Supplemental Online Content

Lenze EJ, Voegtle M, Miller JP, et al. Effects of Mindfulness Training and Exercise on Cognitive Function in Older Adults. *JAMA.* Published online December 13, 2022. doi:10.1001/jama.2022.21680

eFigure 4J. Executive Function Change as a Function of Most vs Least Increase in Lean Body Mass in Exercise+ Group
eFigure 4K. Memory Composite Change as a Function of Most vs Least Increase in Daily Activity in Exercise+ Group
eFigure 4L. Executive Function Change as a Function of Most vs Least Increase in Daily Activity in Exercise+ Group
eFigure 4M. Memory Composite Change as a Function of Most vs Least Increase in Aerobic Fitness in Exercise+ Group
eFigure 4N. Executive Function Change as a Function of Most vs Least Increase in Aerobic Fitness in Exercise+ Group
eFigure 4O. Memory Composite Change as a Function of Most vs Least Increase in Sleep Time in Exercise+ Group
eFigure 4P. Executive Function Change as a Function of Most vs Least Increase in Sleep Time in Exercise+ Group
eFigure 4Q. Memory Composite Change as a Function of Most vs Least Reduction in Time to Fall Asleep in Exercise+ Group
eFigure 4R. Executive Function Change as a Function of Most vs Least Reduction in Time to Fall Asleep in Exercise+ Group
eFigure 4S. Memory Composite Change as a Function of Most vs Least Increase in Mindfulness in MBSR+ Group
eFigure 4T. Executive Function Change as a Function of Most vs Least Increase in Mindfulness in MBSR+ Group
eFigure 4U. Memory Composite Change as a Function of Most vs Least Reduction in Cortisol in MBSR+ Group
eFigure 4V. Executive Function Change as a Function of Most vs Least Reduction in Cortisol in MBSR+ Group
eFigure 4W. Memory Composite Change as a Function of Most vs Least Increase in Sleep Time in MBSR+ Group
eFigure 4X. Executive Function Change as a Function of Most vs Least Increase in Sleep Time in MBSR+ Group
eFigure 4Y. Memory Composite Change as a Function of Most vs Least Reduction in Time to Fall Asleep in MBSR+ Group
eFigure 4Z. Executive Function Change as a Function of Most vs Least Reduction in Time to Fall Asleep in MBSR+ Group
eMethods 5. Grant: Specific Aims and Research Strategy

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods 1. Details of moderate-to-high intensity exercise as exclusionary criteria

Individuals with current moderate-to-high intensity exercise were excluded from trial participation. An extensive phone screening questionnaire (included below) was used to evaluate intensity of exercise. This screening captured information related to total minutes engaged in each type of activity (light vs moderate), ability to hold conversation during the activity (can hold conversation vs difficult to hold conversation), and heart rate (fast vs not fast).

Individuals who engaged in the following were excluded.

- 421 minutes/week or more of light activity
- 61 minutes/week or more of moderate activity
- 421 minutes/week or more of light + moderate activity

Given the complexity of the screening, included below are examples of combinations of activities reported during screening and associated operationalization.

If an individual reported:

- 180 minutes of light activity per week (e.g., walking 1 hour, 3 days per a week)
- 90 minutes of light activity per week (e.g., stretching 30 minutes, 3 days per a week)
- 30 minutes of moderate activity per week (e.g., strength training 30 minutes, 1 day per week)
  Total: 300 minutes light + moderate activity, they could be included.

If an individual reported:

- 420 minutes of light activity per week (e.g., walking 1 hour, 7 days per week)
  Total: 420 light activity, they were included.

If an individual reported:

- 420 minutes of light activity per week (e.g., stretching 1 hour, 7 days per week)
- 30 minutes of moderate activity per week (e.g., strength training 30 minutes, 1 day per week)
  Total: 450 minutes light + moderate activity, they were excluded.

If an individual reported:

- 90 minutes of moderate activity per week (e.g., strength training 30 minutes, 3 days per week)
  Total: 90 minutes of moderate activity, they were excluded.

Phone screening questions and schematic used to evaluate intensity of exercise

17. Have you been participating in any regular physical activity or exercise in the last month? ☐ **Yes** ☐ **No**
If **YES**, describe.

_____

_____

_____

_____

A. Walking: Time: _____ Frequency: _____ days/wk Distance: _____ Speed: _____ MPH

-Can you carry on a conversation? ☐ Yes ☐ No -Do you feel your heart beating faster? ☐ Yes ☐ No

B. Record other activity: _____ Time: _____ Frequency: _____ days/wk

-Can you carry on a conversation? ☐ Yes ☐ No -Do you feel your heart beating faster? ☐ Yes ☐ No

CALCULATE TOTAL TIME PER WEEK OF LIGHT VS. MODERATE ACTIVITY:

	*A. WALKING MIN/WEEK	*B. OTHER MIN/WEEK	TOTAL MIN/WEEK
LIGHT ACTIVITY	*CAN HOLD CONVERSATION; HEART **NOT** BEATING FAST	*CAN HOLD CONVERSATION; HEART **NOT** BEATING FAST	*IF **421 MIN/WEEK** OR MORE- EXCLUDE
MODERATE ACTIVITY	*DIFFICULT TO HOLD CONVO; HEART **IS** BEATING FAST	*DIFFICULT TO HOLD CONVO; HEART **IS** BEATING FAST	*IF **61 MIN/W** OR MORE- EX

•*ADD TOTALS FOR LIGHT AND MODERATE ACTIVITY*

*IF 421 MIN/WEEK OR MORE- EXCLUDE

8

eMethods 2. Details on exercise and mindfulness interventions

Description of Exercise Intervention

The exercise condition was designed to improve aerobic fitness, strength and balance.[1-5] It consisted of facility-based, instructor-supervised 1.5-hour classes twice-weekly for 6 months plus at-home exercise. Sessions consisted of aerobic exercise, resistance training, and functional exercises designed to improve balance, mobility, and flexibility. Classes continued once-weekly during the 12-month maintenance phase plus at-home exercise. Participants were prescribed home exercise by the instructors. The time goal was ≥300 minutes/week combined class + at-home exercise, with a preponderance of aerobic exercise (150+ minutes/week) and the remainder roughly divided between resistance and stretching/balance. Details regarding the exercise intervention are included below.

Description of Exercise Sessions During Acute 6-month Phase

Sessions were 90 minutes in duration split evenly (30 minutes each) between aerobic, strength, and balance/stretching exercises. Classes were generally overseen by 2-3 trained instructors and ran as follows: 15 minutes of metabolic warm-up that included balance challenges; 30 minutes of aerobic conditioning on machine of choice (e.g., treadmill, stationary bike, etc.); 30 minutes of resistance training on standard machines; 15 minutes of cool-down with static stretching, abdominal/core exercises and balance challenges. Once every fifth session, the class engaged in functional training for whole-body conditioning using exercise tools such as dumbbells, 4-8 inch box steps, resistance bands, or body weight alone. Following the standard 15 minute warm up, 60 minutes were completed in this fashion using a "circuit training" approach in which there were 3 to 5 "stations" designed for strength training and heart rate was elevated between stations with brief bouts of relatively high intensity cardiovascular activity. Each station was completed between 30-60 seconds with 15-30 seconds of cardiovascular activity between stations. Rotations were completed twice (i.e. each station was done 2x) with approximately 2 minutes of rest between repetitions. Between 3 and 5 groups of stations were completed each class. These functional training classes ended with a standard 15 minute cool-down.

Monitoring Exercise Intensity

Exercise intensity was monitored by participant report using the Rating of Perceived Exertion scale and by chest-worn heart rate monitors. Staff calculated and provided participants a target heart rate range to reach during aerobic activity in class. Target heart rate ranges were updated as participants progressed through the intervention to increase intensity. Participants recorded heart rate data from the monitor after aerobic sessions.

Intensity was prescribed using percentages of heart rate reserve (HRR) obtained from each participant's baseline resting heart rate and maximal heart rate from the GXT to volitional fatigue gathered in the laboratory. Target heart rate range progressed from 50-55% HHR for the first 2-3 weeks, to 55-65% by week 6, and up to 60-70% beginning week 13 for the duration of the 24 week acute period. High intensity "intervals" were introduced in week 5, beginning with 2 intervals of 1 minute 'on' and 1 minute 'off' of increasing heart rate by 5-10 beats per a minute. These intervals increased in number (up to 5 maximum) and duration (up to 3 minute maximum) from approximately week 6 to 24.

With respect to increasing resistance intensity on standard machines: At baseline and 6 months, one-repetition maximum (1RM) was assessed for lower extremity (leg press) and upper extremity (seated row). Participants' intensity was increased based on the new 1RM for each of those two exercises, such that their relative training intensity was either maintained or increased to maintain a target range of 75-80**%** of their newest 1RM. For the other strength exercises not tested by 1 RM, periodic quick checks were conducted by the trainers by asking the participant to perform as many repetitions as they could at the current machine setting on their program. Those who could perform >10 reps in good form were progressed to a higher machine setting/weight, which was determined somewhat subjectively by the number of repetitions each participant could complete and their perceived effort in doing so, with the goal of maintaining the resistance at an absolute weight/machine setting that would induce temporary failure/fatigue within the target range of 8-10 repetitions.

Home Exercise Practice

Participants were prescribed home exercise. This was monitored during the acute phase using surveys sent daily to participants via their phones or study-provided tablets that asked whether they had exercised on that day, with categorical options for aerobic and strength/balance/stretching each measured. Cardio was split by 20 minute categories (0, 1-19, 20-39, 40-59, 60+ minutes) and strength/balance/stretching by 10 (0, 1-9, 10-19, 20-29, 30+ minutes).

The home exercise program encouraged individual selection of the mode with a focus on aerobic activity (with the remainder divided roughly between strength and stretching/balance activities) with a goal of accumulating 120 minutes each week; during the maintenance phase this home exercise goal was increased to 180-210 minutes/week reflecting the less frequent classes (once weekly, compared to twice weekly during the acute phase) and in order to maintain an overall goal of ~300 minutes/week exercise. Participants were encouraged to exercise with family or friends, and vary their selected exercise to help maintain enthusiasm. Light exercise could include stretching, walking, dancing, or any physical activity. A number of

body weight strength based exercises were also provided in a binder with proper form being taught for these exercises during early functional training classes. Participants were encouraged to complete strength training at home, although they could opt out if they felt unsafe doing so.

Description of Mindfulness Intervention

The mindfulness condition was designed to instruct participants in mindfulness-based stress reduction (MBSR) training and matched the format of the consensus MBSR protocol.[6] Sessions consisted of facility-based, instructor led and supervised classes. After an introductory meeting (orientation), the acute phase was conducted in eight weekly 2.5 hour classes plus a half-day retreat. Sessions consisted of instruction in mindfulness meditation practices and exercises to enhance mindfulness in everyday life. Participants were prescribed home mindfulness practice by the instructors. The time goal was ≥60 minutes/day at-home practice. Classes continued once-monthly for 2.5 hours during the maintenance phase, plus ≥60 minutes/day at-home practice. Details regarding the mindfulness intervention are included below.

Description of Mindfulness Sessions During Acute Phase

Sessions were 2.5 hours in duration and included instruction in key concepts of mindfulness-based stress reduction. Instruction included lecture style presentation, formal practice, and group discussion. Classes were led by 1-2 trained instructors. One half-day (4 hour) retreat was held in the latter half of the eight week course and consisted exclusively of instructor led silent formal practice.

Home Mindfulness Practice

Participants were prescribed home mindfulness practice. This was monitored during the acute phase using surveys sent daily to participants via their phones or study-provided tablets that asked whether they had practiced mindfulness techniques on that day, with categorical options (0, 1-9, 10-19, 20-29, 30+ minutes) for Mindful Movement / Yoga, Body Scan, Mindful Breathing/Meditation, and Mindfulness of Everyday Activities each measured.

The home mindfulness program encouraged individual selection of the technique with a goal of practicing 60 minutes each day; during the maintenance phase this home mindfulness goal remained the same even though classes were less frequent (once monthly, compared to once weekly during the acute phase). Participants were encouraged to use study provided mindfulness recordings, companion books, and other mindfulness resources to maintain their home practice.

eMethods 3. Details on MBSR instructor fidelity assessment by external referees

Two tapes per MBSR group, one from the first four sessions and one from last four sessions, were randomly selected and rated using the Mindfulness-Based Interventions: Teaching Assessment Criteria (MBI:TAC) by Dr. Rebecca Crane at Bangor University, the developer of the MBI:TAC. The MBI:TAC rates mindfulness instructor performance across six domains.[6] These domains include:

(1) Coverage, pacing, and organization of session curriculum[6]

(2) Relational skills (e.g., ability of instructor to relate to participants)

(3) Embodiment of mindfulness

(4) Guiding mindfulness practice

(5) Conveying themes through interactive inquiry and didactic teaching

(6) Holding the group learning environment

An overall rating for the selected sessions was made. The six levels of ratings range from *Incompetent* to *Advanced*. All sessions rated for this trial fell into the top three categories, with 26.1% rated *Competent*, 31.0% rated *Proficient* or *Proficient/Advanced*, and 42.9% rated *Advanced*.

eMethods 4. Summary of Physiological and Performance Measures Used to Evaluate Exercise and Mindfulness-Induced Cognitive Benefits

At 0, 6, and 18-month time points, we evaluated several physiological and performance-based measures to assess mechanisms of mindfulness and exercise-induced cognitive benefits. The table below summarizes measurements used, approach, and units.

Measurement	Approach Used to Measure	Measurement Unit
Aerobic Fitness[8]	Estimated by using a graded treadmill test, measuring the time to reach 85% of age-predicted maximum heart rate	seconds
Insulin Sensitivity[9]	75 gram 2-hour oral glucose tolerance test with sampling of glucose at 0, 90, and 120 minutes and insulin at 0 and 90 minutes	n/a
Homeostatic Model Assessment of Insulin Resistance[10] (HOMA-IR)	Fasting glucose and insulin	n/a
Total Fat Mass[11]	Dual energy X-ray absorptiometry	kilograms
Total Lean Body Fat[11]	Dual energy X-ray absorptiometry	kilograms
Short Physical Performance Battery[12] (SPPB)[a]	Assesses walking speed, lower extremity strength, and balance	Points on scale (range of 1 to 12, with higher scores better)
Plasma Cortisol Levels[13]	Salivary measurements collected at waking, wake+30 minutes, and bedtime on three consecutive days	Area Under the Curve (AUC) cortisol concentration
Daily Physical Activity	Tri-axial accelerometer which participants wore continuously for ten consecutive days	Counts per minute
Time to Fall Asleep	Tri-axial accelerometer which participants wore continuously for ten consecutive days	Minutes (min)
Total Sleep Time	Tri-axial accelerometer which participants wore continuously for ten consecutive days	Minutes (min)
Mindfulness[14]	Measured using the Cognitive and Affective Mindfulness Scale–Revised (CAMS-R)	Points on a scale (range of 12 to 48, with higher scores better)
Strength	One-repetition maximum (1-RM)[b] combining upper and lower body measurements. This represents the maximal weight an individual can lift for only one repetition with correct technique. The number is for arms+legs combined.	kilograms

Abbreviations: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; SPPB, Short Physical Performance Battery; AUC, area under curve; Minutes (min); CAMS-R, Cognitive and Affective Mindfulness Scale-Revised; 1-RM, one-repetition maximum

[a] Modified scoring for the SPPB was used.

[b] 1-RM was only done in exercise+ individuals.

Four-Group Analysis

We examined interaction effects across intervention groups. In eTable 1, we present a four-group analysis (MBSR alone, Exercise alone, combined MBSR+Exercise, and Health Education alone). Reported below are least square means and 95% CIs. Least square means can be thought of as model predicted means. Three-way interactions were tested (described below). This comparison did not change the results of the primary analysis. No significant interaction effects were revealed.

eTable 1. Presentation of Main Results as Four-Group Comparison, and Analysis of 3-Way Interaction Effects

	MBSR Least Square Means (95% CI)	**Exercise** Least Square Means (95% CI)	**MBSR+Exercise** Least Square Means (95% CI)	**Health Education** Least Square Means (95% CI)
Memory Composite Score[a]				
Baseline	-0.06 (-0.22 to 0.09)	-0.10 (-0.26 to 0.06)	-0.16 (-0.32 to 0.00)	-0.18 (-0.33 to -0.02)
Month 3	0.16 (-0.003 to 0.33)	0.11 (-0.06 to 0.29)	-0.03 (-0.20 to 0.14)	-0.04 (-0.20 to 0.13)
Month 6	0.34 (0.17 to 0.51)	0.41 (0.23 to 0.59)	0.31 (0.14 to 0.49)	0.27 (0.10 to 0.44)
Month 18	0.58 (0.41 to 0.75)	0.42 (0.25 to 0.60)	0.41 (0.23 to 0.59)	0.36 (0.19 to 0.53)
Cognitive Control Composite Score[b]				
Baseline	0.09 (-0.07 to 0.24)	-0.002 (-0.16 to 0.16)	0.10 (-0.06 to 0.25)	-0.02 (-0.17 to 0.13)
Month 3	0.24 (0.08 to 0.39)	0.24 (0.08 to 0.40)	0.29 (0.13 to 0.44)	0.18 (0.03 to 0.33)
Month 6	0.41 (0.26 to 0.57)	0.32 (0.16 to 0.48)	0.56 (0.40 to 0.71)	0.28 (0.13 to 0.43)
Month 18	0.32 (0.17 to 0.48)	0.27 (0.11 to 0.44)	0.39 (0.23 to 0.56)	0.32 (0.17 to 0.48)
Hippocampal Volume[c] (mm^3)				
Baseline	3685 (3629 to 3741)	3608 (3547 to 3670)	3675 (3616 to 3733)	3627 (3571 to 3683)
Month 6	3664 (3608 to 3720)	3593 (3532 to 3655)	3654 (3596 to 3713)	3607 (3552 to 3663)
Month 18	3626 (3570 to 3682)	3563 (3502 to 3625)	3599 (3541 to 3658)	3578 (3522 to 3635)
DLPFC Surface Area[d] (mm^2)				
Baseline	12279 (12068 to 12489)	12165 (11934 to 12396)	12310 (12091 to 12530)	12292 (12081 to 12502)
Month 6	12304 (12093 to 12515)	12151 (11920 to 12382)	12288 (12069 to 12508)	12264 (12053 to 12475)
Month 18	12266 (12054 to 12477)	12148 (11917 to 12379)	12333 (12112 to 12553)	12267 (12055 to 12479)
DLPFC Cortical Thickness[e] (mm)				
Baseline	2.77 (2.74 to 2.79)	2.77 (2.74 to 2.79)	2.78 (2.75 to 2.80)	2.77 (2.75 to 2.79)
Month 6	2.75 (2.72 to 2.77)	2.76 (2.73 to 2.79)	2.77 (2.74 to 2.79)	2.76 (2.73 to 2.78)
Month 18	2.75 (2.72 to 2.77)	2.75 (2.72 to 2.77)	2.74 (2.71 to 2.76)	2.75 (2.73 to 2.78)

Abbreviations: MBSR, Mindfulness Based Stress Reduction; DLPFC, dorsolateral prefrontal cortex

3-Way Interaction Effects

Below are analyses of the 3-way interactions. The interaction test evaluated whether the two interventions (Exercise and MBSR) were additive, synergistic, or interfering. None of the interactions were significant at the primary (6 month) or secondary (18 month) endpoints.

