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Original Study

The Study of Mental and Resistance Training (SMART) Study—Resistance Training and/or Cognitive Training in Mild Cognitive Impairment: A Randomized, Double-Blind, Double-Sham Controlled Trial

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A B S T R A C T

Background: Mild cognitive impairment (MCI) increases dementia risk with no pharmacologic treatment available.
Methods: The Study of Mental and Resistance Training was a randomized, double-blind, double-sham controlled trial of adults with MCI. Participants were randomized to 2 supervised interventions: active or sham physical training (high intensity progressive resistance training vs seated calisthenics) plus active or sham cognitive training (computerized, multidomain cognitive training vs watching videos/quizzes), 2–3 days/week for 6 months with 18-month follow-up. Primary outcomes were global cognitive function (Alzheimer's Disease Assessment Scale-cognitive subscale; ADAS-Cog) and functional independence (Bayer Activities of Daily Living). Secondary outcomes included executive function, memory, and speed/attention tests, and cognitive domain scores.

Registry Protocol No: X08-0064 (Australian and New Zealand Clinical Trials Registry; http://www.anzctr.org.au)

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Results: One hundred adults with MCI [70.1 (6.7) years; 68% women] were enrolled and analyzed. Resistance training significantly improved the primary outcome ADAS-Cog; [relative effect size (95% confidence interval) −0.33 (−0.73, 0.06); $P < .05$] at 6 months and executive function (Wechsler Adult Intelligence Scale Matrices; $P = .016$) across 18 months. Normal ADAS-Cog scores occurred in 48% (24/49) after resistance training vs 27% (14/51) without resistance training [$P < .03$; odds ratio (95% confidence interval) 3.50 (1.18, 10.48)]. Cognitive training only attenuated decline in Memory Domain at 6 months ($P < .02$). Resistance training 18-month benefit was 74% higher ($P = .02$) for Executive Domain compared with combined training [z-score change = 0.42 (0.22, 0.63) resistance training vs 0.11 (−0.60, 0.28) combined] and 48% higher ($P < .04$) for Global Domain [z-score change = .0.45 (0.29, 0.61) resistance training vs 0.23 (0.10, 0.36) combined].

Conclusions: Resistance training significantly improved global cognitive function, with maintenance of executive and global benefits over 18 months.

Dementia presents a major challenge to individuals, their caregivers, and the health care system globally, with 135 million persons projected to be affected by 2050.[1] Thus, delay of dementia onset, progression, and severity are among the most pressing challenges for medical research today. Mild cognitive impairment (MCI) is a diagnostic term applied to individuals in the intermediate stage between normal cognitive function and dementia.[2] MCI increases the risk for dementia, with diagnosed individuals progressing at rates up to 6%–10% per year compared with 1%–2% in the general population.[3] Pharmacologic treatments for dementia[4] have not been effective in MCI for either cognitive improvement or reduction of incident dementia or its severity. Therefore, nonpharmacologic investigations addressing cognitive decline are urgently recommended.[5]

There is strong evidence from cross-sectional, prospective cohort, and experimental studies that participation in mentally and physically stimulating activities is associated with decreased dementia prevalence and/or incidence as well as improved cognitive function in healthy individuals and some clinical cohorts.[6–8] Our meta-analysis[9] and review of published randomized controlled trials (RCTs) in older adults[10] suggest effect sizes for cognitive outcomes of approximately 0.60 for cognitive training (CT), 0.59 for aerobic/resistance training, and 0.53 for resistance training, compared with 0.15 for healthy control groups. However, the evidence for efficacy of *any* intervention in those with MCI is less certain. For example, in our systematic review of cognitive outcomes in 14 RCTs of exercise specifically in MCI,[11] 42% of effect sizes were potentially clinically relevant (effect size >0.20), but only 8% statistically significant. Similarly, in our systematic review of 10 cognitive/memory training trials in MCI,[12] only 3 of the 5 RCTs had significant effects, limited to memory. Further, robustly designed trials with longitudinal follow-up have been recommended in MCI to investigate the comparative benefits of isolated and combined physical and mental training.

Progressive resistance training (PRT) has been studied far less extensively than aerobic training in MCI. However, the potential utility of PRT is suggested by its beneficial effects on insulin-like growth factor-1, insulin sensitivity, and anti-inflammatory and brain-derived neurotrophic factor pathways, which are related to both sarcopenia and cognitive decline,[13,14] the observed positive effects of higher muscle/lean mass on cognition[15] and brain size,[16] as well as a small number of positive clinical trials.[11,17,18] Therefore, we designed the Study of Mental Activity and Resistance Training (SMART) trial[19] to examine the isolated and combined benefits of CT and resistance training in MCI.

We hypothesized the following:

(1) Six months of supervised CT or PRT would significantly improve global cognitive function in older adults with MCI, as assessed by our primary outcome: the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog)[20] and independence of function as assessed by the Bayer Activities of Daily Living Scale (BAYER-ADL)[21] at both 6- and 18-month follow-up, relative to sham cognitive and sham exercise control conditions, respectively.
(2) Both CT and PRT would significantly improve secondary cognitive outcomes across memory, executive function, and Attention/Speed Domains.
(3) The combination of CT and PRT would be significantly superior to either intervention alone for cognitive and functional benefits.

