rsFC of the IPL support the role of the parietal cortex in memory function [101]. Taken together, our data are consistent with previous studies showing exercise-specific changes in rsFC, and our findings suggest that exercise-induced changes in rsFC can modulate verbal learning and memory performance. However, these associations were predicated on the combined set of participants who both did and did not participate in exercise intervention. A larger study would allow for investigation of these relationships solely in intervention participants for a more accurate assessment of exercise-specific memory effects.

One may consider that mood state may have influenced memory performance and brain network connectivity, since there is overlap in the brain circuits that mediate mood and memory [74]. For example, stress (via an unpleasant experience) has been shown to disrupt learning and memory performance [102–104] and rsFC [77,105,106]. Previous exercise studies in TRE have shown improvement in emotional/mood states [33] and in psychosocial functioning and QOL [34]. Further, a 12-week randomized controlled trial in PWE with a mixture of individuals who were and were not seizure-free also showed improvement in QOL and reduction in TMD on the POMS in the exercise training group and not in the nonexercise group [35]. In our study, we observed nonsignificant decreases in POMS TMD from baseline to visit 2 in both groups. The reason for the parallel mood state changes is unclear, since none of our study participants had any documented treatment for anxiety or depression either before or during study participation. Thus, it is unlikely that changes in mood state played a role in our results.

4.3. Limitations and future directions

Our study was limited by a small sample size, but it is in line with previous exercise intervention studies in PWE [23,33–35]. The study design was not a true randomization, since participants were able to switch group assignment depending on their availability. This could have potentially biased the patient distribution in the groups, although there were no significant differences in baseline characteristics between groups. Our study was also limited by having a mixture of different types of epilepsy, although the majority in each group was diagnosed with IGE. Coupled with the small sample size, it makes it difficult to discern if cognitive benefit of exercise would be greater in individuals with one type of epilepsy versus another. Our study sample also consisted of individuals who were and were not seizure-free, although the majority was seizure-free for 6 months prior to study procedures. A larger randomized controlled trial is needed for us to address if cognitive benefit of exercise differs between individuals with well-controlled epilepsy and intractable seizures. We were unable to take into account the effects of ASDs or the number of previously used ASDs on cognition or rsFC, given the small sample size and variability of ASDs used among participants, although groups did not differ in the current number of ASDs being taken or in the number of ASDs ever tried, which may also affect cognitive outcome. These will be important to consider in future studies since some ASDs like topiramate and zonisamide have shown associations with cognitive dysfunction while others like levetiracetam have shown cognition-enhancing effects [107–109]. These effects are mitigated somewhat by the within subjects design and the presence of a no-intervention control group that underwent the same MRI and memory assessment procedures at baseline and visit 2. Although two versions of the CVLT-II were utilized to minimize practice effects for our verbal learning and memory testing, we also cannot eliminate this possibility. However, PWE-noE did not show CVLT-II improvement and in the case of their Learning scores and d′ scores, displayed modest score declines, which suggest that PWE-E displayed exercise-induced improvements.

It should be noted that since PWE-noE received no intervention, they were not matched to PWE-E on the number of personal

interactions during the course of the study, and it is possible that this may have influenced some of our observed effects. This methodological limitation should be considered in the interpretation of our findings. However, it is encouraging that our pilot study results are consistent with previous randomized controlled trials of exercise utilizing control interventions (e.g., stretching, toning, or balance exercises) that were matched for personal interactions and showed that the exercise intervention group experienced improvements in memory performance [25,26] and brain network functional connectivity [42,89]. Finally, we do not know how long the memory benefits are sustained after exercise cessation, and we cannot discern if the observed effects are due to the combined endurance and strength training or if each training mode alone would elicit the same effects — a larger randomized controlled trial with multiple intervention arms, including a control intervention, and longitudinal follow-up would be necessary to address these important questions.

5. Conclusions

We conclude that a structured supervised exercise program consisting of intensive endurance and strength training is feasible for adults with epilepsy and that our preliminary data support its efficacy as part of a comprehensive therapy for improving their physical and cognitive health. The findings of this pilot study provide support for a larger randomized controlled trial of exercise for cognitive improvement in PWE.

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Declaration of interests

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