[a] Memory Composite Test of Interaction for MBSR+Exercise: Baseline and Month 6: $t(1604) = 0.08$, $p = 0.93$; Baseline and Month 18: $t(1604) = -0.56$, $p = 0.58$

[b] Cognitive Control (Executive Function) Test of Interaction for MBSR+Exercise: Baseline and Month 6: $t(1605) = 1.06$, $p = 0.29$; Baseline and Month 18: $t(1605) = 1.12$, $p = 0.26$

[c] Hippocampal Volume Test of Interaction for MBSR+Exercise: Baseline and Month 6: $t(922) = -0.30$, $p = 0.76$; Baseline and Month 18: $t(922) = -1.46$, $p = 0.15$

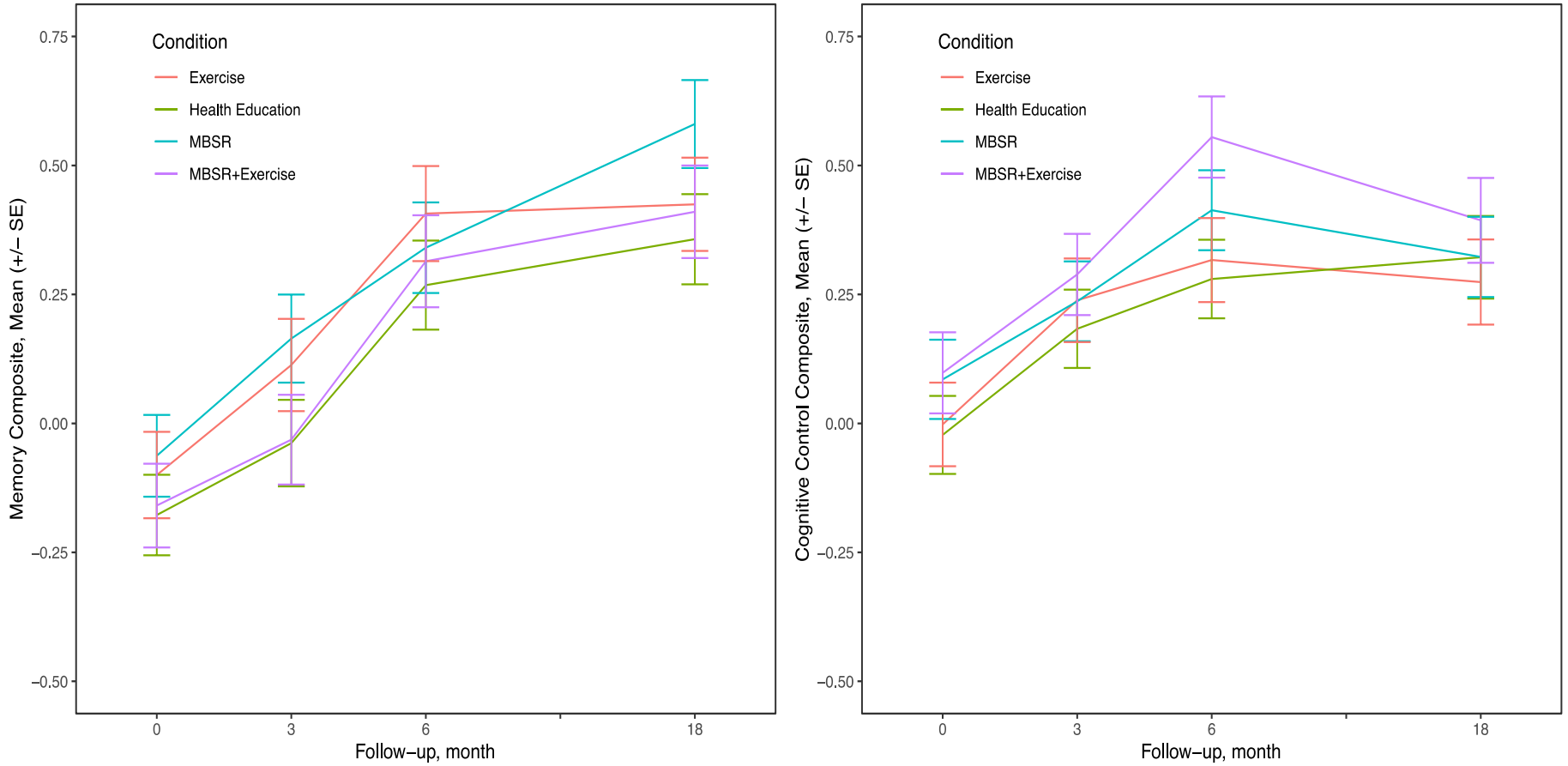
[d] DLPFC Surface Area Test of Interaction for MBSR+Exercise: Baseline and Month 6: $t(922) = -1.32$, $p = 0.19$; Baseline and Month 18: $t(922) = 0.57$, $p = 0.57$

[e] DLPFC Cortical Thickness Test of Interaction for MBSR+Exercise: Baseline and Month 6: $t(922) = 0.64$, $p = 0.52$; Baseline and Month 18: $t(922) = -1.22$, $p = 0.22$

Changes in Memory and Cognitive Control (Executive Function) Composite: 4-Group Comparison

eFigure 1 shows the intervention effects over 18 months for memory and cognitive control (executive function) composites.

eFigure 1. Change in Memory and Cognitive Control (Executive Function) Composite



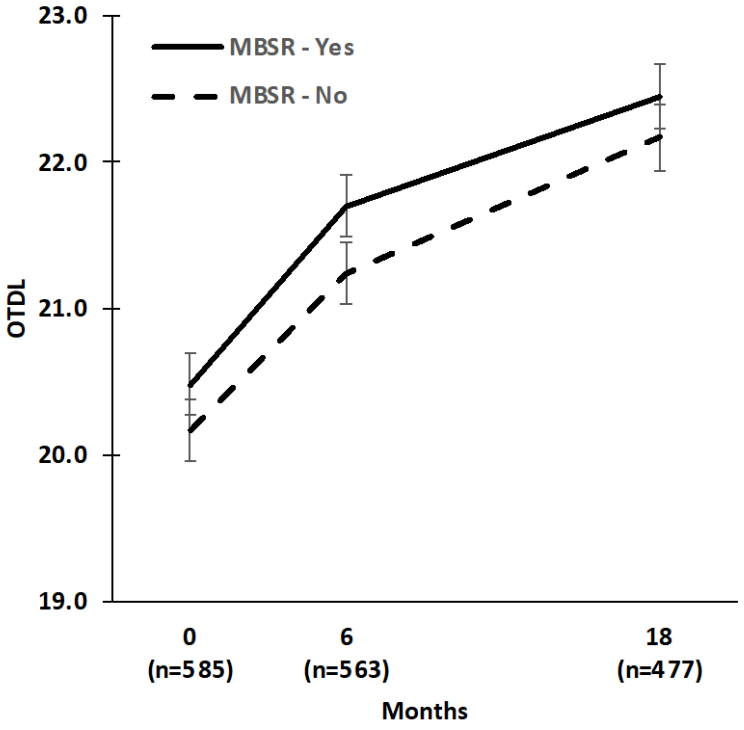
Abbreviations: SE, Standard Error; MBSR, Mindfulness Based Stress Reduction

Changes in Secondary Cognitive Outcomes Over 18 Months

The trial included two secondary cognitive outcomes: (1) the revised Observed Tasks of Daily Living (OTDL), a performance-based measure of functional capacity and (2) the Quality of Life in Neurological Disorders Cognitive Function (NeuroQOL), a self-report measure of cognitive concerns. eFigure 2A and 2B shows the changes in these secondary outcomes over 18 months. Essentially, there were no intervention effects on functional cognition or self-reported cognitive difficulties.

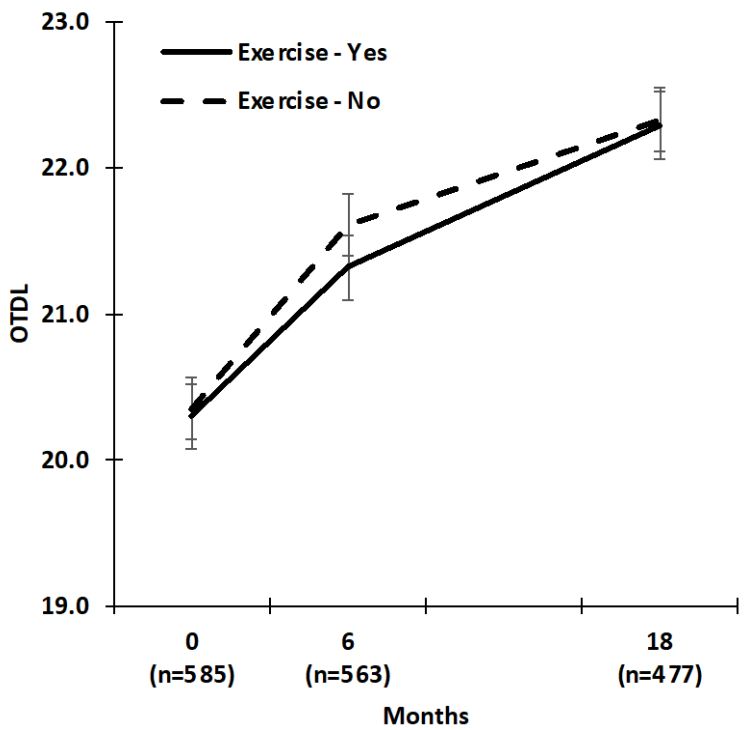
eFigure 2A. Changes in Functional Cognitive Capacity, as Measured by the Observed Tasks of Daily Living (OTDL)

Time by MBSR Intervention



Time x MBSR: F[2,1032] = 0.23, p = 0.80

Time by Exercise Intervention



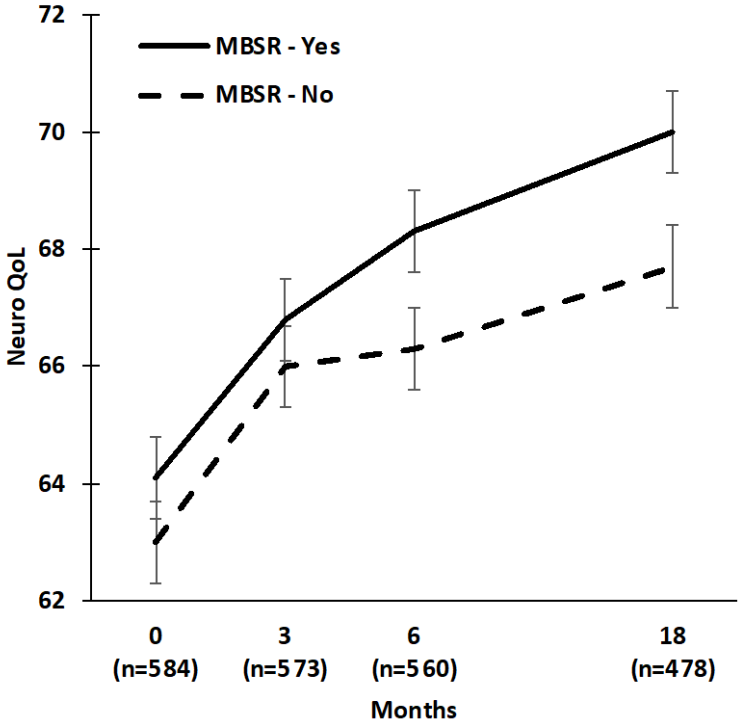
Time x Exercise: F[2,1032] = 0.50, p = 0.60

Note: Main Effect of Time, F[2,1032] = 96.16, p < 0.001

Abbreviations: MBSR, Mindfulness Based Stress Reduction; OTDL, Observed Tasks of Daily Living

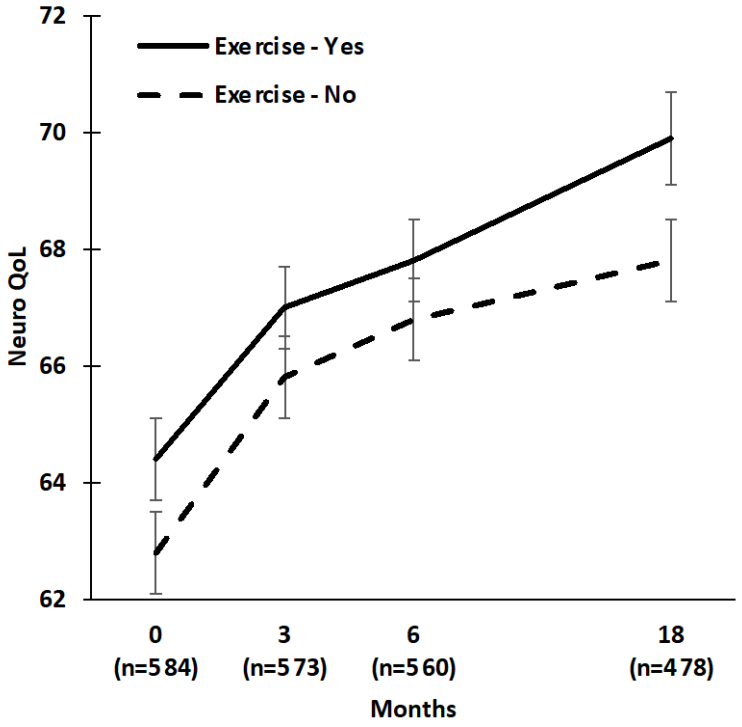
eFigure 2B. Changes in Self-Reported Cognitive Function, as Measured by NeuroQOL

Time by MBSR Intervention



Time x MBSR: F[3,1598] = 1.88, p = 0.13

Time by Exercise Intervention



Time x Exercise: F[3,1598] = 0.75, p = 0.53

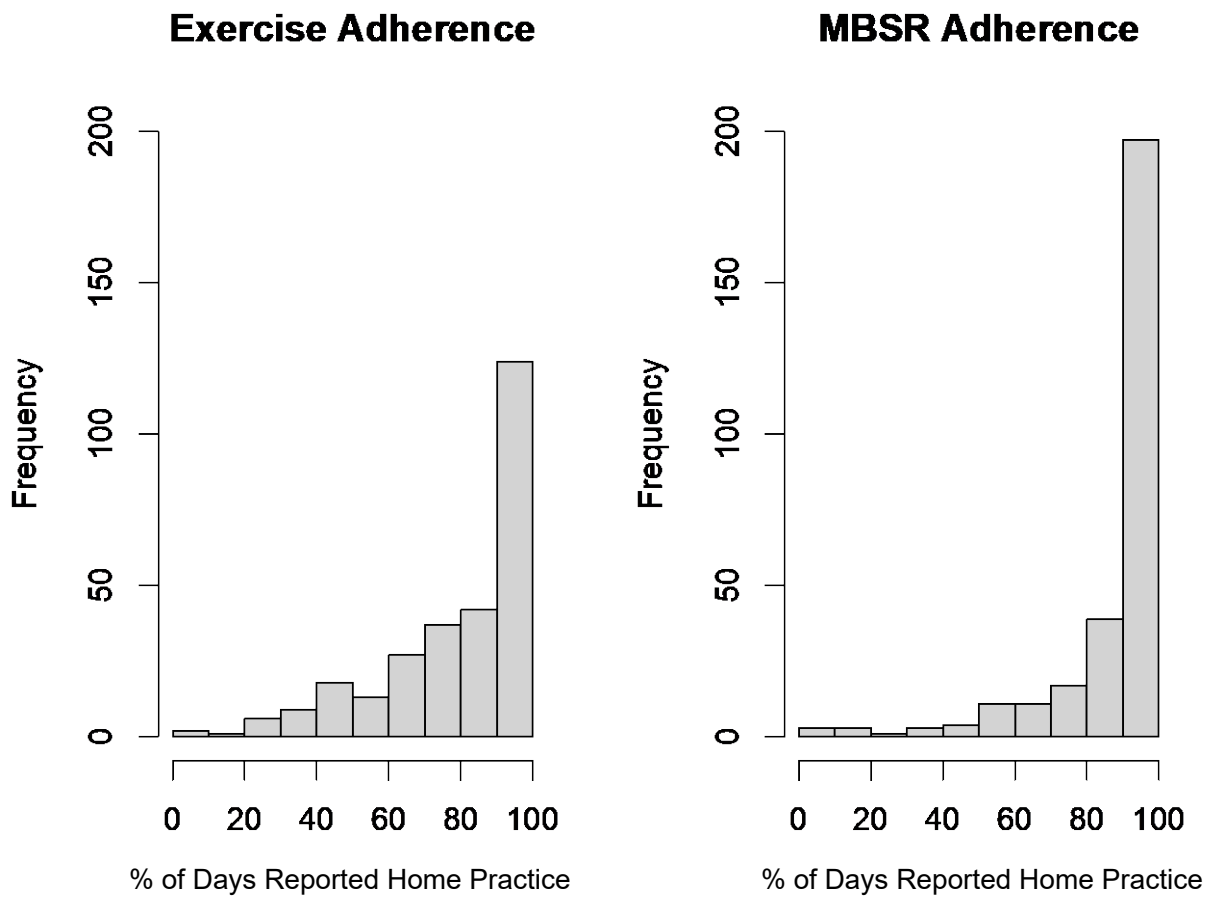
Note: Main Effect of Time: F[3,1598] = 72.11, p < 0.001

Abbreviations: MBSR, Mindfulness Based Stress Reduction; NeuroQOL, Quality of Life in Neurological Disorders Cognitive Function

Participant Adherence to the Interventions

Home Practice Adherence: During the first six months of the interventions, all participants randomized to the MBSR and exercise interventions used either their own smartphone or a study-provided iPad which sent a daily prompt asking how many minutes they practiced mindful movement/yoga, body scan, or mindful breathing/meditation (if randomized to MBSR) and/or aerobic activity, or strength training/balance/stretching (if randomized to exercise). eFigure 3A includes histograms of these participants in terms of each participant's percentage of *Yes* responses (>0 minutes spent on an MBSR or exercise activity) as a percentage of the participant's total responses to the survey (for example, if a participant randomized to exercise answered 100 surveys in the first 6 months and indicated they did exercise on 80 of those days, they would be included in the histogram in the 80% bar). As the histograms show, home practice was generally high, with most participants reporting practice on at least 70% of days.

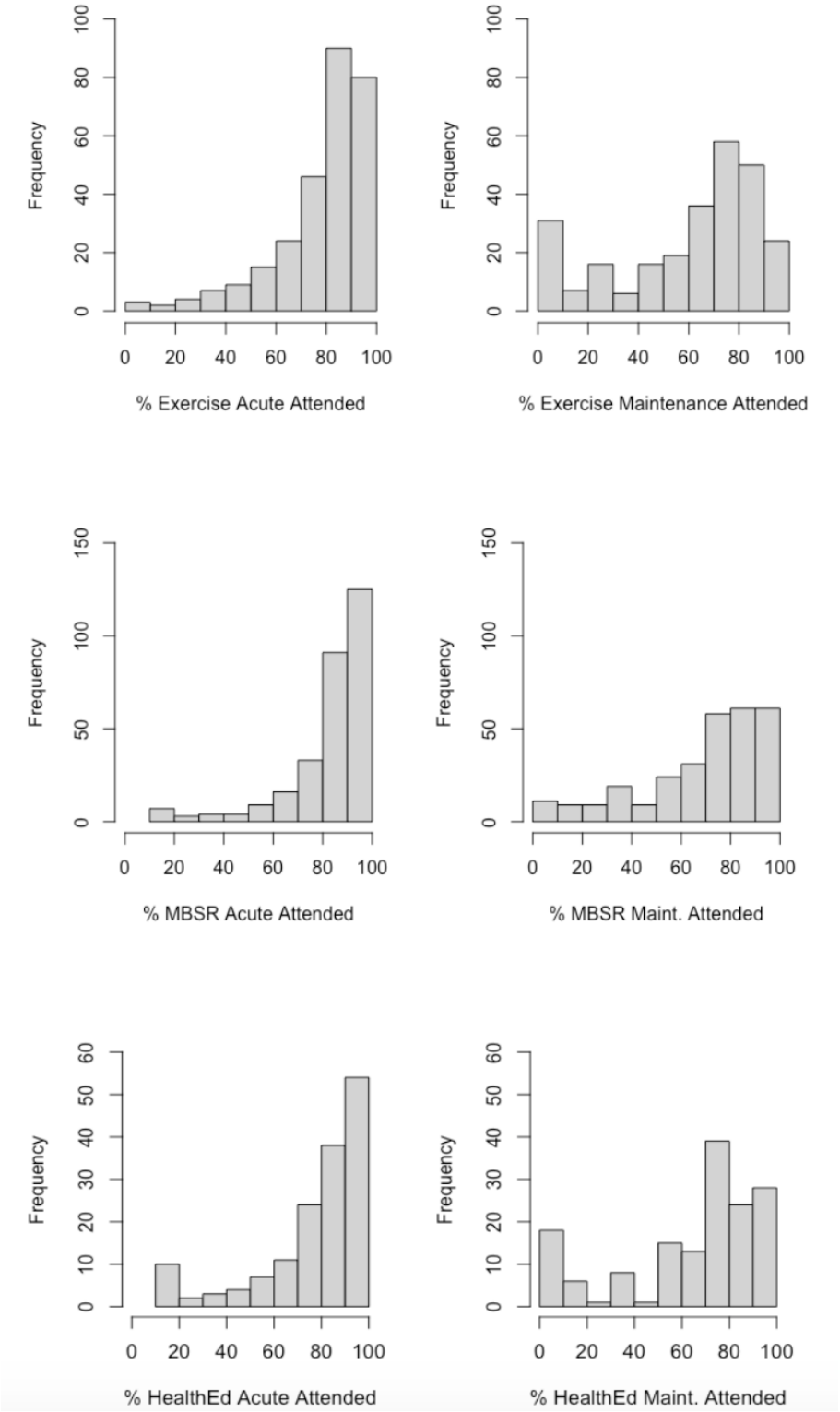
eFigure 3A. Home Practice Adherence Rates During the First Six Months of the Interventions



Note: From 6 to 18 months, participants did not receive daily measurements of practice but were asked if they had any breaks from practicing at home (e.g., due to injury). In the MBSR+Exercise group, participants reported a total of 545 breaks; 67 of these were short (<7 days), 193 were long (>7 days), and 285 were of unknown duration. In the Exercise-only group, participants reported a total of 475 breaks (69 short, 173 long, 233 unknown duration). In the MBSR-only group, participants reported a total of 461 breaks (72 short, 120 long, 269 unknown duration).

Class Attendance: Study staff recorded participant attendance at all classes during both the acute and maintenance phases. As the histograms show in eFigure 3B, class attendance was generally high, with most participants attending at least 70% of classes. Exercise participants attended a median of 83.3% [IQR, 71.7 to 91.7] of classes in the acute phase and 70.6% [IQR, 46.2 to 80.8] of classes in the maintenance phase. MBSR participants attended a median of 90.0% [IQR, 80.0 to 100.0] of classes in the acute phase and 75.0% [IQR, 59.1 to 87.5] of classes in the maintenance phase. Health Education participants attended a median of 90.0% [IQR, 80.0 to 100.0] of classes in the acute phase and 73.3% [IQR, 60.0 to 86.7] of classes in the maintenance phase.

eFigure 3B. Class Attendance Rates During the Interventions



eResults. Assessment of Intervention Contamination

Summary: Participants were asked if they were engaged in any meditative practices if not randomized to MBSR, or moderate-high intensity exercise if not randomized to exercise. Among those not randomized to MBSR, there were 2 reported instances (i.e., people who engaged in meditative practice) at 3 months, 2 at 6 months, and 5 at 18 months. Among those not randomized to exercise there were 11 instances (i.e., people who engaged in regular moderate-high intensity exercise) at 3 months, 5 at 6 months, and 9 at 18 months. Participants were also asked if they were engaging in any brain training games outside of the trial; there were 4 instances at 3 months, 7 at 6 months, and 3 at 18 months. All of these participants were excluded from the per-protocol analyses presented in eTable 2.

Below are tables with the questions asked of participants at the pre-defined time points (3, 6, and 18 months) to evaluate intervention contamination. Each table includes the number of instances, as well as a detailed summary of all *Yes* responses determined to be possible intervention contamination.