Methods

Study Design and Setting

The full protocol for the SMART trial has been published,[19] and the protocol registered with the Australian New Zealand Clinical Trials Registry Protocol No: X08-0064 (ANZCTR; http://www.ansctr.org.au). The SMART trial is a randomized, fully-factorial, double-blind, double sham training-controlled clinical trial adhering closely to Consolidated Standards of Reporting Trials guidelines for the conduct and reporting of clinical trials, as extended to nonpharmacologic interventions.

Study Population and Eligibility Criteria

Participants were community-dwelling men and women aged 55 or above with MCI diagnosis, consistent with the Petersen criteria.[22]

Intervention Arms

Complete intervention details have been published[19] and are summarized below.

Dose and Supervision

All training was fully supervised by research assistants from exercise physiology or physical therapy backgrounds. Initial training frequency of 3 days/week was reduced to 2 days/week after the first 30 participants to minimize burden/transportation difficulties. Each session took approximately 60–100 minutes on average (60 minutes control, 75 minutes PRT, or CT groups, 100 minutes combined), but varied according to the physical frailty or level of cognitive impairment in each participant.

CT Intervention (+Sham Exercise)

CT intervention involved computer-based multimodal and multidomain exercises targeting memory, executive function, attention, and speed of information processing. The training used the

COGPACK program,[23] developed for neuro-rehabilitation and used in a previous research trial with MCI, which no participant had used before. Fourteen progressively more difficult exercises were selected including 6 tasks of visual and verbal explicit memory, advancing to a more difficult task each session. Training sessions were completed in a supervised group setting with up to 10 computer work stations and simple touch screens to avoid training difficulties in the computer-naïve.

PRT (+Sham Cognitive)

PRT was supervised by experienced research assistants (exercise physiologists and physiotherapists) in a physician-supervised clinic at the University of Sydney Exercise campus at a ratio of 1 trainer: 4–5 participants. Pneumatic resistance machines (Keiser Sports Health Equipment, Ltd) were used for training at high intensity, 3 sets of 8 repetitions of each of 5–6 exercises/session for most major muscle groups (chest press, leg press, seated row, standing hip abduction, knee extension).

Combined CT and PRT

This group received both the CT intervention and PRT interventions as above sequentially during the same session.

Control

The control group received both sham cognitive and sham exercise interventions.

Sham Cognitive

Sham CT (sham cognitive) consisted of watching 5 short National Geographic videos, followed by a set of 15 questions (3/video) regarding the presented material, as has been used in previous trials[24] with minimal impact on cognitive outcomes. Feedback was not provided unless requested specifically.

Sham Exercise

This group performed stretching and seated calisthenics designed so as not to notably increase heart rate or aerobic capacity, nor improve balance, enhance strength, or other physiological outcomes.

Adverse Events

Adverse events were defined *a priori* as any exacerbation of underlying disease, or new onset musculoskeletal, cardiovascular, or metabolic abnormality attributed directly to study protocols. Monitoring of adverse events over 18 months was done prospectively by weekly questionnaire/interview with proxy information obtained whenever necessary.

Outcome Assessments

Blinded assessors administered all outcome measures at baseline, 6 and 18 months. Cognitive testing took place at least 72 hours after the previous training session, 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.

Primary Outcomes

Details of cognitive assessments are presented in Supplementary Table 1 and the published protocol.[19] Global cognitive function was assessed via the ADAS-Cog, and mental capacity to perform daily tasks by the Bayer Activities of Daily Living (B-IADL), which has been found to differentiate between normal aging and mild to moderate dementia. Scores ≤ 5 on the ADAS-Cog (the mean score reported in noncognitively impaired volunteers ages 55 to 89) were categorized as normal.

Secondary Cognitive Outcomes

Executive function was assessed by Matrices and Similarities subtests of the Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) and verbal fluency (Controlled Oral Words Association Test (COWAT) and Animal Naming). Memory tests included auditory Logical Memory I (immediate) and II (delayed) subtests of the Wechsler Memory Scale 3rd Edition (WMS-III)[25] and the List Learning subsection of the ADAS-Cog, and visual via Benton Visual Retention Test-Revised 5th Edition (BVRT-R). Attention/speed was assessed via Symbol Digit Modalities Test (SDMT). Cognitive Domain scores were calculated by creating and then averaging the z-scores of component tests at each time point, referenced to whole-group baseline mean and standard deviation. Global Domain included all tests except List Learning, as it was already included within ADAS-Cog total score. Executive Domain included WAIS Similarities and Matrices, COWAT, and Animal Naming. Memory Domain included Logical Memory I and II, List Learning, and BVRT-R.

Randomization, Stratification, Concealment, and Allocation

A concealed, computer-generated sequence of randomly permuted blocks (block size = 8) in a 1:1:1:1 ratio to each of the 4 intervention arms, stratified by sex and age (<75 and 75 + years), was generated by a research assistant not otherwise involved in the study via a statistical website (www.randomization.com created by Dr. Gerard E. Dallal, Tufts University) at the completion of all baseline assessments. Assignments were then placed in sealed opaque envelopes and delivered to participants by the recruitment officer.

Results

Recruitment and Retention

As shown in Figure 1, from the 2094 people contacted (primarily via electoral roll), the majority were not interested/did not respond (76%) or ineligible (3%) after telephone screening, or placed on hold primarily for being too physically active (10%). Notably, among the 135 individuals diagnosed with MCI, 75% (100) were interested and enrolled. Dropout rate was much lower than expected (8% and 12% at 6 and 18 months, respectively) because of commitment (5%), dissatisfaction (3%), or health (4%) issues. Six percent (n = 6) discontinued training, all because of commitment issues, not health or adverse events.

Training Adherence and Fidelity

There were no group differences in the median training duration of 26 (0–28) weeks. Absolute exercise adherence (number of sessions) was equivalent between PRT and sham exercise: mean (standard deviation) 42 (19) vs 42 (20); $P = .96$). The intended increase in total tonnage (total weight lifted) over 6 months averaged 48 (49%), with a nonsignificantly greater increase in the Combined Training Group than isolated PRT [56 (46%) vs 38 (51%), respectively, $P = .21$]. Absolute cognitive session adherence was higher in CT than sham cognitive: [52 (19) vs 42 (22); $P = .02$].

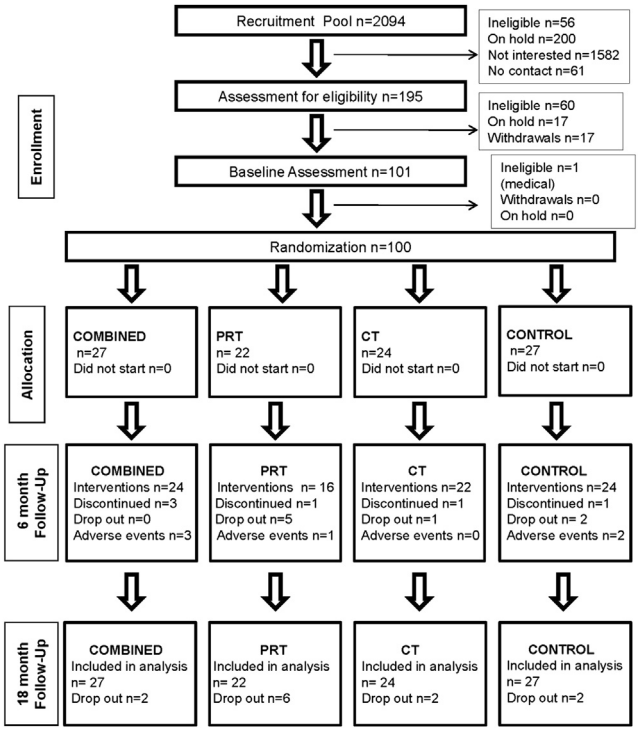

Fig. 1. Flow of participants through the study. Participants were randomized into 1 of 4 treatment groups in a fully factorial design so that all participants received either active or sham cognitive intervention plus either active or sham exercise intervention. CT (+sham exercise) = Computerized cognitive training plus stretching exercise; PRT (+sham COG) = Progressive resistance training plus video watching; Combined (CT + PRT) = Computerized cognitive training plus progressive resistance training; Control (sham COG + sham exercise) = video watching plus stretching exercise

Adverse Events

There were 6 adverse musculoskeletal events over 18 months (3 falls during assessments and 3 exacerbations of pre-existing arthritis symptoms during strength testing/training, with 1 unresolved (exacerbation of an underlying rotator cuff tear).

Participants

Baseline characteristics of participants are shown in Supplementary Table 2; there were no significant group differences ($P > .05$). All 100 participants and 93% of their informants reported concern over memory/cognitive decline. The most common chronic conditions were osteoarthritis (73%), hypertension (42%), hyperlipidemia (30%), osteoporosis (21%), diabetes (11%), and coronary artery disease (6%).

Primary Outcomes

Global cognition: ADAS-Cog

Primary outcomes (ADAS-Cog and BAYER-ADL) are reported in Tables 1 and 2. Resistance training significantly improved ADAS-Cog compared with sham exercise ($P < .05$) over 6 months, with a trend for benefit persistent over 18 months ($P = .08$). The proportion of participants with normal ADAS-Cog scores after resistance training doubled from 24% to 48% (absolute increase of 24%), compared with an increase from 20% to 27% (absolute increase of 7%) with sham exercise [$P < .03$; adjusted odds ratio (OR; 95% confidence intervals) 3.50; (1.18, 10.48)]; Figure 2. By contrast, there was no difference between CT and sham cognitive (absolute increase of 19% vs 13%, respectively) in the proportion with normal ADAS-Cog scores after training [$P > .99$; adjusted OR 1.00 (0.34, 2.90)].

Functional independence: BAYER-ADL

Functional impairment was minimal at baseline (consistent with MCI criteria) and improved slightly over time ($P < .001$), as shown in Tables 1 and 2, without group effects.

Secondary Cognitive Outcomes

Secondary outcomes are presented in Tables 1 and 2.

Executive Function

Resistance training significantly improved executive function test WAIS Matrices ($P < .02$) with trend for improvement in overall Executive Domain score as well ($P < .07$), both over 18 months (Tables 1 and 2). By contrast, there was no significant effect of CT on Executive Domain.

Contrary to our hypothesis, the Combined Group did not perform better than the single intervention arms. Instead, there was a significant RESISTANCE × COGNITIVE × TIME interaction term in the mixed models for both Category Fluency (Animal Naming; $P < .02$ and $P = .003$ over 6 and 18 months, respectively), as well as for overall Executive Domain ($P = .01$ and $< .02$ over 6 and 18 months, respectively), see Tables 1 and 2. This interaction was due to the PRT Group improving 60% more than the Combined Group on Executive Domain changes at 6 months [mean z-score change of 0.426 (0.249, 0.603) vs 0.168 (0.026, 0.310), respectively, $P < .03$]. The Executive Domain difference between PRT Group [mean z-score change 0.424 (0.215, 0.632)] and the Combined Group [mean z-score change 0.109 (−0.060, 0.278)] was even greater at 18 months, with the PRT benefit 74% higher than the Combined Group ($P = .02$), (Figure 3a).

Memory

The effects of resistance training on memory were mixed. Resistance training attenuated the decline in visual/constructional memory (BVRT-R; $P = .04$) but was associated with worse delayed auditory memory at 6 months ($P < .03$) and had no significant effect on Memory Domain score; see Tables 1 and 2. On the other hand, CT did not significantly improve any individual memory test, but maintained the Memory Domain z-score (+0.036) compared with z-score declines without CT (−0.196) at 6 months [z-score mean difference 0.23 (−0.06, 0.52); $P = .01$].

Speed/Attention

All participants improved slightly but significantly over time, without group effects (Tables 1 and 2).

Global Function Domain

There was a very small but significant improvement in Global Domain in the whole cohort over 6 months, with no group differences [mean z-score change 0.119 (0.055, 0.183); $P < .001$, Tables 1 and 2]. Similar to the findings for both Category Fluency and Executive Domain above, there was a trend for an interaction of RESISTANCE × COGNITIVE × TIME over 18 months ($P < .07$). As shown in Figure 3b, this was due to the PRT Group having a 48% higher benefit [mean z-score change 0.452 (0.291, 0.614)] compared with the Combined Group [mean z-score change 0.233 (0.103, 0.363)] on Global Domain changes at 18 months ($P < .04$).

Table 1
Mean Scores (95% CIs) for Primary Outcomes at all Time Points for Each Randomization Group

Outcome Measures		Randomization Group			
	Time Point	CT (+sham Exercise)	PRT (+sham Cognitive)	Combined (CT + PRT)	Control (Sham Cognitive + Sham Exercise)
Global cognition					
ADAS-Cog*	Baseline	8.79 (7.57, 10.02)	8.29 (7.02, 9.56)	8.02 (6.87, 9.17)	8.09 (6.95, 6.93)
	6 months	7.31 (6.08, 8.54)	5.56 (4.2, 6.91)	6.26 (5.11,7.41)	7.14 (5.97, 8.30)
	18 months	6.49 (5.24, 7.75)	4.97 (3.55, 6.38)	5.76 (4.59. 6.92)	5.75 (4.58, 6.93)
Global Cognition Domain	Baseline	−0.044 (−0.276, 0.187)	0.082 (−0.159, 0.323)	−0.077 (−0.295, 0.141)	−0.113 (−0.330, 0.104)
	6 months	0.109 (−0.247, 0.342)	0.259 (−0.010, 0.509)	0.072 (−0.146, 0.290)	−0.116 (−0.335, 0.103)
	18 months	0.312 (0.077, 0.548)	0.536 (0.279, 0.794)	0.165 (−0.055, 0.385)	0.108 (−0.113, 0.328)
Executive Function					
WAIS-III Similarities	Baseline	19.11 (17.28, 20.95)	19.83 (17.92, 21.74)	19.05 (17.32, 20.77)	17.84 (16.12, 19.56)
	6 months	21.52 (19.67, 23.37)	22.35 (20.31, 24.39)	20.57 (18.84, 22.29)	19.02 (17.27, 20.77)
	18 months	21.91 (20.03, 23.80)	22.15 (20.01, 24.28)	20.79 (19.04, 22.55)	20.72 (18.96, 22.49)
WAIS-III Matrices	Baseline	11.98 (10.14, 13.81)	13.24 (11.31, 15.17)	12.04 (10.31,13.76)	11.53 (99.81, 13.25)
	6 months	11.82 (9.97, 13.67)	14.98 (12.93, 17.03)	13.26 (11.54, 14.98)	11.27 (9.52, 13.03)
	18 months	13.17 (11.29, 15.06)	14.16 (11.97, 16.35)	12.06 (10.30, 13.82)	11.65 (9.88, 13.42)
Category Fluency	Baseline	20.2 (18.3, 22.1)	18.3 (16.3, 20.2)	17.9 (16.1, 19.6)	18.4 (16.7, 20.2)
(Animal Naming)	6 months	20.5 (18.6,22.4)	20.4 (18.3, 22.5)	18.2 (16.5, 20.0)	17.7 (15.9, 19.5)
	18 months	20.8 (18.9, 22.7)	21.3 (19.1, 23.5)	17.4 (15.6, 19.2)	17.5 (15.7, 19.3)
COWAT	Baseline	38.24 (33.34, 43.14)	38.98 (33.88, 44.08)	36.40 (31.79, 41.01)	35.23 (30.64, 39.82)
	6 months	41.85 (36.91, 46.78)	43.28 (37.92, 48.64)	37.88 (33.27,42.49)	41.09 (36.43, 45.74)
	18 months	42.71 (37.71, 47.72)	44.78 (39.20, 50.36)	39.22 (34.54, 43.89)	40.93 (36.23, 45.62)
Executive Function Domain	Baseline	0.066 (−0.201, 0.332)	0.080 (−0.197, 0.357)	−0.089 (−0.340, 0.162)	−0.169 (−0.418, 0.081)
	6 months	0.264 (−0.004, 0.532)	0.484 (0.196, 0.772)	0.096 (−0.155, 0.346)	−0.053 (−0.305, 0.199)
	18 months	0.392 (0.122, 0.663)	0.504 (0.206, 0.803)	0.026 (−0.227, 0.280)	0.034 (−0.220, 0.288)
Memory					
List Learning Memory	Baseline	18.59 (17.09, 20.10)	20.96 (19.40,22.53)	20.13 (18.71, 21.54)	18.84 (17.43, 20.25)
Sum from ADAS-Cog	6 months	19.72 (18.20, 21.24)	22.61 (20.90, 24.32)	20.79 (19.38, 22.21)	19.09 (17.64, 20.53)
	18 months	21.02 (19.47, 22.58)	22.42 (20.64, 24.10)	21.90 (20.45, 23.35)	20.91 (19.45, 22.37)
BVRT	Baseline	5.98 (5.31,6.65)	6.20 (5.49, 6.90)	5.86 (5.23, 6.49)	6.51 (5.88, 7.14)
	6 months	5.88 (5.20, 6.56)	6.15 (5.38, 6.93)	6.27 (5.64, 6.90)	5.46 (4.81, 6.11)
	18 months	6.57 (5.87, 7.27)	6.41 (5.59), 7.24)	6.12 (5.47, 6.77)	6.07 (5.42, 6.72)
Logical Memory I (immediate)	Baseline	10.13 (8.49, 11.78)	10.17 (8.34, 12.00)	9.46 (7.93, 10.99)	9.60 (8.04, 11.16)
	6 months	10.61 (8.98, 12.24)	12.00 (10.31, 13.70)	10.42 (8.89, 11.95)	10.99 (9.46, 12.51)
	18 months	11.83 (10.16, 13.50)	13.03 (11.16, 14.89)	11.96 (10.39, 13.52)	11.00 (9.44, 12.56)
Logical Memory II (delayed)	Baseline	8.17 (6.32, 10.12)	10.71 (8.80, 12.63)	8.71 (6.98, 10.48)	8.17 (6.44, 9.89)
	6 months	9.08 (7.22, 10.94)	8.62 (6.58, 10.66)	8.04 (6.31, 9.77)	7.75 (6.00, 9.51)
	18 months	10.20 (8.32, 12.08)	12.53 (10.45, 14.60)	10.23 (8.47, 11.99)	10.03 (8.28, 11.79)
Memory Domain	Baseline	−0.197 (−0.488, 0.094)	0.199 (−0.104, 0.501)	−0.108 (−0.381, 0.166)	−0.091 (−0.363, 0.182)
	6 months	−0.125 (−0.418, 0.168)	0.056 (−0.264, 0.376)	−0.107 (−0.381, 0.166)	−0.333 (−0.610, −0.056)
	18 months	0.231 (−0.066, 0.529)	0.531 (0.196, 0.865)	0.208 (−0.070, 0.486)	0.077 (−0.202. 0.357)
Attention/Speed					
SDMT	Baseline	45.58 (41.43, 49.73)	44.25 (39.92, 48.58)	44.94 (41.05, 48.83)	41.68 (37.79, 45.57)
	6 months	46.87 (42.68, 51.06)	46.29 (41.66, 50.92)	47.42 (43.53, 51.32)	44.11 (40.15, 48.07)
	18 months	46.40 (42.21, 50.59)	47.54 (42.97, 52.12)	47.55 (43.63, 51.47)	44.83 (40.90, 48.76)
Functional status					
BAYER-ADL scale*	Baseline	0.3 (0.2, 0.3)	0.3 (0.2, 0.3)	0.2 (0.2, 03)	0.2 (0.2, 0.3)
	6 months	0.1 (0.1, 0.2)	0.2 (0.1, 0.2)	0.2 (0.1, 0.2)	0.1 (0.1, 0.2)
	18 months	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.2 (0.1, 0.2)	0.1 (0.1, 0.2)

n = 100 for all outcomes. All data were normally distributed and raw data used except for BAYER-ADL, which was logged prior to analyses.
Data represent the estimated marginal means and 95% confidence intervals (CIs) from repeated measures linear mixed models including all 3 time points, with fixed effects of time, resistance, cognitive, and their interactions, and adjusted for age, sex, and highest level of education.
Domain results are calculated as the average of the z-scores of the component tests.
Z-score at baseline = individual value at baseline minus mean value for baseline cohort/SD for baseline cohort.
Z-score at 6 and 18 months = individual value at 6 or 18 months minus mean value for baseline cohort/SD for baseline cohort.
Memory Domain was calculated by averaging the z-scores of component memory tests: ADAS-Cog List Learning Memory Sum, Logical Memory I (immediate), Logical Memory II (delayed), and BVRT.
Executive Domain was calculated by averaging the z-scores of component executive function tests: WAIS-III Similarities, WAIS-III Matrices, COWAT, and Category Fluency.
Global cognition Domain was calculated by averaging the z-scores of all tests except ADAS-Cog Memory Sum, as this is a subscale within the ADAS-Cog and, therefore, already included. The sign was reversed on the ADAS-Cog z-score so that positive z-score changes indicate improvement for all tests and Domains.
*Lower score indicates better function; n = number of errors (ADAS-Cog[20]) or magnitude of deficits in function reported by informant (BAYER-ADL[21]). For all other tests, higher score indicates better function, n = number correct.

Discussion

We have reported the primary outcomes of SMART, the first fully factorial trial of high intensity PRT and computerized multidomain CT in older adults with MCI. As hypothesized, PRT significantly improved measures of global and executive function after training, as well as at 18-month follow-up. CT did not improve any individual test result at either time point, but transiently attenuated decline in overall Memory Domain score at 6 months. Contrary to our hypotheses, the training and long-term benefits of PRT alone were significantly greater for both global and executive function compared with PRT combined with CT.

Efficacy of Resistance Training

The clinical relevance of the significant improvement in our primary outcome of global function (ADAS-Cog) with PRT is supported

Table 2
Repeated Measures Linear Mixed Model Analysis and Relative Effect Sizes for all Outcomes

Statistical Effect	TIME	COGNITIVE × TIME		RESISTANCE × TIME	
	P Value	*P* Value	Relative Effect Size (95% CIs)	*P* Value	Relative Effect Size (95% CIs)
Global Function					
ADAS-Cog*					
Treatment (0,6)	<.001	.66	0.07 (−0.32, 0.46)	<.05	−0.33 (−0.73, 0.06)
Long-term (0,6,18)	<.001	.69	0.18 (−0.21, 0.57)	.08	−0.15 (−0.55, 0.24)
Global Domain					
Treatment (0, 6)	<.001	.32	0.07 (−0.17, 0.30)	.17	0.09 (−0.50, 0.32)
Long-term (0,6,18)	<.001	.12	−0.04 (−0.27, 0.19)	.37	0.06 (−0.17, 0.29)
Executive Function					
WAIS-III Similarities					
Treatment (0, 6)	<.001	.89	0.02 (−36, 0.41)	.77	0.05 (−0.35, 0.45)
Long-term (0,6,18)	<.001	.84	−0.07 (−0.46, 0.32)	.39	−0.18 (−0.57, 0.22)
WAIS-III Matrices					
Treatment (0, 6)	.15	.79	−0.05 (−0.43, 0.34)	.06	0.37 (−0.03, 0.77)
Long-term (0, 6, 18)	.27	.91	0.02 (−0.37, 0.41)	<.02	−0.04 (−0.44, 0.36)
Category Fluency					
Treatment (0, 6)	.17	.62	−0.08 (−0.47, 0.31)	<.06	0.32 (−0.08, 0.71)
Long-term (0, 6, 18)	.37	.62	−0.20 (−0.59, 0.19)	.15	0.31 (−0.09, 0.71)
COWAT					
Treatment (0, 6)	<.001	.14	−0.20 (−0.59, 0.19)	.29	−0.15 (−0.55, 0.25)
Long-term (0, 6, 18)	<.001	.31	−0.17 (−0.56, 0.22)	.48	−0.06 (−0.46, 0.33)
Executive Domain					
Treatment (0, 6)	<.001	.39	−0.07 (−0.33, 0.20)	<.09	0.14 (−0.13, 0.40)
Long-term (0, 6, 18)	<.001	.63	−0.09 (−0.36, 0.17)	<.07	0.01 (−0.26, 0.27)
Memory Function					
List Learning Memory Sum					
Treatment (0, 6)	.02	.95	−0.01 (−0.40, 0.35)	.53	0.12 (−0.28, 0.52)
Long-term (0, 6, 18)	<.001	.88	0.09 (−0.30, 0.48)	.33	−0.17 (−0.57, 0.23)
BVRT					
Treatment (0, 6)	.29	.06	0.41 (0.01, 0.80)	.04	0.45 (0.05, 0.85)
Long-term (0, 6, 18)	.13	.14	0.31 (−0.08, 0.70)	<.06	0.10 (−0.30, 0.49)
Immediate Memory I					
Treatment (0, 6)	.002	.23	0.21 (−0.17, 0.60)	.55	0.12 (−0.28, 0.51)
Long-term (0, 6, 18)	<.001	.28	0.21 (−0.18, 0.60)	.47	0.28 (−0.12, 0.60)
Delayed Memory II					
Treatment (0, 6)	.12	<.06	0.29 (−0.10, 0.68)	<.03	−0.35 (−0.75, 0.05)
Long-term (0, 6, 18)	<.001	.16	−0.04 (−0.43, 0.35)	.08	−0.06 (−0.46, 0.33)
Memory Domain					
Treatment (0, 6)	.10	<.02	0.23 (−0.06, 0.52)	.88	0.01 (−0.28, 0.30)
Long-term (0, 6, 18)	<.001	<.08	0.12 (−0.17, 0.41)	.98	0.03 (−0.26, 0.31)
Speed/Attention					
SDMT					
Treatment (0, 6)	.001	.84	−0.03 (−0.42, 0.36)	.89	0.04 (−0.36, 0.43)
Long-term (0, 6, 18)	.001	.38	−0.14 (−0.53, 0.25)	.71	0.09 (−0.30, 0.49)
Functional status					
BAYER-ADL*					
Treatment (0, 6)	<.001	.31	0.31 (−0.09, 0.70)	.72	0.10 (−0.30, 0.50)
Long-term (0, 6, 18)	<.001	.40	0.27 (−0.12, 0.66)	.86	−0.02 (−0.41, 0.38)

WAIS = Wechsler Adult Intelligence Scale; N = 100 for all outcomes.
All data were normally distributed and raw data used in analyses except for BAYER-ADL, which was logged.
Domain scores represent the average of the z-scores of each component test.
Z-score at baseline = individual value at baseline minus mean value for baseline cohort/SD for baseline cohort.
Z-score at 6 and 18 months = individual value at 6 or 18 months minus mean value for baseline cohort/SD for baseline cohort.
Memory Domain was calculated by averaging the z-scores of component memory tests: ADAS-Cog List Learning Memory Sum, Logical Memory I (Immediate), Logical Memory II (Delayed), and BVRT.
Executive Domain was calculated by averaging the z-scores of component executive function tests: WAIS-III Similarities, WAIS-III Matrices, COWAT, and Category Fluency.
Global Cognition Domain was calculated by averaging the z-scores of all tests except ADAS-cog Memory Sum, as this is a subscale within the ADAS-Cog and, therefore, already included. The sign was reversed on the ADAS-Cog z-score so that positive z-score changes indicate improvement for all tests and domains.
Two separate repeated measures linear mixed models were constructed for each cognitive outcome (dependent variable).
Intervention fixed effects in mixed models were:
RESISTANCE = PRT and combined groups vs no resistance training (CT and control groups)
COGNITIVE = CT and combined groups vs no cognitive training (PRT and control groups)
The first model included baseline and 6-month data (Treatment Effect). The second model included baseline, 6- and 18-month data (Long-term Effect). All models were adjusted for age, sex and highest educational level achieved and included main effects of TIME, RESISTANCE, COGNITIVE, and the interaction terms: RESISTANCE × TIME, COGNITIVE × TIME, AND RESISTANCE × COGNITIVE × TIME.
P values are from the mixed model Type III Sum of Squares tests of these fixed effects.
Relative Hedges' Bias Corrected Effect Sizes (ES) and 95% CI[40] were calculated for each time point and main treatment effects for each cognitive outcome using the estimated marginal means and standard deviations (SD) from the mixed models:
Relative effect size (ES) = (post-test minus Baseline) INTERVENTION − (Post-test minus Baseline) NO INTERVENTION/pooled baseline SD of cohort.
For the domain ESs, which are already standardized z-scores, the formula was:
Relative ES = post-test domain z-score minus baseline z-score (95% CIs).
*Lower score indicates better function, n = number of errors on the ADAS-Cog[20] or magnitude of deficits in function by informant on the BAYER-ADL scale.[21] For all other tests, higher score indicates better function, n = number correct.

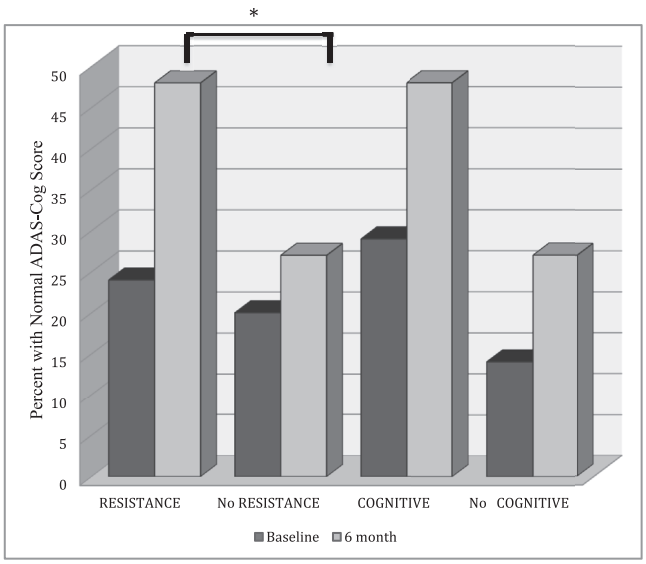

Fig. 2. Proportion of participants with ADAS-Cog total score within normal range at baseline and after 6 months of training. *Resistance training was associated with a significantly increased proportion of participants with normal ADAS-Cog scores (increasing from 24% at baseline to 48% after training compared with 20% to 27% in the nonresistance training participants: adjusted OR (95% CIs) = 3.50 (1.18, 10.48), $P < .03$). By contrast, there was no significant effect of CT on ADAS-Cog status at 6 months (increasing from 29% to 48% normal) compared with noncognitive training participants (increasing from 14% to 27% normal; OR 1.00 (0.34, 2.95; $P > .99$).

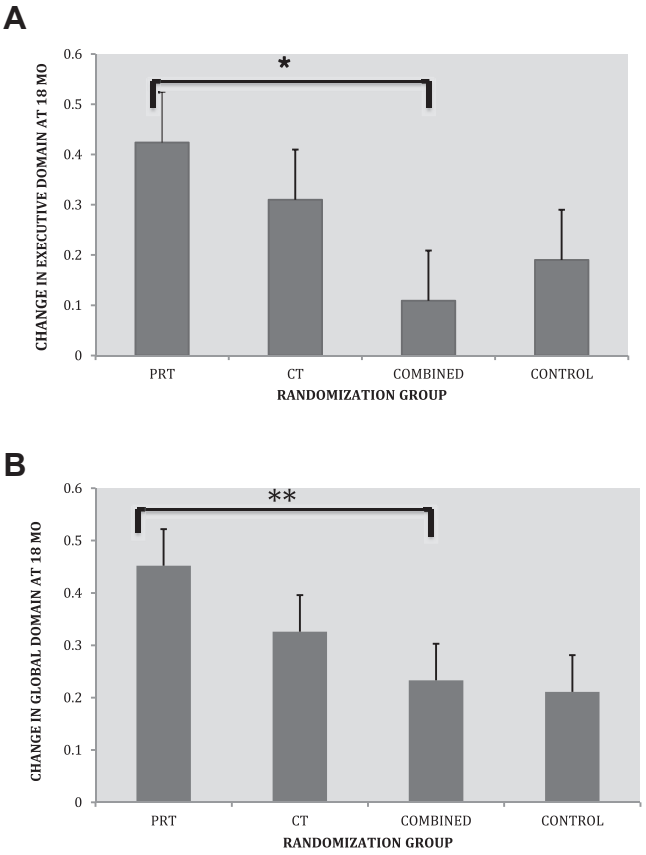

Fig. 3. Changes in Executive and Global Domain scores at 18 months by randomization group. Data represent the 18-month z-score change and standard error for each group. COMBINED = PRT + CT; CONTROL = sham cognitive and sham exercise. Greater z-score changes indicate more improvement. A, Executive Domain changes at 18 months. The PRT Group improvement was significantly greater than the Combined Group improvement (*$P = .02$). No other comparisons were significant ($P > .05$). B, Global Domain changes at 18 months. The PRT Group improvement was significantly greater than the Combined Group improvement (**$P < .04$). No other comparisons were significant ($P > .05$).

by the observed doubling of the number of individuals scoring within the normal range of ADAS-Cog (absolute increase from 24% to 48% of participants), as well as by the persistence of benefit for executive and global function even 12 months after cessation of supervised training.

Prior systematic reviews and meta-analyses of exercise and cognition have mainly focused on aerobic exercise and linked it most closely to improved executive function in healthy older adults.[10,26,27] By contrast, in our recent review of RCTs specific to individuals with MCI,[11] the benefit of aerobic exercise was limited to verbal fluency (no other executive function), and did not benefit memory in any trial.[18,28–31] Furthermore, the 2 trials of isolated moderate-high intensity resistance training resulted in large significant effects on memory,[17,18] whereas the effect of lower intensity resistance training combined with other exercise modalities was inconclusive.[32–35] These prior systematic reviews, along with the current SMART findings of significantly improved global function, executive function, and verbal/constructive memory in MCI after PRT provide evidence of the utility of this specific exercise modality at high intensity to address cognitive decline in this cohort.

Efficacy of CT

CT prevented objective memory decline during the intervention period only, suggesting that the benefits from CT in this cohort are contingent upon sustained training. Very few RCTs of multidomain CT such as used in SMART have been reported in individuals with MCI[12] or cognitive complaints,[36] and the results are mixed, with most effect sizes being negligible or small. Thus, our findings and review of the literature suggest that there is currently no evidence-based CT training paradigm to recommend for global cognitive improvement in MCI.

Combined PRT and CT

Contrary to our hypothesis, the Combined Training Group, receiving full doses of each active intervention, performed significantly worse compared with isolated PRT on Executive and Global Domains; differences which were sustained at 18 months. This paradoxical negative effect of combined physical and CT we observed stands in contrast to large beneficial effects reported in two previous small studies of combined physical/CT in healthy cohorts,[37,38] as well as to the neutral effect seen in the recent Mental Activity and eXercise (MAX)[36] trial in older adults with cognitive complaints.

The mechanism of this significant blunting of PRT benefit when CT was added is not known. The combined intervention, which was both mentally and physically challenging, could have resulted in excessive stress, less engagement in home or community-based activities, or other changes that inhibited rather than promoted neural plasticity and cognitive benefits. Concurrent aerobic and resistive exercise has been shown to negatively impact anabolic adaptations to isolated PRT such as strength gain, thought to be due to interference at the molecular level.[39] It is possible that a similar interference with neural/cognitive adaptations to PRT could occur with concurrent CT, a novel hypothesis warranting further investigation.

Conclusions

We have shown for the first time that 6 months of high intensity PRT improved the primary outcome of global cognition, as well as executive function and verbal/constructional memory in older adults

with MCI, with some maintenance of global and executive function benefit 12 months after cessation of training. By contrast, CT had no significant effects on global function, individual tests, or any Cognitive Domains other than memory, and it attenuated Memory Domain decline during the period of active training only. Combined Training unexpectedly significantly reduced the benefits of isolated PRT on executive and global function. Further large-scale trials are warranted to confirm and extend our findings, explore the mechanism of cognitive/neural adaptations to PRT, and most critically to demonstrate that PRT can reduce incident dementia in this high-risk cohort.

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Supplementary Data

Supplementary Data related to this article can be found online at http://dx.doi.org/10.1016/j.jamda.2014.09.010.

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