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Study protocol for the BRAIN Training Trial: a randomised controlled trial of Balance, Resistance, And INterval training on cognitive function in older adults with mild cognitive impairment

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ABSTRACT

Introduction Epidemiological evidence suggests that both poor cardiovascular fitness and low muscle mass or strength markedly increase the rate of cognitive decline and incident dementia in older adults. Results from exercise trials for the improvement of cognition in older adults with mild cognitive impairment (MCI) have reported mixed results. This is possibly due to insufficient exercise intensities. The aim of the Balance, Resistance, And INterval (BRAIN) Training Trial is to determine the effects of two forms of exercise, high-intensity aerobic interval training (HIIT) and high-intensity power training (POWER) each compared with a sham exercise control group on cognition in older adults with MCI.

Methods and analysis One hundred and sixty community-dwelling older (≥ 60 years) people with MCI have been randomised into the trial. Interventions are delivered supervised 2–3 days per week for 12 months. The primary outcome measured at baseline, 6 and 12 months is performance on a cognitive composite score measuring the executive domain calculated from a combination of computerised (NeuroTrax) and paper-and-pencil tests. Analyses will be performed via repeated measures linear mixed models and generalised linear mixed models of baseline, 6-month and 12-month time points, adjusted for baseline values and covariates selected a priori. Mixed models will be constructed to determine the interaction of GROUP × TIME.

Ethics and dissemination Ethical approval was obtained from the University of Sydney (HREC Ref.2017/368), University of Queensland (HREC Ref. 2017/HE000853), University of British Columbia (H16-03309), and Vancouver Coastal Health Research Institute (V16-03309) Human Research Ethics. Dissemination will be via publications, conference presentations, newsletter articles, social media, talks to clinicians and consumers and meetings with health departments/managers.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Balance, Resistance, And INterval Training Trial is a world first: a double-blind, multinational (Australia, Canada), parallel group, randomised controlled trial of two very different and robust experimental exercise interventions (high-intensity aerobic interval training (HIIT) and high-intensity power training (POWER)) for the improvement of cognition in older adults with mild cognitive impairment (MCI).

⇒ This study will provide evidence into the differential systemic and central pathways that may mediate improvements in cognition after 12 months of HIIT and POWER training, compared with a sham-control intervention. The evaluation of changes in brain morphology and function will allow to explore the link to cognitive and functional performance over time.

⇒ Strength of this multicentre trial lie in the rigour of the 12-month exercise intervention. All exercise sessions (active and sham control) will be supervised to ensure that the correct exercise intensity is achieved.

⇒ Primary endpoint data will be collected at baseline, 6 and 12 months (end of intervention period); additional secondary endpoint data will include a yearly follow-up over the 5 years following the intervention period to explore the legacy effect of the intervention.

⇒ We hypothesise that cognition will improve in both HIIT and POWER intervention relative to the SHAM control group and have not powered the study to compare the two active interventions (HIIT vs POWER) directly, which would require a much larger sample size.

It is expected that communication of results will allow for the development of more effective evidence-based exercise prescription guidelines in this population while

investigating the benefits of HIIT and POWER on subclinical markers of disease.

Trial registration number ACTRN12617001440314 Australian New Zealand Clinical Trials Registry.

INTRODUCTION

Dementia is a leading cause of disability and dependence globally.[1 2] Mild cognitive impairment (MCI), defined as objective and subjective cognitive decline with preserved function,[3 4] increases the risk of incident dementia from 1%–2% to 10%–15% annually.[5] Approximately 39% of those diagnosed with MCI in specialist settings and 22% in population studies develop dementia over the subsequent 3–10 years,[6] compared with 3% of the population without MCI at the same age.[7] Lifestyle factors, in particular engagement in physical activity and associated physiological adaptations, are increasingly recognised as important contributants to cognitive health across the lifespan.[8]

Epidemiological evidence suggests that cardiorespiratory fitness (CRF) and cardiovascular (CV) risk profile (eg, adiposity, insulin resistance, inflammation, blood pressure, arterial stiffness) predict cognitive decline and brain pathology.[9–12] Change in CRF is also an independent risk factor for incident dementia and dementia mortality.[13] In a metaregression of exercise intervention studies in healthy adults, change in aerobic capacity was a much better predictor of cognitive gains than exercise volume.[14] This is supported by the only study to date of high-intensity continuous aerobic exercise in MCI,[15] which reported much larger improvements in executive function (ES=0.68) than other studies in MCI,[16] as well as a significant relationship between changes in CRF and changes in cognition. High-intensity aerobic interval training (HIIT) is the most effective exercise to improve CRF and CV risk profile,[17 18] and therefore theoretically may confer the most robust cognitive adaptations as well. Given this superior physiological profile of HIIT, and its demonstrated safety in elderly and clinical cohorts,[17 19] there is strong rationale for testing its efficacy for cognitive improvement in MCI for the first time.

In addition to the relationship of CRF to cognition noted above, epidemiological data also show markedly increased rates of cognitive decline and incident dementia in older adults with low muscle mass or strength.[20 21] Only three trials of progressive resistance training (PRT) have been conducted in people with MCI[22–24] and all have demonstrated significant improvements in cognition. Notably, the Study of Mental and Resistance Training (SMART) trial,[25] the only trial using high-intensity PRT, demonstrated that increases in lower body strength explained 64% of the benefits of PRT on cognition (ADAS-Cog), indicating that robust anabolic adaptations mediated much of the improvement in brain function after PRT. As with aerobic training, high PRT training intensity (working at approximately 80% of peak load capacity) results in the largest physiologic adaptations,[26] thus supporting the use of this training paradigm in studies of cognitive impairment. In addition to the benefits of high loading, PRT performed at high concentric velocity (power training) has been shown to be particularly relevant to older adults due to its contribution to functional independence[27–30] and ability to attenuate the well-known atrophy of type II fibres with ageing underpinning sarcopenia.[31] Although not yet studied for its benefits on cognitive health, high-intensity power training may represent the best strategy for simultaneous improvements in whole-body peak power and strength in older adults,[32 33] functional independence, and potentially cognitive health.

Therefore, the existing literature demonstrates dose–response relationship between fitness and cognitive adaptations in MCI, and suggests that aerobic and resistance exercise work through different pathways (CV vs anabolic adaptations) to improve brain health. This underscores the need to identify the specific components of the CV, hormonal and musculoskeletal systems involved in these training adaptations to optimise the exercise prescription for cognitive improvement in older adults with MCI. No studies have ever studied high-intensity interval training or high-intensity power training for their cognitive benefits, nor examined the differential systemic and central pathways that may mediate improvements in cognition after these training modalities in this cohort (figure 1).

The primary aim of the Balance, Resistance, And INterval (BRAIN) Training Trial is to determine the effects of 12 months of high-intensity aerobic interval training (HIIT) or high-intensity power training (POWER) compared with a sham exercise control group (SHAM) on executive function in older adults with MCI. Primary hypotheses are that both HIIT and POWER training will significantly improve executive function compared with the SHAM control group; the cognitive benefits of POWER (but not HIIT) will be mediated by anabolic adaptations (increased muscle size, strength and insulin-like growth factor-1) and improved morphology, perfusion and function of the posterior cingulate cortex; and the cognitive benefits of HIIT (but not POWER) will be mediated by CV adaptations (increased aerobic capacity and decreased vascular stiffness) and improved morphology, perfusion and function of the hippocampus. Secondary aims of the study are to determine the effect of POWER and HIIT on global cognition and secondary outcomes of cognitive function, CV and vascular profiles, physiological function, disability, functional limitations, sleep quality, physical activity participation, biomarkers of brain pathology and cognitive function, nutritional status and body composition, psychosocial measures and quality of life.

METHODS

Trial design

The BRAIN Training Trial is a multisite, longitudinal, double-blind, sham training-controlled, randomised clinical trial. Trial protocol was prepared in accordance with

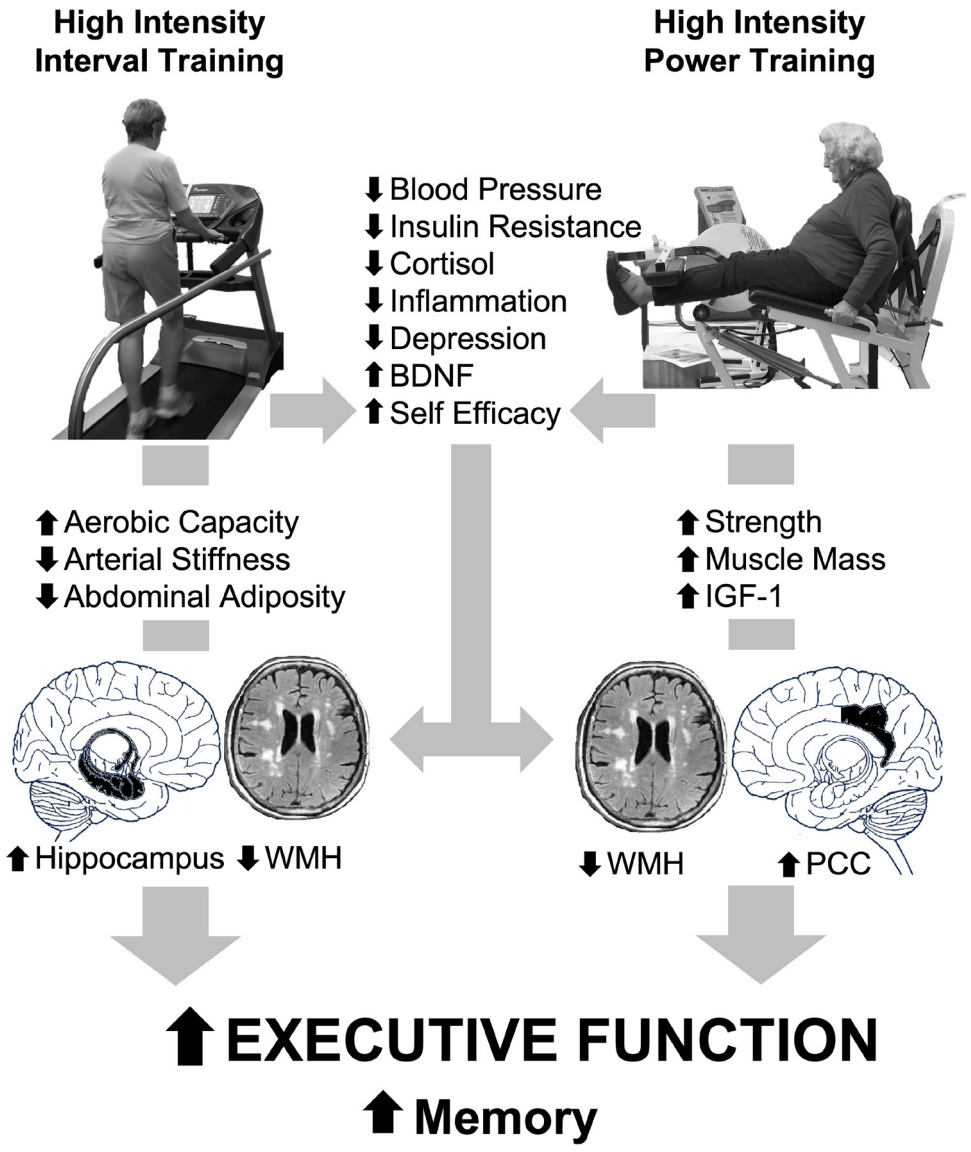

Figure 1 Theoretical model of differential systemic and central pathways that may mediate improvements in cognition after high-intensity interval training and high-intensity power training in older adults with mild cognitive impairment. BDNF, brain-derived neurotrophic factor; IGF-1, Insulin-like growth factor-1; WMH, white matter hyperintensities; PCC, posterior cingulate cortex. This is to confirm that one of the author illustrates the figure.

the Standard Protocol Items: Recommendations for Interventional Trials Statement[34] for the reporting of clinical trial protocols. The trial protocol was prospectively registered (ACTRN12617001440314, online supplemental table 1). The study is conducted at the University of Sydney (USYD), University of Queensland (UQ), and University of British Columbia (UBC) and signed informed consent was obtained from all participants. Participants are from the Greater Sydney Metropolitan Area and Greater Brisbane Area (Australia), and Metro Vancouver Area (Canada). Figure 2 shows the trial design. An overview of the schedule of enrolment, interventions and assessments is presented in table 1.[34] Participant recruitment commenced in January 2018. Five-yearly follow-up assessments are currently underway and the trial is expected to be completed in March 2026. Online supplemental table 2 details the clinical trial support structure. See online supplemental note 1 for additional sources of funding.

Recruitment and screening

The inclusion and exclusion criteria are in table 2.[35–40] Recruitment is from newsletters, information sessions and mail drops at retirement villages and independent living aged care facilities, seniors clubs, community centres, libraries, local health service facilities, community programmes, social media, contact with participants from previous studies who provided consent for such contact, and word of mouth. Recruitment at USYD will be aided by an online recruitment company.

The screening process is presented in figure 3. People interested in the study contact a recruitment officer at each site who provides information about the study and

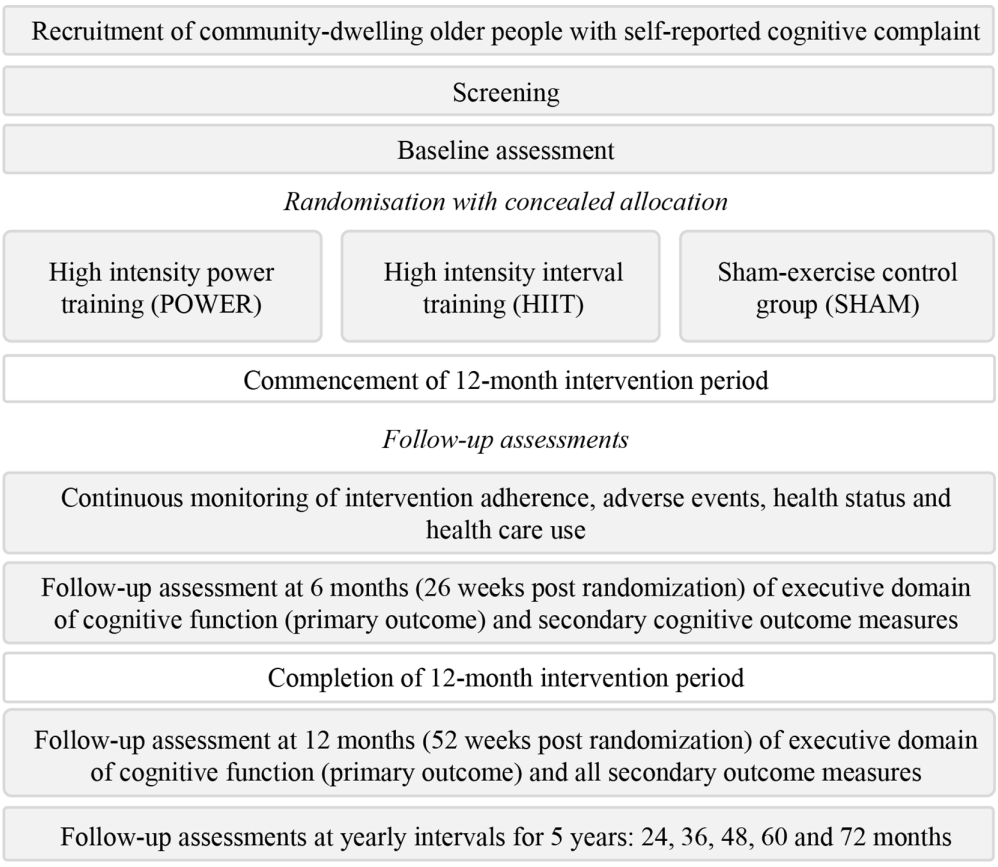

Figure 2 Study design.

screens for eligibility after verbal consent. If screening criteria are met, the participant information statement and consent form are sent via email. An appointment with study personnel for signing the informed consent and performing a face-to-face clinical interview and cognitive screening is made during a second call. Participants who meet inclusion criteria are scheduled to attend physician screening. If eligible after physician screening, the remainder of the baseline cognitive and physical performance tests are completed. If following screening a participant is excluded for an unstable medical condition, acute illness, or abnormal stress test, he/she may enter the study following appropriate treatment and medical review.

Group allocation

Participants are randomised after completion of all baseline assessments, except for the MRI scan which is performed after randomisation but prior to commencement of the intervention by a third person not aware of group allocation. Randomisation is performed using an online randomisation module in the clinical trial management system WebCRF3, hosted by the Norwegian University of Science and Technology. A concealed, computer-generated sequence of permuted blocks with randomly varying block sizes (6 or 8), stratified by gender, age (60-74; ≥75), and study site is generated by the system and masked for trialists. Stratification for gender and age is in anticipation of the greater prevalence of women in the targeted cohort, and potential age effects on adaptation to training. Stratification by study site is carried out to ensure near equal number of participants in each group across study sites. Required strata information is entered into WebCRF3 by the recruitment officer at each site, and group assignment is presented to the participants on the screen. People living in the same household are allocated together to prevent contamination and randomisation takes place after both people have completed baseline assessment.

Blinding

As this is an exercise intervention, trial participants cannot be blinded to group assignment. Participants are informed that they will be randomly assigned to one of three exercise training groups and will be blinded to the investigators' hypothesis as to which are the preferred training groups. All outcome measures collected at baseline, 6-month, and 12-month follow-up timepoints will be obtained by blinded assessors. Annual follow-up assessments over 5 years will be performed by unblinded assessors, as participants will have completed the study intervention.

Study interventions

Training sessions are conducted 2–3 days per week depending on intervention arm and supervised by experienced research assistants (exercise physiologists and physiotherapists). Training logs are used to capture

Table 1 Schedule of enrolment, interventions and assessments*

	Study period					
	Enrolment	Allocation	Post allocation			
Timepoint	Weeks −3 to −1	Week 0	Week 1	Follow-up week 26	Follow-up week 52	5-yearly follow-up†
Enrolment						
Criteria for mild cognitive impairment	All sites			All sites	All sites	All sites
Health status and lifestyle behaviours	All sites				All sites	All sites
Sociodemographic characteristics	All sites					
Informed consent	All sites					
Allocation		All sites				
Interventions						
High-intensity aerobic interval training (HIIT)			◆—	—	—◆	
High-intensity power training (POWER)			◆—	—	—◆	
Sham-exercise control (SHAM)			◆—	—	—◆	
Assessments						
Cognitive function	All sites			All sites	All sites	All sites
Nutritional status/body composition	All sites				All sites	All sites
Cardiovascular profile	All sites				All sites	All sites
Vascular profile	UQ				UQ	
Physiological function	All sites				All sites	All sites
Disability	All sites				All sites	All sites
Functional limitations	All sites				All sites	All sites
Sleep quality	All sites				All sites	All sites
Frailty	All sites				All sites	All sites
Physical activity participation	All sites				All sites	All sites
Biomarkers of brain pathology and cognitive function	USYD, UQ				USYD, UQ	
Psychosocial and quality of life	All sites				All sites	All sites
Perceptions of the intervention					All sites	
Brain MRI			USYD		USYD	
Intervention adherence, adverse events			◆— All sites	—	—◆	
Change in health status and medications			◆— All sites	—	—◆	All sites

*Using the template from Standard Protocol Items: Recommendations for Interventional Trials Group.[34]
†Five yearly follow-up=24, 36, 48, 60 and 72 months.
UBC, University of British Columbia; UQ, University of Queensland; USYD, University of Sydney study.

prescribed and completed training volumes at every session. SHAM training will be delivered in a different room from POWER and HIIT to avoid participants observing the intervention protocols. Participants are asked not to engage in any planned exercise routine involving>150 min of moderate or high intensity exercise while undertaking the study. Table 3[41] details the active and sham-control group intervention protocols. Training of study personnel is described in online supplemental note 2.

High-intensity power training (POWER)

POWER training sessions consist of seven exercises using pneumatic resistance machines. The 'power' variant of

Table 2 Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age≥60	Pre-existing diagnosis of dementia
Criteria for mild cognitive impairment: *Absence of dementia:* Clinical Dementia Rating (CDR) Scale score≤1.0[35] *No or minimal functional impairment due to cognition:* Amsterdam Independent Activities of Daily Living Questionnaire score≥40 rated by informant or participant if no informant available *Subjective memory complaint:* participant or informant reported concerns about their memory based on three questions used in the Sydney Memory and Ageing Study[36] OR they scored 3 ('some change') or greater (over 5 years) on a 5-point Likert Scale on three or more cognitive items on the 20-item Cognitive Change Index (eg, 'remembering things that have happened recently'; 'expressing myself when speaking')[37] *Objective cognitive impairment:* Montreal Cognitive Assessment score>18 and <26[38] Community dwelling, including retirement villages and other independent living senior housing No unstable disease precluding planned exercise* Ambulatory without the assistance of a person Native English speaker, or if classified as from a non-English speaking background, attended some schooling in English Absence of known organic or psychiatric condition affecting cognition Able to see and hear sufficiently to undertake cognitive and physical assessments and participate in planned exercise training Willing to participate in a study which involves attending supervised exercise sessions 3 days per week for 12 months	High-level residential care Non-ambulatory or requiring person to assist when walking Stroke within past 12 months, or ≥2 strokes in a lifetime Transient ischaemic attack within past 6 months Myocardial infarction or cardiac surgery within past 6 months Degenerative neurological disorder Unstable medical condition* or terminal disease Participation in>150 min/week of moderate or greater intensity planned exercise of any kind, PRT or HIIT Rapidly progressive or terminal illness Psychotic illness or substance abuse (DSM-IV) Traumatic brain injury within past year Current major depressive episode (Patient Health Questionnaire-9[39]) score>9 Current alcohol abuse (responded 'yes' to questions 3 and 4 of the CAGE questionnaire for alcohol use,[40] and reported risky drinking behaviour using NHMRC standard criteria) Unrepaired abdominal or other known aneurysm Chronic heart failure NYHA Class IV Seizures (>2 in past 12 months) From a non-English speaking background (NESB) without any education in English Planned move, or planning to be away for 4 or more consecutive weeks during the study period Inability to read and identify objects on a computer screen and draw on a piece of paper due to vision impairment

*Examples of unstable conditions include angina, uncontrolled arrhythmias, hypertension and hyperglycaemia, symptomatic enlarging hernia, acute pulmonary embolism, deep venous thrombosis, recent or unstable fracture, inflammatory or traumatic joint injuries, recent retinal haemorrhage, or detachment/ proliferative retinopathy and so on. Such individuals may become eligible if medical or surgical treatment stabilizes their condition.

resistance training used is characterised by rapid concentric muscular contractions. Participants are instructed to contract concentrically 'as fast as possible' and then 3–4 s of control through the eccentric phase, satisfying the requirements of a power training protocol.[32] Mindful focusing is encouraged by asking participants to focus on the muscles involved in each exercise. During training, rate of perceived exertion (RPE) is rated by both the trainer and the participant on completion of the first repetition of every set. The trainer's rating is used to guide progression when the trainer and participant's RPE do not match. This protocol was chosen as the most appropriate to produce optimal adaptations in muscular strength and power in older adults.[32 33 42] During all sessions, RPE, workload and number of repetitions performed will be documented to monitor protocol adherence.

High-intensity aerobic interval training

HIIT training sessions consist of a single 4-min high-intensity interval working up to 85%–95% of peak heart rate (HRpeak) with additional warm-up and cool-down periods. Peak HR is determined by electrocardiography recorded during the cardiopulmonary exercise test at baseline. Heart rate (Polar M200) and RPE are recorded during the last 10 s of every minute. RPE rating is reported by both participants and trainers. Although percentage of HRpeak is used as a guide for exercise intensity, RPE is used when there is discordance between HR targets and RPE. This is particularly relevant for participants taking beta-blocker medications who will likely be guided by lower HR ranges, reflective of their lower HR peak during maximal exercise testing. The trainer's rating is used to guide progression when the trainer and participant's RPE do not match. During all sessions, RPE and HR will be documented to monitor protocol adherence.

Sham-exercise control group

SHAM sessions will be conducted similarly to what older adults anticipate receiving in senior group exercise classes, and include stretching, seated and standing callisthenics and pseudo balance exercises designed so as not to notably increase HR, aerobic capacity, muscle strength or balance due to emphasis on low intensity and minimally progressive exercises. This group will also serve to control

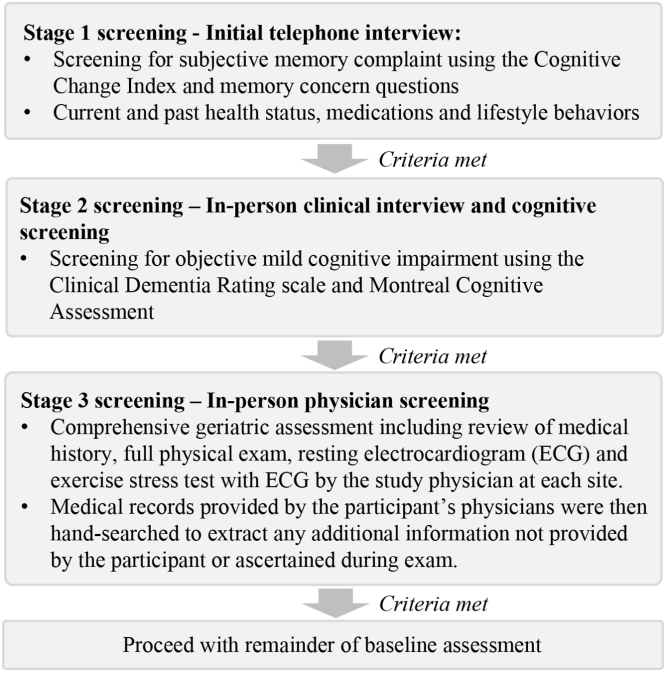

Figure 3 Screening procedure.

for confounding variables such as social interaction and changes in lifestyle secondary to the study. Furthermore, in contrast to strength training and aerobic activity, such a regimen has been shown recently to have no effects on brain volume in older adults.[23 43]

Outcomes

Outcomes will be assessed at baseline, 6 and 12 months (end of intervention period). Five-yearly follow-up assessments will also be performed. Each assessment timepoint comprises four facility-based visits of approximately 4 hours each. In addition, participants from USYD and UQ sites will attend a fifth visit to undergo a brain MRI scan and vascular assessments, respectively. Testing sessions will end prematurely if participants show signs of fatigue and make up sessions scheduled accordingly. Online supplemental table 3 presents an example of the assessment schedule. Participants will be informed of preparation requirements for the assessments, which will be checked prior to the assessments being conducted (see online supplemental note 3).

Primary outcome

Executive domain of cognitive function

The primary outcome is change in executive domain of cognitive function (table 4).[44–48] The executive domain score will be calculated from a combination of computerised (NeuroTrax)[44] and paper-and-pencil tests: NeuroTrax Stroop Interference Test, NeuroTrax Go-No-Go Test, NeuroTrax Catch Game, Trail Making Test (TMT) Part A and B (TMT-B minus TMT-A),[46] Category Fluency Test,[47] and Wechsler Adult Intelligence Scale 4th Edition (WAIS-IV) Matrix Reasoning Test.[48] Individual test scores will be converted to standard scores (z-scores) using the means and SD of the cohort at baseline as the reference sample for each assessment occasion. The executive domain z-score will then be calculated by first averaging the z-scores of the index tests for the domain, and restandardising that average z-score using the means and SDs of the sample at baseline, for each assessment occasion.

Secondary outcomes

Cognitive function/status

Secondary outcomes of cognitive function are shown in table 5.[35–37 44–46 48–51] A composite measure of global cognition and individual cognitive domains will be computed using z-scores as described above. Clinical cognitive status will be assessed via the Clinical Dementia Rating scale[35]; subjective memory complaint will be assessed via the Cognitive Change Index[37] and a set of questions developed to measure subjective memory complaint.[36] Change in executive domain of cognitive function at 24, 36, 48, 60 and 72 months follow-up will also be a secondary outcome measure. See online supplemental table 4 for a description of the tests used to calculate secondary domains of cognitive function.

Physical health and functional status

Physical health and functional status are assessed across 10 domains: nutritional status and body composition, CV profile, vascular profile, physiological function, disability, functional limitations, frailty, sleep quality, habitual physical activity level and biomarkers of brain pathology and cognitive function (see online supplemental table 5).

Psychosocial and quality of life

Psycho-social well-being and quality of life are assessed via the Geriatric Depression Scale,[52] Duke Social Support,[53] Oxford Happiness Questionnaire,[54] Attitudes to Ageing Questionnaire,[55] Toronto Empathy Questionnaire,[56] Core Self-Evaluations Scale,[57 58] Ewart's Self-efficacy Scale,[59] Iconographical Falls Efficacy Scale,[60] Outcome Expectancy Questionnaire, and the Physical and Mental Health Short-36 Summary Scales[61] (see online supplemental table 6). Perceptions of the intervention is assessed using semistructured interviews with participants randomised to POWER and HIIT (see online supplemental note 4).

Brain imaging

MRI data are acquired at baseline and 12 months follow-up in participants from the USYD study site using a 3.0T GE DiscoveryTM MR750w Wide Bore MRI scanner (GE Healthcare, Milwaukee, Wisconsin, USA) with a 32-channel Nova Head Coil and a software version of DV26.0_R01_1725.a, located at Macquarie Medical Imaging, New South Wales, Australia. A comprehensive set of imaging sequences is administered to the participants after screening for contraindications. Imaging derived phenotypes will include brain volumetric measures, integrity of white matter microstructures, functional connectivity, measures of brain vascular burdens and cerebral blood flow. Summary and detailed scanning parameters are described in online supplemental tables

Table 3 Active and sham-control group intervention protocols

Exercise modality and equipment	Frequency; duration; supervisory ratio	Volume	Intensity and progression
High intensity power training group (POWER)			
Seated leg press, seated chest press, knee extension, seated row, knee flexion, triceps extension, hip abduction. Equipment: *USYD and UBC Study sites:* Digital K400 Keiser pneumatic resistance machines (Keiser Sports health Equipment, Fresno, California). *UQ Study site:* HUR SmartTouch pneumatic resistance machines.	2 sessions per week; 60–90 min per session; 1 trainer to 1–4 participants	24 repetitions per exercise prescribed as 3 sets of 8 repetitions or 6 sets of 4 repetitions to avoid fatigue and maintain form and intensity. Ten seconds of rest between repetitions, and 2–3 min of rest between sets.	Sessions 1–5 include familiarisation, 1RM testing, and increasing in target intensity from 50%, 60%, 70% 1RM in each successive session. From session 6 onwards, intensity set at 80% of the most recently measured 1RM (or RPE 15-18/20 when strength reassessment not feasible) and progressed each session by approximately 3% guided by RPE 15-18/20), and 1RM repeated every sixth session throughout the 12-month intervention.
High-intensity aerobic interval training group (HIIT)			
Treadmill walking. Recumbent stepper or bike if unable to safely walk on a treadmill. Equipment: *USYD study site:* Spirit Fitness XT685 Corporate Treadmill (Spirit Fitness, Jonesboro, Arkansas) and Spirit MS300 Semi-Recumbent Medical Stepper (Spirit Fitness). *UQ Study site:* LifeFitness 95Te Treadmill, h/p/cosmos pulsar 3p Treadmill and T4r NuStep recumbent cross trainer. *UBC Study site:* Bodyguard T360 Treadmill (Bodyguard Fitness, Saint-Georges, Quebec) and Bodyguard T320 Treadmill (Bodyguard Fitness). All sites: Polar M200 wrist worn heart rate monitors (Polar Electro, Kempele, Finland).	3 sessions per week*; 15 min per session; 1 trainer to 1–2 participants	Total exercise time: 15 min ► 8 min warm up ► 1×4 min interval ► 3 min cool down	Sessions 1–3 serve as familiarisation, with time spent at the target 85%–95% HRpeak increasing from 30, 60, to 90 s in each successive session. From session 4 onwards, 120 s are spent at target intensity 80%–95% HRpeak. *Warm up:* 8 min at 60% HRpeak *1×4 min interval:* ► Minute 1: 70%–80% hour peak (RPE 13-14/20) ► Minute 2: 80%–85% hour peak (RPE 14-15/20) ► Minute 3 and 4: 85%–95% hour peak (RPE 15-17/20 Intensity progressed each session using RPE and modified by adjusting treadmill incline and speed and reducing hand support.
Sham exercise control group (SHAM)			
Stretching, seated and standing callisthenics, pseudo balance exercises. Pseudo balance exercises were performed with hand support. *Equipment:* very light resistance bands, chairs, handrail, field markers, different sized balls, floor mats.	2 sessions per week; 30 min per session; 1 trainer to 4–6 participants	Total exercise time: 30 min including 5 min warm-up and 5 min cool-down.	Low intensity, minimally progressive exercises.

RPE, Ratings of perceived Exertion Borg Scale[41]; 1RM, one repetition maximum.
*Participants randomised to HIIT who are unable to attend 3 training sessions per week are offered to perform two training protocols on 1 day, with a 30-min break between training bouts, and the third one on another day.

7 and 8. MRI processing plans are described in online supplemental note 5.

Assessment of adherence

Attendance will be quantified as the number of sessions attended of the total number of sessions offered, reported as a percentage (%). Reasons for missing sessions will be recorded. Adherence to POWER and HIIT interventions will be calculated based on the participant's ability to adhere to the prescribed training volume expressed as both absolute and relative prescribed and completed training volumes. Global adherence to the POWER and HIIT interventions will be assessed as≥70% attendance at sessions where training was at the prescribed intensity and volume (POWER: 24 repetitions per exercise at≥80% 1 RM; HIIT: 4-min interval with average HRpeak for end of minutes 3 and 4 of ≥85%HRpeak or RPE≥15/20).

Table 4 Primary outcome measure

Executive domain of cognitive function	
Outcome measure	**Description**
NeuroTrax Go-No Go Response Inhibition Test[44 45]	A series of large coloured stimuli are presented at pseudorandom intervals. Participants are instructed to respond as quickly as possible by pressing a mouse button if the colour of the stimulus is any colour except red, for which no response is to be made. *Outcome measure:* composite score((accuracy/RT) *100).
NeuroTrax Stroop Interference Test[44 45]	The Stroop is a well-established test of response inhibition. The NeuroTrax Stroop test consists of three levels. Participants are presented with a pair of large coloured squares, one on the left and the other on the right side of the screen. In each level, participants are instructed to choose as quickly as possible which of the two squares is a particular colour by pressing either the left or right mouse button. First, participants are presented with a general word in coloured letters. In the next level, participants are presented with a word that names a colour in white letters. In the final level (the Stroop interference level), participants are presented with a word that names a colour, but the letters of the word are in a colour other than that named by the word. The instructions for the final level are to choose the colour of the letters, and not the colour named by the word. *Outcome measure:* composite score level 3 (colour vs meaning).
NeuroTrax Catch Game Test[44 45]	The Catch game is a novel screen that assesses psychomotor function. Participants must 'catch' a rectangular white object falling vertically from the top of the screen before it reaches the bottom of the screen. Mouse button presses move a rectangular green 'paddle' horizontally so that it can be positioned directly in the path of the falling object. The test requires hand-eye coordination, scanning and rapid responses. *Outcome measure:* total score (weighted accuracy).
Trail Making Test (TMT) A & B[46]	Individuals are asked to draw lines connecting consecutive numbers (TMT-A), and numbers and letters (TMT-B) alternating between the two sequences, as quickly as possible. TMT-A and TMT-B measure attention, processing speed, and visual search, while TMT-B additionally assesses working memory, and set switching, an executive function. The mental flexibility, an executive function. The difference score (TMT-B – TMT-A) is thought to be a relatively pure indicator of executive control abilities. *Outcome measure:* time to complete TMT-B (ms) minus time to complete TMT-A (ms).
Category Fluency Test[47]	Category Verbal Fluency measures speeded verbal production of animal names (in 1 min) from semantic memory. Performance involves executive control abilities including effortful initiation, monitoring, strategic search and inhibition. *Outcome measure:* total correct score.
WAIS-IV Matrix Reasoning test[48]	Visual pattern completion and analogy problems in which participants select item that completes the array. Assesses visual reasoning, a component of executive function involving visual perception, organisation, and synthesis of visual spatial information. *Outcome measure:* total score.

Sample size calculation

The study is powered for the primary hypothesis that both POWER and HIIT will improve Executive function domain relative to the control group. Our sample size calculations (estimated at 70 participants per group for a total sample size of 210 across the 3 sites) will allow us to demonstrate a relative ES of 0.48 (POWER vs Control and HIIT vs Control) assuming alpha less than 0.05 and beta of 0.2. The ES is obtained from the only two published studies of high-intensity progressive resistance training (SMART[23]) or vigorous intensity aerobic exercise (Baker[15]) reporting executive function changes in older adults. Relative ES for executive function in the PRT trial at 6 months was+0.3,[23] and for vigorous intensity aerobic exercise at 6 months was+0.68 (average=0.49 relative ES for these comparisons).[15] Sample size has not been inflated for loss to follow-up, as we will perform intention-to-treat analyses including all randomised participants irrespective of dropout or adherence. We do not intend to compare POWER to HIIT as we hypothesise both to be effective; therefore, the comparisons are for intervention versus control only. We believe that this is conservative for several reasons: (1) BRAIN study intervention period is twice as long as in SMART (12 months vs 6 months), (2) BRAIN intervention uses high-intensity power training with mindful focusing which is potentially more effective than slow velocity PRT (used in SMART), (3) BRAIN HIIT intensity at 85%–95% peak heart rate is more intense than vigorous intensive aerobic exercise at 75%–85% peak heart rate (used in Baker's study), (4) the SHAM control group in BRAIN (2 days/week of low intensity non-progressive pseudo balance, seated and standing callisthenics) is less stimulating than the SMART control group (3 days/week callisthenics plus 'sham cognitive' training). We anticipate less of an improvement or even a decline in the BRAIN SHAM control group at 12 months compared with the SMART control group.

Statistical analysis

All data analysis will occur without knowledge of intervention assignment. An intention-to-treat analytic strategy has been designed with statistician consultation, inclusive of all participants randomised, regardless of dropout. We will analyse all outcomes via LMM or GLMM with

Table 5 Secondary cognitive and functional outcome measures

Outcome measure	Description
Global cognition	Composite measure of global cognition is calculated by averaging the z-scores of all cognitive domains (executive, memory, attention/ working memory, visual spatial, verbal function, information processing and motor skills), and then transforming it to a z-score using the whole sample at baseline.
Secondary domains of cognitive function	
Memory domain	
NeuroTrax Verbal Memory test[44 45]	*Outcome measures:* immediate recognition, total (average) accuracy (%); delayed recognition, accuracy (%).
NeuroTrax Non-Verbal Memory test[44 45]	*Outcome measures:* immediate recognition, total (average) accuracy (%); delayed recognition, accuracy (%).
Hopkins Verbal Learning Test Revised[49 50]	*Outcome measures:* total learning score (sum scores of trials 1+2+3); delay recall (trial 4 score).
Attention/working memory domain	
NeuroTrax Go-No Go test[44 45]	*Outcome measures:* response time (ms) (average); response time standard deviation (ms).
NeuroTrax Stroop Interference test[44 45]	*Outcome measure:* no interference, word meaning (level 2) and response time (ms) (average).
NeuroTrax Staged Information Processing test[44 45]	*Outcome measures:* single digit, slow speed (level 1.2), response time (ms) (average); single digit, fast speed (level 1.3), composite score ((accuracy/RT)*100).
WAIS-IV Digit Span Test[48]	*Outcome measures:* total forward score; total backward score.
Visual-spatial domain	
NeuroTrax Visual Spatial Processing test[44 45]	*Outcome measure:* accuracy (%).
Language/ verbal function domain	
NeuroTrax Verbal Function test[44 45]	*Outcome measure:* rhyming, accuracy (%).
Information processing speed domain	
NeuroTrax Staged Information Processing test[44 45]	*Outcome measures*: single digit, slow speed [1.1], composite score ([accuracy/RT]*100); single digit, fast speed [1.3], composite score ([accuracy/RT]*100); 2-digit arithmetic, slow speed [2.1], composite score ([accuracy/RT]*100); 2-digit arithmetic, medium speed [2.2], composite score ([accuracy/RT]*100).
WAIS-IV Coding test[48]	*Outcome measure:* total score.
Trails Making Test form A[46]	*Outcome measure:* time taken to complete Trails form A (ms).
Motor skills domain	
NeuroTrax Finger Tapping test[44 45]	*Outcome measures:* inter-tap interval (ms) (average); tap interval standard deviation (ms).
NeuroTrax Catch Game test[44 45]	*Outcome measure:* time to make first move (ms) (average).
Clinical cognitive status	Assessed using the Clinical Dementia Rating Scale (CDR).[35] A commonly used clinical tool for the global assessment of dementia severity. Completed by a clinician after synthesising information obtained from the patient, informants and any other sources.
Subjective memory complaint	Assessed using the following instruments: 20-item Cognitive change Index (CCI)[37] and a set of three questions developed to measure subjective memory complaint including having noticed memory difficulty and concern level around this.[36]
Functional impairment due to cognition	Assessed using the Amsterdam Instrumental Activity of Daily Living Questionnaire (A-IADL-Q).[51] Scores attained for instrumental activities of daily living (IADL) related to cognitive deficit only will be used for this outcome. The A-IADL-Q is an adaptive and computerised questionnaire designed to assess impairments in IADL in (early) dementia. Reported by informant (or participant if no informant available).

repeated measures as appropriate to the distribution of the data of baseline, 6-month and 12-month time points. Fixed effects specified will include GROUP, TIME and GROUP × TIME, stratification variables (age, sex, study site) and education, as well as any found to be prognostic of the dependent variable of interest. Mixed models will

be constructed to determine the interaction of GROUP × TIME (ie, POWER vs Control and HIIT vs Control). A random slope and intercept will also be specified. We hypothesise that cognition will improve in both POWER and HIIT relative to SHAM in these models and have not powered this as a non-inferiority study to compare the two active interventions (POWER vs HIIT) directly, which would require a much larger sample size. Therefore, primary post hoc comparisons will include the effect of intervention versus control (ie, POWER vs Control and HIIT vs Control), while any comparison of POWER versus HIIT will be considered a secondary outcome. We will report estimated marginal means (95% CIs), mean differences between groups and Hedges' bias corrected effect sizes (95% CIs) for all primary and secondary outcomes. A two-tailed alpha level of 0.05 will be used to determine statistical significance for the primary outcome of executive function as well as the above prespecified secondary outcomes. Unspecified secondary outcomes will undergo Bonferroni adjustment for multiple comparisons. Mediation analysis will be conducted to test the hypotheses that CV and muscular fitness and other central and systemic adaptations differentially mediate the cognitive benefits of POWER and HIIT. Clinical meaningfulness will be assessed in accord with available data on the expected annual rates of change and minimal clinically important differences in this cohort for all outcomes where these differences have been defined. Secondary exploratory analyses will include per protocol and complete case analysis based on attendance rate or adherence to the training protocol.

Data management and confidentiality

The study is being conducted in compliance with the conditions of ethics committee approval, the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research and the Handbook for Good Clinical Research Practice. Information collected from participants is in a reidentifiable form and any information collected for, used in, or generated by this project will not be used for any other purpose. All data are stored using identification codes. Electronic copies of all information are stored in a secure server at USYD and in REDCAP Digital. Data entry is conducted by trained staff and data quality will be assessed before statistical analysis. All missing and ambiguous data will be queried. Individual data sets will be checked at regular intervals and discrepancies highlighted for review by the Trial Management Group. Tissue samples will be identified by participant number using barcodes and stored in a secure location.

Patient and public involvement

No patient was involved in the design of this study.

Safety monitoring

Adverse events (AEs) are monitored using weekly questionnaires with proxy information obtained whenever necessary to minimise missing data. All AEs are collected and reported, independent of potential relationship to the study protocol. Adjudication of relationship to the study is made by the study physician. AEs include exacerbation of underlying diseases, or new onset musculoskeletal, CV or metabolic abnormality. In addition, participants are asked to report all changes in medications, healthcare professional visits, new diagnoses, acute illnesses, or any new symptoms at weekly intervals. Serious AEs, defined as any event related or unrelated to the study resulting in hospitalisation, persistent or permanent disability, or death, are reported to the CI and the HREC at the respective university where the event took place as well as USYD for review within 24 hours after becoming aware of the event. In cases where participants develop a medical or surgical illness during the study, the study physician in cooperation with the participant's general practitioner will ascertain continuation in the intervention.

Impact of COVID-19 pandemic

See online supplemental note 6 for the impact of the COVID-19 pandemic on the trial.

Ethics and dissemination

Ethical and research and governance approval were obtained from the University of Sydney (HREC Ref. 2017/368), UQ (HREC Ref. 2017/HE000853), UBC (H16-03309) and Vancouver Coastal Health Research Institute (V16-03309) research ethics. Results of this trial will be submitted for publication in peer-reviewed scientific journals and presented at national and international conferences. We will also disseminate the results via newsletter articles, social media, talks to clinicians and consumers and meetings with health departments/managers.

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Competing interests JMH, JSC and TL-A report funding received from a subcontract between USYD and their institutions to support the conduct of this study; PSS receives funding from a NHMRC Investigator Grant and is a member of Advisory Committee for Biogen Australia and Roche Australia.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Supplementary Table 1. Trial registration data

Category	Information
Protocol version	Version 1
Primary registry and trial identifying number	anzctr.org.au: ACTRN12617001440314
Date of registration in primary registry	11 October 2017
Secondary identifying numbers	National Health and Medical Research Council (NHMRC) grant: APP1121409
Source of support	National Health and Medical Research Council (NHMRC) grant: APP1121409
Primary sponsor	University of Sydney Susan Wakil Health Building D18, Western Avenue, Camperdown NSW 2006, Australia
Contact for public and scientific queries	Professor Maria Fiatarone Singh, maria.fiataronesingh@sydney.edu.au Susan Wakil Health Building D18, Western Avenue, Camperdown NSW 2006, Australia
Public title	BRAIN Training Trial: Balance, Resistance, And INterval Training Trial: A Randomised Controlled Trial of Three Exercise Modalities in Mild Cognitive Impairment
Scientific title	BRAIN Training Trial: A randomised controlled trial of Balance, Resistance, And INterval training on cognitive function in older adults with Mild Cognitive Impairment
Countries of recruitment	Australia, Canada
Health problem studied	Mild cognitive impairment
Intervention(s)	Interventions: high intensity power training (POWER); high-intensity interval training (HIIT) Comparator: Sham exercise control group: Balance, toning and mobility (SHAM)
Key inclusion and exclusion criteria	Ages eligible for the study: ≥60 years; gender eligible: male and female. Inclusion criteria: Mild Cognitive Impairment (MCI) defined as the presence of all four generally accepted criteria including: (1) *absence of dementia:* Clinical Dementia Rating scale (CDR) score <1; *no or minimal functional impairment due to cognition:* Amsterdam Independent Activities of Daily Living Questionnaire (Amsterdam IADL) score ≥40, rated by informant or participant if no informant available; (3) *subjective memory/cognitive complaint:* Cognitive Change Index (CCI) scale: participant or informant responds to 3 or more statements with a rating of 3, 4 or 5 ('mild to severe problem'); OR Subjective memory complaint questionnaire: participant or informant responds 'yes' to question 1 and 'yes' to questions 2 OR 3 (Q1 'Have you noticed difficulties with your memory?', Q2 'Have you been concerned about your memory?, (Q3) Have you mentioned any concerns about memory to anyone? as per recommendations for the assessment of subjective memory complaint; (4) *objective cognitive impairment:* Score between 19 and 25 on the Montreal Cognitive Assessment (MoCA); ambulatory without the assistance of a person; if from non-English speaking background, must have completed some education in English; residing in the community, including retirement villages and other senior housing or activity sites (independent level of care); willing to participate in a study which involves attending supervised exercise sessions 3 days per week for 12 months Exclusion criteria: Diagnosis of dementia; high level residential care; non-ambulatory or requiring person to assist when walking; 1 stroke in the past 12 months or ≥2 strokes in a lifetime; cardiovascular event/surgery in the past 6 months; progressive neurological disease;

	inability to read and identify objects on a computer screen and draw on a piece of paper due to vision impairment; current major depressive episode (Patient Health Questionnaire-9 (PHQ-9) score of ≤9); psychosis; alcohol abuse (responded 'Yes' to questions 3 and 4 of the CAGE Questionnaire for alcohol use, and reported risky drinking behaviour using the National Health and Medical Research Council (NHMRC) standard criteria); from a non-English speaking background (NESB) without any education in English; already practicing ≥150 minutes of moderate intensity exercise, progressive resistance training or high-intensity interval training regularly; medical contraindications to the planned exercise due to chronic or unstable or terminal diseases; planned move, or planning to be away for ≥4 consecutive weeks during the study period
Study type	Interventional Allocation: randomised; intervention model: parallel; masking: double blinded Primary purpose: treatment Type of endpoint: efficacy
First and last enrolment date	29 January 2018; 02 March 2020
Target sample size	210
Recruitment status	Closed. Recruitment ended early with 160 participants enrolled due to the inability to carry out participant assessments and interventions due to COVID-19 restrictions.
Anticipated date of last data collection	02 March 2026
Primary outcome	Change in overall executive domain of cognitive function score (composite measure) at 26 and 52 weeks after randomisation
Key secondary outcomes	Change in individual tests scores of secondary domains of cognitive function (memory, attention/working memory, visual-spatial, language, information processing speed, motor skills), global cognition, clinical cognitive status, subjective cognitive complaint, and functional impairment due to cognition. Time frame: 26- and 52-weeks post intervention, and long-term follow-up at 24-, 36-, 48- and 72-months post randomisation. Other secondary outcomes: Nutritional status and body composition, cardiovascular and vascular parameters, physiological function (muscle strength and power, maximal aerobic capacity, functional mobility, balance), disability, functional limitations, frailty status, sleep quality, habitual physical activity, biomarkers of brain pathology and cognitive function, psychosocial measures, quality of life, brain morphology and cerebral perfusion, health status. Time frame: 52 weeks post intervention, and long-term follow-up at 24-, 36-, 48- and 72-months post randomisation. Adherence to the training protocol and adverse events (time frame: weekly until 52-weeks post randomisation), attitudes towards the intervention (time frame: 52-weeks post randomisation).

Supplementary Table 2. Cinical trial support structure

Support structure	Composition, roles and responsabilities
Coordinating Centre	The University of Sydney is the coordinating centre of the BRAIN multi-national clinical trial. A clinical trial co-ordinator/ project manager was appointed prior to comencement of the trial (TV). Roles of the clinical trial coordinator include: preparation of ethics application and trial governance documentation, maintenance of trial documentation and master database, reporting of all adverse events, serious adverse events and suspected unexpected serious adverse reactions to the Ethics Committee (in accordance with HREC requirements), development of quality assurance protocols, development of manual of procedures, responsible for assessment of intra and inter reliability, assistance in the development of screening, intervention and assessment protocols, oversight of recruitment and screening of participants, performance of site initiation visits and training of staff across sites in all study related procedures, data analysis and interpretation, preparation of manuscripts.
Principal Investigator and Study Physician	Professor Maria Fiatarone Singh, MD, FRACP (Geriatrician) is the principal investigator and study physician. She is the acting study physician for the USYD study site. She is responsible for confirming eligibility of subjects across sites in relation to their past and current medical history, medications, outcome of physician assessments and signs and symptoms presented during any baseline physical assessments. She is also responsible for providing case-by-case tailoring of the exercise intervention when required for participants who are unable to complete an exercise due to pain or limitation in their range of motion, or due to a change in their medical status during the study intervention period.
Trial Management Committee (TMC)	The trial management committee is composed of the principal investigator at each study site (MFS, JC, TLA). The TMC is responsible for providing the annual S/AE report to HREC and clinical trial governance, responsible for trial master file, budget administration and contractual issues with individual centres, overall data verification and randomisation. The TMC work with the clinical trial co-ordinator and oversee the study site coordinators. The TMC is responsible for organising Steering Committee meetings. All members of the TMC will have access to the final trial dataset.
Study Site Co-ordinator	In each study site a site co-ordinator is nominated to be responsible for recruitment, participant identification, management of data collection, follow-up of study participants and adherence to study protocol and study manual of procedures. The study site co-ordinators report to the PI of the respective study sites. The study site co-ordinators are responsible for providing site specific updates as required to the clinical trial co-ordinator. Weekly meetings (virtual) are held between the TMC, the clinical trial co-ordinator and the study site coordinators.
Steering Committee	The steering committee (SC) is composed of all the lead investigators. The steering committee provided input in the development of the study protocol, and agreed to the final study protocol. The SC is responsible for reviewing the progress of study and if necessary agreeing changes to the protocol to facilitate the smooth running of the study.
Data Safety Monitoring Committee	A data safety monitoring committee composed of Professor Maria Fiatarone Singh, MD, FRACP (Geriatrician) and Professor Jaqueline Close (Geriatrician) from UNSW was established prior to commencement of the study. This committee meets virtually biannually and as needed to triage study events. After each review, the DSMC makes recommendations regarding the conduct of the study. Weekly conference calls are held with all principal investigators, clinical trial co-ordinator and site-specific study coordinators to discuss information related to the study participants, adverse events, and exercise interventions across sites.

Trial data management plan	Data is collected over the phone (telephone screening) and in person (assessments), using researcher-administered questionnaires, and physical testing at each participating site. Data gathered from the screening process, assessment, and training sessions is entered by the research staff into a central database created in REDCap web application hosted by The University of Sydney. Data is entered in a re-identifiable form using unique identifying numbers. All data entered into the database is stored on a secure server of the University of Sydney. Access to the database is provided only to research staff working on the study. User privileges and data access groups are used to limit the viewing and/or editing access that research members have within the database. The REDCap database, including management of access rights are managed by the clinical trial co-ordinator at the University of Sydney. Efforts will be made to gather all outcome measures for study participants who discontinue the intervention. All data will be de-identified prior to depositing in a repository at the end of the study, as required by the National Health and Medical Research Council.
Adverse event managment plan	The standard USYD HREC process for reporting adverse events are followed throughout the conduct of the trial: ▪ The PI and/or sub-investigators review all AE information which may be gathered via any of the following means: - Spontaneous reports by participants at their study visits or via phone or email - Observations by clinical research staff - Reports to research staff by family or medical care providers - Reports collected in participant diaries - Possible AEs documented in medical records, progress notes, hospitalisations etc. - Reports of a participant death within four weeks after stopping treatment or during the protocol-defined follow-up period, whichever is longer, whether considered treatment-related or not ▪ All subjects enrolled in the study are required to complete a weekly health status report to indicate whether there have been changes to their health status, medical conditions, or adverse events. In addition, participants are asked to classify the cause of the event to different diseases/incidents. ▪ Adverse events categorised as serious adverse event (SAE) occurring in research participants at the University of Sydney are reported to the Principal Investigator immediately and to HREC within 72 hours of study staff becoming aware of the SAE by completing the study specific SAE form using IRMA. ▪ All SAE's at sites other than the University of Sydney and where the event materially impacts the continued ethical acceptability of the trial or indicates the need for a change to the trial protocol including changes to safety monitoring in the view of the investigator or sponsor will be reported to HREC as soon as practical study staff at USYD become aware of the SAE using IRMA, and also to Clinical Trial Governance. ▪ AE information is immediately recorded in the participant's medical records and reported to HREC annually using IRMA. A SAE follow up report is provided to the HREC and Governance as required. ▪ The PI and/or sub-investigators provide further information if requested to the University of Sydney as sponsor of the clinical trial for related adverse events that could result in an insurance claim. ▪ All S/AEs are recorded and reported within the established period for safety. The study PI Prof Maria Fiatarone Singh, MD, will follow-up on participants suffering from harm related to participation in the study to ensure that adequate medical

	care is provided to a subject for any adverse events related to the trial. This encompasses the time from baseline assessment prior to intervention commencement, until follow-up is completed for each participant. ▪ The study physician in conjunction with the PI at each intervention site will inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed. ▪ The study physician will inform subjects when medical care is needed for intercurrent illness(es). ▪ Although subjects are not obliged to give reason(s) for withdrawing prematurely from a trial, the investigators will make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Reasons for withdrawal will be reviewed and rates of drop out compared between groups at each biannual virtual board meeting.

Supplementary Table 3. Baseline assessment schedule

DAY 1 (4hrs)		
MORNING	**AFTERNOON**	**Morning (8:30am-12:30pm) or Afternoon (1:00-5:00)**
8:30 9:30	13:00 14:00	Gait under usual and dual task conditions Habitual and Maximal Gait Speed Test Six-Minute Walk Test (Trial 1)
9:30-10:30	14:00-15:00	Physician Screening
10:30-11:30	15:00-16:00	ECG Stress Test
11:30 12:30	16:00 17:00	Provide home-based questionnaire package and 7 day Axivity monitor and log
DAY 2 (4hrs)		
MORNING ONLY		**Morning only: FASTING (8:30 to 12:30)**
8:30-10:30		Collect Axivity monitor and log Weight and height; waist, mid-arm, and mid-cuff circumference Preparation for haemodynamic measures: 10 minutes resting in supine Heart rate variability, Pulse Wave Analysis Pulse Wave Velocity Orthostatic Blood Pressure Dual-energy X-ray absorptiometry scan Peripheral quantitative computed tomography (UQ study site only) Blood collection (USYD and UQ study sites only)
10:30 11:00		*Breakfast*
11:00 11:30		Clinic-based questionnaires
11:30 12:00		Static and dynamic balance assessment Five Times Sit-to-stand
12:00 12:30		Maximal muscle strength test (Trial 1)
DAY 3 (4hrs)		
MORNING	**AFTERNOON**	**Morning (8:30am-12:30pm) or Afternoon (1:00-5:00)**
8:30 9:30	13:00 14:00	Hand grip strength and isometric muscle strength test
9:30 9:45	14:00 14:15	Six-Minute Walk Test (Trial 2)
9:45 11:45	14:15 16:15	Maximal muscle strength test (Trial 2)
11:45 12:30	16:15 17:00	Provide 24h ambulatory blood pressure monitor and log
DAY 4 (4hrs)		
MORNING ONLY		**Morning only (8:30 to 12:30)**
8:30-10:30		Cognitive Assessment (Neurotrax battery) *15-minute break* Paper-based cognitive assessment
10:30 11:30		Muscle power test
11:30 12:00		Randomization
DAY 5 (2 hrs)		
MORNING ONLY		**Morning only (8:30 to 10:30)**
8:30 10:30		Brain MRI (USYD study site only) or cerebral blood flow and brachial flow mediated dilation (UQ study site only)

Supplementary Table 4. Description of tests used to calculate secondary domains of cognitive function

Cognitive test	Description
Memory domain	
NeuroTrax Verbal Memory test [1, 2]	Ten pairs of words are presented, followed by a recognition test in which one member (the target) of a previously presented pair appears together with a list of four candidates for the other member of the pair. Participants must indicate which word of the four alternatives was paired with the target when presented previously. Four consecutive repetitions of the recognition test are administered during the 'learning' phase. An additional recognition test is administered following a delay of approximately 10 minutes.
NeuroTrax Non-Verbal Memory test[1, 2]	Eight pictures of simple geometric objects are presented, followed by a recognition test in which four versions of each object are presented, each oriented in a different direction. Participants are required to remember the orientations of the originally presented objects. Four consecutive repetitions of the recognition test are administered during the 'learning' phase of the test. An additional recognition test is administered following a delay of approximately 10 minutes.
Hopkins Verbal Learning Test Revised [3, 4]	Repeat a verbally-presented list of 12 words from three semantic categories over three learning trials; delayed recall after 20-25 minutes.
Attention/working memory domain	
NeuroTrax Go-No Go test[1, 2]	A series of large coloured stimuli are presented at pseudo-random intervals. Participants are instructed to respond as quickly as possible by pressing a mouse button if the colour of the stimulus is any colour except red, for which no response is to be made.
NeuroTrax Stroop Interference test[1, 2]	The Stroop is a well-established test of response inhibition. The NeuroTrax Stroop test consists of three levels. Participants are presented with a pair of large coloured squares, one on the left and the other on the right side of the screen. In each level, participants are instructed to choose as quickly as possible which of the two squares is a particular colour by pressing either the left or right mouse button. First, participants are presented with a general word in coloured letters. In the next level, participants are presented with a word that names a colour in white letters. In the final level (the Stroop interference level), participants are presented with a word that names a colour, but the letters of the word are in a colour other than that named by the word. The instructions for the final level are to choose the colour of the letters, and not the colour named by the word.
NeuroTrax Staged Information Processing test[1, 2]	This test comprises three levels of information processing load: single digits, two-digit arithmetic problems (e.g., 5-1), and three-digit arithmetic problems (e.g., 3+2-1). For each of the three levels, stimuli are presented at three different fixed rates, incrementally increasing as testing continues. Participants are instructed to respond as quickly as possible by pressing the left mouse button if the digit or result is less than or equal to 4 and the right mouse button if it is greater than 4.
WAIS-IV Digit Span Test[5]	Two subtests are administered. In the first part (digits forward) the individual is read a series of numbers and is required to repeat the sequence in order to the examiner. In the second part (digits reversed) he/she is again read a series of numbers but this time she/he is required to repeat the sequence in reverse order.
Visual-spatial domain	
NeuroTrax Visual Spatial Processing test[1, 2]	Computer-generated scenes containing a red pillar are presented. Participants are instructed to imagine viewing the scene from the vantage point of the red pillar. Four alternative views of the scene are presented as choices.
Language/ verbal function domain	
NeuroTrax Verbal Function test[1, 2]	Pictures of common objects are presented. Participants are instructed to select the word that best rhymes with the name of the picture from among four choices. In

	another test level, participants are instructed to match the picture with its name by choosing the name from among four choices.
Information processing speed domain	
NeuroTrax Staged Information Processing test[1, 2]	Test described earlier within attention/ working memory domain.
WAIS-IV Coding test[5]	In this subtest individuals are asked to quickly write symbols paired with numbers according to a key, within a 120 second time limit.
Trails Making Test form A[6]	Individuals are asked to draw lines connecting consecutive numbers (TMT-A) as quickly as possible.
Motor skills domain	
NeuroTrax Finger Tapping test[1, 2]	Participants are instructed to tap on a single mouse button for 12 seconds with their dominant hand. This task is repeated twice.
NeuroTrax Catch Game test[1, 2]	The Catch game is a novel screen that assesses psychomotor function. Participants must "catch" a rectangular white object falling vertically from the top of the screen before it reaches the bottom of the screen. Mouse button presses move a rectangular green "paddle" horizontally so that it can be positioned directly in the path of the falling object. The test requires hand-eye coordination, scanning and rapid responses.

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Supplementary Table 5. Secondary outcome measures: Physical health and functional status

Outcome measure	Name of scale	Description
Nutritional Status/ Body composition	Mini Nutritional Assessment Short form (MNA-SF)	Validated nutritional screening that can identify geriatric patients age 65 and above who are malnourished or at risk of malnutrition.[1]
	Mediterranean Diet and Culinary Index (MediCul)	Short survey index tool developed to assess adherence to a 'traditional' Mediterranean dietary pattern and certain aspects of cuisine, within a Western population. It includes a blend of frequency and serve questions spanning seventeen main elements and assesses their exposure over the past 6 months.[2]
	CAGE Questionnaire	Widely used screening test for problem drinking and potential alcohol problems.[3]
	Anthropometrics	Measures include standing height, body weight and waist, cuff, and arm circumferences. Body mass index (BMI) is calculated as fasting body weight kg/ height m^2.
	Dual-energy X-ray absorptiometry (DXA) and Peripheral quantitative computed tomography (pQCT)	Measures include whole body and regional lean and adipose tissue; and bone density in the lumbar spine and hip.
Cardiovascular profile	Arterial stiffness	Measures include carotid-femoral pulse wave velocity (PWV), pulse wave analysis (PWA), central aortic systolic blood pressure, central pulse pressure, and augmentation index (AIx) assessed using SphygmoCor Xcel.
	Heart rate variability	Changes in Heart Rate Variability (HRV) assessed using SphygmoCor CvMS.
	Blood Pressure (BP)	Orthostatic blood pressure and orthostatic hypotension assessed in a fasted state and after rising from a five-minute rest in supine position using SunTech automatic blood pressure monitor. Twenty-four-hour ambulatory BP monitoring, awake and nocturnal means and circadian rhythm also obtained using Oscar 2 with Sphygmocor inside.
Vascular profile	Cerebral blood flow	Cerebral blood flow assessed using Transcranial Doppler Ultrasound.
	Braquial Flow Mediated Dilation (FMD)	Flow Mediated Dilation assessed using reactivity of the brachial artery via 2D Ultrasound.
Physiological function	Muscle strength	Maximal dynamic muscle strength assessed using 1 repetition maximum (1RM) on pneumatic resistance machines: bilateral leg press, unilateral knee extension, bilateral chest press, bilateral triceps extension.
		Maximal isometric muscle strength assessed using stand-held dynamometer: unilateral hip abduction, unilateral knee extension, unilateral triceps extension, unilateral ankle dorsiflexion. Maximal isometric handgrip strength of the non-dominant hand assessed using a JAMAR handgrip dynamometer (Sammons Preston, Bolingbrook, IL).
	Muscle power	Maximal muscle power assessed using pneumatic resistance machines: bilateral leg press, unilateral knee extension, bilateral chest press, bilateral triceps extension.

	Aerobic Capacity	Maximal exercise capacity assessed by indirect calorimetry during a maximal walking treadmill exercise test to fatigue.
	Short Physical Performance Battery (SPPB)	Objective measurement instrument of balance, lower extremity strength, and functional capacity in older adults. It is a powerful predictor of disability, institutionalization, and mortality.[4]
	Static Balance	Assessed while standing without the use of assistive devices and with feet in different positions for 20 seconds (eyes open: feet apart in parallel stance, feet together in parallel stance, half tandem stance, tandem stance, and single leg stance; eyes closed: tandem stance and single leg stance). Two trials performed at each stance. Total static balance calculated by summing the time recorded for the best trial at each stance.
	Tandem walk	Assessed with a 3 meter forward tandem walk along a marked course. Dynamic balance score calculated based on time to complete and number of errors recorded.
Disability	KATZ Index of Independence in Activities of Daily Living	Instrument used to assess functional status as a measurement of the person's ability to perform activities of daily living independently.[5]
	Use of Community & Health Services	Instrument used to measure a person's use of community and health care services during the year preceding the assessment.
	Use of assistive devices	Instrument used to measure a person's use of assistive devices during the week preceding the assessment.
	Amsterdam Instrumental Activity of Daily Living Questionnaire	Adaptive and computerized questionnaire designed to assess impairments in instrumental activities of daily living (IADL) in early dementia. The questionnaire is completed by an informant if available. Scores are attained for IADL related to cognitive deficit as well as non-cognitive deficits.[6]
	Life space assessment	Instrument used to evaluate mobility by measuring a person's usual pattern of mobility during the month preceding the assessment.[7]
Functional limitations	Gait speed	Habitual gait speedand maximal gait velocities assessed over a 4-metre distance.
	Gait under usual and dual task condition	Distance covered at habitual walking speed over 1 minute under the following conditions in random order: 1) Gait at usual speed without cognitive task; 2) gait at usual speed with a subtraction task; 3) gait at usual speed with a verbal fluency task. A seated letter fluency task is administered either prior or after the three gait trials (determined at random).
	Five Times Sit-to-Stand Test	Used as a proxy for lower extremity power and has a predictive value of subsequent disability.[8]
	6-minute walk distance (6MWD)	Walking endurance was assessed using the six-minute walk test which is a proxy for overall cardiovascular endurance capacity (aerobic capacity) and in the elderly subject it may be determined by muscle strength and endurance, balance, orthopaedic or neurologic abnormalities, and other problems.[9]
Frailty	FRAIL Scale	Simple tool for the identification of frailty in older people comprising 5 yes-or-no questions—Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight. It has predictive value for disability[10] and mortality.[11]

	Fried phenotype	Tool for the assessment of frailty in older adults based on the presence of five components: weakness, slowness, exhaustion, low physical activity, and unintentional weight loss. [12]
Sleep quality	Motion Watch 8 actigraphy	Objective sleep quality measurement assessed over 7 days using a Motion Watch 8 actigraphy system (MW8; Comtech) together with a 7-day Consensus Sleep Diary (CSD)
	Pittsburgh Sleep Quality Index (PSQI)	Subjective measure of sleep quality and patterns. The tool looks at seven areas: The tool looks at seven areas including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, the use of sleep-promoting medication, and daytime dysfunction.[13]
Habitual physical activity level	Axivity MEMS 3-axis accelerometer	Objective measure of physical activity participation assessed over 7-days using an Axivity MEMS 3-axis accelerometer positioned on the person's lower back.
	Paffenbarger Physical Activity Questionnaire	Self-report measure of physical activity. Activities assessed include number of flights of stairs climbed and blocks walked in a typical day as well as duration of weekly sports and recreational activities.[14]
	Physical Activity Scale for the Elderly (PASE)	Brief survey designed to assess physical activity in older adults during the week preceding the assessment. It includes a section on leisure time activities, household activities and work-related activities.[15]
	Australian National Health Questionnaire (physical activity module)	Brief survey which is part of the Australian Bureau of Statistics 2017-18 National Health Survey. The survey is designed to assess physical activity which consists of four domains, walking for transport, walking for fitness, sport or recreation, moderate exercise and vigorous exercise, which was undertaken in the last week.[16]
Biomarkers of brain pathology and cognitive function	Serum samples for nutritional, biochemical and hormonal factors, pro- and anti-inflammatory Cytokines	BDNF, IGF-1, IGF-1 Binding protein 3, HOMA (insulin and glucose), APOE, Serum Cortisol, Epigenetic analysis, GWAS, Nitric Oxide, Vitamin D, Vitamin B12

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Supplementary Table 6. Secondary outcome measures: psycho-social and quality of life

Outcome measure	Name of scale	Description
Psycho-social	Geriatric Depression Scale (GDS) 30-item	The GDS is used to assess an older person's level of depression with simple yes/no response set and the fifteen-item screening test has been reported to be satisfactory.[1]
	Duke Social Support (DSS)	The DSS is used to assess perceived adequacy and size of social support network on a 3-point scale with higher total scores reflecting higher levels of social support.[2]
	Oxford Happiness Questionnaire (OHQ)	The OHQ is a compact scale for the measurement of psychosocial well-being derived from the Oxford Happiness Inventory (OHI). It includes 29 items each presented as a single statement which are answered on a uniform six-point Likert scale (1=''strongly disagree'' to 6=''strongly agree'').[3]
	Attitudes to Ageing Questionnaire (AAQ)	The AAQ is a self-administered questionnaire consisting of 24 items scored on a 5-point Likert scale which capture general attitudes towards the ageing process and personal experience of ageing. [4]
	Toronto Empathy Questionnaire (TEQ)	The TEQ is a short scale for the measurement of empathy. It contains 16 items that represent a wide variety of empathy-related behaviors. Items are presented as a single statement which are answered on a uniform five-point Likert scale (1=''Never'' to 5=''Always"). Scores are summed to derive total for the Toronto Empathy Questionnaire.[5]
	Core self evaluations scale (CSES)	The 12-item CSES is a direct and relatively brief measure of the core-self-evaluations personality trait which has been described as a basic, fundamental appraisal of one's worthiness, effectiveness, and capability as a person, and has shown to be significantly correlated to life satisfaction. This is the only current CSE scale and is known to have sound psychometric properties. The CSE scale measures a single factor that is the intersection of self-esteem, locus of control, generalized self-efficacy, and emotional stability. Responses for each item are recorded on a 5-point Likert type scale ranging from 1 (disagree strongly) to 5 (agree strongly). Sample items from this scale are "Sometimes I feel depressed," "I am capable of coping with most of my problems," and "I determine what will happen in my life."[6]
	Ewart's Self-efficacy Scale	The Ewart's Self-efficacy scale is a measure of self-perceived ability to perform a variety of exercise related activities. Each activity is scaled by presenting the subject with a list of increasingly difficult behavioural tasks. For example, the walking scale includes: walk 1/2 mile (approximately 10 minutes); walk 1 mile (20 min); walk 1.5 miles (30 min),…walk 6 miles (2 h). Altogether there are 12 levels of task difficulty for each scale. Subjects indicate how certain they are that they can perform each of the levels on a scale ranging from 0 (completely uncertain) to 100 (completely certain).[7]
	Iconographical Falls Efficacy Scale (Icon-FES)	The 30-item Icon-FES questionnaire is used to assess concern about falling in older people during a wide range of daily activities and situations using pictures and brief text.[8]
	Outcome expectancy training questionnaire	Older adults are asked to indicate how confident they are that three different types of exercise (namely resistance exercise, aerobic exercise, and balance, toning and mobility exercises) will result in improved memory and thinking rated using a 10-item Likert scale.
Quality of life	Physical and Mental Health Summary Scales (SF-36)	The Physical & Mental Health Summary Scales include eight generic health concepts, selected from 40 included in the Medical Outcomes Study (MOS), and MOS researchers selected and adapted questionnaire items and developed new measures for a 149-item Functioning and Well-Being Profile the source for SF-36® items.[9]

Perception of the intervention	Semi-structured interview	Attitudes towards the intervention assessed using semi-structured interviews with participants allocated to HIIT and POWER intervention groups.

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Supplementary Table 7. Summary of MRI scanning parameters

	Acquisition duration (min:sec)	Acquisition matrix size (mm^3)	Voxel size (mm^3)	TR (ms)	TE (ms)	TI (ms)	FA (degree)
3D MPRAGE	4:32	198×256×256	1×1×1	8.388	3.168	900	8
3D FLAIR	5:55	198×256×256	1×1×1 (interpolated to 1×0.5×0.5)	6502	91.481	1753	90
Blipped DWI	0:43	240×240×132	2×2×2	5430	107.1	-	90
2D DWI	11:51	240×240×132	2×2×2	4772	107.1	-	90
3D SWAN	3:35	240×240×150	0.4688×0.4688×3	53.2	8 readouts (5, 8.756, 12.512, 16.268, 20.024, 23.78, 27.536, 31.292 ms)	-	15
3D ASL	4:35	240×240×144	1.875×1.875×4	4854	10.7	2025	111
2D resting-state BOLD	7:20	240×240×165	3.243 × 3.243 × 3	1100	30	-	70
Field map	1:53	256×256×140	1×1×4	860	Dual echo (8 and 20 ms)	-	15

TR, repetition time; TE, echo time; TI, inversion time; FA, flip angle; MPRAGE, magnetization-prepared rapid acquisition gradient echo; FLAIR, T2-weighted fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; SWAN, susceptibility-weighted angiography; ASL, resting-state arterial spin labelling imaging; BOLD, resting-state blood oxygenation level dependent imaging.

Supplementary Table 8. Detailed MRI scanning parameters

Imaging modality	Description
T1-weighted images	T1-weighted scans were acquired with a Magnetization-prepared Rapid Acquisition Gradient Echo (MPRAGE) pulse sequence with prospective motion correction (PROMO). The following scanning parameters have been used: repetition time (TR) = 8.388 ms, echo time (TE) = 3.168 ms, inversion time (TI) = 900 ms, flip angle (FA) = 8°, pixel bandwidth = 244.141 Hz, acquisition matrix = 256 × 256, 198 slices, yielding 1 mm isotropic voxels. Autocalibrating Reconstruction for Cartesian imaging (ARC) was applied for parallel imaging (acceleration factor = 3 in the phase encoding direction).
T2-weighted fluid-attenuated inversion recovery (FLAIR)	T2-FLAIR was acquired with a 3D fast spin echo sequence (sagittal slices) and variable flip-angle readouts (CUBE). TR/TE = 6,502/92 ms, TI = 1,745 ms, FA = 90°, acquisition matrix = 256 × 256 (being interpolated to 512 × 512), 198 sagittal slices, 1 mm isotropic voxels (being interpolated to 1.0 × 0.5 × 0.5 mm3).
Diffusion-weighted imaging (DWI)	Diffusion data were acquired with a multiband, multishell pulse sequence. A phase offset was applied to each multiband component. The following scanning parameters were used: TR = 4,671 ms, TE = 108.7 ms, acquisition matrix 120 × 120, 66 slices, 2 mm isotropic voxels, FA=90°, multiband factor = 3, phase encoding direction=AP. The acquisition includes 8 non-diffusion weighted volumes (b=0 s/mm2; one b0 each 20 volumes), as well as 25 (b=700 s/mm2), 38 (b=1000 s/mm2), and 77 (b=2800 s/mm2) unique directions. A separate diffusion-weighted acquisition with 1 non-diffusion weighted volume (b=0 s/mm2) and 6 diffusion directions (b=700 s/mm2) was achieved with PA phase encoding direction to correct for distortion.
Susceptibility-weighted angiography (SWAN)	3D gradient-echo T2*-weighted enhanced SWAN was acquired with TR = 53.2 ms, multi-TE readout technique (8 readouts at TE = 5, 8.756, 12.512, 16.268, 20.024, 23.78, 27.536, 31.292 ms), FA=15°, acquisition matrix = 256 × 256 (interpolated to 512 × 512), 50 slices, voxel size=0.4688 × 0.4688 × 3 mm3 (after interpolation).
Resting-state Arterial spin labelling (ASL) imaging	Pseudo-continuous ASL images were acquired with 3D multi-shot spiral sequence. Sixteen TRs were acquired to construct 1 tag-control pair (8 TRs for tag and 8 TRs for control image) (number of excitations (NEX) = 1, spiral arms = 8). TR/TE = 4,854/10.7 ms, FA = 111°, acquisition matrix = 128 × 128, 36 slices with slice thickness of 4 mm and no gap between slices, 1.875 × 1.875 × 4.0 mm3 voxel size, label duration = 1,450 ms, post-label delay = 2,025 ms. A proton density weighted image was also acquired with the same TR/TE and spatial resolution as control-tag pairs as a reference for cerebral blood flow quantification.
Resting-state blood oxygenation level dependent (BOLD) imaging	To acquire resting-state BOLD maps, T2*-weighted gradient-echo echo-plan sequence was applied with TR = 1,100 ms, TE = 30 ms, FA = 70°, acquisition matrix = 74 × 74, 54 slices, 400 timepoints, voxel size = 3.2432 × 3.2432 × 3 mm3, 2 × in-plane acceleration, multiband factor = 3, and acquisition direction = AP. Dual-echo field maps with phase maps were also acquired to assess any field drift for distortion correction (TR = 860 ms, TE = 8 and 20 ms (dual echo), FA = 15°, acquisition matrix = 256 × 256, 35 slices, 1 × 1 × 4 mm3 voxel size).

Supplementary Note 1: Additional sources of funding

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Supplementary Note 2: Training of study personnel

Study Site Coordinators and Exercise Instructors are trained on all aspects of the intervention protocol by the Trial Coordinator during trial initiation phase. Training is carried out in the form of a 7-day face-to-face study site initiation visit. Topics covered during the training include familiarisation with the exercise equipment used to deliver the exercise protocols, correct exercise technique, assessment of exercise intensity (including Borg rate of perceived exertion scale, percentage of 1 repetition maximum and percentage of maximum heart rate, use of exercise logs, and safety monitoring of participants during exercise sessions.

Sites are provided with a detailed manual of procedure covering all aspects of the trial protocol, including videos demonstrating correct protocol administration. In addition, training sites are required to periodically provide video recordings of training sessions and exercise logs to the Trial Coordinator for quality assurance purposes.

Supplementary Note 3: Assessment procedures

NEUROPSYCHOLOGICAL MEASURES

Cognitive testing takes place in the morning in a quiet and isolated room, with participants in a fed state (after breakfast), and before any physical testing on that day to standardize known effects of fasting and acute exercise on cognitive performance. Participants are asked to avoid exercise for the 48 hours prior to the assessment. Cognitive testing is administered by trained research assistants. The cognitive assessments target a wide range of cognitive domains, including executive function, memory (verbal and non-verbal), visual spatial skills, verbal fluency, attention, information processing, and motor skills. Testing is conducted using pen-and-paper-based assessments as well as a computerised battery (NeuroTrax™ (http://www.neurotrax.com)).[1] The computerised battery is delivered using a standard computer screen and responses are made using the mouse or the number pad on the keyboard (common to all assessment sites). Participant are seated approximately 70 cm away from the computer screen. Participants are familiarized with these input devices at the beginning of the battery, and each test is preceded by a practice session where participants are taught the mechanics of the test while the cognitive task remains trivial. In addition, visual acuity and colour discrimination are tested to the degree necessary for valid completion of the NeuroTrax tests. Research assistants are trained not to assist participants during actual testing, but rather to ensure that they sufficiently understood the instructions prior to each test. Tests are run in the same fixed order for all participants with the computer-based tests administered first, followed by the pen-and-paper-based tests. Duration of the neurocognitive assessment battery is approximately 2 hours including a 20-minute break between the two testing batteries (computerised and paper-based) and additional breaks as provided as required by the participants.

ANTHROPOMETRY & BODY COMPOSITION

Stature

Stature will be measured in a fasted state in the morning suing a wall-mounted stadiometer (Holtain stadiometer, Holtain Limited, Crymych Pembs., UK (USYD site); Seca 284 stadiometer, Hanburg., Germany (UQ and UBC sites)). Participants are assessed barefoot, in light clothing, with feet together and the head positioned in the Frankfort plane. Feet, buttocks, and shoulder blades are against the stadiometer, or as close as possible so that the body remains in a non-distorted vertical posture. The headboard is lowered onto the participants head, depressing any hair to attain the correct height. The measurement is taken as the average of three attempts, and to the nearest 0.1cm.

Body mass

Body mass is measured three times to the nearest 0.01kg, and in both naked and clothed conditions. Naked body mass [body mass in gown (kg) – body mass of gown (kg)] is measured in the morning, with the participant fasting at least 10 hours, and in a supplied gown which is weighed prior to being worn. Clothed body mass requires participants to be weighed immediately prior to the maximal exercise stress test and used when calculating outcome variables of indirect calorimetry. Participants wear self-selected clothing and shoes and are not fasted for this measurement.

Circumferences

Waist, arm, and calf circumferences are measured fasting in the morning and according to International Society for the Advancement of Kinanthropometry Standards.[2] Arm and calf circumferences are measured on the non-dominant limb unless it is impractical due to injury or swelling. Waist circumference is measured at the end of normal expiration, and in line with the mid-point of the lowest rib and iliac crest on each side. Three measurements (with a maximum of 1% difference from each other) are taken for each outcome and the average of the three values calculated and expressed to the nearest 0.1cm.

Body composition

Body composition, including the distribution of fat mass, fat-free mass and bone, will be assessed by dual x-ray absorptiometry (DXA) (General Electric Prodigy DXA scanner (GE Healthcare, MA, USA) (USYD site); Hologic Horizon A DXA scanner, (Hologic, USA) (UQ site); and Discovery DXA System, Hologic, Mississauga, ON

(UBC site). A single, whole body DXA scan, and a lumbar and bilateral hip scan are performed at each timepoint in supine position, with the participant in a fasted state and a supplied gown. Two whole body scans are performed on participants who do not fit within the DXA scanner bed.

CARDIOVASCULAR PROFILE

Arterial stiffness, heart rate variability and blood pressure

Measurements will be performed following at least 10 minutes of supine rest in a quiet environment. Pulse wave analysis and pulse wave velocity will then be measured at the right-sided carotid and femoral arteries using automated technology (SphygmoCor XCEL, AtCor Medical, IL, USA (USYD and UQ sites; and Sphygmocor EM3, AtCor Medical, IL, US (UBC site) and validated techniques appropriate to the device.[3] For pulse wave analysis, a cuff will be placed around the right arm, between the elbow and shoulder, and will be partially inflated to obtain the augmentation index. For pulse wave velocity, a cuff will be placed around the right thigh on the femoral artery to capture the femoral waveform, and a tonometer pressure sensor on the right-sided carotid artery to capture carotid waveform. The velocity of pulse transfer from the carotid artery to the femoral artery will be measured. Pulse wave analysis and pulse wave velocity will be each assessed three times. Central haemodynamics will be assessed with a single brachial cuff on the right arm. By measuring the brachial pulse waves, the device estimates key haemodynamic measures at the aorta including systolic and diastolic pressure. In addition, pulse pressure will be reported as the difference between systolic and diastolic aortic pressures, augmented pressure will be reported as the pressure difference between the first and second systolic peaks of the pulse wave, and the augmentation index will be reported as augmented pressure as a percentage of the pulse pressure[3] Heart rate variability will be measured using continuous electrocardiogram recorded for 5 min (SphygmoCor, AtCor Medical Pty Ltd., West Ryde, Australia).

VASCULAR PROFILE

Outcomes related to vascular profile are only performed at the University of Queensland study site.

Cerebrovascular blood flow and function

During all assessments of cerebrovascular blood flow and function, cerebral blood flow is measured using Transcranial Doppler (TCD) ultrasound (Spencer Technologies) to assess blood velocity at the middle cerebral artery (MCA). Insonation of the cerebral arteries follow standard protocols. [4, 5] The maximal cerebral blood flow velocity through the MCA is recorded at a depth of 30-60mm.

Continual monitoring of beat-by-beat blood pressure is assessed using finger photo plethysmography (Finapres), heart rate is measured using 3 lead ECG (lead II), and a facemask with gas and flow analysis is attached for the measurement of inspired and expired oxygen and carbon dioxide concentrations (AD Instruments) and inspiratory flow along with MCAv continually recorded (Powerlab, Labchart, AD Instruments). End tidal CO2 (PETCO2) is calculated from the following formula: $\frac{Barometric\ pressure-47}{Peak\ CO2*100}$. All data is collected second by second using Powerlab, and data is exported and stored for later offline analysis.

Resting Cerebral Blood Flow

Following 10 min of semi-supine rest, resting cerebral blood flow is monitored for 10 min used to assess the following: 1) Middle cerebral artery blood flow velocity; 2) Cerebrovascular conductance index (CVCi): $(\frac{CBF}{MAP})$; 3) Pulsatility index (PI): $((\frac{systolic\ CBF-diastolic\ CBF}{mean\ CBF})/_{MAP})$; and 4) Cerebrovascular resistance (CVRi): $(\frac{MAP}{CBF})$.

Cerebrovascular reactivity using hyper and hypocapnia

After 10 minutes of resting the participants undergo a test of both hypercapnia and hypocapnia by manipulating changes in carbon inhaled carbon dioxide concentrations. For the hypercapnic test, the subject is connected to a breathing tube to a gas mix with 5% CO_2, with balanced oxygen and nitrogen. The participant inhales this gas mix for 5 minutes at a recommended breathing rate of 12-15 breaths per minute to measure the increase in bilateral middle cerebral artery velocity. After this, the participant breathes room air until the $PETCO_2$ returns to baseline levels. The participant is then instructed to increase the depth of their breathing and slowly increase the rate, they were coached to reduce their $PETCO_2$ to 10mmHg below resting levels, not going any lower than 20mmHg [6].

The results are presented as: MCAv Reactivity (%mmHg) = $\frac{\Delta\ \%\ MCAv}{\Delta\ PETCO2}$; MCAv Reactivity (slope) = linear regression analysis (MCAv vs $PETCO_2$); and CVCi Reactivity = $\frac{\Delta\ \%\ CVCi}{\Delta\ PETCO2}$.

All results will include the respective reactivity calculations for three separate calculations: Hypercapnia – Hypocapnia; Hypercapnia – Normocapnia; and Normocapnia – Hypercapnia.

Brachial flow-mediated dilation (FMD)

Endothelial function will be assessed as flow-mediated dilation (FMD) using high-resolution vascular ultrasound (Usmart 3300, Teratech Corporation, Burlington, USA) in accordance with guidelines for a nitric oxide dependent approach.[7] A 7.5 Hz probe will be used to capture B-mode images of the brachial artery in the right arm. The probe will be placed on the distal third of the upper arm (proximal to the antecubital fossa) and orientated to the longitudinal plane. Following image optimization, continuous images will be recorded to measure vessel diameter and blood velocity, using the lowest possible insonation angle (≤60°). Baseline images will be continuously recorded for 1 min to capture diameter and velocity. A sphygmomanometer cuff, placed directly distal to the olecranon, will be subsequently inflated to 220 mmHg (or 50 mmHg above systolic blood pressure). The cuff will remain inflated for 5 min, with continuous recordings of the brachial artery commencing 30 s before deflation, and for 3 min thereafter. Hyperemic velocity will be assessed via mid-artery pulsed Doppler signal obtained upon immediate release of the cuff. All recordings will be analysed offline by specialized, automated edge detection and wall tracking software to provide an objective measure of peak diameter and calculation of shear rate as previously described [8]. Arterial diameter, flow and shear rate will be analysed using the 1-min baseline recording prior to cuff inflation and 3-min recording following cuff deflation. FMD response will be reported as absolute (in millimetres) and relative (in %) change in post-stimulus brachial artery diameter from baseline diameter. Shear rate stimulus (area under the curve until peak diameter) will also be reported.

PHYSIOLOGICAL FUNCTION

Maximal dynamic muscular strength and power

Maximal muscular strength (1RM) is measured on four pneumatic-resistance machines including leg press, knee extension, chest press and triceps extension (Keiser Sports Health Equipment, Ltd., Fresno, CA (USYD and UBC sites); and HUR Premium Line, HUR, Finland and HUR Functional Trainer Pulley, HUR, Finland (UQ site). The participant is first asked to complete four repetitions with the resistance set at the lowest possible setting, so the assessor can establish technical proficiency for each movement and provide the participant with some basic instructional cues. Thereafter, the resistance is progressively increased following each successful attempt until two unsuccessful attempts have been made at the same load. A successful attempt encompasses both technical proficiency and a full range of motion on each machine, whereas an unsuccessful attempt is defined as failure of either the technical and/or range of motion components. Participant RPE is recorded following each attempt and is used to guide the assessor's resistance increases such that maximal strength should be determined within approximately 10-14 attempts. The highest successful resistance load is deemed the 1RM. The assessment is conducted on two separate assessment days one week apart at baseline to ensure precise measurement and account for any potential learning effects. The higher of the two 1RMs is recorded as the baseline measure.

Muscular power is assessed on the same four resistance machines, and on a separate assessment day to ensure sufficient muscular recovery. Using the highest recorded 1RM, values are calculated for 20, 30, 40, 50, 60, 70, 80, 90, 100% of 1RM. The participant is asked to complete two attempts at 20% 1RM and one attempt at each of the remaining eight levels and is encouraged to move 'as fast as possible' during the concentric phase of each movement. Peak velocity and power are recorded after each repetition. If an attempt is unable to be completed due to muscular or volitional fatigue, the participant is encouraged to make one more attempt. If the second attempt is unsuccessful, the remainder of the test for that exercise is stopped.

Maximal isometric muscle strength

Maximal isometric muscle strength is assessed for knee extension, triceps extension, hip abduction and ankle dorsiflexion exercises using a portable Chatillon CSD200 dynamometer mounted on a stand. The assessments are performed unilaterally on both right and left limbs. Three measurements are taken at each assessment site with 1 minute rest between trials, and the highest of the three values used.

Maximal isometric handgrip strength of the non-dominant hand is assessed using a JAMAR handgrip dynamometer (Sammons Preston, Bolingbrook, IL). Assessment is conducted with the participant seated with the back against the backrest and the arm bent at the elbow at 90° degrees and touching the side of the body. Three measurements are taken with 1 minute rest between trials, and the highest of the three values used.

Aerobic Capacity

The maximal exercise stress test is performed under direct physician supervision on a treadmill using 12-lead ECG (for rate, rhythm, and S-T segment morphology evaluation) and indirect calorimetry. Prior to commencement of the test, a minimum of 3 minutes of resting ECG data is recorded with participants seated. Seated and standing heart rate and blood pressure measures are taken at the end of three minutes. A modified Balke protocol is used, with speed set at 80-100% of habitual gait speed (depending on the participant's comorbidities, balance ability and participant's confidence/ experience walking on a treadmill), and gradient increased by 2% every minute (and speed by 0.5km/h per min only after 24% gradient is reached) until volitional fatigue is reached or test is stopped by the supervising medical doctor. Participants are asked to lightly grasp the handrails for balance throughout the test. Habitual walking speed is measured by asking participants to walk 6 meters on an unobstructed path at their habitual walking speed, and the time taken to travel 2 meters (not including 2 meters for acceleration and 2 meters for deceleration) is measured and converted to kilometres per hour (km/h; Australia) or miles per hour (mph/h; Canada). Heart rate and rate of perceived exertion (RPE) are recorded at the end of every minute, and blood pressure recorded at end of every second minute. At test termination, participants remain walking at 1.0 km/h (and 0% incline) with indirect calorimetry for the initial 60 seconds, and then are seated with only ECG and blood pressure monitoring for the duration of recovery, until any dysrhythmia or ST changes have reverted to baseline, blood pressure and heart rate has returned to baseline values (standing measure), and heart rate is within 10 beats per minute of resting value (standing measure). The automated stress test peak heart rate is used for intensity prescription unless there are high levels of artefact or arrhythmias in which case a manual calculation is performed.

Test preparation: Participants are advised to take their regular medications but avoid caffeine, alcohol, cigarettes, and strenuous exercise on the day of testing; and not to eat and drink only water in the 2 hours prior to the test. Prior to commencement of the test, the system is calibrated according to the manufacture instructions; height and weight of the participants is recorded; and the participant's habitual gait speed is measured to calculate treadmill walking speed.

Equipment:

Study site	**Treadmill**	**ECG System**	**Blood pressure device**	**Indirect Calorimetry System**
USYD	TM55; Quinton Cardiology Systems Inc, WI, USA	Norav Medical Ltd., Mainz-Kastel, Germany	Tango; Suntech Medical Inc., NC, USA (automated)	MGC Diagnostics Corporation, MN, USA
UQ	h/p/cosmos, Germany	CASE, GE healthcare, USA	WelchAllyn, USA (manual BP)	MetaMax3B, Cortex Biophysik, Leipzig, Germany
UBC	Trackmaster (Model No: TMX428 110), Full Vision Inc, Kansas, USA	Nasiff CardioCard, Nasiff Associates Inc, New York, USA	Nasiff CardioCard, Nasiff Associates Inc, New York, USA (automated BP)	K4 b2 Data Management Software, Cosmed, Rome, Italy

Calculation of aerobic metabolism variables:

Variables of focus will be peak oxygen consumption (VO_2peak; L/min, mL/kg/min), oxygen uptake efficiency slope (OUES) and workload (METS). Unaveraged test data will be exported as standard temperature pressure dry (STPD) variables. All data will be exported breath-by-breath and then transformed as 30-second rolling averages over the course of the exercise and recovery stages. Resting data will be removed from analyses so relevant

variables are not artificially influenced by any stress-related hyperventilation by participants. VO_2peak is a measure of cardiorespiratory fitness (CRF) and will be defined as the highest 30-second averaged value occurring during the test or in early recovery (calorimetry will be continued for the first 60 seconds of active recovery at 0.1 km/hr and 0% grade). Oxygen uptake slope efficiency (OUES) is a submaximal measure of cardiorespiratory efficiency derived from the relationship between oxygen uptake and minute ventilation.[9] It
will be determined within the exercise portion of the test by the following equation, where n =OUES ,VO_2 is expressed in millilitres/minute and VE in litres/minute: $VO_2 = n \log VE + b$
Peak workload (METS) will be estimated based on peak treadmill speed and grade using validated equations from the American College of Sports Medicine,[10] where speed is expressed in metres/minute and grade in percentage (as a decimal). Workload will be estimated as VO_2 using the following equation, and then converted to METS by dividing by 3.5:

estimated VO2(ml/Kg/min) = (0.1 x *speed*) + (1.8 x *speed* x *grade*) + 3.5

estimated METS = estimated VO_2/ 3.5

BIOMARKERS OF BRAIN PATHOLOGY AND COGNITIVE FUNCTION

Blood samples will be collected at baseline and 12-month follow-up at the University of Sydney and the University of Queensland study sites only. Bloods will be collected and stored to be analysed at the completion of the study. Up to 50 ml of venous blood will be collected into plasma (with anticoagulant agent) and serum (with clot activator) vacutainers from the antecubital vein according to standard phlebotomy procedures. Samples will be collected between 8 and 9am after an overnight fast (≥12 h). Samples will be logged in Sample log sheet and a barcode will be generated for each sample. Missed samples will be noted. Samples will be centrifuged for 10 min at 4 °C and 3000 rpm. After centrifugation, samples will be divided into aliquots of plasma and serum and then stored in an organized freezer box system at −80 °C for later analysis for the following investigations (not exclusively): BDNF, IGF-1, IGF-1 Binding protein 3, HOMA (insulin and glucose), APOE, Serum Cortisol, Epigenetic analysis, GWAS, Nitric Oxide, Vitamin D, Vitamin B12.

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Supplementary Note 4: Supplementary interview guide 12 month follow up

Interview guide administered to a subsample of participants randomised to POWER and HIIT at 12-month follow-up timepoint.

Interviewer: Thank you agreeing to take part in this interview. The aim of this interview is to explore your experiences with the BRAIN training program and to learn how we can improve our program for future implementation.

This interview should resemble a natural conversation. I will ask you a couple of questions, but the idea is for you to speak freely about your experience in the BRAIN exercise study.

1. Can you tell me about the reasons why you decided to join the program?

2. Can you start by telling me about your experience participating in the Brain study?
Prompt for the following areas:
   - Motivations to join the BRAIN study
   - Facilitators and barriers to exercise adherence (discuss exercise adherence)

3. Can you tell me about your previous experiences with exercise participation? How did your previous experiences compare with your experience now?
Prompt for:
   - Perceptions of exercise mode, dose and perceived exercise intensity

4. Can you tell me about the way you feel when you exercise? How about after you exercise? Has the way you feel changed over time? If so, in what ways has it changed?

5. Can you tell me about the things you like the most and the least of the training program? Can you think of anything you would like to see changed in the program? If so, what?
Prompt for:
   - Perceived strengths and weaknesses of the BRAIN training program
   - Perceived benefits of the program

6. What are your thoughts regarding the implementation of a program like the BRAIN exercise program outside of the research setting?

7. Is there anything else you would like to tell me about?

Closing interview:

I will now summarise the main points I gathered from our conversation. I would like you to please tell me if there is anything you do not agree with as it is possible that I may have misunderstood something that you said. Please also feel free to add anything else you wish to say.

Supplementary Note 5: MRI processing methods

STRUCTURAL IMAGING PROCESSING

To study the within-subject brain morphological changes during the follow-up, MPRAGE PROMO T1-weighted images are automatically processed with the longitudinal stream [1] in FreeSurfer v7.1.1. T2-FLAIR will be used to aid the parcellation of the pial surface. Changes in cortical thickness, volume, and area, as well as in the volumes of subcortical structures and their subfields (e.g., hippocampus), will be calculated for future analyses. Vertex-based longitudinal changes on cortical thickness will also be compared between baseline and follow-up using mixed effects model.

White matter lesions (WML) will be segmented and quantified by using the longitudinal pipeline of our UBO Detector.[2] WML loadings on strategic white matter tracts will also be quantified by using the Toolbox for Probabilistic Mapping of Lesions (TOPMAL).[3]

DWI data will be processed and analysed by the FMRIB's Diffusion Toolbox (FDT). Specifically, diffusion data will first be visualized to remove those with artefacts due to motion effects. Susceptibility-induced distortion correction is then conducted by using FSL's TOPUP, which is followed by correction for subject motion and eddy currents using FSL's EDDY. For microstructural analyses, a tensor model will be fit to eddy-corrected data, and Tract-Based Spatial Statistics (TBSS) will be applied to compare maps of white matter microstructure, including fractional anisotropy (FA) and mean diffusivity (MD). To study the tractography, eddy-corrected data will be fit with a probabilistic diffusion model using Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX) and registered to a standard space. This is followed by a probabilistic tractography on the output from BEDPOSTX using Probabilistic Tracking with Crossing Fibres (PROBTRACKX). Further analyses, such as structural network, can then be carried out using the tractography results.

SWAN images will be visually inspected for microbleeds. SWAN data are also processed by using the MATLAB script available at http://pre.weill.cornell.edu/mri/pages/qsm.html to generate quantitative susceptibility mapping (QSM) data.[4]

FUNCTIONAL IMAGING PROCESSING

Oxford_asl [5] from FSL will be applied to process the ASL data and generate cerebral blood flow (CBF) maps. Briefly, after motion correction, adaptive spatial smoothing,[6] and partial volume correction,[7] voxel-by-voxel calibration, as recommended by the white paper,[8] will be conducted with the M0 map. The resultant CBF maps will then be used to study changes in both global and regional CBF.

Resting state BOLD images will first be visually checked for quality. Images with significant signal loss and/or geometric distortion will be removed from further analyses. The remaining data will be preprocessed with FSL, SPM12, and AFNI. Briefly, FSL's FUGUE will be used to process the field map and correct for the spatial distortion in BOLD data. The 4D BOLD data will first be despiked. After removing the first 5 volumes to allow for magnetic equilibrium, motion correction, slice timing correction, non-brain tissue removal, and spatial smoothing with FWHM = 6 mm, will be administered. Scans with excessive movement, defined as translations over 2 mm and/or rotations over 2°, will be identified and removed from the following processing. Subject-level independent component analysis (ICA) is then performed by using FSL MELODIC (multivariate exploratory linear optimised decomposition into independent components). FMRIB's ICA-based Xnoiseifier (FIX) v1.06 will then be applied to classify subject-level independent components (ICs). Specifically, 40 scans will be randomly selected for training the FIX classifier. Subject-level IC maps of these 40 individuals will be visually inspected and labelled as signal ICs or noise ICs of different types according to the guideline.[9] The FIX classifier will then be applied to the rest of scans with a threshold of 20. The preprocessed BOLD data can then be used for further analyses.

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Supplementary Note 6: Impact of COVID-19 pandemic

As a result of the COVID-19 pandemic and the associated public health order mandating national lockdown, all three study sites were forced to cease all trial activities requiring on-site activities in March 2020. This included participant enrolment, conduct of follow-up assessments and delivery of study intervention. Study participants were informed of the need to end all face-to-face activities via email and phone correspondence. Collection of data relating to adverse events and change in health status continued to be collected via telephone at weekly intervals for the duration of the 12-month intervention period. Face-to-face trial related activities were allowed to recommence in February 2021 at the University of Queensland study site, and in July 2021 at the University of British Columbia study site. The University of Sydney study site was not able to resume activities until February 2021 due to the relocation of the campus where the study was being conducted. By this date the 12-month follow up period had elapsed for the remaining trial participants, thus no remaining 12-month follow up assessments were completed. Five-yearly follow up assessments resumed but were later temporarily stopped between June and October 2021 due to a second national lockdown. Assessments have since resumed and are expected to be completed by March 2026.

No modifications to the planned statistical methods are required as an intention-to-treat analytic strategy inclusive of all participants randomised, regardless of dropout was planned. Planned secondary exploratory analyses also include per protocol and complete case analysis based on attendance rate or adherence to the training protocol.