Possible Intervention Contamination Among Participants Not Randomized to MBSR

Question	Month	Number of Instances	Description
"Have you engaged in any meditative practices, including formal meditation, yoga or focused breathing exercises outside of your participation in this study since your last in-person visit with research staff?"	3	2	• Did 1 meditation class once then stopped • Was doing some yoga and meditation prior to study. Decreased yoga, but meditation is the same (one time per a week).
	6	2	• 10 minutes of meditation every morning. Started this up again around March. Did it before the study, but stopped for first 3 months. • Praying meditate once a week for an hour & do chair yoga
	18	5	• Focused breathing, visualization/focusing on the breath. 5-10 minutes 4 times a week. • Meditation: 1 time per day. Imagines floating on the ocean and trying to be calm and peaceful. • Meditates 3 times a week on his own for years & did not stop • Mindful & stretching yoga 2 times a week for an hour • "Oriental" meditation, never stopped, every night 15 minutes

Possible Intervention Contamination Among Participants Not Randomized to Exercise

Question	Month	Number of Instances	Description
"Have you engaged in any structured exercise outside of your participation in this study since your last in-person visit with research staff?"	3	11	• Had a stent placed, so started intensive cardiac rehab on March 23, 2017. Goes 3 times a week, for about 1 hour. Does mostly aerobic (treadmill, elliptical), some light weights (5 lbs) • Joined a health club, does weights, machines, treadmill for 1 hour a week. • Resumed senior fitness classes at YMCA 2 times a week for 55 minutes; workout at YMCA 1 time a week on own using machines. Was in walking boot at time of enrollment due to injury but reported was doing all these activities before the injury • Returned to gym for weights/cardio 2 times a week starting March 26. • Silver sneakers • Sit-ups, lifts, and line dancing; 2 times a week • Started body sculpt class 1 time a week for 60 minutes in November 2017. Started yoga class 1 time a week for 60 minutes in November 2017 • Starting gym workouts. Trying to go 3 to 4 times per a week (treadmill, weights, started about 1 month ago) • Strength & balance class 55+ with weights, circuit bootcamp 1 to 2 times a week started back up in February 2018 • Stretching class for 50 minutes once a week started 4 weeks ago • Zumba, hip hop dance class, weights, yoga, cycling & all for about 1 hour.
	6	5	• Gym 3 times a week treadmill, weights 30 - 60 minutes/ session • Gym 5 days a week 60 minutes & include cycling & zumba 2 times a week 60 minutes • Gym class once a week • Started going to the YMCA 1 month ago, 2x/week, aerobic activity (class: Silver sneakers) • Zumba – 2 times/week
	18	9	• 30 minutes a day with an instructor in a fitness class. She does balance, stretching, toning. She does this 4 times a week up from 2 times a week when she joined the study. • Cardiac rehab: All the following exercises are completed once a week. 1. Sitting elliptical 12 min 2. Treadmill 12 min at 2.5 MPH 3. Arm pedaling machine 10 min 4. light weight lifting for 6 min 5. Stretching • Dance exercise 'aerobic' in her apartment complex. 45 minutes, 2 times a week. Lightweight dumbbells, tension bands, dancing to music. The class is taught by an instructor and there are about 20 people in the class. • Lap swimming 30 min three times per week. • One hour exercise class 3 times per week. • Exercises 5 days a week, 1-2 hours a day • Exercises 3 times per a week, 45 minutes, starting 2 months ago • Zumba class 3 times per week, one hour, for past 1 year • Treadmill twice a week for 1 hour

Possible Intervention Contamination Among Participants Engaging in Brain Training Games Outside of Trial

Question	Month	Number of Instances	Description
"Have you engaged in any brain training games, such as Lumosity or NeuroNation, outside of your participation in this study since your last in-person visit with research staff?"	3	4	• Every day • In 3 studies and he gets brain training games. Gets one every few months • Luminosity. Every night (started last week) • Started Brain HQ 3 months ago 2- to 3 times a week, 15 minutes each
	6	7	• Brain HQ computer games 20 minutes 2x a month • Brain HQ, an online class from SD Community College SD Continuing Ed. 3 to 4 times a week, 0.5 hours at a time • Have done Luminosity once a week not regularly • Lumosity 1 time a week since the 3mo assessment (instructor said it was ok) • Lumosity twice a month, 30 minutes, irregularly • Started Lumosity 2 to 3 months ago (was doing this prior to the study but stopped for 3 months) • Word game - computer daily 2 hours a day, about a year
	18	3	• Driving course - computer once a day for 10 minutes. 7 days a week for 1 year • Lumosity on and off for a year. Participant will use the app for about 2 hours a week. • Started Lumosity 6 months ago, uses once every 2 weeks, 30 minutes per session

eTable 2. Intervention Effects on Study Outcomes in Full Sample vs. Per-Protocol Subsamples

Shown are intervention effects expressed as difference in outcome between those who received vs did not receive the intervention on cognitive and MRI changes. Shown are the full sample (n=585) and two per-protocol sub-samples. These sub-samples were created based on (i) home practice: practicing mindfulness and/or exercise on ≥70% of days (months 0-6), and; (ii) class attendance: attending ≥70% of classes. The per-protocol samples also excluded individuals who engaged in interventions they were not randomized to (details proceeding this table, eResults). Based upon home practice, the per-protocol sample sizes were: MBSR+ (n=192); MBSR- (n=223); Exercise+ (n=190); and Exercise- (n=225). Based upon class attendance, the per-protocol sample sizes were: MBSR+ (n=226); MBSR- (n=221); Exercise+ (n=211); and Exercise- (n=236).

	Baseline/6 Months			Baseline/18 Months			Baseline/6 Months			Baseline/18 Months		
	MBSR Vs No MBSR Difference	95% CI	P-Value (DF)	MBSR Vs No MBSR Difference	95% CI	P-Value (DF)	Exercise Vs No Exercise Difference	95% CI	P-Value (DF)	Exercise Vs No Exercise Difference	95% CI	P-Value (DF)
Primary Outcomes												
Memory Composite Score[1]												
Full Sample	-0.04	(-0.15 to 0.07)	0.50 (1604)	0.08	(-0.04 to 0.19)	0.18 (1604)	0.07	(-0.04 to 0.17)	0.23 (1604)	-0.04	(-0.15 to 0.07)	0.47 (1604)
Per Protocol (Based on Practice)	0.02	(-0.11 to 0.14)	0.80 (1168)	0.08	(-0.05 to 0.21)	0.23 (1168)	0.09	(-0.04 to 0.21)	0.17 (1168)	-0.04	(-0.17 to 0.09)	0.55 (1168)
Per Protocol (Based on Class Attendance)	-0.02	(-0.14 to 0.10)	0.77 (1264)	0.08	(-0.05 to 0.20)	0.24 (1264)	0.07	(-0.05 to 0.20)	0.24 (1264)	0.00	(-0.13 to 0.12)	0.96 (1264)
Cognitive Control Composite[2]												
Full Sample	0.08	(-0.02 to 0.19)	0.12 (1605)	-0.04	(-0.15 to 0.07)	0.44 (1605)	0.07	(-0.03 to 0.18)	0.17 (1605)	-0.01	(-0.12 to 0.11)	0.93 (1605)
Per Protocol (Based on Practice)	0.11	(-0.02 to 0.23)	0.09 (1168)	-0.03	(-0.16 to 0.10)	0.68 (1168)	0.06	(-0.07 to 0.18)	0.37 (1168)	-0.07	(-0.20 to 0.06)	0.30 (1168)
Per Protocol (Based on Class Attendance)	0.09	(-0.02 to 0.21)	0.11 (1264)	-0.01	(-0.13 to 0.11)	0.82 (1264)	0.06	(-0.05 to 0.18)	0.29 (1264)	-0.04	(-0.16 to 0.08)	0.55 (1264)
Hippocampal Volume (mm^3)												
Full Sample	-3.46	(-14.27 to 7.34)	0.53 (922)	-20.16	(-33.88 to -6.44)	0.004 (922)	3.04	(-7.76 to 13.85)	0.58 (922)	-6.26	(-19.98 to 7.46)	0.37 (922)
Per Protocol (Based on Practice)	-4.15	(-16.94 to 8.65)	0.52 (677)	-18.44	(-34.25 to -2.62)	0.02 (677)	2.35	(-10.45 to 15.14)	0.72 (677)	-6.05	(-21.87 to 9.76)	0.45 (677)
Per Protocol (Based on Class Attendance)	0.01	(-12.10 to 12.11)	1.00 (748)	-14.26	(-29.18 to 0.66)	0.06 (748)	5.06	(-7.04 to 17.16)	0.41 (748)	-2.26	(-17.18 to 12.66)	0.77 (748)
DLPFC Surface Area (mm^2)												
Full Sample	22.71	(-22.95 to 68.36)	0.33 (922)	25.35	(-23.18 to 73.88)	0.31 (922)	-17.18	(-62.83 to 28.48)	0.46 (922)	21.11	(-27.41 to 69.64)	0.39 (922)
Per Protocol (Based on Practice)	23.67	(-29.94 to 77.27)	0.39 (677)	34.66	(-10.79 to 80.11)	0.13 (677)	-4.14	(-57.74 to 49.47)	0.88 (677)	16.31	(-29.14 to 61.76)	0.48 (677)
Per Protocol (Based on Class Attendance)	27.45	(-23.79 to 78.69)	0.29 (748)	15.43	(-27.29 to 58.15)	0.48 (748)	-9.71	(-60.95 to 41.53)	0.71 (748)	23.05	(-19.67 to 65.77)	0.29 (748)
DLPFC Cortical Thickness (mm)												
Full Sample	-0.01	(-0.02 to 0.01)	0.37 (922)	-0.01	(-0.02 to 0.00)	0.10 (922)	0.01	(0.00 to 0.02)	0.21 (922)	-0.01	(-0.02 to 0.00)	0.09 (922)
Per Protocol (Based on Practice)	0.00	(-0.01 to 0.01)	0.91 (677)	0.00	(-0.02 to 0.01)	0.64 (677)	0.01	(-0.01 to 0.02)	0.40 (677)	-0.01	(-0.03 to 0.00)	0.12 (677)
Per Protocol (Based on Class Attendance)	0.00	(-0.02 to 0.01)	0.69 (748)	-0.01	(-0.02 to 0.01)	0.40 (748)	0.00	(-0.01 to 0.02)	0.73 (748)	-0.01	(-0.03 to 0.00)	0.05 (748)

Abbreviations: CI, confidence interval; DF, degrees of freedom; DLPFC, dorsolateral prefrontal cortex

Effects of Exercise and MBSR on Key Physiological/Performance Variables Putatively Influential for Cognitive Health

Shown are (a) exercise-induced changes and (b) MBSR-induced changes in key variables identified in the literature as potentially influential on cognitive health. As eTable 3A shows, exercise (compared to no exercise) significantly increased physical performance, lean body mass, and aerobic fitness, and reduced fat mass and sleep latency (time to fall asleep; a measure of sleep quality); there were trends towards greater total daily activity and total sleep time; but, there were no effects on insulin sensitivity (either via OGIS or HOMA-IR) or cortisol level. As eTable 3B shows, MSBR (compared to no MBSR) did not significantly influence any variable.

eTable 3A. Effects of Exercise on Key Physiological/Performance Variables

	Exercise		Baseline/6 Months			Baseline/18 Months		
	Yes Least Square Mean (SE)	No Least Square Mean (SE)	Exercise Vs No Exercise Difference	95% CI	P-Value	Exercise Vs No Exercise Difference	95% CI	P-Value
Physical Performance (SPPB) (points on a 1-12 scale)								
Baseline	8.9 (0.1)	8.8 (0.1)	0.30	0.04 to 0.56	0.02	0.36	0.09 to 0.64	0.01
Month 6	9.1 (0.1)	8.7 (0.1)						
Month 18	9.0 (0.1)	8.6 (0.1)						
Total Lean Body Mass (kg)								
Baseline	43.4 (0.6)	44.0 (0.5)	0.72	0.51 to 0.94	< 0.001	0.43	0.15 to 0.71	0.002
Month 6	43.9 (0.6)	43.8 (0.5)						
Month 18	43.6 (0.6)	43.8 (0.5)						
Total Fat Mass (kg)								
Baseline	31.9 (0.6)	30.9 (0.6)	-1.17	-1.64 to -0.69	< 0.001	-0.91	-1.61 to -0.20	0.01
Month 6	30.7 (0.6)	30.9 (0.6)						
Month 18	30.7 (0.6)	30.6 (0.6)						
Insulin Sensitivity (OGIS)								
Baseline	346 (4.0)	350 (3.8)	1.01	-6.58 to 8.59	0.79	------	------	------
Month 6	353 (4.0)	355 (3.9)						
Month 18	------*	------*						
HOMA-IR								
Baseline	3.00 (0.13)	2.81 (0.12)	0.01	-0.02 to 0.04	0.62[a]	0.01	-0.03 to 0.04	0.63[a]
Month 6	2.90 (0.13)	2.80 (0.12)						
Month 18	3.13 (0.13)	2.99 (0.13)						

Daily Activity (counts per minute)								
Baseline	1917 (32)	1935 (31)	44.76	-9.99 to 99.51	0.11	61.57	-6.00 to 129.14	0.07
Month 6	1943 (32)	1916 (31)						
Month 18	1904 (33)	1861 (32)						
Strength (1-RM)[b] (kg)								
Baseline	215 (5.1)	------*	53.37	47.34 to 59.40	< 0.001	61.14	53.13 to 69.16	< 0.001
Month 6	269 (6.3)	------*						
Month 18	276 (6.8)	------*						
Cortisol Area Under Curve (AUC)								
Baseline	6079 (188)	5644 (178)	0.02	-0.02 to 0.06	0.34[a]	0.004	-0.04 to 0.05	0.88[a]
Month 6	6259 (190)	5826 (186)						
Month 18	6149 (204)	5602 (202)						
Aerobic Fitness (Time to 85% HR) (seconds)								
Baseline	339 (10.1)	357 (9.7)	42.34	22.50 to 62.18	< 0.001	------	------	------
Month 6	423 (10.4)	398 (10.1)						
Month 18	------*	------*						
Time to Fall Asleep (minutes)								
Baseline	6.8 (0.3)	6.0 (0.3)	-0.09	-0.16 to -0.01	0.02[a]	-0.08	-0.16 to -0.01	0.04[a]
Month 6	5.9 (0.3)	6.4 (0.3)						
Month 18	5.8 (0.3)	5.9 (0.3)						
Total Sleep Time (minutes)								
Baseline	382 (3.5)	384 (3.4)	7.06	-0.18 to 14.30	0.06	9.84	2.08 to 17.61	0.01
Month 6	387 (3.6)	382 (3.5)						
Month 18	394 (3.7)	386 (3.6)						

eTable 3B. Effects of MBSR on Key Physiological/Performance Variables

	MBSR	Baseline/6 Months	Baseline/18 Months

	Yes Least Square Mean (Standard Error)	No Least Square Mean (Standard Error)	MBSR Vs No MBSR Difference	95% CI	P-Value	MBSR Vs No MBSR Difference	95% CI	P-Value
Mindfulness (CAMS-R) (points on a scale)								
Baseline	37.9 (0.3)	36.9 (0.3)	-0.28	-1.01 to 0.45	0.45	-0.41	-1.21 to 0.39	0.32
Month 3	37.7 (0.3)	36.9 (0.3)						
Month 6	38.8 (0.3)	38.1 (0.3)						
Month 18	39.3 (0.3)	38.6 (0.3)						
Cortisol Area Under Curve								
Baseline	6040 (181)	5683 (184)	0.001	-0.04 to 0.04	0.96[a]	-0.02	-0.06 to 0.03	0.49[a]
Month 6	6214 (187)	5870 (189)						
Month 18	5862 (199)	5888 (207)						
Time to Fall Asleep (minutes)								
Baseline	6.5 (0.3)	6.4 (0.3)	0.03	-0.04 to 0.10	0.40[a]	0.04	-0.04 to 0.11	0.36[a]
Month 6	6.2 (0.3)	6.1 (0.3)						
Month 18	5.9 (0.3)	5.8 (0.3)						
Total Sleep Time (minutes)								
Baseline	383 (3.4)	382 (3.5)	2.12	-5.12 to 9.36	0.57	-1.60	-9.37 to 6.16	0.69
Month 6	386 (3.5)	383 (3.5)						
Month 18	389 (3.6)	390 (3.7)						

Abbreviations: SPPB, Short Physical Performance Battery; kg, kilograms; OGIS, Oral Glucose Insulin Sensitivity; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; 1-RM, One Repetition Maximum; HR, heart rate; MBSR, Mindfulness Based Stress Reduction; CAMS-R, Cognitive and Affective Mindfulness Scale-Revised

[a] P-values obtained after log-transforming the variable.

[b] 1-RM is upper plus lower body strength combined.

*Insulin sensitivity (OGIS) and aerobic fitness were not measured at 18 months, and 1-RM was only measured in exercise+ participants.

Subgroups of Most vs. Least increase in Physiological/Performance Variables Putatively Influential for Cognitive Health

Shown below is from the entire sample of MEDEX. We examined each of the key physiological and performance variables also shown in eTable 3, for which prior literature suggested that change in these variables with intervention could affect cognitive performance (e.g., an exercise-induced increase in insulin sensitivity could putatively improve cognitive performance). For each of these variables, the sample was divided into three tertiles, with the top tertile showing the greatest increase in this variable and the bottom tertile showing the least increase (generally a decrease) in this variable. These tertiles were constructed to examine effects of exercise and MBSR on cognitive performance outcomes as a function of change in these variables (see eFigure 4A through eFigure 4Z, pages 25-37).

eTable 4. Subgroups of Most vs. Least increase in Physiological/Performance Variables Putatively Influential for Cognitive Health

	Top Tertile				Bottom Tertile			
	0 to 6 Month Change		Baseline Mean (From)	Month 6 Mean (To)	0 to 6 Month Change		Baseline Mean (From)	Month 6 Mean (To)
	Average	Range			Average	Range		
Strength (1-RM) (kg)	+97	65 to 230	248	345	+16	-60 to 35	211	226
Physical Performance (SPPB) (points on a scale)	+1.6	1.0 to 4.0	8.2	9.8	-1.0	-6.0 to 0.0	9.3	8.4
Insulin Sensitivity (OGIS)	+51	23 to 119	329	380	-39	-196 to -12	367	327
Total Body Fat (kg)	+1.9	0.4 to 15.5	31.5	33.4	-3.4	-22.8 to -1.3	33	29.6
Lean Body Mass (kg)	+1.6	0.7 to 5.3	42.9	44.5	-1.3	-6.4 to -0.4	46.7	45.3
Daily Activity (counts per minute)	+323	117 to 1306	1853	2176	-314	-2362 to -100	2078	1764
Aerobic Fitness (seconds)	+180	103 to 479	304	484	-50	-347 to 14	391	341
Mindfulness (CAMS-R) (points on a scale)	+5.7	3.0 to 17.0	34.2	39.8	-3.5	-16.0 to -1.0	40.1	36.6
Cortisol Area Under Curve	+3131	924 to 21226	5149	8281	-2520	-16719 to -766	7364	4843
Total Sleep Time (minutes)	+47	18 to 175	359	405	-44	-170 to -15	399	355
Time to Fall Asleep (minutes)	+5.2	1.1 to 35.5	4.3	9.5	-5.6	-30.9 to -2.0	9.9	4.3

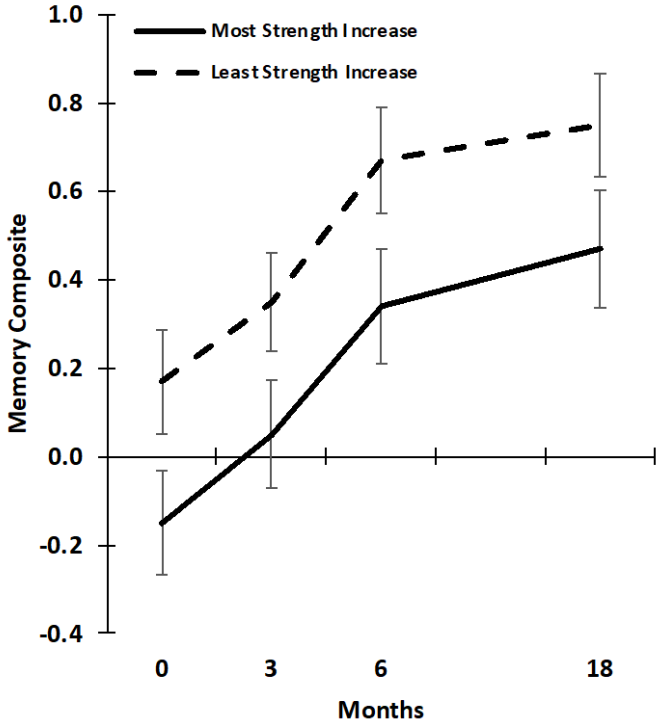
Abbreviations: 1-RM, One Repetition Maximum (upper and lower body combined); kg, kilograms; OGIS, Oral Glucose Insulin Sensitivity; CAMS-R, Cognitive and Affective Mindfulness Scale-Revised

Intervention Effects on Cognitive Outcomes as a Function of Influencing Putatively Beneficial Physiological/Performance Variables

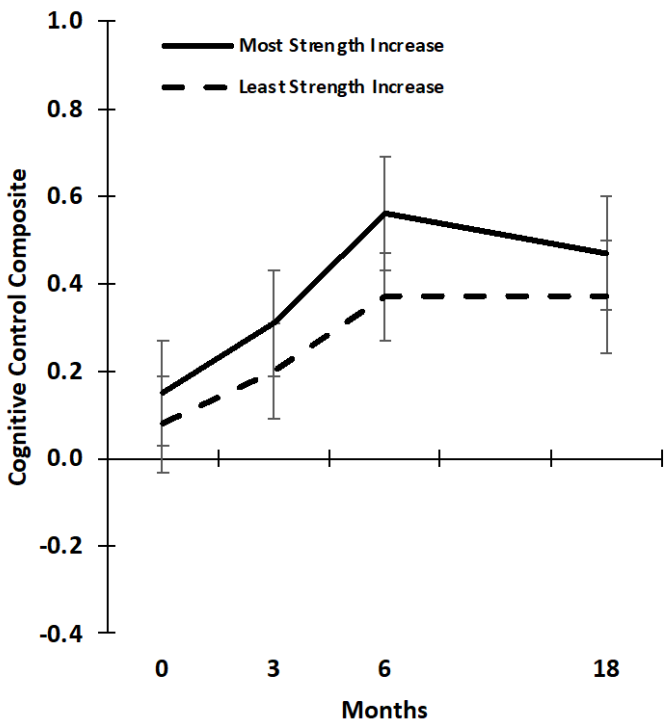
Shown below are line graphs of the cognitive change over time (for each primary outcome: Memory Composite and Executive Function (Cognitive Control Composite), within the relevant intervention group (e.g., Exercise+ group) as a function of whether they showed the most vs. least change in a potentially beneficial variable from baseline to 6 months. For example, the first figure shows whether cognitive improvement is greater among those randomized to exercise who showed the greatest increase in strength (compared to those who showed the least increase in strength). As the figures show, there are at most marginal, and in most cases no, differences in subgroups, suggesting that these interventions did not improve cognitive function in certain selected individuals who changed most physiologically/performance-wise from the interventions. Sample sizes in the top vs bottom tertile are below the figure.

Exercise+ Group

eFigure 4A. Memory Composite Change as a Function of of Most vs Least Increase in Strength in Exercise+ Group



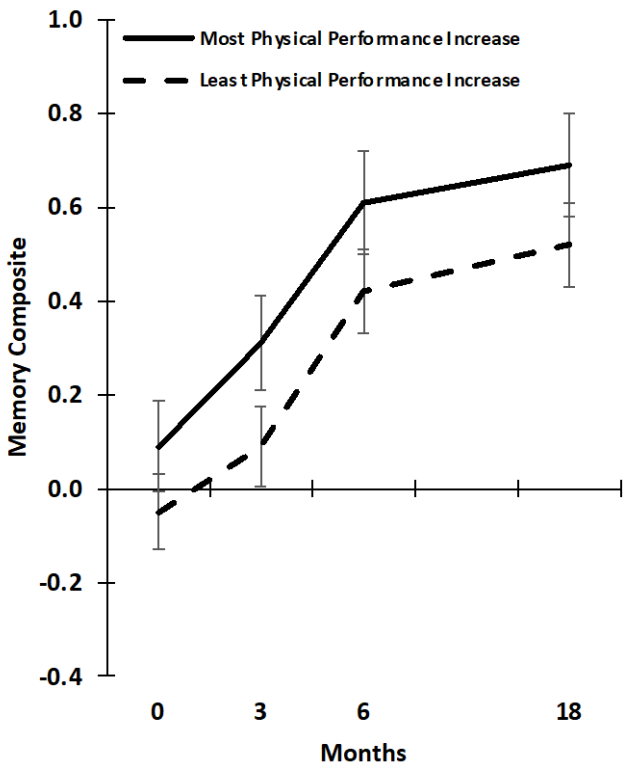
eFigure 4B: Executive Function Change as a Function of Most vs Least Increase in Strength in Exercise+ Group



No. of participants in each tertile

Top	66	66	66	62
Bottom	68	68	68	53

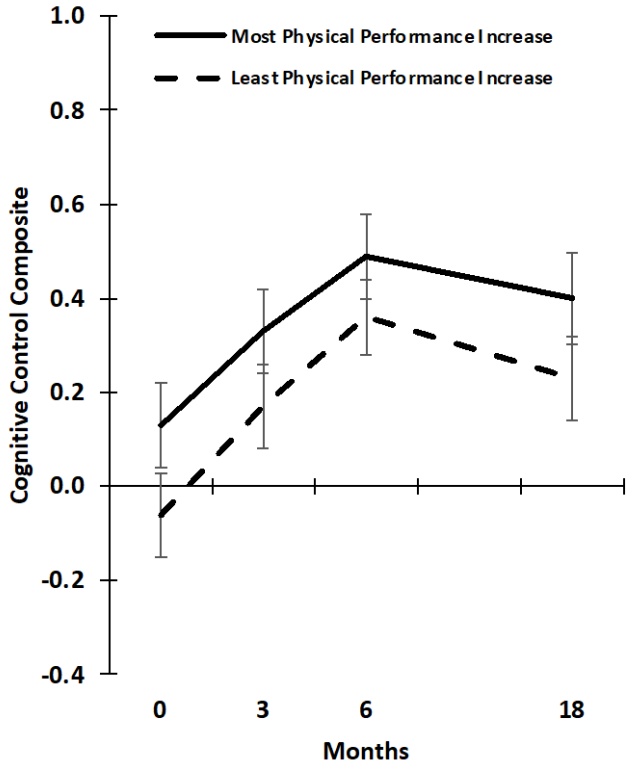
eFigure 4C. Memory Composite Change as a Function of Most vs Least Increase in Physical Performance in Exercise+ Group



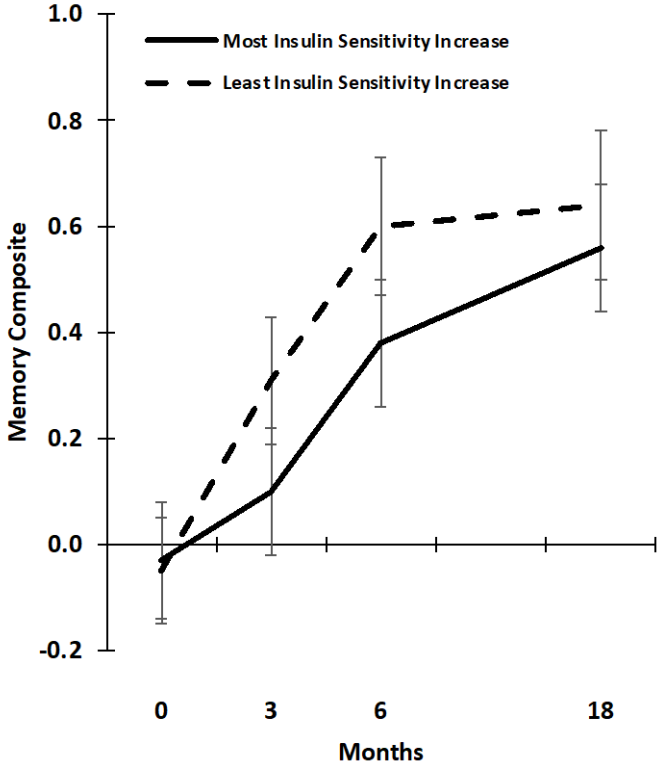
No. of participants in each tertile

Top	115	115	115	100
Bottom	148	148	147	122

eFigure 4D. Executive Function Change as a Function of of Most vs Least Increase in Physical Performance in Exercise+ Group



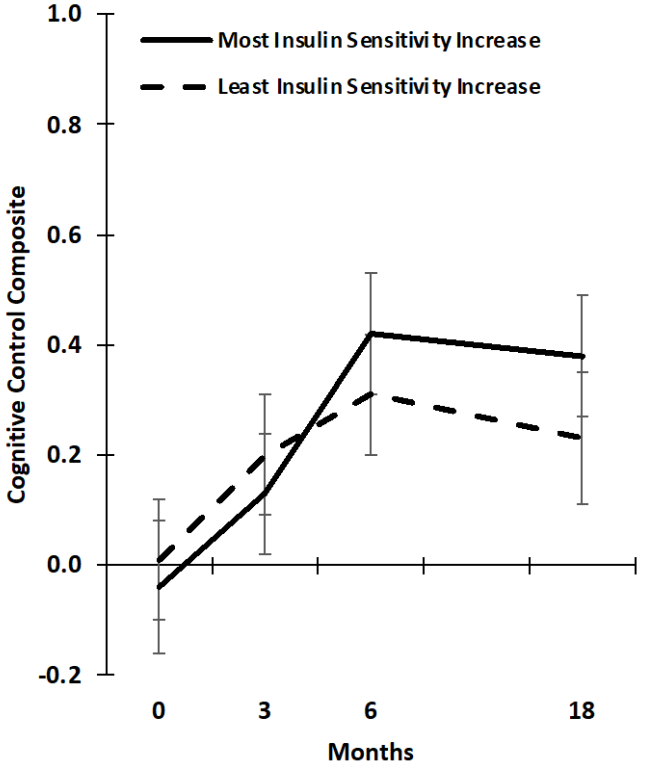
eFigure 4E. Memory Composite Change as a Function of Most vs Least Increase in Insulin Sensitivity in Exercise+ Group



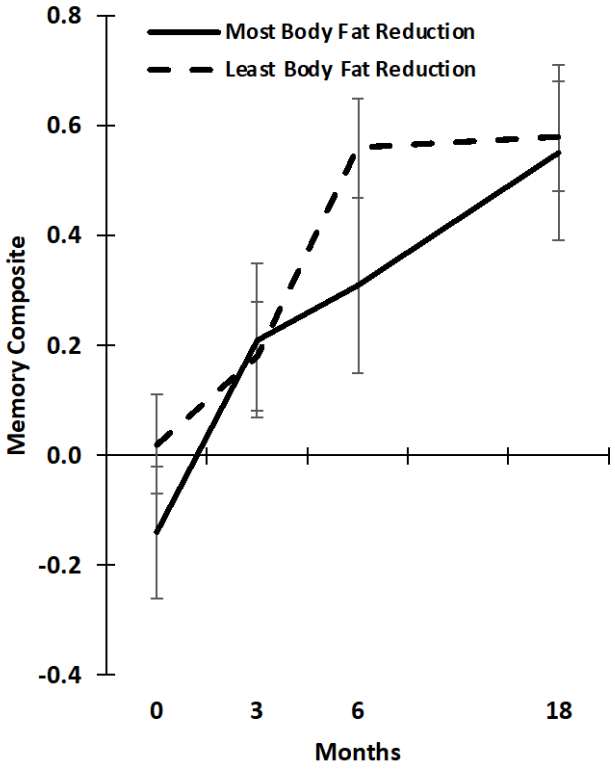
No. of participants in each tertile

Top	85	85	85	70
Bottom	78	78	77	66

eFigure 4F. Executive Function Change as a Function of of Most vs Least Increase in Insulin Sensitivity in Exercise + Group



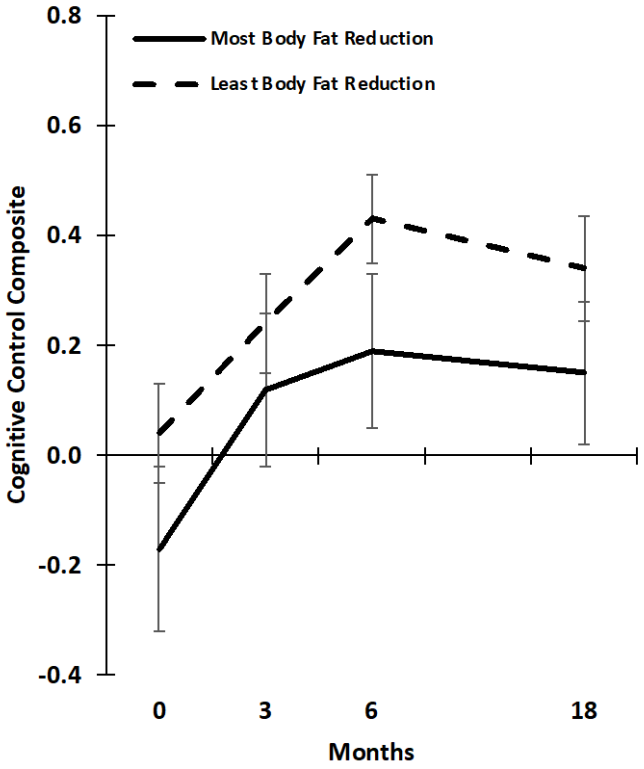
eFigure 4G. Memory Composite Change as a Function of Most vs Least Reduction in Body Fat in Exercise+ Group



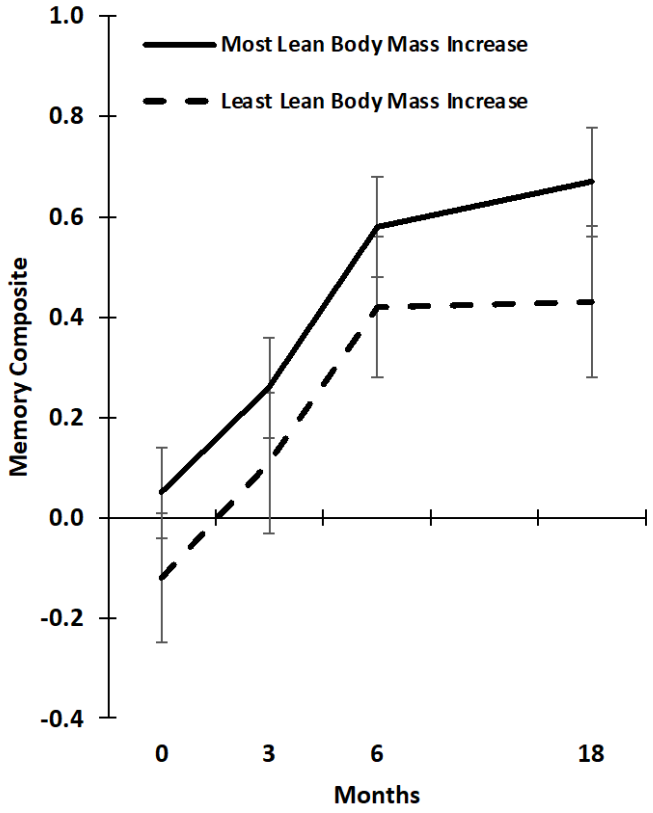
No. of participants in each tertile

Top	66	66	65	50
Bottom	122	122	122	105

eFigure 4H. Executive Function Change as a Function of of Most vs Least Reduction in Body Fat in Exercise+ Group

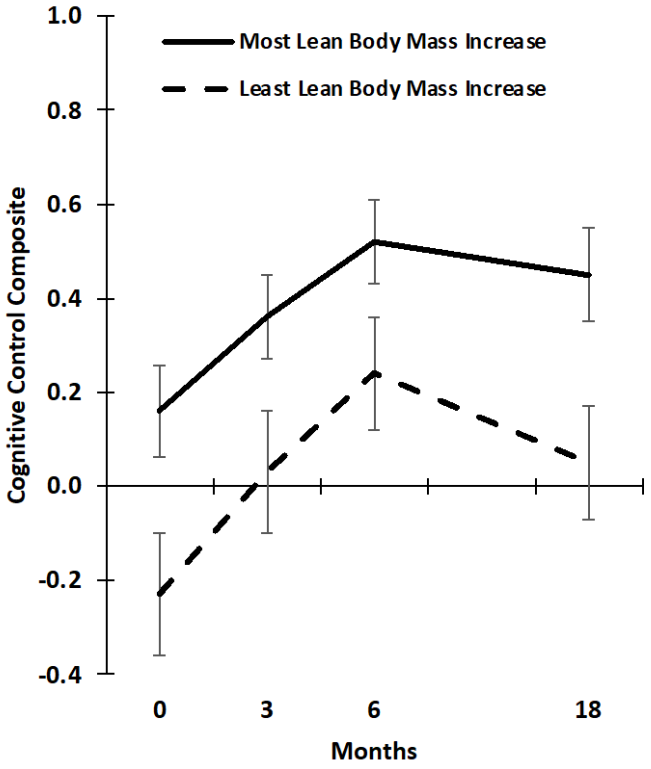


eFigure 4I. Memory Composite Change as a Function of Most vs Least Increase in Lean Body Mass in Exercise+ Group

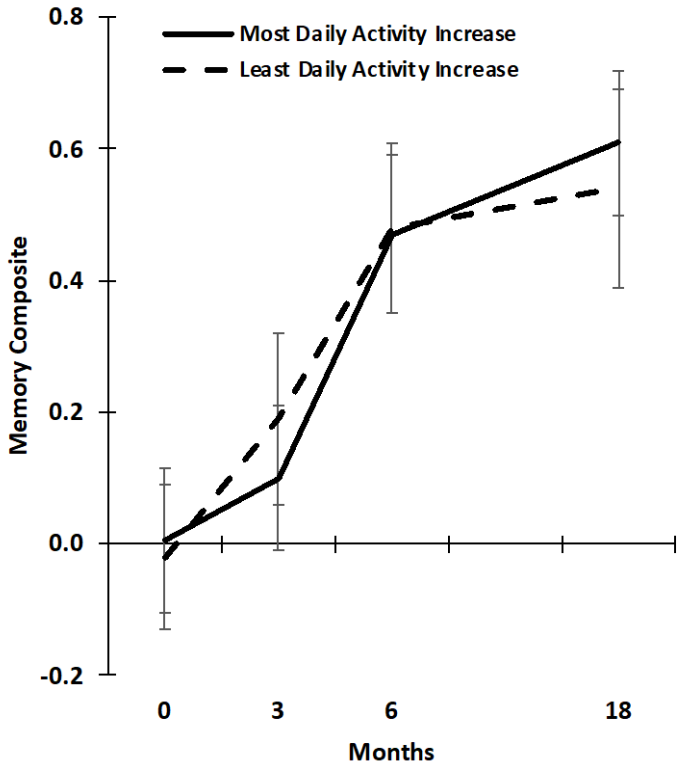


No. of participants in each tertile				
Top	117	117	117	98
Bottom	59	59	59	50

eFigure 4J. Executive Function Change as a Function of Most vs Least Increase in Lean Body Mass in Exercise+ Group



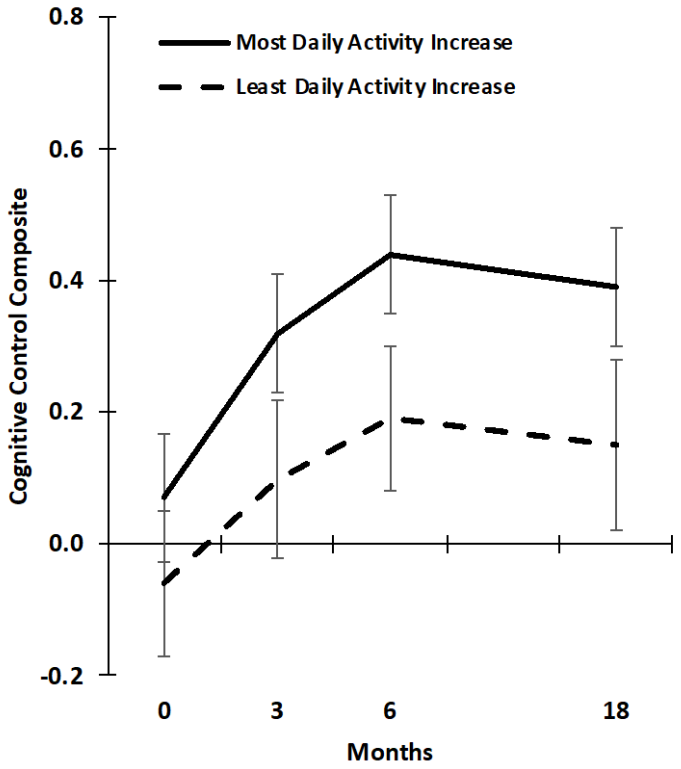
eFigure 4K. Memory Composite Change as a Function of Most vs Least Increase in Daily Activity in Exercise+ Group



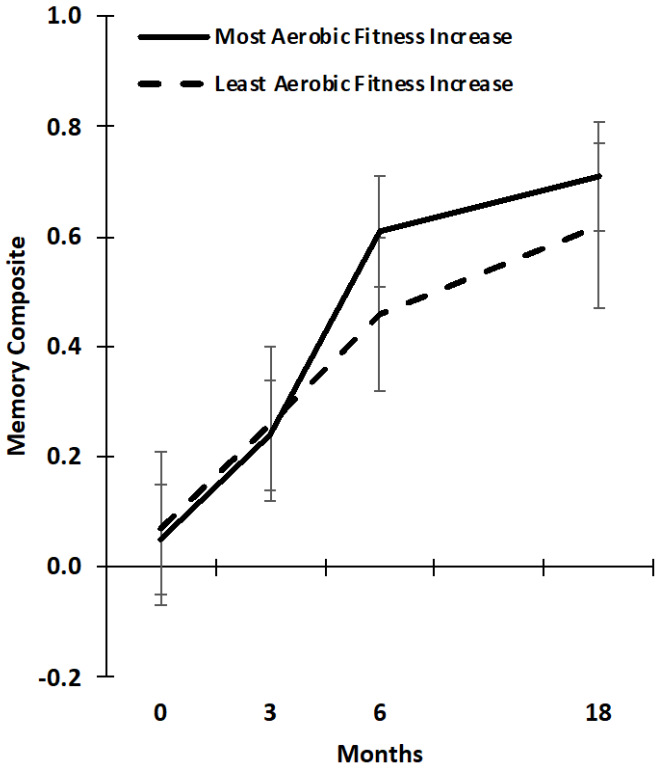
No. of participants in each tertile

Top	96	96	96	85
Bottom	77	77	76	62

eFigure 4L. Executive Function Change as a Function of Most vs Least Increase in Daily Activity in Exercise+ Group



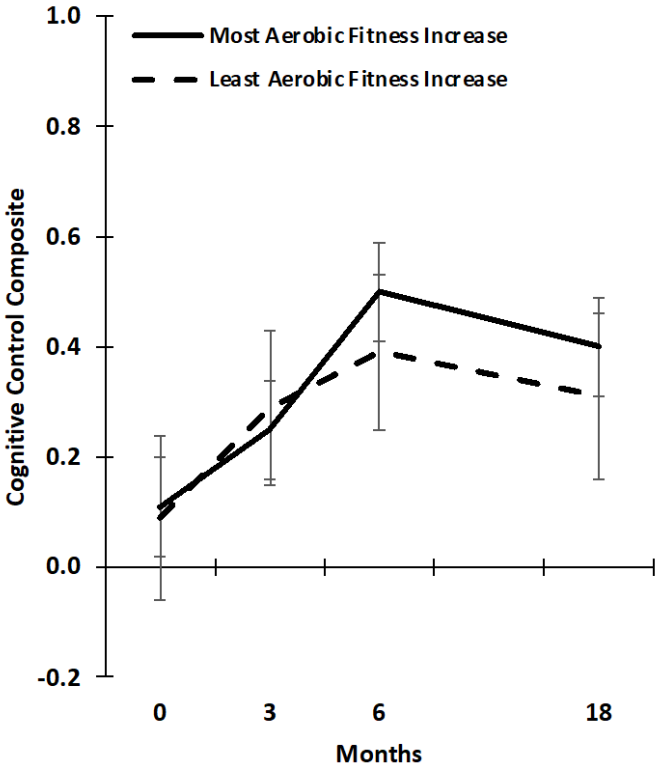
eFigure 4M. Memory Composite Change as a Function of Most vs Least Increase in Aerobic Fitness in Exercise+ Group



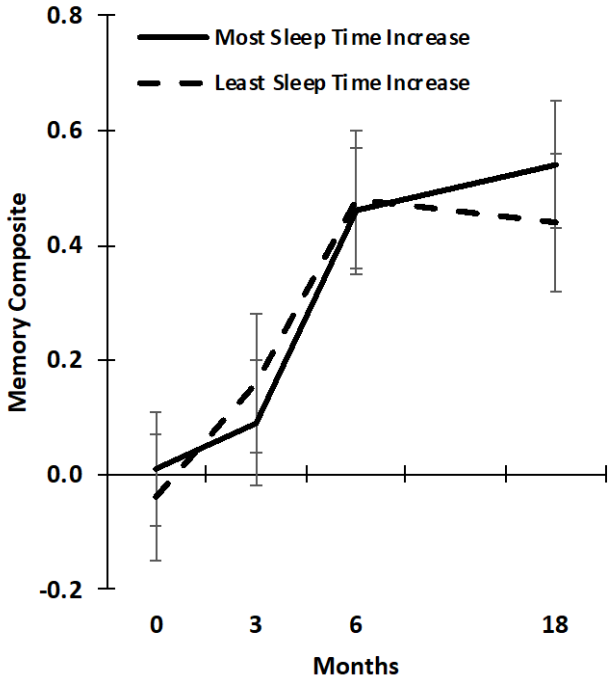
No. of participants in each tertile

Top	92	92	92	84
Bottom	55	55	54	42

eFigure 4N. Executive Function Change as a Function of Most vs Least Increase in Aerobic Fitness in Exercise+ Group



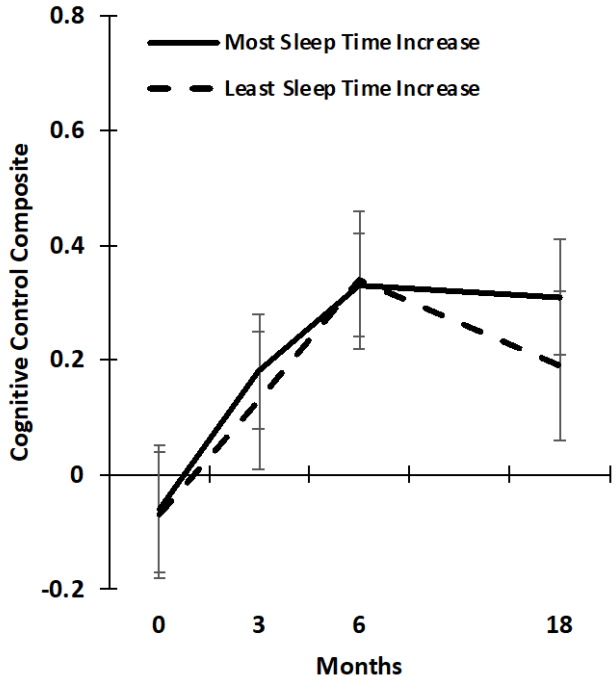
eFigure 4O. Memory Composite Change as a Function of Most vs Least Increase in Sleep Time in Exercise+ Group



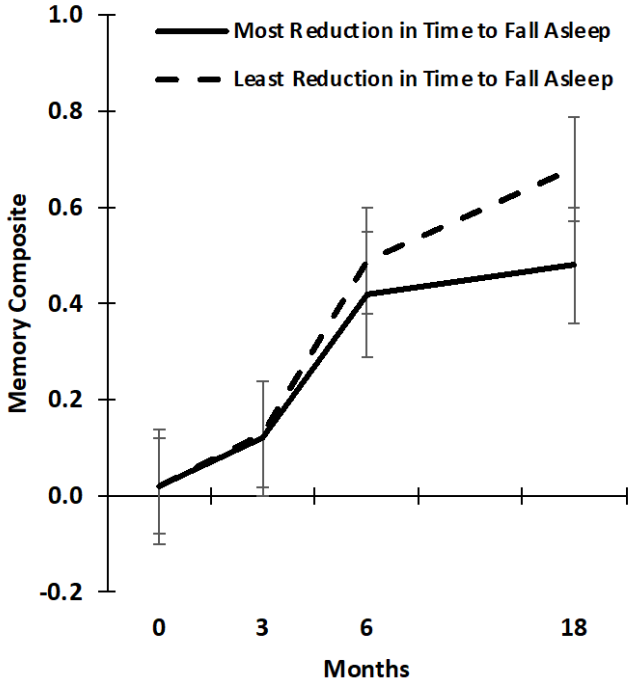
No. of participants in each tertile

Top	101	101	101	86
Bottom	81	81	80	66

eFigure 4P. Executive Function Change as a Function of Most vs Least Increase in Sleep Time in Exercise+ Group



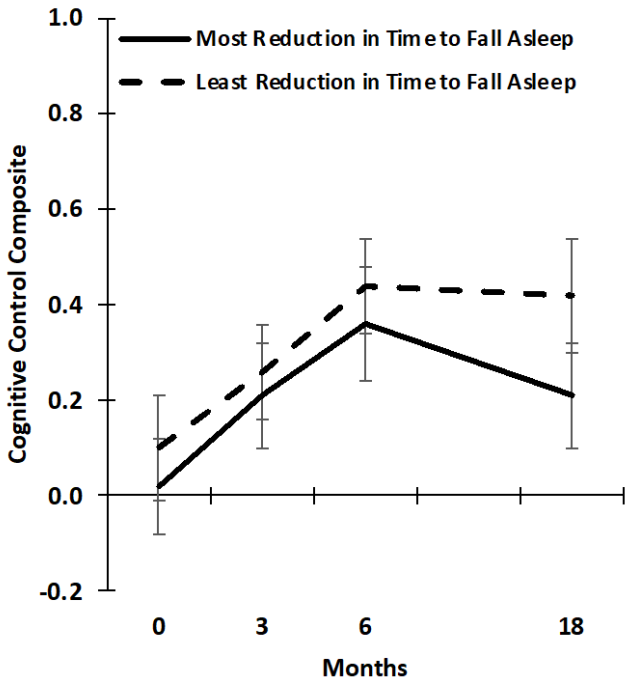
eFigure 4Q. Memory Composite Change as a Function of Most vs Least Reduction in Time to Fall Asleep in Exercise+ Group



No. of participants in each tertile

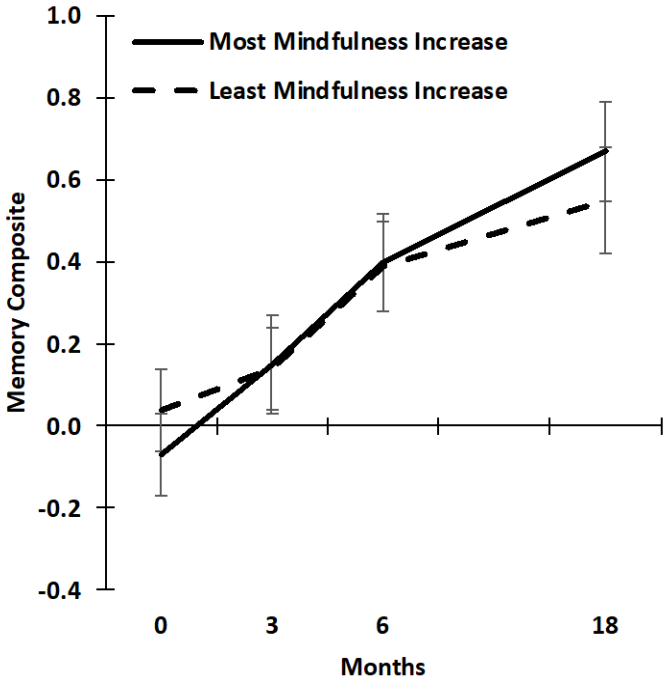
Top	76	76	76	67
Bottom	101	101	101	86

eFigure 4R. Executive Function Change as a Function of Most vs Least Reduction in Time to Fall Asleep in Exercise+ Group



MBSR+ Group

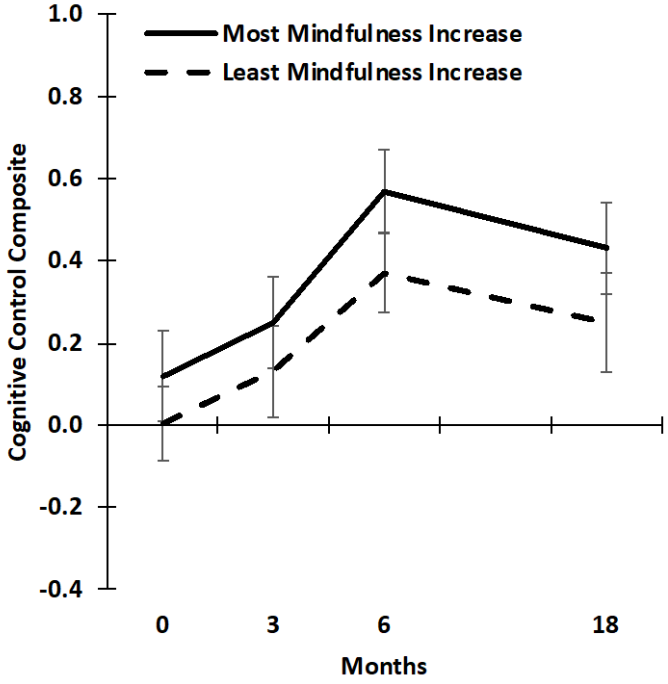
eFigure 4S. Memory Composite Change as a Function of Most vs Least Increase in Mindfulness in MBSR+ Group



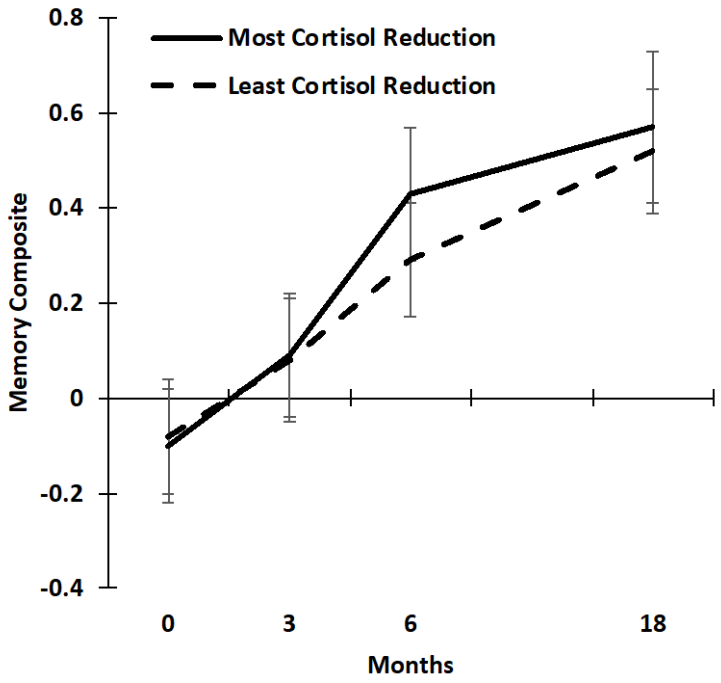
No. of participants in each tertile

Top	95	95	95	81
Bottom	100	99	100	85

eFigure 4T. Executive Function Change as a Function of Most vs Least Increase in Mindfulness in MBSR+ Group



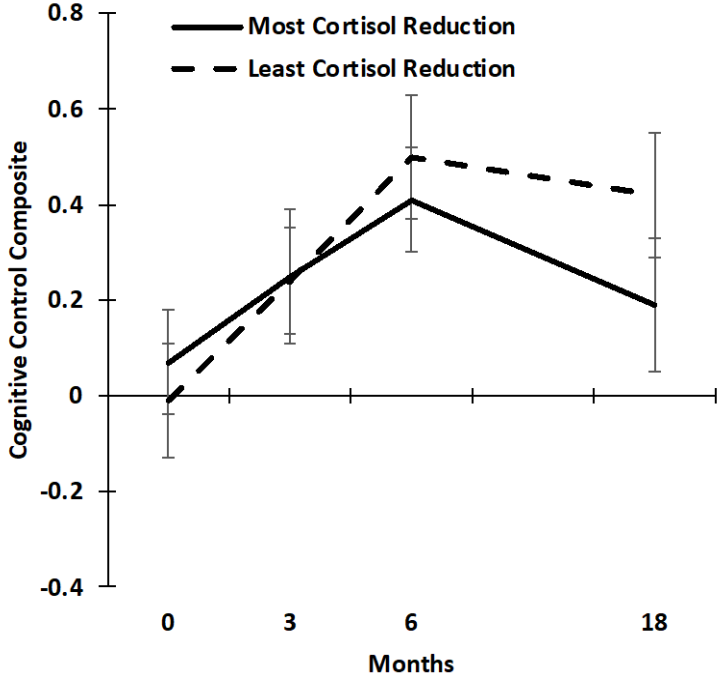
eFigure 4U. Memory Composite Change as a Function of Most vs Least Reduction in Cortisol in MBSR+ Group



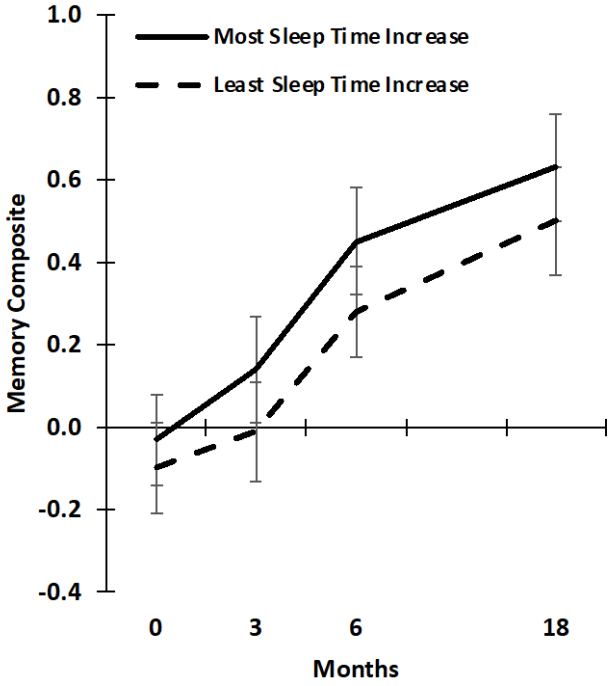
No. of participants in each tertile

Top	69	68	69	62
Bottom	76	76	76	66

eFigure 4V. Executive Function Change as a Function of Most vs Least Reduction in Cortisol in MBSR+ Group



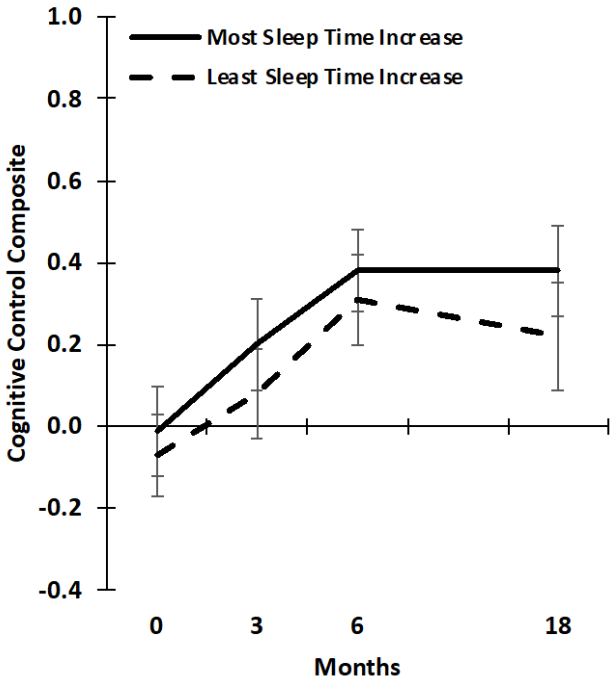
eFigure 4W. Memory Composite Change as a Function of Most vs Least Increase in Sleep Time in MBSR+ Group



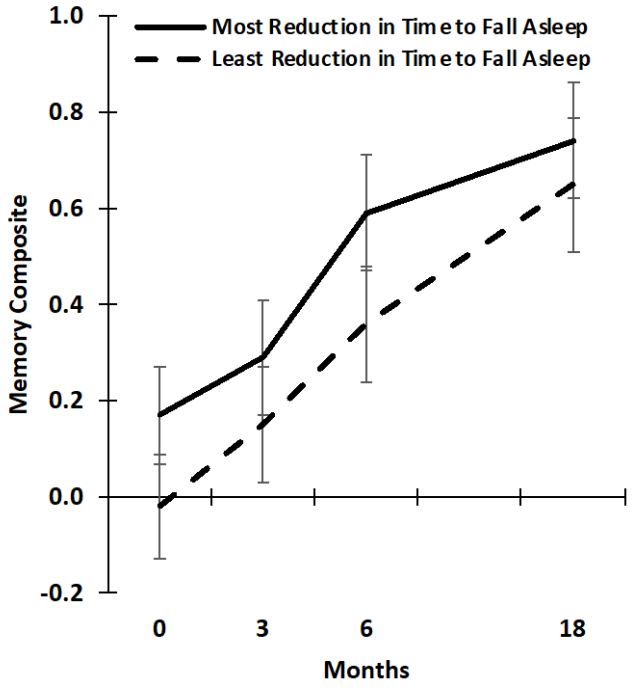
No. of participants in each tertile

Top	90	90	90	78
Bottom	79	79	79	65

eFigure 4X. Executive Function Change as a Function of of Most vs Least Increase in Sleep Time in MBSR+ Group



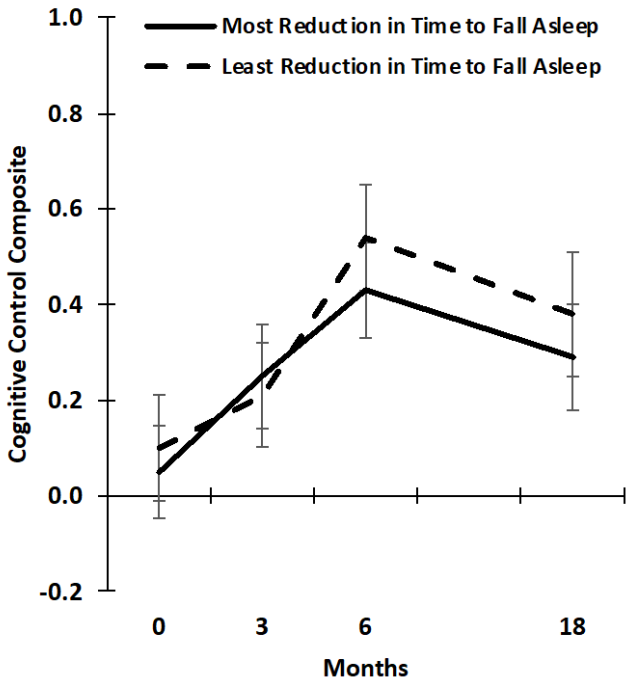
eFigure 4Y. Memory Composite Change as a Function of Most vs Least Reduction in Time to Fall Asleep in MBSR+ Group



No. of participants in each tertile

Top	92	92	92	84
Bottom	84	84	83	70

eFigure 4Z. Executive Function Change as a Function of of Most vs Least Reduction in Time to Fall Asleep in MBSR+ Group

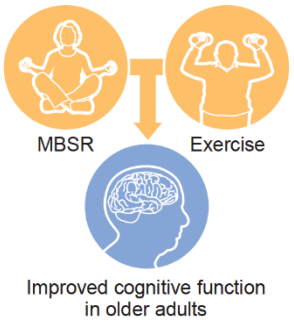


References

1. Nichols JF, Hitzelberger LM, Sherman JG, Patterson P. Effects of resistance training on muscular strength and functional abilities of community-dwelling older adults. *Journal of aging and physical activity*. 1995;3(3):238-250.
2. Nichols JF, Omizo DK, Peterson KK, Nelson KP. Efficacy of heavy-resistance training for active women over sixty: muscular strength, body composition, and program adherence. *J Am Geriatr Soc*. Mar 1993;41(3):205-10.
3. Stevens JA, Burns E. A CDC Compendium of Effective Fall Interventons: What Works for Community-Dwelling Older Adults. 3rd ed: National Center for Injury Prevention and Control of the Centers for Disease Control and Prevention; 2015.
4. Villareal DT, Banks M, Sinacore DR, Siener C, Klein S. Effect of weight loss and exercise on frailty in obese older adults. *Archives of Internal Medicine*. Apr 24 2006;166(8):860-6. doi:10.1001/archinte.166.8.860
5. Villareal DT, Chode S, Parimi N, et al. Weight loss, exercise, or both and physical function in obese older adults. *New England Journal of Medicine*. Mar 31 2011;364(13):1218-29. doi:10.1056/NEJMoa1008234
6. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry*. Apr 1982;4(1):33-47. doi:10.1016/0163-8343(82)90026-3
7. Crane R. Mapping mindfulness-based teaching skills. Bangor University website. 2022. https://mbitac.bangor.ac.uk/
8. Clausen JP, Trap-Jensen J. Heart rate and arterial blood pressure during exercise in patients with angina pectoris. Effects of training and of nitroglycerin. *Circulation*. Mar 1976;53(3):436-42. doi:10.1161/01.cir.53.3.436
9. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. *Diabetes Care*. Mar 2001;24(3):539-48. doi:10.2337/diacare.24.3.539
10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. Jul 1985;28(7):412-9.
11. Kamel EG, McNeill G, Van Wijk MC. Usefulness of anthropometry and DXA in predicting intra-abdominal fat in obese men and women. *Obes Res*. Jan 2000;8(1):36-42. doi:10.1038/oby.2000.6
12. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *The Journals of Gerontology*. Mar 1994;49(2):M85-94.
13. Kraemer HC, Giese-Davis J, Yutsis M, et al. Design decisions to optimize reliability of daytime cortisol slopes in an older population. *Am J Geriatr Psychiatry*. Apr 2006;14(4):325-33. doi:14/4/325 [pii] 10.1097/01.JGP.0000201816.26786.5b
14. Feldman G, Hayes A, Kumar S, Greeson J, Laurenceau JP. Mindfulness and emotion regulation: The development and initial validation of the Cognitive and Affective Mindfulness Scale-Revised (CMS-R). *J Psychopathol Behav*. 2007;29(3):177-190.

eMethods5: Grant

We propose a responsive application for RFA *"Plasticity and mechanisms of cognitive remediation in older adults."* This RFA seeks to test the benefits of interventions for age-related cognitive decline. Our group has promising findings from two such interventions, and so we are well-positioned to undertake this study.



(1) Mindfulness Based Stress Reduction (MBSR) teaches mindfulness, or the focusing of attention and awareness, through various meditation techniques. Mindfulness meditation practices appear to produce neurocircuitry changes that are the reverse of those seen in age-related cognitive decline. MBSR also appears to alter stress-related biological pathways that contribute to cognitive changes in older adults, such as Hypothalamic-Pituitary-Adrenal (HPA) axis hyperactivity. In recent studies of MBSR, we showed that this mechanism contributes to cognitive remediation.

(2) Exercise – specifically, intense, multi-component exercise that seeks to achieve or exceed 70% of age-predicted heart rate – also appears to affect brain structure and function and improve cognitive performance. We postulate that improvements in aerobic fitness and insulin sensitivity and increased Brain-Derived Neurotrophic Factor (BDNF) underlie exercise's cognitive benefits in older adults. Our team has extensive research experience with intensity-focused exercise in older adults demonstrating its cognitive benefit and mechanisms.

Our main hypothesis is that MBSR and exercise each improve cognitive function in older adults, including memory and executive function. We also hypothesize that greater cognitive benefits result from the combination because of the complementary nature of their mechanisms, such as decreased cortisol with MBSR and improved insulin sensitivity with exercise. Finally, we hypothesize that enhanced neuroplasticity, as shown through changes in structural and functional neuroimaging, explain the cognitive improvements.

We will randomize 580 non-demented healthy adults aged 65+, in a 2x2 factorial design, to one of four conditions: MBSR alone, exercise alone, MBSR + exercise, or a health education control condition. The study will consist of a 6-month acute intervention phase followed by a 12-month maintenance phase with monthly classes and other prompts to maintain intervention behaviors.

Assessments include cognitive tests, biomarkers, neuroimaging assessments, functional assessments to examine real-world benefits of the interventions, and other behavioral assessments to characterize participants and pave the way for further exploratory analyses.

The most important aim of this project is to carry out a high-quality clinical trial with careful recruitment, reliable measurement, high-fidelity interventions with good adherence, and quality neuroimaging data and biosamples with a plan to make these data and samples readily available to the scientific community.

Specific Aims are well-supported by data from our preliminary studies, and those of other research groups:

Aim 1. Examine effects of MBSR, exercise, and their combination for remediation of memory and cognitive control, with secondary outcomes of everyday cognition, functional performance, and social participation and engagement.

H1: MBSR and exercise will each produce benefits in healthy older adults' cognitive performance, and combined MBSR + exercise will show greater cognitive improvements than either intervention alone.

Aim 2. Examine mechanistic changes that underlie cognitive remediation from MBSR and exercise.

H2: (a) Decrease in peak cortisol accounts for improvements with MBSR.
(b) Increased insulin sensitivity, aerobic fitness, and BDNF account for improvements with exercise.

Aim 3. Examine whether the interventions cause changes in brain structure and functional connectivity and whether these plastic changes help explain the cognitive improvements.

H3: Improved functional connectivity within and across specific cognitive networks and increased volume of hippocampal and lateral prefrontal regions account for improved cognitive function with the interventions.

Aim 4. Examine predictors of variability in response to the interventions.

H4: Baseline cortisol and insulin sensitivity will predict degree of cognitive remediation from MBSR and exercise; that is, high baseline cortisol will predict greater improvement from MBSR, while low insulin sensitivity will predict greater improvement from exercise.

RESEARCH STRATEGY

1. SIGNIFICANCE

Age-related cognitive decline is a widespread, urgent, and growing public health issue. The vast majority of older adults will experience deteriorating cognitive function. The decay affects many domains, particularly memory and cognitive control (also called executive function),[1,2] which are key to participating and engaging in meaningful daily activities.[3-5] These cognitive losses match age-related changes in brain structure, such as volume loss, and function, including reduced functional connections within cognitive circuits.[6,7]

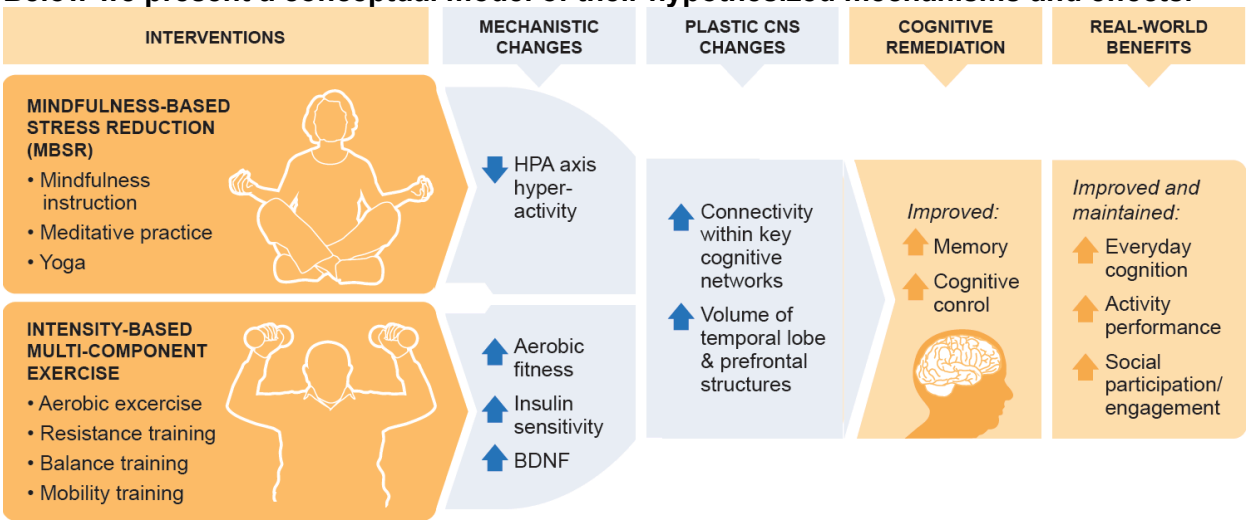
We need interventions that remediate age-related cognitive decline. The brain retains the potential for neuroplasticity in old age,[8-14] so interventions that enhance neuroplasticity may remediate age-related cognitive decline. Neuroimaging advances allow us to study neuroplasticity changes in intervention research, including precise structural measurements and resting state functional MRI (rs-fMRI).[15]

Stress and (in)activity are key predictors of decline,[7,16-21] putatively via neuroendocrine, immune, metabolic, and neurotrophin changes that are targets for intervention.[17,22-24] **Therefore, two promising interventions are Mindfulness-Based Stress Reduction (MBSR) and exercise.**

MBSR: Mindfulness meditation emphasizes focused, nonjudgmental awareness of present moment experiences.[25] MBSR is a mindfulness/meditation protocol developed by Jon Kabat-Zinn, Ph.D. at the University of Massachusetts.[26,27] It is a group-based instruction that introduces the concept of mindfulness and develops it through techniques such as informal mindfulness, yoga, mindful breathing, and various forms of meditation. There are two key reasons to predict that MBSR may remediate cognitive function in older adults: (1) the practice of mindfulness and meditation, including MBSR, enhances attentional processes[28] and has been shown to produce changes in brain circuitry[29-33] that are the opposite of the disruptions of large-scale brain systems in aging;[34] and (2) as implied by the name, MBSR also reduces stress and improves psychological health, [27,35-41] with a resulting decrease in HPA-axis hyperactivity and a downstream effect on cognition.[42-48] These stress-reduction and cortisol-lowering effects of MBSR map onto basic research regarding stress, glucocorticoid excess, and cognitive impairment in aging.[49-52]

Multi-component intensity-based exercise seeks to improve aerobic fitness, strength, mobility, and balance. Particularly in older adults, fitness ties closely to cognitive function,[53] and in recent years several groups have published promising findings demonstrating beneficial cognitive effects from exercise. They correlate with brain changes that are both structural and functional and that putatively show enhanced plasticity.[54-56] Improved insulin sensitivity, increased aerobic capacity, and increased Brain Derived Neurotrophic Factor (BDNF) are recognized pathways to exercise-induced cognitive improvements.[7,57] All of these mechanisms support basic research regarding neurobiological mechanisms and outcomes leading to cognitive improvements with exercise training, through increased hippocampal volume and synaptic density.[24,58-64]

Their complementary nature suggests that MBSR and exercise may be highly effective in combination. Below we present a conceptual model of their hypothesized mechanisms and effects.



2. INNOVATION There are numerous innovative aspects to our proposed project:

- This will be a definitive test of exercise, mindfulness/meditation, and their combination for age-related cognitive decline within a single clinical trial.
- The project will test long-term cognitive benefits with a regimen to maintain these interventions.
- The project will examine biological pathways that underlie cognitive remediation with these interventions.
- State-of-the-art neuroimaging methods will evaluate functional and structural brain changes that help explain the cognitive benefits of these interventions.
- A novel application of smart phone-based ecological momentary assessment (EMA) will precisely measure patient-reported outcomes, including everyday cognition, function, and participation.

3. APPROACH

The investigative team has a track record of success and expertise in every aspect of this research. The PI, Eric Lenze, M.D., is a geriatric psychiatrist experienced with clinical trials in older adults from numerous investigator-initiated projects[65-78] including NCCAM-funded studies of MBSR for older adults[79] described below. Additionally, Dr. Lenze has been PI or Co-I of several behavioral intervention RCTs, including 2x2 factorial design studies,[76,77] and large and/or multi-site studies with long-term collection of biobehavioral data.[75-77,80]

The PI of the UCSD site, Julie Wetherell, Ph.D., is a geriatric psychologist who has conducted numerous behavioral clinical trials in older adults. She brings expertise in mindfulness interventions as PI or Co-I of five federally-funded trials of treatments with mindfulness components in a variety of stress-related conditions, as well as leading numerous federally-funded studies of behavioral interventions in older adults.[77,81-84]

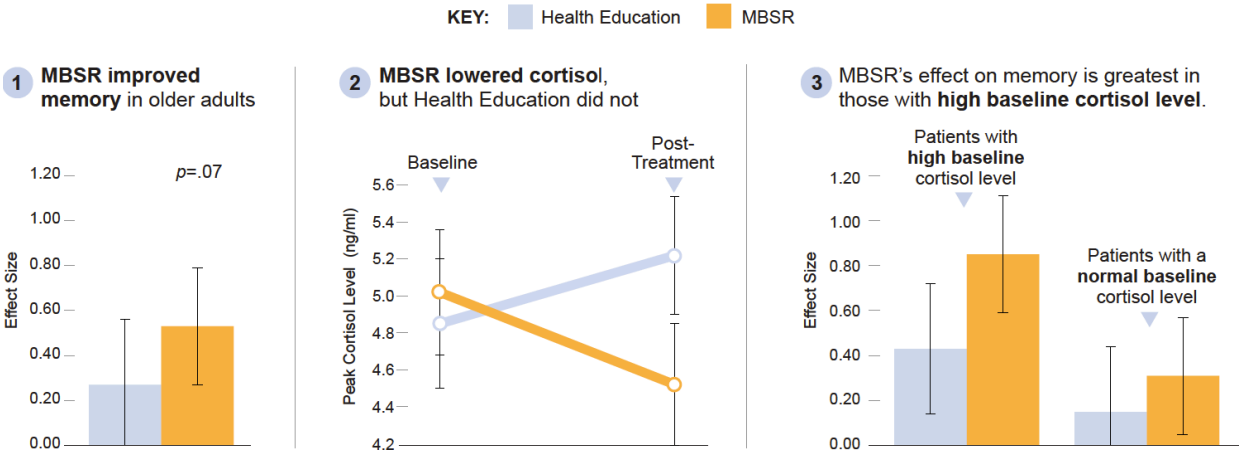
The team's exercise intervention researchers are experts in every aspect of this component of the project: Sam Klein, M.D., David Sinacore, P.T., Ph.D., Jeanne Nichols, Ph.D., and Kevin Patrick, M.D.

The neuroimaging team expertise includes: (1) Experience with high-throughput imaging acquisition, analysis, and storage methods using the WU Central Neuroimaging Data Archive (CNDA) and (2) Extensive testing of the NIH Toolbox, gained from coordination of multi-site projects such as the Human Connectome Project (HCP), the Dominantly Inherited Alzheimers Network project, and participation in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Similarly, UCSD is a coordinating or participating site in the Functional BioInformatics Research Network (fBIRN), ADNI, and Pediatric Imaging, Neurocognition, and Genetics (PING).

Our sites have a history of successful and productive collaboration in complex interventions[65,77,79,83,85] **including the WU/UCSD collaborative studies of MBSR for cognitive remediation:**

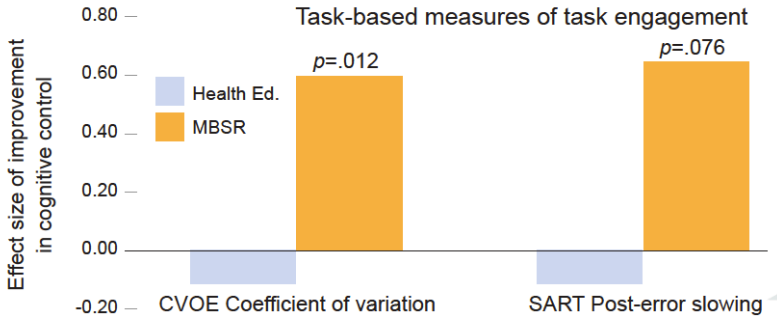
a. In an initial study,[79] we piloted MBSR in 34 older adults and developed methods to examine cognitive remediation: (i) A neuropsychological battery sufficiently sensitive to detect changes in memory and cognitive control with MBSR; (ii) More accurate assessment of patient-reported outcomes and behaviors, including mindfulness, using EMA (see Research Design and Methods).

b. We used these measures in a second study, in which we randomized 103 older adults to MBSR or a Health Education condition. We measured salivary cortisol, as high cortisol is understood to be a sign of HPA axis hyperactivity[86] and a mechanism of cognitive impairment in aging.[18,87-100] **Our four key findings:** [101-106]



4 MBSR improves cognitive control in older adults.

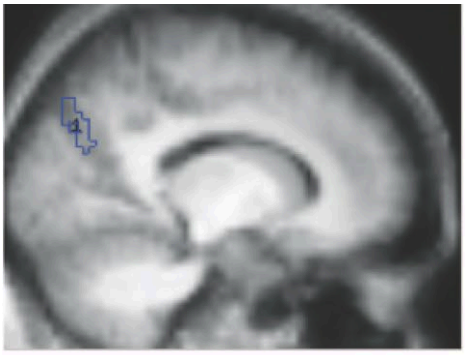
MBSR participants showed improvements in these tasks indicating improved cognitive control. The implication is that MBSR promotes the robust maintenance of complex task sets over time. Similar results with meditation training have been reported by other groups studying older[103,104] and younger[105,106] adults.



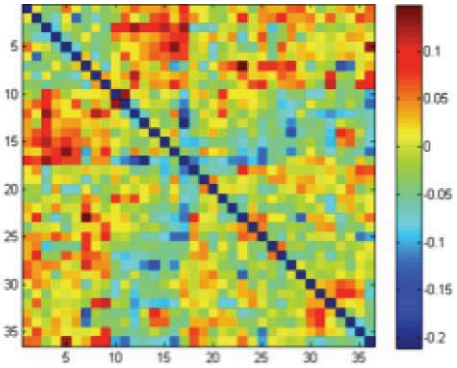
Two cognitive control tasks were:

- Consonant Vowel Odd Even (CVOE),[101] a task of attentional control and task switching.
- Sustained Attention Response Task (SART),[102] a Go/No-Go attentional control task.

c. In the third study, we examined **rs-fMRI changes** in 13 older adults who underwent MBSR. This study shows that our group can use rs-fMRI functional connectivity changes to assess plastic CNS changes with the interventions in this project, consistent with findings from other groups.[33,56,107-109] **Key findings**:



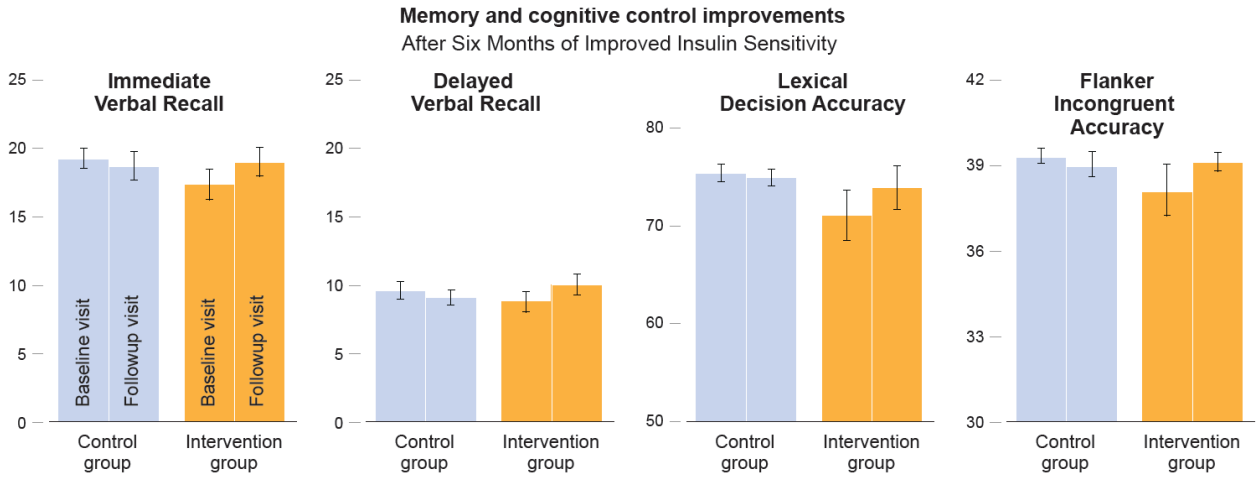
1. Significantly increased connectivity within a node of the Default Mode Network (DMN)
2. Pre-post correlation matrix (described in data analysis section) showed changes within and among cognitive networks.



Studies of exercise, fitness, and cognitive remediation in older adults:

a. We have shown[107,108] that an intense, multi-component exercise intervention (as proposed in this application) improves aerobic fitness, understood to be a key mechanism of cognitive remediation,[55] possibly because it increases neuronal proliferation, dendritic complexity, and the vascularization of brain structures.[7]

b. Improved insulin sensitivity aids memory and cognitive control in older adults. We have carried out several studies in older adults using both exercise and weight loss to successfully improve insulin sensitivity.[110-112] **In the figure below from a recent study, we show that a six-month intervention to improve insulin sensitivity in older adults improves memory and cognitive control.**



Note: all pre-post changes were p<0.05 for the intervention group

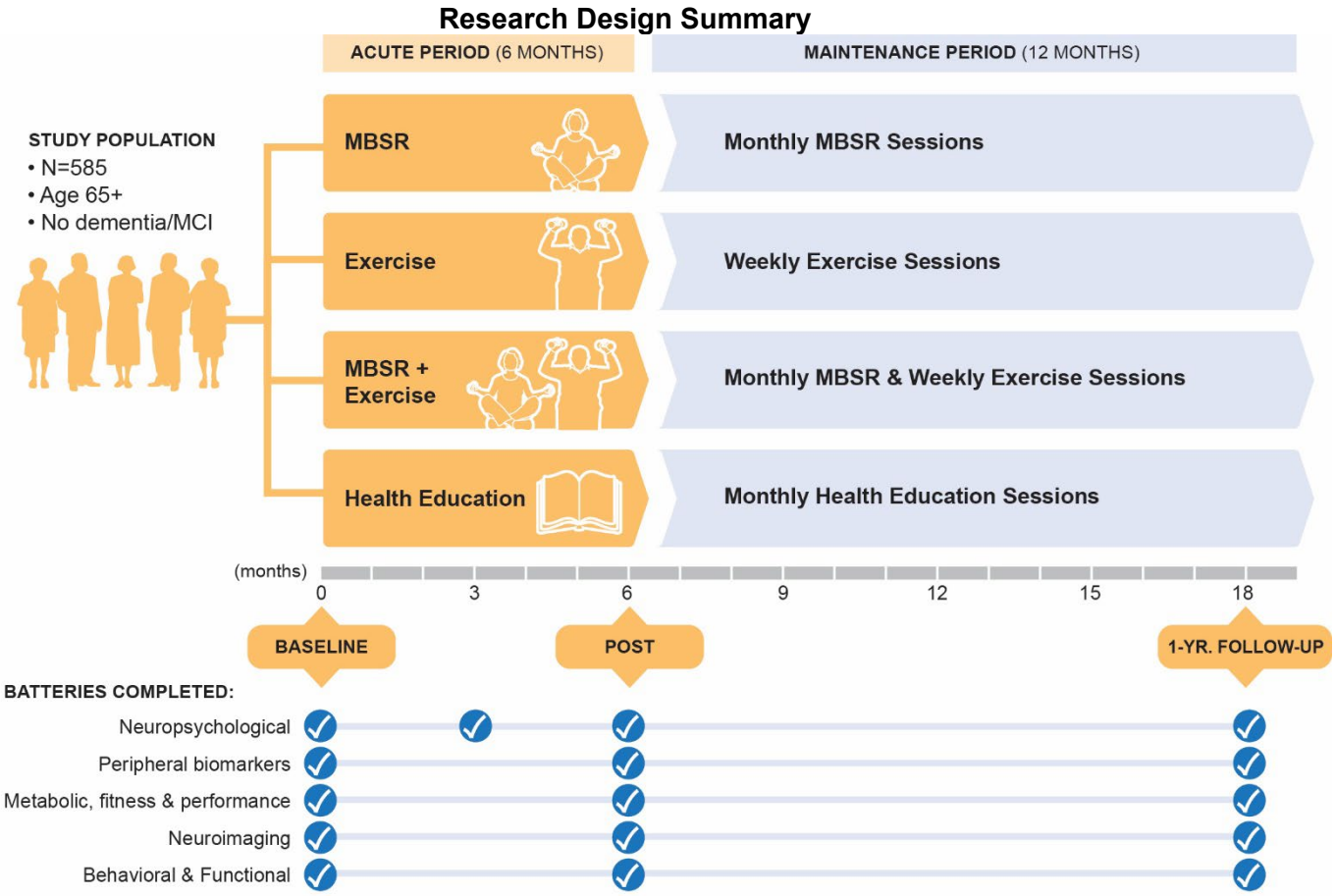
c. Exercise and fitness in older adults is associated with regional brain volumes on structural MRI. Co-Investigator Denise Head, Ph.D., found that healthy older adults who engaged in vigorous and frequent exercise had higher medial temporal lobe volume than those engaged in little or no exercise.[113] In another study, Dr.

Head demonstrated that aerobic fitness in older adults correlates with processing speed, executive function, and hippocampal volume, with some correlation with lateral prefrontal gray matter volume.[114] Though correlational, these findings are similar to findings from other researchers[55,115] and provide support for H3.

MBSR benefits may be complemented by exercise: In preparation for this project, we explored in the RCT (1) MBSR's effects on BDNF serum levels and IL-6 plasma levels and (2) moderation of MBSR benefits for cognition by ApoE and BDNF val66met genotypes. We found: (1) BDNF level did not change with MBSR (26.9 →26.0ng/ml) nor was MBSR's effect size influenced by BDNF genotype; (2) IL-6 did not change with MBSR (2.0→2.0pg/ml); (3) ApoE ε4 carriers had 1/3rd the effect size of memory improvement (MBSR>Health Ed) than did ApoE ε4 noncarriers. It is notable the contrast between these findings and observations that exercise's cognitive benefits appear to be both correlated with BDNF increases[56,116,117] and mitigating Apo E ε4 effects.[118] These findings suggest complementary mechanisms of MBSR vs. exercise, generating the hypothesis that the two interventions combined may have more beneficial effects.

In summary, our preliminary studies in older adults provide support for our hypotheses regarding cognitive remediation from MBSR and exercise and their biomarker and neuroimaging mechanisms and moderators.

RESEARCH DESIGN AND METHODS: The design is responsive to the guidelines of the RFA and is optimal for achieving all of our objectives. We will test the efficacy for cognitive remediation of MBSR and exercise, using a 2x2 factorial design. We will randomize 580 healthy adults aged 65+ to six months of acute intervention followed by a 12-month maintenance phase.



Note: This figure has been modified from the original grant to show that exercise sessions in maintenance phase were weekly and there was no 12 month neuropsychological battery.

Participant selection: All participants will complete a phone screen, then an in-person screen which includes a medical history, physical examination, standard blood chemistries, and an exercise stress test, as in our previous studies.[110,119] **Inclusion criteria:** (1) Community-living men and women age 65 and older; (2) No current

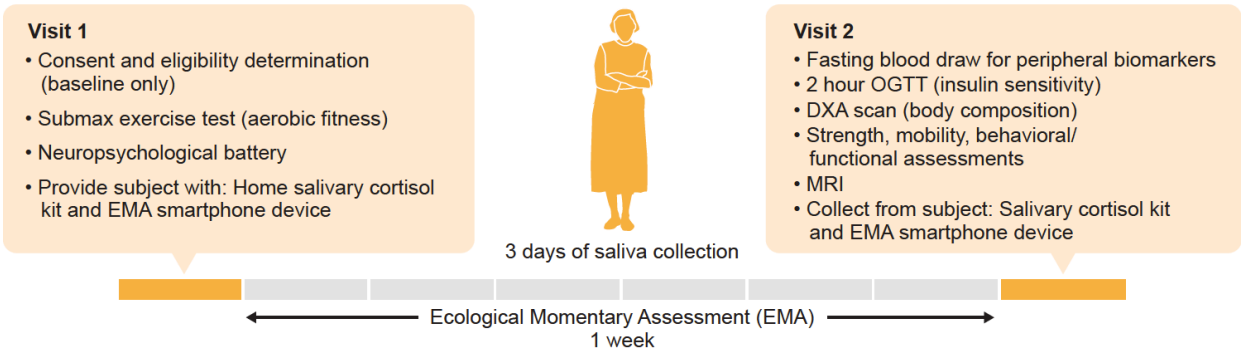
meditation practice nor prior training in it; (3) Sedentary (no current or recent participation in exercise).

Exclusion criteria: (1) Dementia, mild cognitive impairment, or other clinical neurodegenerative illness (e.g., Parkinson's disease, cerebrovascular disease) per self-report,[120] medical records, or unable to complete neuropsychological testing. (2) Psychotic disorder or any unstable psychiatric condition. (3) Medical conditions that suggest shortened lifespan, such as metastatic cancer; or would prohibit safe participation in the interventions, including cardiovascular disease or musculoskeletal conditions; or with the assessments, such as diabetes, inflammatory disease, or ferromagnetic metal/bridgework that would interfere with MRI signal. (4) Sensory impairment that would prevent participation. (5) IQ < 70 as estimated by the Wechsler Test of Adult Reading.[121] (6) Alcohol or substance abuse within 6 months. (7) Concurrent cognitive training, such as brain-training software, or other interventions expected to affect neuroplasticity. (8) Medications that interfere with measurements, including cancer chemotherapy, glucocorticoids, and interferon.

Rationales: (1) Allowing preclinical Alzheimer's Disease (AD): Data[122,123] report that roughly one-third of older adults with a Clinical Dementia Rating (CDR) of 0 (that is, non-MCI, non-demented) have preclinical evidence of AD (abnormal amyloid markers with or without neuronal injury markers). We will not exclude such individuals, improving study generalizability. (2) Allowing a diversity of participants: A "supernormal" population devoid of significant medical or mental health concerns is not ideal as older adults with anxiety, depression, and pain are the most likely to participate in mind-body treatments.[124,125] We will assess medical and psychiatric comorbidities[126,127] which can be included as potential covariates.

Recruitment and Retention: As recruitment must be completed by the middle of the fourth year, 39 months of recruitment (after a startup period) requires 7-8 participants randomized each month at each site. Both sites have robust recruitment resources including Volunteers for Health, a WU research registry. High retention will be obtained by our successful methods from numerous prior RCTs (e.g., 94% of MBSR RCT participants were completers).

Detailed view of baseline, post-acute, and post-maintenance assessments:



Randomization: The order of the intervention conditions will be randomized and balanced across the study. Our statistician will generate the randomization table using blocks of varying size.

Interventions: The four intervention conditions in this study are (1) MBSR, (2) intensity-focused multi-component exercise, (3) combined MBSR and exercise, and (4) Health Education (a control condition). All interventions will be held in groups of 10-11 participants, totaling 56 groups (14 groups of each condition), carried out at the available WU/UCSD facilities (see Facilities and Resources).

1. MBSR Intervention: This condition matches the consensus MBSR protocol: after a brief introductory meeting, it is conducted in eight weekly 2.5-hour classes plus a retreat.[128] Content includes instruction in mindfulness meditation practices, gentle mindful movement, and exercises to enhance mindfulness in everyday life. We use *A Mindfulness-Based Stress Reduction Workbook*[129] as a companion guide. Participants get daily at-home assignments with CDs of meditative practices. See Appendix A for manual.

2. Exercise Condition: The exercise protocol is optimal for improving aerobic fitness and insulin sensitivity in older adults, as well as improving strength and balance and reducing indices of frailty.[119,130-132] It consists of classes twice weekly, building up to 1.5 hr, under the direct supervision of trained exercise instructors (three instructors per group). Each session consists of aerobic exercises and resistance training to improve fitness and

insulin sensitivity, and exercises to improve balance, mobility, and flexibility which are an essential part of an exercise program in this age group.[133] The rationale for our focus on multiple components rather than only one, such as aerobic exercise alone, is that aerobic exercise and resistance training each change these putative pathways[134] and have been shown to improve cognitive function in older adults.[7,135]

Type	Exercises	Description
Aerobic	Treadmill, elliptical, bikes	Participants exercise so that their heart rate is approximately 65% of their peak heart rate and gradually increase the intensity of exercise so that their heart rate is between 70 and 85% of their peak heart rate.
Progressive resistance training	Weight-lifting machines and functional movements	Participants perform 1- or-2 sets at a resistance of approximately 65% of their one-repetition maximum, with 8-to-12 repetitions of each exercise; they gradually increase the volume and intensity to 2-to-3 sets at a resistance of approximately 80% of their one-repetition maximum, with 6-to-8 repetitions of each exercise. Also functional resistance training using whole body movements with either light weights or body weight as resistance.
Balance/mobility	Dynamic movements that challenge postural stability and mobility	Various gait patterns; walking on uneven terrain (simulated indoors, or outside); maneuvering around obstacles; use of stability balls for seated 'core' work; weight transfer forward/backward, side-to-side; eye tracking movements while seated, standing, slow walking.

Participants will also be prescribed an hour of home exercise twice weekly. The aerobic component will consist of walking and/or using exercise DVDs; additionally, participants will be given a rotation of exercise cards for strength and balance-training exercises practiced in class that can be done safely at home. We will ask if they are adhering to their home exercise and also monitor via actigraphy in real time and intervene with prompts and counseling for those not keeping up with their home exercise.

3. MBSR and Exercise condition: This condition will receive both MBSR and exercise as described above. Participants in this condition will come in once weekly to receive MBSR and twice weekly to receive exercise class, with at-home exercise the other two days as well as daily, at-home mindfulness practice.

4. Health Education: A control condition that matches for group setting, time, and attention is necessary to minimize the chance that study findings might be attributable to non-specific differences in conditions rather than the active ingredients of MBSR and exercise. Health Education (manual in Appendix B) is a group-based intervention that increases health-related knowledge and action (similar to the control condition developed by the University of Wisconsin for MBSR[136]). Health Education improves chronic disease management, but it does not teach mindfulness techniques and does not involve exercise. It matches MBSR in time and number of sessions. In our RCT of MBSR in older adults, participants found Health Education credible (high scores on a credibility and expectations for improvement scale[137]) and showed small and non-significant improvements in memory and some measures of cognitive control, as expected in a control condition. We considered a double-sham control – stretching as a control for exercise plus Health Education as a control for MBSR – but were concerned about a stretching control confounding or interfering with the mindful-movement aspect of MBSR.

Attaining, maintaining, and measuring fidelity: Fidelity refers to whether instructors consistently perform the interventions with a high level of adherence to and competence with the intervention protocols. Low fidelity is a common and often unrecognized problem leading to "failed" intervention studies. We will apply expertise from numerous intervention studies, including intersite WU/UCSD studies: (1) Attaining fidelity – we have a pool of trained instructors in the interventions (MBSR, exercise, and Health Education) who implement them with high fidelity. (2) Measuring and maintaining fidelity – Co-investigators will have weekly supervisory calls with instructors. All sessions will be videotaped, and a random sample of 25% will be reviewed by the supervisors and rated according to the standards established during our most recently completed studies. Research assistants will also monitor adequacy of all sessions in terms of number in attendance, timed length of sessions, and material covered. The PIs are the ultimate fidelity supervisors; they will be in weekly contact with the supervisors, study coordinators, and research assistants to promptly detect and correct problems.

Maintenance phase: In both MBSR and exercise, the acute interventions are meant to develop skills, knowledge, and/or improvements in fitness that are maintained long-term. For maintenance practice after the

completion of the 8-week course in MBSR, consensus recommendations[26,129,138] are: (1) a regular follow-up retreat to reinforce mindfulness/meditation skills; (2) daily meditative practice and everyday practice of mindfulness. Therefore, MBSR participants will follow up once monthly as a group for a 2.5-hour "mini-retreat" and will be prompted to continue a daily meditative practice. To match for non-specific effects of attention and group participation during the maintenance phase, the Health Education participants will also meet monthly. After the acute exercise phase, the regimen will undergo a gradual fade – weekly, then biweekly, then monthly classes – plus reinforcements and support such that individuals can exercise on their own. Research assistants will assess maintained MBSR/exercise practice via monthly phone calls to participants.

STUDY MEASUREMENTS AND ASSESSMENTS include the NIH Toolbox for Assessment of Neurological and Behavioral Function (www.nihtoolbox.org)[139] and NIH Patient Reported Outcomes Measurement Information System (PROMIS; www.nihpromis.org). All outcome measures will be carried out by blinded raters.

Neuropsychological measures included (total test battery time=90 minutes):

NIH Toolbox tests:	**Domain:**
Flanker Inhibitory Control	Measures attention and inhibitory control by requiring participant to focus on a given stimulus while inhibiting attention to stimuli flanking it.
Dimensional Change Sort	Measure of cognitive flexibility. Participants must match a series of bivalent test pictures to the target pictures, switching between dimensions.
List Sorting Working Memory	Participants order objects (either food or animals) in size from smallest to largest. Then, they are presented food + animals and report the food in size followed by the animals.
Picture Sequence Memory	Participants recall increasingly lengthy series of illustrated objects and activities that are presented in a particular order on the computer screen.
Oral Reading Recognition	Language task. Participants read and pronounce letters and words.
Picture Vocabulary	Language task. Participants are presented with an audio recording of a word and four picture and are asked to select the picture that most matches the meaning of the word.
Pattern Comparison Processing	Measures speed of processing by asking participants to discern whether two side-by-side pictures are the same or not, in a 90-second period.
Legacy measures:	**Rationale:**
Paragraph recall	Developed and validated specifically to detect stress-related cognitive dysfunction[140] and sensitive to change in our preliminary studies. Multiple forms are available.
List recall	16-word list validated at WU ADRC; sensitive to change and absent ceiling effects in our preliminary studies. Multiple forms are available.
Color Word Interference	Computerized Stroop task (inhibitory control) which we have used in prior studies.[141]
Consonant Vowel Odd Even (CVOE)[101]	Attentional control and task switching paradigm; Participants alternate between vowel-consonant vs odd-even judgments. Sensitive to change in our preliminary studies.
Sustained Attention Response Task (SART)[102]	Go/No-Go attentional control task specific to the construct of mind-wandering;[142] sensitive to change in our preliminary studies. Both accuracy and post-error slowing are assessed.

Primary outcome measures: We will create two co-primary outcome measures: (1) A memory composite variable using the list recall, paragraph recall, and picture sequence memory tasks. For each memory variable, a z score is computed for each participant [(participant score - mean)/standard deviation]. Then the composite memory variable is created by summing up z scores. (2) A cognitive control composite variable using the CVOE, SART, Color Word Interference, flanker, and list-sorting tasks. Composites provide robust estimates of underlying constructs (compared to single tasks). Other tasks provide additional characterization.

Biomarker assessments will test mechanisms/moderators of interventions and generate a biorepository as a resource for the scientific community. Quality assurance will follow National Cancer Institute Best Practices for Biospecimen Resources guidelines (http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf).

ELISA and flow cytometry on 10% of samples will verify quality and cell type. Biomarkers are subject to circadian/metabolic effects; therefore, blood draws will take place at about 9am after fasting.

Biomarker assessments:

Measure	Rationale
Cortisol levels	Home salivary collection method developed by our team for reliable assessment[143] assays cortisol at wake, 30 minutes after waking (= peak cortisol), and bedtime for 3 consecutive days.
IL-6, IL-17, eotaxin levels	Well-validated markers of inflammatory pathways implicated in age-related cognitive decline.
Brain-Derived Neurotrophic Factor (BDNF) serum level	Explanatory variable for exercise benefits on cognitive function in aging (H2b).
Genotyping: Apolipoprotein E; BDNF (Val66Met)	These two genotypes are needed for adequate characterization of the sample in keeping with past research on brain function and aging.[116,118,144-146] We will store DNA for future studies.
Biorepository	We will store serum, plasma, and cellular samples (detailed in Appendix C) for projects such as an examination of the age-relevant communicome (peripheral factors reflecting the CNS[147]).

Metabolic/fitness/physical performance assessments:

Measure	Rationale
Aerobic fitness: estimated VO_2 max	Assessed via submaximal graded exercise test (GXT), a low-burden alternative to VO_2 max.[148,149]
Insulin sensitivity: modeled from OGTT	We will use a 2-hour oral glucose tolerance test (OGTT) with frequent sampling of glucose and insulin levels to calculate an insulin sensitivity index as in our past research.[112]
Body Composition scan	Measure of total and regional fat and lean body mass; will characterize participants and will be examined in exploratory analyses. Measured with dual-energy x-ray absorptiometry (DXA).
9-Hole Pegboard Dexterity Test (NIH Toolbox)	This test of manual dexterity records the time required for the participant to accurately place and remove 9 plastic pegs into a plastic pegboard.
Standing Balance Test (NIH Toolbox)	Participant assumes and maintains up to 5 poses for 50 seconds each. Postural sway is recorded for each pose on a force platform.
Short Physical Performance Battery	This test includes graded balance tasks, a timed test of gait speed (8-ft walk) and 5 timed chair stands (lower extremity strength/power).[150]

Neuroimaging battery: (a) covers structural and functional measures of plasticity, (b) is brief and feasible, with a scan time of 45 minutes, and (c) has excellent measurement characteristics with sequences adapted at multiple sites and types of hardware. Because of diurnal variation in brain metabolism,[151] MRIs are done mid-afternoon.

Structural MRI: T1-weighted 3D	High-resolution (1×1×1mm) T1-weighted sagittal, magnetization-prepared rapid gradient echo (MP-RAGE; repetition time (TR)=2300 ms; inversion time (TI)=900 ms, echo time (TE)=2.95 ms, flip angle=9°) with real-time motion correction (PROMO[152]). Analysis with FreeSurfer[153] obtains validated, objective, and semi-automatic regional volumes. Key variables are hippocampal and prefrontal gray matter volumes.[116,154] Acquisition time=5 minutes.
T2-weighted 3D space	T2-weighted space (1×1×1 mm, TR=3200 ms, TE = 455 ms, flip angle= 120°). Anatomic scan that primarily aids in co-registration of functional images to T1-weighted images. Secondarily, evaluation of regions of elevated T2 signal in white matter provides an estimation of white matter integrity.[155] This can serve as an exploratory predictor of response to interventions.[31,156] Acquisition time = 8 minutes.
Functional MRI: Resting state BOLD imaging	Gradient recalled echo-planar sequence (EPI) (TR=2000ms, TE=30ms, flip angle=80°, 3×3×3 mm voxels) while participants are awake in the scanner, performing no task, and keeping their eyes open and loosely fixated on a cross.[157] We will collect three 10-min runs to enhance both within and between session reliability.[158] Key variables are connectivity within frontal-parietal (FP), dorsal attention (DAN) and default mode networks (DMN), and anticorrelations between FP/DAN and DMN.
Gradient Echo Field Mapping	Gradient echo (1.7×1.7×3.0 mm, TR = 488 ms; TE1=4.92 ms; TE2=7.38 ms; flip angle = 60°). For distortion correction in the processing of the rs-fMRI data. Acquisition time = 2 minutes.

Evidence supports rs-fMRI to reliably assay neuroplasticity in age-related cognitive decline: Adding to studies of exercise and MBSR,[33,56,107-109] performance measures linked to rs-fMRI measures include general intelligence,[159,160] working memory capacity,[161,162] performance on a flanker task,[163] numerical ability[164] and

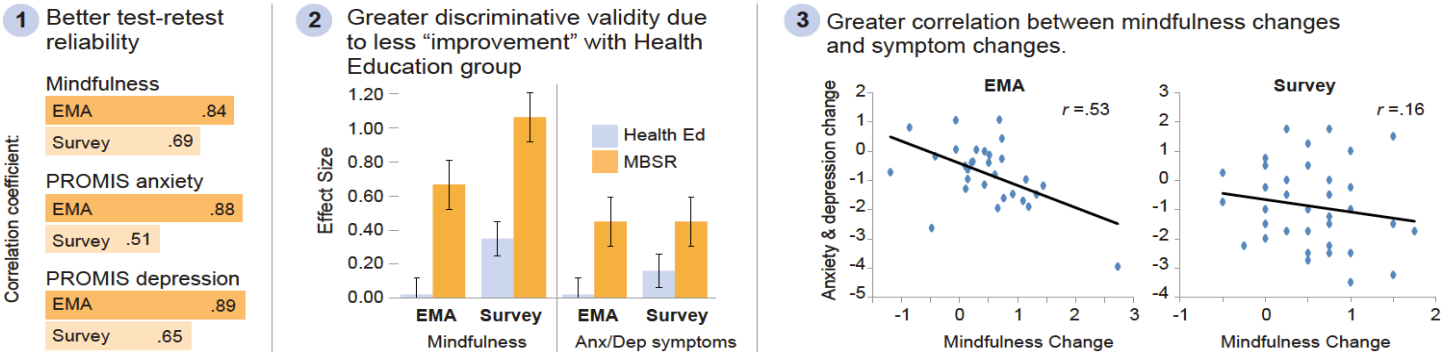
musical ability.[165] Reading proficiency has been related to functional connectivity within brain areas known to instantiate language function,[166] and rs-fMRI has been reported to change in response to reading remediation.[167] Similarly, several studies have shown that intensive training over several days, alters functional connectivity.[168-170] In contrast, task-based fMRI is complicated by findings that fMRI responses to memory paradigms are *greater* than normal early in the course of cognitive decline[171-173] while task-induced responses do decline in parallel with clinical status.[174] These paradoxical results are interpreted as reflecting compensatory hyperactivity in early stages of cognitive impairment followed by ultimate failure. Yet, hypoactive responses may indicate low difficulty, low effort, or impaired circuitry, and therefore are difficult to interpret for this project. Putatively because rs-fMRI eliminates the task-related performance confound, rs-fMRI findings of reduced connectivity in default mode network (DMN) are consistently seen at all stages of age-related cognitive decline.[175,176] Test-retest reliability of structural[177-180] and rs-fMRI[158,181-183] is adequate for this project.

Behavioral/functional measures:

Measure	Rationale
Cognitive and Affective Mindfulness Scale-Revised (CAMS-R)[184]	Measure of mindfulness specifically designed for ease of understanding and found to be sensitive to change in our preliminary studies.
Cognitive concerns and Executive function (short forms)	Secondary outcome variable (everyday cognition).
Anxiety, Depression, Insomnia (short forms)	Exploratory analyses of heterogeneity of response, and exploratory outcomes of psychological health.
Satisfaction with social roles and activities (short form)	Secondary outcome variable (participation/engagement).
Ability to participate in social roles, activities (short form)	Secondary outcome variable (participation/engagement).
Observed Tasks of Daily Living[185] (OTDL)	Performance-based Instrumental Activities of Daily Living measure; potentially more sensitive to intervention effect (compared to self-report).

Ecological Momentary Assessment will improve measurement: The self-report measures are typically assessed via retrospective surveys – "in the last 7 days…" – which require participants to recall, average, and summarize their experiences. These are prone to bias and error,[186-188] and the resultant low assay sensitivity leads to conclusions that interventions have smaller effects – a notorious problem both in geriatric clinical trials[17] and studies of mindfulness/meditation[189] – and interferes with examination of mechanisms. A good example is that MBSR is thought to increase mindfulness, or attention to present moment experience,[190-193] which is particularly ill-suited for retrospective assessment: "in the past, how much were you in the present?"

Ecological Momentary Assessment (EMA) is a solution to this problem.[194-201] EMA queries about present moment experience in real time multiple times throughout the day. In our recent NCCAM-funded grant, we developed an application which turns cell phones into EMA data-capture devices, and we tested EMA against standard retrospective surveys of mindfulness (CAMS-R) and symptoms (PROMIS anxiety and depression short forms) in the same participants before and after intervention. **EMA showed:**



For EMA, we will select items from measures of mindfulness, everyday cognition, anxiety, depression, and participation in social roles and activities, up to 15 total, and sample subjects three times daily for one week at each assessment as in our preliminary study. In addition to precision,[176,180,181] EMA will provide rich data so we can model mechanisms among momentary stress, behavior, and cognition, in relationship to daily activity.[202-204]

Details of the WU-UCSD collaboration for this project:

Study function	Site	Areas of Primary Responsibility
Coordinating Center	WU	• Prepare reports for DSMB and NIA/NCCAM. • Overall study management. • Training and reliability testing in measures. • Precise implementation of the Toolbox at both sites. • Data management and analysis. • Biomarker storage.
MBSR and Health Education supervision	UCSD	• Supervise MBSR and Health Education. • Oversee fidelity/competence in the protocol.
Exercise supervision	WU, UCSD	• Supervise exercise. • Collaborate to ensure fidelity to the protocol.

Study start-up: Key personnel from WU will visit the UCSD site at the beginning of the project period for a study start-up meeting. A highly detailed Manual of Operations, adapted from our existing inter-site protocols for MBSR and exercise studies, will detail each aspect of the project. Once recruitment has begun and the first groups have been randomized and begun interventions, the PI (Lenze) and WU/overall coordinator (Voegtle) will again visit the UCSD site to ensure that both sites act in complete compliance with the protocol and not at variance with each other. The same study site visit will recur yearly throughout the project.

Cross-site Reliability: ***(1) General measurement:*** WU will organize and initiate inter-site meetings to review progress as well as safety and data monitoring. All investigators and raters will participate in phone meetings that will be weekly for PIs and coordinators, with Co-Investigators and other staff participating less frequently. Raters and site coordinators will also participate in monthly phone conferences that will ensure that the study protocol is implemented consistently at each site. All intervention supervisors will hold weekly adherence phone calls with all relevant instructors participating. Interrater reliability of cognitive assessments will be assessed at the start of the study and yearly thereafter. Each site will videotape interviews, and raters will assess the tapes, testing them for reliability and retraining staff to prevent rater drift. ***(2) Neuroimaging:*** The scanning protocol will be imported from WU's Siemen site to the UCSD GE site to ensure exact protocol comparability. To empirically establish reliability across sites, each will collect five sets of phantom data on different days employing our proposed functional sequence, using phantom data and analyses recommended by the fBIRN (Function Bioinformatics Research Network) to assess fundamental parameters of image quality and stability.[205] We will compare these results with fBIRN-recommended QA values. Once the study has started, we will continue to acquire phantom data monthly at each site and compute fBIRN QA parameters. In the analysis of the imaging data, we will use methods suggested by the fBIRN to reduce site influences.[205] To conduct QA studies for structural data, sites will utilize the ADNI structural phantom.[206] Finally, an investigator will be a traveling phantom scanned at both sites at the beginning of the study and annually thereafter.

Data management: We will utilize the same infrastructure from our previous WU/UCSD collaboration. A custom project management database tracks the flow of each participant through the study, recording every contact and data collection point. Study meetings will use real-time assessment of project progress and data monitoring and cleanup. The **Central Neuroimaging Data Archive** (CNDA) will facilitate common data management and productivity tasks for neuroimaging and associated data (see Resources for description).[207]

Data analysis: The 2x2 factorial design is optimal for testing the effects of each intervention and for testing the combined and interactive effects.[208,209] Prior to inferential testing, baseline characteristics will be examined, frequency distributions will be produced, and measures of central tendency and variability will be estimated on each continuous measure. We will follow the intention-to-treat rule for main effects hypotheses, and we will include site as a factor in all of the analyses. All power analyses were conducted with G*Power 3.1 and assume 15% attrition for power calculations. Consistent with conventions for factorial designs,[208,209] we Bonferroni-adjust for number of primary outcomes (two-tailed α=0.025) but not for number of conditions.

Hypothesis testing:
H1: MBSR and exercise will each produce benefits in healthy older adults' cognitive performance, and participants randomized to combined MBSR + exercise will show greater cognitive improvements than those randomized to either intervention alone.

We test (1) main effects of each intervention and (2) interactive effects of the interventions for co-primary dependent variables (memory and cognitive composites). Importantly and in response to the RFA, the sample is well-powered for detection of interactive effects: synergistic effects (e.g., exercise is a therapeutic permissive for MBSR) or interfering effects (e.g., exercising reduces ability or motivation to engage in meditation). Without sufficient power to discern such interactive effects, such a factorial design could provide inconclusive results regarding main effects of each intervention. We have 80% power to detect an interaction of ≥0.2 (Cohen's d), a small effect size. Equally, the sample is well-powered for main effects (80% power to detect main effect of ≥0.2 effect size). Thus, we will provide definitive test of these interventions for cognitive remediation.

Our primary outcome timepoint is 6 months, although this is approximately three months after the end of acute MBSR, because (1) MBSR's benefits are not expected to end immediately after the acute intervention; all of our preliminary studies found retained or increased benefits at three-month follow-up; (2) the project addresses neuroplasticity changes which are not fully obtainable until an intervention has been maximally effective for at least three months, which is the time stem cells need to differentiate into neurons.[210] We also assess cognition at 3 months to provide an "acute" MBSR endpoint, consistent with literature comparing interventions with different time scales.[211] Secondary outcomes test intervention effects on everyday cognition (Cognitive concerns and Executive function), activity performance (OTDL), and social participation/engagement scales.

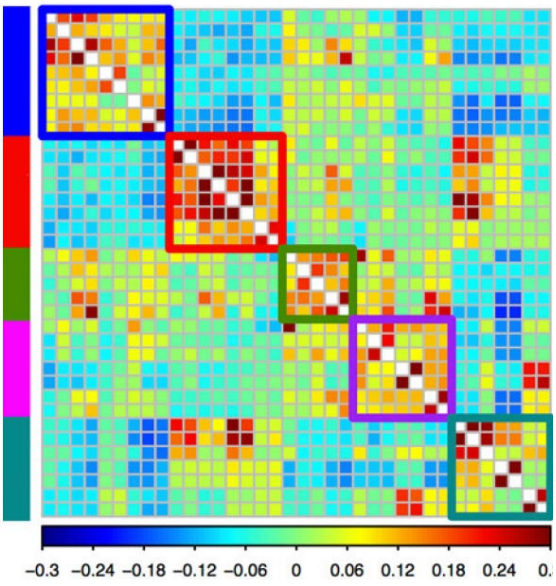
The analytic strategy is mixed-effects modeling. This modeling assumes normality of data, even slight deviations from which can greatly reduce power.[212] Therefore we will also use modern robust methods for between-group testing, as described by Wilcox.[213] Specific techniques are a percentile bootstrap method using a 20% trimmed mean and a running interval smoother. Any pre-test variables may be treated as covariates.

H2: (a) Decrease in peak cortisol accounts for improvements with MBSR.
(b) Increased insulin sensitivity, aerobic fitness, and BDNF account for improvements with exercise.

H3: Improved functional connectivity within and across specific cognitive networks and increased volume of hippocampal and lateral prefrontal regions account for improved cognitive function with the interventions.

For H1a/b analyses that are supported, we will test whether changes in the explanatory variable reduce the size of the relationship between condition and outcome. We will use methods suggested by Preacher and Hayes[214] with bootstrapped estimates of direct and indirect effects. Our power is 80% to detect an indirect effect explaining at least 10% of the relationship between a condition and cognitive outcome. Hence our project will be well powered for any explanatory variable that is clinically significant.

Preprocessing of rsfMRI: Preprocessing of rsfMRI data will be performed using standard techniques.[215,216] This preprocessing will include compensation for slice-dependent time shifts, elimination of systemic odd-even slice intensity differences due to interleaved acquisition, and rigid body correction for head movement within and across runs. Atlas transformation will be achieved by composition of affine transforms connecting the rsfMRI volumes with the T2-weighted and MPRAGE structural images, resulting in a volumetric time series in 3 mm^3 atlas space. Additional preprocessing will include spatial smoothing, voxelwise removal of linear trends over each run, temporal low pass filtering that retaining frequencies <0.1 Hz, and reduction of spurious variance by regression of nuisance waveforms derived from head motion correction and extraction of the time series from regions of white matter and CSF. Regression of whole brain signal will also be performed.[217] Quality control will be performed to ensure that the study objectives are not compromised by subject head motion.[218] This includes removing frames with high root mean squared (rms) head displacement derived from the motion correction procedure, removing frames with excessively high whole brain rms signal change, and removing frames with excessive time series standard deviation averaged across the whole brain.



rs-fMRI Connectivity matrix: Each small square represents a correlation value between two ROIs. The networks are represented as groups of ROIs in larger colored squares along the diagonal, top to bottom are DMN, DAN, FPC, SAL, and SMN.

Functional connectivity changes: As per Brier and Power[215,216] we will use a collection of 36 canonical regions of interest (ROIs) that represent key nodes in the following resting state networks (RSN): Default mode network (DMN), Dorsal attention networks (DAN), FrontoParietal control (FPC), Salience (SAL), and somatomotor (SMN). The first 4 RSN are part of H3 testing since they relate to cognitive control and memory. The last RSN (SMN) can be used as a comparison. Variables of interest are within FPC, DAN, and SAL connectivity which we expect to increase as a function of the interventions.

As the **figure** above shows, a correlation matrix will be generated for each of the 3 time points by calculating the correlation value between each pair of ROIs. The Pearson correlation coefficients will be converted to a z-score. To perform statistical tests for differences while avoiding sampling error at the level of node pairs, we will compute composite scores for each network by averaging the correlations between nodes that belong to that network. For example, the composite score for the DMN will be computed as the average of the z transformed correlations between the pairs of ROIs of the DMN (e.g., posterior cingulate, medial prefrontal, lateral parietal areas). The blue box in the figure shows the DMN ROI. Additionally, cross network composite scores can be computed, providing information on the interaction between networks.

Neuroanatomical changes: Primary analyses will focus on hippocampal and ventral/dorsal-lateral prefrontal (i.e., combined inferior frontal gyrus and caudal middle frontal gyrus) volumes, as these regions underlie memory and cognitive control and have been associated with meditation/mindfulness and exercise effects (e.g.,[29,55]). Primary visual cortex will be a comparison region. Volumes will be adjusted for estimated intracranial volume using covariance to adjust for body size differences.[219,220] We will examine neuroanatomical changes based on longitudinal T1-weighted images acquired with real-time, or prospective, motion correction (PROMO)[152] to improve quality and reliability of scans in this project. PROMO uses three orthogonal spiral navigators along with a recursive image-based estimation strategy based on the Extended Kalman Filter for motion measurement. Images are re-acquired during the course of the scan if motion exceeds a predetermined threshold. The PROMO sequence is available at UCSD and WU and has been used in previous multi-site studies (e.g., PING). PROMO increases success of Freesurfer cortical reconstructions and improves longitudinal reliability of subcortical segmentation, including for the hippocampus.[221] Automated cortical and subcortical parcellations of the T1-weighted images will be obtained using the Freesurfer 5.3.0 image analysis suite;[153] this processing includes motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Once the cortical models are complete, the cerebral cortex is parcellated into units based on gyral and sulcal structure.[153,222,223] Neuroanatomical labels are applied to each voxel based on a probabilistic atlas derived from a manually labeled training set that included older adults.[222] We have experience with quality control procedures for Freesurfer.

H4: Baseline cortisol and insulin sensitivity will predict degree of cognitive remediation with MBSR and exercise, respectively, such that high baseline cortisol will predict greater improvements from MBSR, whereas low insulin sensitivity will predict greater improvements from exercise.

Insulin sensitivity and cortisol are well-suited for hypothesis-testing as moderators, because they are validated systemic constructs that reliability affect cognitive function and neuroplasticity in aging.[18,87-100] Moreover, both are expected (based on our studies and others') to be reversed by exercise and MBSR, respectively.

Robust ANCOVA is the preferred analysis to test moderation, because this technique avoids assumptions of linearity associated with the moderators, allowing the potential detection of threshold levels (at what levels of the variable is the moderator effect greatest). Using this strategy, power for each of these two moderator tests is 80% to detect a moderator effect size (analogous to Cohen's d) = 0.2; thus we are well powered to detect anything above a small effect size. The same robust ANCOVA strategy will allow us to explore other biobehavioral markers as potential treatment moderators, starting with the explanatory variables in H2-H3.

The next set of analyses would examine all time points: baseline (month 0), month 3 and 12 for cognitive variables, end of acute intervention (month 6), and end of one-year maintenance (month 18) using the same models to examine support for H1-H4 with respect to longer-term changes and mechanisms.

Additional exploratory analyses will ensue, including (1) unbiased tests of neuroimaging changes with interventions and (2) functional outcomes and their mediation by neuropsychological changes and improved everyday cognition. The end-product is a comprehensive picture of the benefits of cognitive remediation from MBSR, exercise, and their combination, the underlying plastic changes and mechanisms, and sources of heterogeneity, as requested in the RFA and providing the maximal public health impact from this project.

1. Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. Review. *Ageing research reviews*. Nov 2004;3(4):369-82. doi:10.1016/j.arr.2004.05.001
2. Hedden T, Gabrieli JD. Insights into the ageing mind: a view from cognitive neuroscience. Research Support, U.S. Gov't, P.H.S. Review. *Nature reviews Neuroscience*. Feb 2004;5(2):87-96. doi:10.1038/nrn1323
3. Parslow RA, Jorm AF, Christensen H, Mackinnon A. An instrument to measure engagement in life: factor analysis and associations with sociodemographic, health and cognition measures. *Gerontology*. 2006;52(3):188-98. doi:10.1159/000091829
4. Hultsch DF, Hammer M, Small BJ. Age differences in cognitive performance in later life: relationships to self-reported health and activity life style. Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. *Journal of Gerontology*. Jan 1993;48(1):P1-11.
5. Hillman CH, Motl RW, Pontifex MB, et al. Physical activity and cognitive function in a cross-section of younger and older community-dwelling individuals. Research Support, Non-U.S. Gov't. *Health Psychol*. Nov 2006;25(6):678-87. doi:10.1037/0278-6133.25.6.678
6. Mora F. Successful brain aging: plasticity, environmental enrichment, and lifestyle. Research Support, Non-U.S. Gov't Review. *Dialogues Clin Neurosci*. Mar 2013;15(1):45-52.
7. Erickson KI, Gildengers AG, Butters MA. Physical activity and brain plasticity in late adulthood. *Dialogues Clin Neurosci*. Mar 2013;15(1):99-108.
8. Kheirbek MA, Hen R. (Radio)active neurogenesis in the human hippocampus. *Cell*. Jun 6 2013;153(6):1183-4. doi:10.1016/j.cell.2013.05.033
9. Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. *Annu Rev Neurosci*. 2005;28:377-401.
10. Boyke J, Driemeyer J, Gaser C, Buchel C, May A. Training-induced brain structure changes in the elderly. *J Neurosci*. Jul 9 2008;28(28):7031-5. doi:10.1523/jneurosci.0742-08.2008
11. Lovden M, Bodammer NC, Kuhn S, et al. Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia*. Nov 2010;48(13):3878-83. doi:10.1016/j.neuropsychologia.2010.08.026
12. Mozolic JL, Hayasaka S, Laurienti PJ. A cognitive training intervention increases resting cerebral blood flow in healthy older adults. *Front Hum Neurosci*. 2010;4:16. doi:10.3389/neuro.09.016.2010
13. Park DC, Bischof GN. The aging mind: neuroplasticity in response to cognitive training. *Dialogues Clin Neurosci*. Mar 2013;15(1):109-19.
14. Wenger E, Schaefer S, Noack H, et al. Cortical thickness changes following spatial navigation training in adulthood and aging. Research Support, Non-U.S. Gov't. *Neuroimage*. Feb 15 2012;59(4):3389-97. doi:10.1016/j.neuroimage.2011.11.015
15. Ferreira LK, Busatto GF. Resting-state functional connectivity in normal brain aging. Research Support, Non-U.S. Gov't Review. *Neurosci Biobehav Rev*. Mar 2013;37(3):384-400. doi:10.1016/j.neubiorev.2013.01.017
16. Head D, Singh T, Bugg JM. The moderating role of exercise on stress-related effects on the hippocampus and memory in later adulthood. *Neuropsychology*. Mar 2012;26(2):133-43. doi:10.1037/a0027108
17. Lenze EJ, Wetherell JL. Bringing the bedside to the bench, and then to the community: a prospectus for intervention research in late-life anxiety disorders. *Int J Geriatr Psychiatry*. Jan 2009;24(1):1-14. doi:10.1002/gps.2074 [doi]
18. Peavy GM, Salmon DP, Jacobson MW, et al. Effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. *Am J Psychiatry*. Dec 2009;166(12):1384-91. doi:appi.ajp.2009.09040461 [pii]10.1176/appi.ajp.2009.09040461
19. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci U S A*. Apr 10 2001;98(8):4770-5. doi:10.1073/pnas.081072698081072698 [pii]
20. Sotiropoulos I, Catania C, Pinto LG, et al. Stress acts cumulatively to precipitate Alzheimer's disease-like tau pathology and cognitive deficits. *J Neurosci*. May 25 2011;31(21):7840-7. doi:10.1523/jneurosci.0730-11.2011
21. Wilson RS, Begeny CT, Boyle PA, Schneider JA, Bennett DA. Vulnerability to stress, anxiety, and development of dementia in old age. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *Am J Geriatr Psychiatry*. Apr 2011;19(4):327-34. doi:10.1097/JGP.0b013e31820119da

22. Franceschi C, Capri M, Monti D, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev*. Jan 2007;128(1):92-105. doi:S0047-6374(06)00249-1 [pii]10.1016/j.mad.2006.11.016 [doi]
23. Yaffe K. Metabolic syndrome and cognitive disorders: is the sum greater than its parts? *Alzheimer Dis Assoc Disord*. Apr-Jun 2007;21(2):167-71. doi:10.1097/WAD.0b013e318065bfd6
24. Vivar C, Potter MC, van Praag H. All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. *Curr Top Behav Neurosci*. 2013;15:189-210. doi:10.1007/7854_2012_220
25. Bishop SR. What do we really know about mindfulness-based stress reduction? *Psychosom Med*. Jan-Feb 2002;64(1):71-83.
26. Kabat-Zinn J. *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*. Dell Publishing; 1990.
27. Kabat-Zinn J, Massion AO, Kristeller J, et al. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Am J Psychiatry*. Jul 1992;149(7):936-43.
28. Lutz A, Slagter HA, Rawlings NB, Francis AD, Greischar LL, Davidson RJ. Mental training enhances attentional stability: neural and behavioral evidence. *J Neurosci*. Oct 21 2009;29(42):13418-27. doi:10.1523/jneurosci.1614-09.2009
29. Holzel BK, Carmody J, Vangel M, et al. Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Res*. Jan 30 2011;191(1):36-43. doi:10.1016/j.pscychresns.2010.08.006
30. Tang YY, Lu Q, Fan M, Yang Y, Posner MI. Mechanisms of white matter changes induced by meditation. *Proc Natl Acad Sci U S A*. Jun 26 2012;109(26):10570-4. doi:10.1073/pnas.1207817109
31. Tang YY, Lu Q, Geng X, Stein EA, Yang Y, Posner MI. Short-term meditation induces white matter changes in the anterior cingulate. *Proc Natl Acad Sci U S A*. Aug 31 2010;107(35):15649-52. doi:10.1073/pnas.1011043107
32. Farb NA, Segal ZV, Mayberg H, et al. Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. Research Support, Non-U.S. Gov't. *Soc Cogn Affect Neurosci*. Dec 2007;2(4):313-22. doi:10.1093/scan/nsm030
33. Wells RE, Yeh GY, Kerr CE, et al. Meditation's impact on default mode network and hippocampus in mild cognitive impairment: a pilot study. *Neurosci Lett*. Nov 27 2013;556:15-9. doi:10.1016/j.neulet.2013.10.001
34. Andrews-Hanna JR, Snyder AZ, Vincent JL, et al. Disruption of large-scale brain systems in advanced aging. *Neuron*. 2007;56(5):924-935.
35. Miller JJ, Fletcher K, Kabat-Zinn J. Three-year follow-up and clinical implications of a mindfulness meditation-based stress reduction intervention in the treatment of anxiety disorders. *Gen Hosp Psychiatry*. May 1995;17(3):192-200. doi:016383439500025M [pii]
36. Goldin PR, Gross JJ. Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. *Emotion*. 2010;10(1):83-91.
37. Deyo M, Wilson KA, Ong J, Koopman C. Mindfulness and rumination: does mindfulness training lead to reductions in the ruminative thinking associated with depression? *Explore (NY)*. Sep-Oct 2009;5(5):265-71. doi:S1550-8307(09)00210-9 [pii]10.1016/j.explore.2009.06.005 [doi]
38. Matousek RH, Dobkin PL. Weathering storms: a cohort study of how participation in a mindfulness-based stress reduction program benefits women after breast cancer treatment. *Curr Oncol*. Aug 2010;17(4):62-70.
39. Lengacher CA, Johnson-Mallard V, Barta M, et al. Feasibility of a Mindfulness-Based Stress Reduction Program for Early-Stage Breast Cancer Survivors. *J Holist Nurs*. Nov 1 2010;doi:0898010110385938 [pii] 10.1177/0898010110385938
40. Shapiro SL, Oman D, Thoresen CE, Plante TG, Flinders T. Cultivating mindfulness: effects on well-being. *J Clin Psychol*. Jul 2008;64(7):840-62. doi:10.1002/jclp.20491 [doi]
41. Jain S, Shapiro SL, Swanick S, et al. A randomized controlled trial of mindfulness meditation versus relaxation training: effects on distress, positive states of mind, rumination, and distraction. *Ann Behav Med*. Feb 2007;33(1):11-21. doi:10.1207/s15324796abm3301_2 [doi]
42. Brand S, Holsboer-Trachsler E, Naranjo JR, Schmidt S. Influence of mindfulness practice on cortisol and sleep in long-term and short-term meditators. *Neuropsychobiology*. 2012;65(3):109-18. doi:10.1159/000330362
43. Branstrom R, Kvillemo P, Akerstedt T. Effects of mindfulness training on levels of cortisol in cancer patients. *Psychosomatics*. