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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

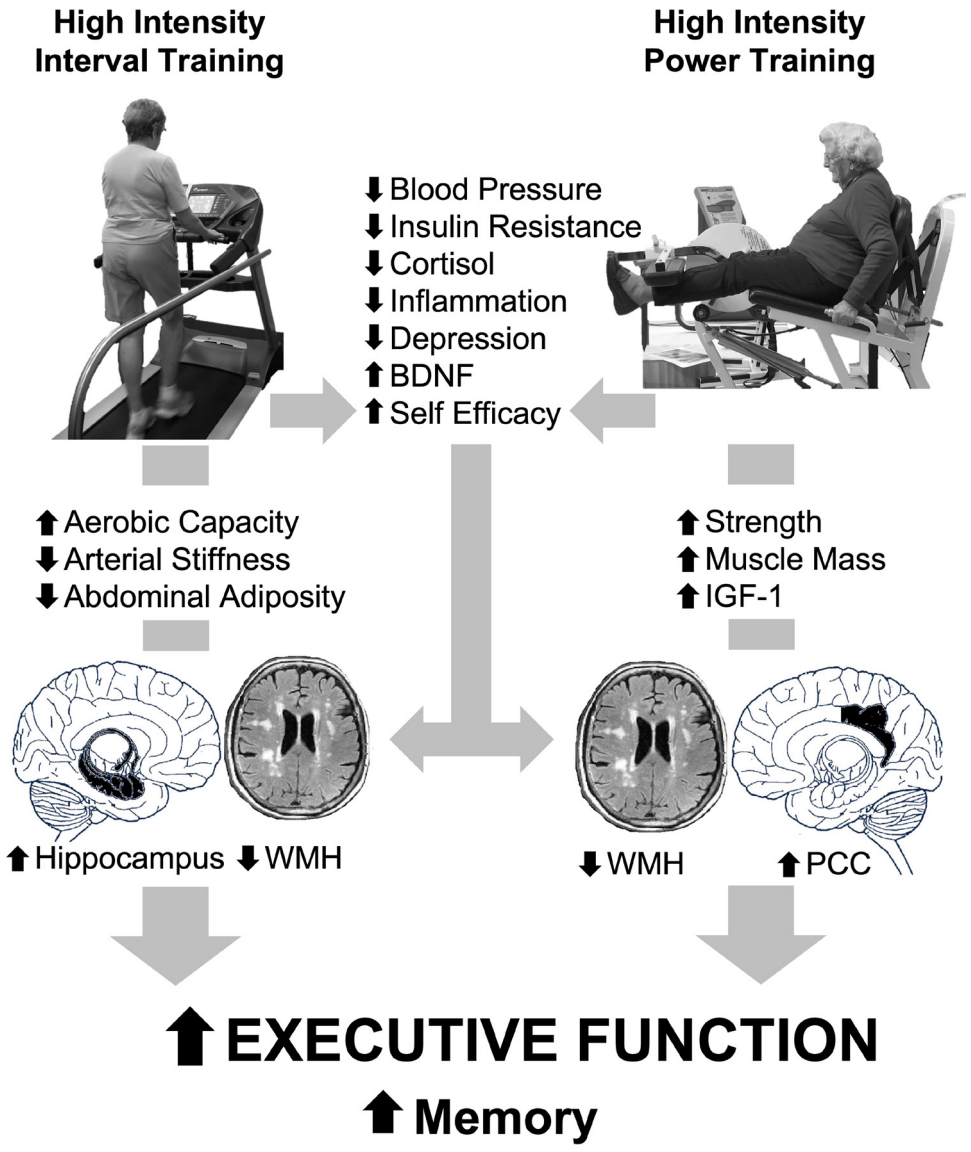

Figure 1 Theoretical model of differential systemic and central pathways that may mediate improvements in cognition after high-intensity interval training and high-intensity power training in older adults with mild cognitive impairment. BDNF, brain-derived neurotrophic factor; IGF-1, Insulin-like growth 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

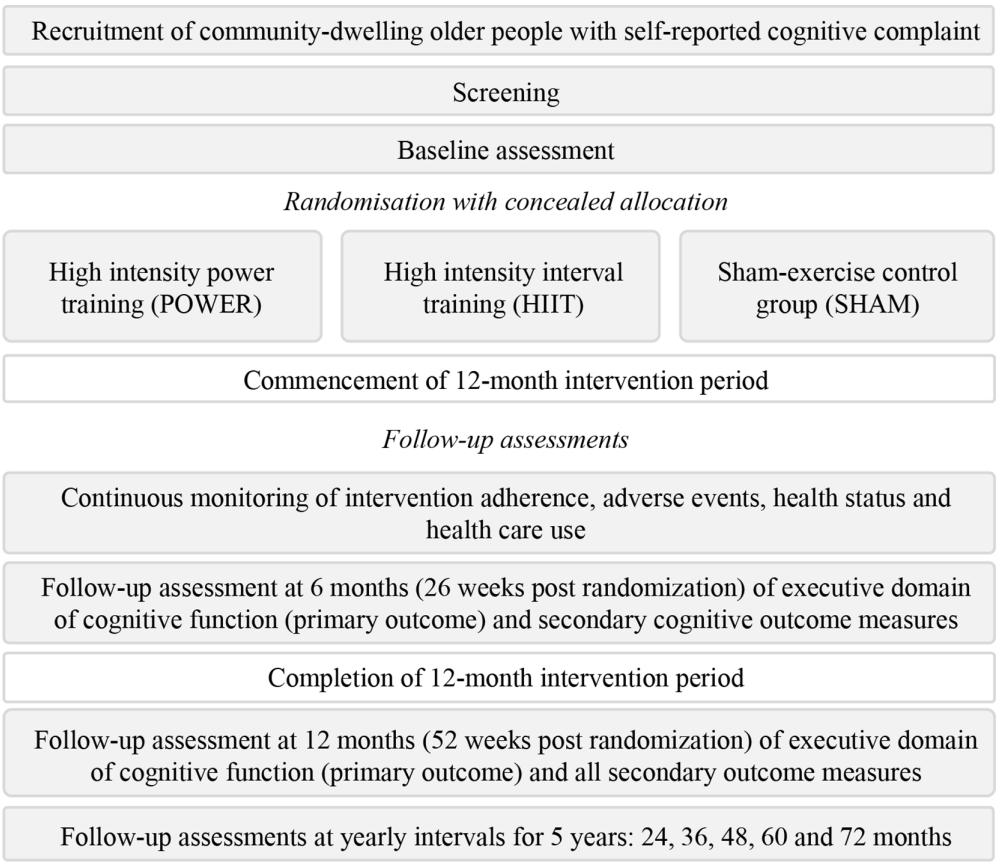

Figure 2 Study design.

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

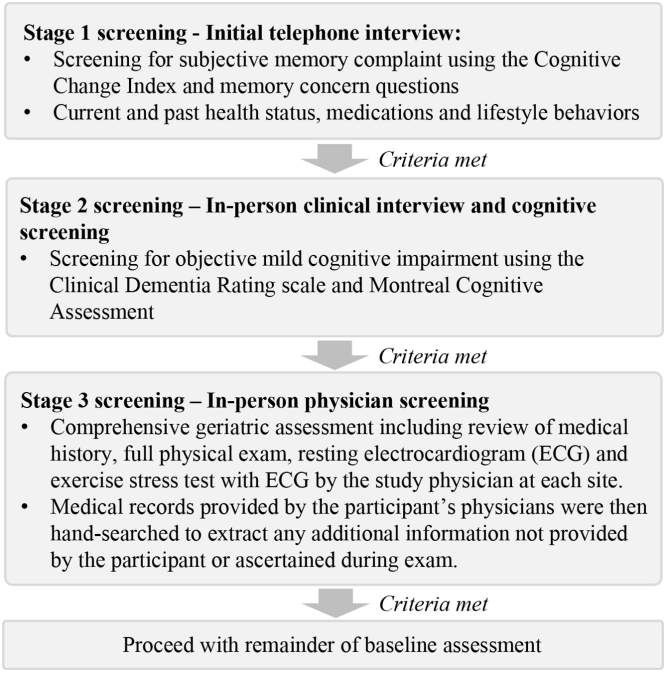

Figure 3 Screening procedure.

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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