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Title:

Changes in cognition and brain function following 26 weeks of progressive resistance training in older adults at risk for diabetes: A pilot randomized controlled trial

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Key Messages:

- Older adults with prediabetes and/or obesity experience neurocognitive deficits and are at risk of further decline associated with type 2 diabetes.
- In our pilot study, six months of resistance training improved multiple cognitive abilities and brain function in this at-risk population.

Abstract

Introduction: Type 2 diabetes is associated with deficits in cognition and brain health. Individuals with 1 or more risk factors for diabetes (i.e., obesity, prediabetes) already experience some neurocognitive impairment and are at risk for further decline. One way to combat these deficits is through exercise; however, whether resistance exercise can improve these functions in this at-risk group is unknown.

Methods: This study was a pilot randomized controlled trial. Participants were aged 60-80 and had prediabetes (fasting capillary glucose 6.1-6.9 mmol/L) and/or were overweight or obese (body mass index of 25 or above). Participants completed resistance training or balance and stretching exercise (control) thrice-weekly for 6 months. Neuropsychological tests were used to assess cognitive ability, while functional magnetic resonance imaging was used to examine brain activation patterns.

Results: Resistance training led to improvements in task-switching, attention, and conflict resolution, as well as improved patterns of brain activation that may mimic healthy older adults.

Conclusions: Resistance exercise may serve as an effective behavioural strategy to improve neurocognition in older adults at risk for type 2 diabetes. A large-scale powered trial is needed to further explore these findings.

Introduction

Globally, over 55 million people suffer from dementia including Alzheimer's disease (AD) [1]. One of the largest modifiable risk factors for dementia is type 2 diabetes (T2D), defined as having elevated blood glucose as a result of insulin resistance and dysregulation. Individuals with T2D are known to experience both cognitive and functional brain abnormalities. A meta-analysis found that those with T2D have deficits across multiple cognitive domains (e.g., attention, memory, processing speed) when compared to diabetes-free individuals [2]. Further, functional magnetic resonance imaging (fMRI) work shows that people with T2D have reduced neural activation (i.e., blood-oxygen-level dependent (BOLD) signalling) in task-related brain areas compared to healthy controls, correlating with worse cognitive performance [3]. While the relationship between T2D and neurocognitive dysfunction is complex, it may be explained by cardiovascular-related abnormalities seen in T2D, including hypertension, atherosclerosis, and systemic inflammation [4]. Moreover, there is evidence showing that those with T2D exhibit white matter hyperintensities, which are associated with the buildup of amyloid on the arterial walls of the brain [5]. Such hyperintensities may contribute to hyperglycemia in T2D and are linked to cognitive impairments in many domains [5].

Two interrelated diseases that are major risk factors for T2D are obesity and prediabetes; the former is defined as having abnormal fat levels with an associated health risk, while the latter occurs when one's blood glucose is above normal but below the diabetes level. These comorbidities occur frequently in old age when the body undergoes physiological declines due to aging. Older adults experience a natural decline in both cardiovascular abilities and neurocognition with age that can be exacerbated by T2D. Most T2D cases, in fact, occur in older

adults aged 60+ compared to other ages [6]. Given the evidence demonstrating that cognitive and brain deficits occur in T2D, people with obesity and prediabetes, especially late in life, are at high risk of such impairment. Indeed, these at-risk individuals are known to already experience some deficits in neurocognition. For example, a review found that those with obesity have impaired executive function (e.g., response inhibition, working memory) [7]. In a separate study, obesity was associated with atrophy of the hippocampus and frontal lobes [8]. Systemic inflammation and impairments in cerebral metabolism common in obesity may underlie these brain deficits [9], [10]. Similarly, van Bussel and colleagues showed that those with prediabetes display altered functional brain networks [11], and other work demonstrates that cognitive functions including global cognitive ability are disrupted in prediabetes [12]. These deficits may be the result of disruptions in cerebral glucose metabolism seen in diabetes [13]. In addition, studies have shown that the brains of people at risk for diabetes appear older, suggesting that these diseases accelerate age-related decline [14].

Evidently, there is a need for targeted lifestyle interventions to improve cognitive function and brain health in older adults at risk for diabetes. A previous study found that 6 months of aerobic exercise (which is exercise aimed at improving cardiovascular function) resulted in improvements in cognitive function including selective attention among older adults at risk for T2D [15]. However, whether resistance training (RT), defined as exercise intended to increase muscle mass and endurance, would have similar effects in this population, and whether these individuals would improve in brain health as well, is unknown. Nevertheless, RT has been shown to have positive effects among other populations of older adults. For example, a study in older adults with mild cognitive impairment (MCI) found that 6 months of twice-weekly RT

improves memory [16]. In this study, RT also led to increased brain activation in regions involved in memorizing associations (lingual and occipital-fusiform gyri, frontal pole). [16]. In a systematic review of RT interventions, all included studies had improvements in at least one or more cognitive or neurophysiological domain [17]. In these studies, RT led to considerable positive functional brain changes accompanied by improvements in cognition in both healthy and cognitively impaired older adults [17]. These positive changes in neurocognition may be from the release of insulin-like growth factor-1 (IGF-1) from exercise which promotes the growth and survival of neurons [18]. Importantly, RT has also been shown to improve diabetes-related health outcomes for those with T2D, including insulin action and blood glucose regulation [19]. This may be due to increased muscle mass as a result of RT leading to improved glucose uptake in T2D [20].

Despite evidence that RT has positive effects on the brain in older adult populations, research has not yet examined whether this type of exercise can improve cognition and brain function in older adults at risk for T2D. As such, we conducted a pilot randomized controlled trial (RCT) to evaluate the preliminary efficacy of an RT program in this at-risk population. Feasibility outcomes were also of interest in this study to inform future trials and have been reported elsewhere [21].

Methods

Study overview

Details of our study design and sample (including full inclusion and exclusion criteria) have been described previously [21], [22]. Briefly, this study was a 6-month RCT in older adults

93 at risk for T2D. Twenty-four participants were randomly assigned to thrice-weekly RT or
94 balance and tone (BAT; control group) training; the BAT group served to control for possible
95 confounding variables (e.g., commitment to an exercise program). Participants were community-
96 dwelling older adults aged 60 to 80 who were overweight or obese (body mass index (BMI) ≥
97 25) or had prediabetes (fasting blood glucose (FBG; refers to capillary glucose levels measured
98 via a glucometer following 8 hours of fasting) 6.1-7.0 mmol/L based on the World Health
99 Organization's disease criteria [23]) and did not participate in regular exercise (i.e., one or less
100 times per week; thus did not meet the Canadian Society for Exercise Physiology's
101 recommendations of activity) [24] within the past 6 months; this was self-reported. Cognitive
102 and physical assessments were completed at baseline, midpoint (3 months), and trial completion;
103 fMRI using a 3T scanner was completed at baseline and trial completion. Written consent was
104 collected from all participants.
105
106 The 60-minute exercise sessions (both RT and BAT) were instructor-led and held in
107 small groups in-person on campus (2-5 participants). Participants in the RT group performed 2
108 sets of 6-8 repetitions of exercises (e.g., leg press, chest press, bicep curl) targeting major muscle
109 groups (e.g., quadriceps, pectoralis major, biceps) and loading was increased over time when
110 exercises were performed with correct form and without discomfort; all participants reached 80%
111 of their predicted 1-repetition maximum (1RM; maximum amount of load that can be lifted).
112 Predicted 1RM, which takes into account the weight being applied and number of repetitions that
113 can be done comfortably for the participant [25], was calculated in place of true 1RM, as
114 measuring the latter in older adults who do not exercise regularly may be unsafe due to fragility.
115 For this, participants used a weight that they felt comfortable with and were guided by research

personnel to avoid injury. The validated formula used to calculate predicted 1RM was weight ÷ (1.0278 - (0.0278 × Number of repetitions)) [25]. The BAT protocol consisted of balance, stretching, and range of motion exercises with no additional loading; examples of such exercises include standing on one leg, tandem standing, and light ball toss.

Outcome measures

Cognitive function was assessed using the following standardized measures: Stroop Test (condition C – B) to measure selective attention and response inhibition [26]; Trail Making Test (TMT; Part B – A) to measure task-switching [27]; Digit Span Test to measure working memory [28]; Rey Auditory Verbal Learning Test (RAVLT; 20-minute delay) to measure long-term auditory-verbal memory [29]; and the Alzheimer's Disease Assessment Scale–Cognitive 12 (ADAS-Cog 12) to measure various functions implicated in dementia risk (e.g., language, constructional praxis, orientation) [30]. Lower scores indicate better performance for all measures except the RAVLT.

In addition, participants completed an associative memory task during fMRI. For this task (described in detail elsewhere) [22], participants viewed a series of photos and had to recall either faces or scenes (item memory) or faces paired with scenes (associative memory). Participants completed 3 blocks of the task. Task performance was assessed via d prime, a measure of signal detection that accounts for response bias [31]; larger values indicate better performance. Regional patterns of brain activity were assessed during BOLD imaging (TR = 1000, TE = 30, slice thickness =2.5 mm; fMRI analysis described in detail below). T1-weighted images (TR = 2300, TE = 2.98, voxel size =1 x 1 x 1 mm) were also taken for each participant.

In T1-weighted imaging, the signal of fatty tissue is enhanced while the signal of water (fluid) is suppressed [32]. These images are produced by using short Time to Echo (TE) and short Repetition Time (TR) during standard MRI processing steps [32].

Physical function assessments included measures of 1RM, BMI, and FBG. Aerobic capacity and endurance was also measured via the 6-Minute Walk Test (which measures the distance that an individual can walk comfortably in 6 minutes (in meters)) [33], and the Physical Activity Scale for the Elderly (PASE) was used to assess levels of leisure, household, and occupational physical activity outside of the structured exercise program [34]. Demographic information (age, sex, education, income) was also collected.

Data analysis

Since pilot studies are used to estimate possible effects rather than formally testing hypotheses, we used descriptive statistics and estimation (means, standard errors (SEs), medians, confidence intervals (CIs)) to infer the possible size and direction of effects, and thus did not use p-values to report findings [35]. As such, cognitive and physical results are presented as means, SEs, and medians at baseline, midpoint, and trial completion; change over time is presented as means and 95% CIs. This method of presenting data has been used previously in pilot intervention work [36].

Functional MRI analysis was performed using FSL (FMRIB's Software Library; Version 5.0.10). Within FSL, data were preprocessed using FEAT (FMRI Expert Analysis Tool) (motion-corrected [37], registered using FLIRT (FMRIB's Linear Image Registration Tool) [38], and

spatially smoothed with a Gaussian kernel of 5.0 mm full width at half maximum). During first-level analysis, each functional block for each participant was analyzed using only correct response data. Next, second-level fixed-effects analysis was performed to combine all blocks for each participant. Any blocks with head motion > 3 mm were excluded from analysis. This threshold was chosen in order to exclude participants with the greatest amount of motion while ensuring that we maintained the largest sample size possible; we also manually inspected all data to ensure motion during scans did not impact image quality. For the third-level fixed-effects analysis, changes from baseline to trial completion were examined for each participant. Finally, during the 4^{th}-level mixed-effects analysis using FLAME (FMRIB's Local Analysis of Mixed Effects), data from all participants were combined at the group level. Significant clusters of activation were identified using a cluster threshold of $Z > 1.65$, $p = 0.05$. For all levels of analysis, signal contrasts of interest were as follows: item (face or scene) encoding, item recognition, associative (face-scene) encoding, associative recognition, associative > item encoding, associative > item recognition. Regions of interest were created based on identified clusters with significant activation, and percent signal change (PSC) by group across the trial was calculated using FSL's Featquery.

Results

Baseline characteristics of participants (mean age = 68.7 years ± 5.7; 50% female) are shown in Table 1. All participants were overweight or obese at baseline, 4 of whom also had prediabetes (2 in each experimental group). Thirteen participants were randomized to the RT group and 11 to the BAT group. All participants completed the full intervention, apart from 1

BAT participant who dropped out at week 10 (thus did not complete midpoint or trial completion assessments).

At baseline, 2 participants had 1 of 3 associative memory task blocks excluded and 1 participant had 2 of 3 blocks excluded, all due to excess head motion. Similarly, at trial completion, 1 participant had 2 of 3 blocks excluded due to motion. One additional participant was excluded from both timepoint analyses as a result of motion. Altogether, we analyzed fMRI data from 23 participants at baseline (20 with all 3 blocks, 3 with 1-2 blocks) and 22 at trial completion (21 with all 3 blocks, 1 with 1-2 blocks). Within each usable block, some additional task data was missing due to task error or premature withdrawal from the MRI scanner (due to participant discomfort). As a result, 9 participants at baseline and 7 at trial completion were missing small amounts of data from usable blocks. Finally, some cognitive and physical data were also missing due to assessor errors, or were purposely not collected (e.g., 1RM due to participant discomfort) (see Table 2).

Changes in cognitive and physical outcomes over time are presented in Table 2. Participants in the RT group improved in task-switching (TMT) ability compared to the BAT group. Contrarily, those in the BAT group improved in long-term auditory-verbal memory (RAVLT) and working memory (Digit Span Test). Both groups had comparable improvements in selective attention and response inhibition (Stroop Test) at midpoint relative to baseline, however the RT group had greater improvements at trial completion. Additionally, both groups slightly improved on the ADAS-Cog 12 over time, but these changes are not considered clinically significant in the literature [39]. Participants in the RT group saw very small

improvements in item memory (based on d prime), but both groups had small decreases in associative memory performance (Table 3). For physical measures, those in the RT group had larger increases in 1RM and higher PASE scores, as well as larger improvements on the 6-Minute Walk Test at both midpoint and trial completion. No sizable changes were seen in FBG or BMI for either group.

When assessing changes in functional brain activity across the intervention (Figure 1), the RT group had an 0.11% increase in activation in the postcentral gyrus (PoCG) during associative > item encoding compared to the BAT group. The RT group also had an 0.13% increase in activation in the precentral gyrus (PCG) and an 0.11% increase in the posterior middle temporal gyrus (MTG) during associative > item recognition compared to the BAT group. However, those in the BAT group had an increase in activation in the anterior supramarginal gyrus (SMJ) by 0.18% and juxtapositional lobule cortex (JLC) by 0.12% during associative > item encoding when compared to the RT group. No other brain areas were identified as having significant between-group differences in activation for any of the remaining 4 signal contrasts (item encoding, item recognition, associative encoding, associative recognition) at trial completion relative to baseline. Specific clusters that were identified as being significantly more active across the trial are presented in Supplementary Tables 1-3.

Discussion

The current pilot study assessed the preliminary effects of 6 months of thrice-weekly RT on cognition and brain function in older adults at risk for T2D. Cognitive results suggest that RT may benefit certain cognitive domains over others in this population. The largest improvement in

cognition was seen in task-switching performance, of which the size of change parallels what has been found in a previous RT intervention in older adults [40]. Our additional finding that RT improves selective attention and response inhibition also corroborates previous work in older adults. Liu-Ambrose and colleagues found that older adults who performed RT twice per week for 12 months significantly improved in these functions as measured by the Stroop Test [40]. While our study found even greater improvements on the Stroop task than this study did, the frequency/duration of RT differed between studies. Importantly, improvements in these executive functions have meaningful implications to everyday life for older adults, as they are essential to activities of daily living.

Although we did find improvements in executive function following RT, no sizable effects were found for memory. This is in line with a previous study that found no improvements in memory as measured by the Digit Span Test, but did find improvements in executive function, following 12-months of RT in older adults [40]. One possible explanation is the potential use of higher-order cognitive functions to perform RT (e.g., learning new equipment, using attention and concentration during movements), which may strengthen one's executive function ability in itself. Additionally, while we did expect to see improvements in associative memory based on previous research in older adults with MCI [16], it is possible that our sample (those at risk for diabetes) do not experience as large of associative memory impairments, and thus may benefit less from exercise compared to other older adult groups. Cross-sectional studies examining associative memory in our target population compared to both healthy older adults and other clinical populations could help shed light on potential group differences.

An unexpected finding was that BAT training led to some improvements in cognitive function relative to RT. This differs from a previous RT study in older adults that used a similar BAT protocol but found much smaller or no improvements in cognitive function (e.g., on the Digit Span Test) for control participants [40]. Given that our study only measured quadricep muscle strength and included no other measure of muscle function in the BAT group, it is possible that this group improved in muscle strength in an undetected way. Research has shown that balance and stretching exercises can in fact improve muscle strength that may be positively related to cognition [41], [42]. As such, future trials may benefit from including additional tests of muscle function (e.g., lean body mass measures) and further exploring the potential benefits that BAT exercise may have in older adults at risk for diabetes.

While RT did lead to some improvements in cognition, changes in BMI or FBG were not seen. It has been suggested that high-intensity RT, which results in glucose uptake in skeletal muscle, is needed to see such changes. This is important as the majority of insulin-stimulated glucose uptake, which reduces blood glucose levels, occurs in skeletal muscle [43]. Based on this, it is possible that our RT group did not exercise at a high enough intensity to allow for increased glucose uptake over time. Although participants did exercise at 80% of their predicted 1RM, it has been shown that predicted 1RM may underestimate true 1RM values in older adults [44], and thus participants may have been exercising at a lower intensity than intended. Nevertheless, participants in the RT group did improve in aerobic function. Future trials with additional tests of aerobic capacity may help explain this potential relationship.

When examining fMRI outcomes, we did not see significant changes in activation in brain areas that have previously responded positively to RT [11]. However, those in the RT group did have increased activation during associative memory recollection relative to item memory (i.e., associative > item) in the PoCG during encoding and in the PCG and MTG during recognition. Previous research has found greater activation in these areas in younger versus older adults [45]. Similarly, a study showed that healthy individuals have greater activation in the PCG during a memory task compared to patients with AD [46]. Based on these findings, it appears that patterns of increased activation in our RT group may reflect that of younger, healthy adults. While previous studies assessing PSC following resistance training in older adults is limited, one study found an 0.09% increase in brain activation overtime (in the left anterior insula extending into the lateral orbital frontal cortex) [40]. By comparison, our study found larger increases in functional activation across the intervention but in differing brain areas, as mentioned. However, it should be noted that this previous study differed from ours in various ways (e.g., participants were healthy older adults who exercised twice per week for one year, and the cognitive test used during fMRI was a response inhibition task). On the contrary to the RT findings in our study, individuals in the BAT group had increased activation in the SMG and JLC during encoding conditions. Activation in the SMG has previously been implicated in the use of rehearsal strategies during working memory encoding [47], and thus those in our BAT group may have used this strategy to memorize images. Finally, impairments in working memory are associated with less activation in the JLC [48], therefore it is possible that BAT exercise selectively improves memory function (which is in line with our cognitive findings).

There are several limitations to the current study. Firstly, given that this was an underpowered pilot study, results should be interpreted with caution. Furthermore, as we did not use inferential statistics, we cannot conclude that trends (both between-group and across timepoints) are significant, and it remains possible that no effects are present. Additionally, we were unable to control for variables that may affect results. For example, our PASE data suggests that those in the RT group may have benefitted from additional physical activity outside of the exercise program, which may have affected results. We also did not measure diet which could have an effect on cognitive and brain health overtime. A large limitation to our study is that there were missing data (e.g., due to errors in assessment delivery; the use of computerized cognitive tests or additional quality checks may help prevent this in a future large-scale trial). Since we did not use a BMI cut-off that is more inclusive of varying cultures (e.g., Asian cultures in which there is a lower threshold for being overweight or obesity), we may have inadvertently excluded individuals who would classify as being overweight or obese. In addition, we cannot conclude whether our changes in cognition and functional activity are clinically significant, given that a threshold for this (e.g., minimum clinically important difference) is currently unknown. Finally, since we were only able to recruit a very limited number of people with prediabetes (who were all also overweight or obese), we were unable to examine potential differences between these 2 diseases in response to RT. We also acknowledge that there are multiple risk factors for T2D and in this study we primarily focused on obesity. Future research should examine additional risk factors including differences between prediabetes and obesity.

In the future, research should also assess the underlying neurophysiological mechanisms that may explain the benefits of RT on cognition and brain function. For example, at the

molecular and cellular level, RT leads to the release of neurochemicals (including insulin-like growth factor 1) that stimulate the growth of new neurons and blood vessels, as well as strengthen neuronal connections [49]. Resistance exercise also leads to increased cytokines such as interleukin-6 which reduces beta-amyloid levels in the brain that disrupts brain cell function [50]. Understanding these mechanisms may also help link changes in cognition and brain function together as a result of RT. Future studies could also examine potential sex differences in response to RT, as cognitive performance may vary based on hormones and body composition.

Conclusion

Based on our pilot RCT findings, being at-risk of T2D may represent a window of opportunity to improve neurocognition through a lifestyle intervention, and prevent further decline associated with possible progression to T2D. While our trial demonstrates that RT may lead to some important improvements in cognition and brain function in older adults at risk for diabetes, a full-scale powered RCT is needed to further explore these possible effects. Ultimately, this research has the potential to help prevent T2D-related brain complications as well as dementia, and in turn help reduce the global burden that these diseases have.

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Author Contributions

Joyla A. Furlano and Lindsay S. Nagamatsu devised the study. Joyla A. Furlano led the data collection and analysis with support from Becky R. Horst and Lindsay S. Nagamatsu. Joyla A. Furlano prepared the manuscript, with edits and contributions from all authors. All authors approved of the final manuscript draft.

Author Disclosures

The authors declare no conflicts of interest.

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Tables

Table 1: Baseline characteristics of participants.

Variable	Total (*n* = 24)	RT (*n* = 13)	BAT (*n* = 11)
Age, years	68.7 ± 5.7	68.2 ± 6.0	69.3 ± 5.6
Female – n (%)	12 (50)	6 (46.2)	6 (54.5)
Education – n (%)			
High school diploma	2 (8.3)	2 (15.4)	0 (0)
Some college	6 (25.0)	3 (23.1)	3 (27.3)
College/trade degree	3 (12.5)	2 (15.4)	1 (9.1)
Bachelor's degree	8 (33.3)	4 (30.8)	4 (36.4)
Graduate degree	5 (20.8)	2 (15.4)	3 (27.3)
Annual income			
Under $20,000	4 (16.7)	3 (23.1)	1 (9.1)
Over $20,000	20 (83.3)	10 (76.9)	10 (90.9)
FBG, mmol/L	5.3 ± 0.8	5.2 ± 0.9	5.3 ± 0.8
BMI, kg/m^2	31.4 ± 5.0	30.9 ± 3.0	31.9 ± 6.7

Note. All data expressed as mean ± standard deviation unless otherwise indicated.

FBG = fasting blood glucose; BMI = body mass index; RT = resistance training group; BAT = balance and tone group.

Table 2: Cognitive and physical outcomes by group.

Variable	Baseline		Midpoint		Trial completion		Δ Baseline to midpoint		Δ Baseline to trial completion	
	Mean (SE)	Median	Mean (SE)	Median	Mean (SE)	Median	Mean (95% CI)	Median	Mean (95% CI)	Median
RT										
Stroop (C-B)	44.1 (7.2)	43.5	40.2 (4.0)	36.9	36.9 (3.8)	33.4	-3.8 (-18.7, 11.0)	-8.9	-7.2 (-23.5, 9.8)	-9.7
TMT (B-A)	[a]33.7 (5.0)	[a]35.3	[a]25.3 (3.8)	[a]19.4	[c]23.1 (3.6)	[c]23.6	-11.9 (-19.6, -4.1)	-12.3	-9.6 (-21.8, 2.5)	-3.2
Digit Span (F-B)	2.5 (1.1)	3.0	2.2 (0.8)	2.0	3.5 (0.7)	4.0	-0.3 (-3.1, 2.5)	-1.0	1.1 (-1.2, 3.4)	0.0
RAVLT (20-minute delay)	[a]7.0 (1.2)	[a]7.5	8.5 (1.2)	9.0	[c]9.0 (1.6)	[c]10.5	1.2 (-0.9, 3.2)	2.0	1.7 (-0.5, 3.8)	2.0
ADAS-Cog 12	7.1 (1.1)	6.3	5.0 (0.7)	4.5	5.6 (0.9)	4.7	-2.0 (-3.5, -0.5)	-1.7	-1.4 (-2.9, 0.1)	-1.7
1RM	49.5 (3.9)	50.0	61.5 (4.9)	64.0	70.7 (3.5)	69.0	12.0 (4.9, 18.9)	9.0	21.2 (15.8, 26.5)	22.0
FBG, mmol/L	5.2 (0.3)	5.1	5.3 (0.2)	5.1	5.5 (0.2)	5.4	0.1 (-0.3, 0.5)	0.0	0.2 (-0.3, 0.8)	0.3
BMI, kg/m^2	30.9 (0.8)	30.7	30.7 (0.9)	31.3	30.3 (1.1)	30.5	-0.2 (-1.0, 0.6)	0.2	-0.6 (-1.8, 0.7)	0.1
6-Minute Walk Test, m	478.9 (11.9)	465.0	503.0 (20.7)	507.0	513.3 (16.0)	510.0	24.1 (-21.1, 69.3)	32.0	34.4 (-6.7, 75.5)	48.0
PASE	[a]109.5 (10.2)	[a]101.0	135.9 (17.6)	136.7	144.8 (19.0)	138.0	28.0 (-17.0, 73.0)	12.7	35.9 (4.7, 67.1)	PASE
BAT										
Stroop (C-B)	52.4 (6.1)	49.6	43.6 (6.7)	50.7	41.6 (2.8)	41.4	-3.8 (-20.6, 12.9)	-3.3	-5.8 (-13.4, 1.7)	-7.5
TMT (B-A)	40.9 (11.8)	24.0	27.4 (4.0)	28.7	[c]41.5 (6.0)	[c]41.2	-2.4 (-14.4, 9.6)	-0.4	11.0 (-2.6, 24.5)	13.1
Digit Span (F-B)	1.9 (0.7)	2.0	-0.2 (0.4)	0.0	1.0 (0.7)	1.0	-2.3 (-3.9, -0.7)	-1.5	-1.1 (-3.0, 0.8)	-0.5

RAVLT (20 minute delay)	[a]7.0 (1.5)	[a]5.0	[b]12.1 (1.5)	[b]14.0	[c]12.5 (1.1)	[c]14.0	4.3 (0.1, 8.4)	4.5	5.3 (2.1, 8.5)	5.0
ADAS-Cog 12	5.3 (1.1)	5.7	4.1 (0.8)	3.5	3.1 (0.4)	3.2	-0.6 (-2.6, 1.5)	0.0	-1.5 (-3.3, 0.4)	-1.5
1RM	[a]50.4 (6.2)	[a]51.5	[b]64.2 (6.2)	[b]72.0	[b]66.4 (6.8)	[b]64.0	9.1 (-2.6, 20.8)	13.0	9.1 (-3.2, 21.4)	8.0
FBG, mmol/L	5.3 (0.2)	5.6	[b]5.1 (0.2)	[b]5.2	5.6 (0.2)	5.8	0 (-0.5, 0.5)	-0.1	0.3 (-0.3, 0.9)	0.4
BMI, kg/m^2	31.9 (2.0)	29.9	[c]32.0 (2.8)	[c]30.4	32.3 (2.4)	30.7	0.4 (-0.7, 1.5)	0.1	0.0 (-1.2, 1.2)	0.0
6-Minute Walk Test, m	468.8 (25.0)	485.0	[b]454.3 (21.5)	[b]480.0	474.4 (21.7)	484.5	1.2 (-56.5, 58.9)	-5.0	7.4 (-52.6, 67.3)	9.5
PASE	[a]115.9 (15.2)	[a]133.9	97.5 (11.0)	92.3	[b]117.9 (12.0)	[b]116.0	-10.1 (-59.4, 39.1)	15.0	5.2 (-25.2, 35.7)	-4.4

Stroop (C-B) = Stroop Test condition C minus condition B; TMT (B-A) = Trail Making Test part B minus part A; Digit Span (F-B) = Digit Span Test Forward minus Backward; RAVLT (20-minute delay) = Rey Auditory Verbal Learning Test 20-minute delay condition; ADAS-Cog 12 = Alzheimer's Disease Assessment Scale–Cognitive 12; 1RM = one repetition maximum (predicted) – quadricep; FBG = fasting blood glucose; BMI = body mass index; PASE = Physical Activity Scale for the Elderly; RT = resistance training group; BAT = balance and tone group; SE = standard error; CI = confidence interval.

[a] Missing data for n = 1.

[b] Missing data for n = 2.

[c] Missing data for n = 3.

Table 3: Percent change in d prime by group.

Variable	**Baseline**	**Trial completion**	**Δ Baseline to trial completion**
	Mean (SE)	Mean (SE)	Percent change (95% CI)
RT			
d prime (associative)	2.0 (0.2)	1.8 (0.2)	-0.2 (-1.0, 0.5)
d prime (item)	1.5 (0.2)	1.7 (0.3)	0.2 (-0.2, 0.7)
BAT			
d prime (associative)	2.5 (0.8)	2.3 (0.5)	-0.3 (-2.0, 1.3)
d prime (item)	1.0 (0.1)	1.0 (0.1)	-0.1 (-0.4, 0.2)

RT = resistance training group; BAT = balance and tone group; SE = standard error; CI = confidence interval.

Figures

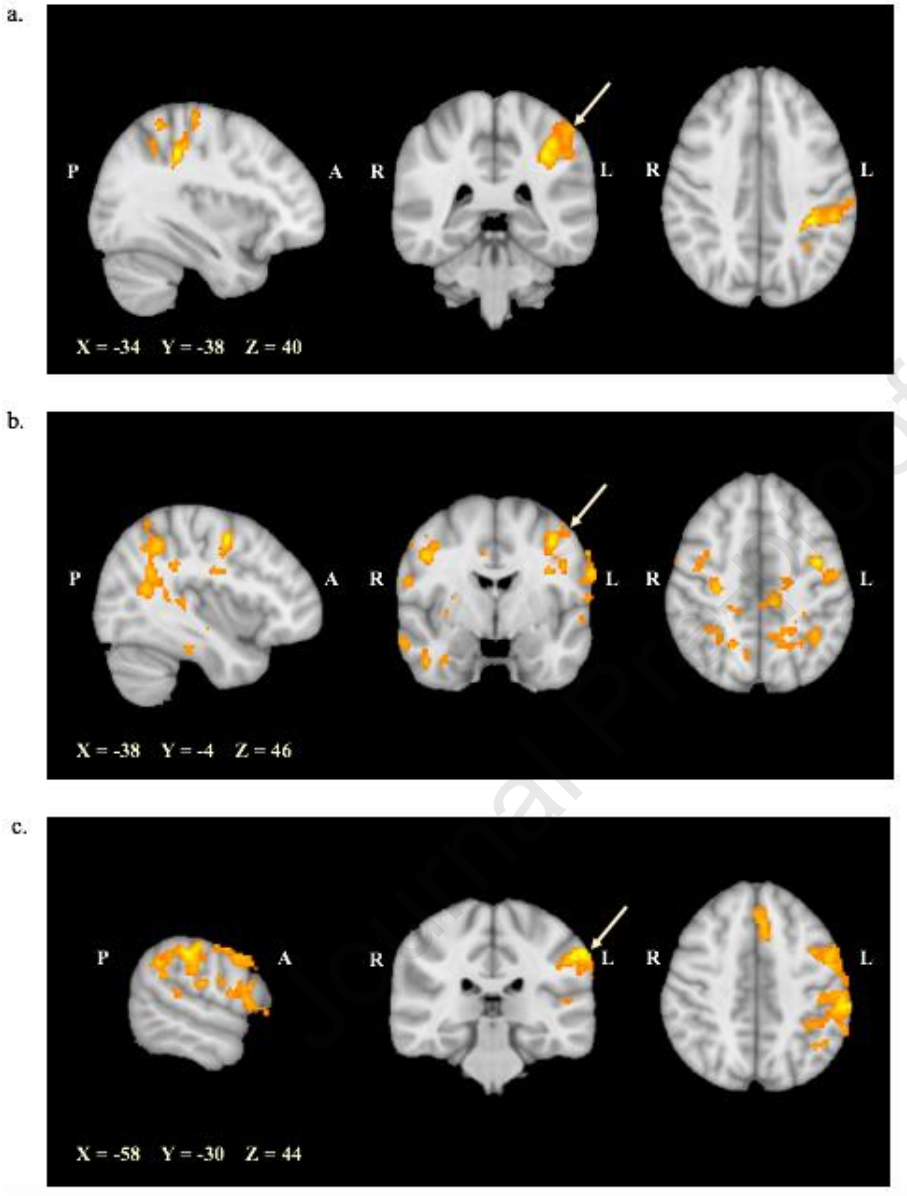

Figure 1: Significant changes in activation during the associative memory task (trial completion > baseline).
a. Resistance training group, associative > item encoding; main activation is found in the left postcentral gyrus (arrow).
b. Resistance training group, associative > item recognition; main activation is found in the left precentral gyrus. (arrow).
c. Balance and tone group, associative > item encoding; main activation is found in the left anterior supramarginal gyrus (arrow).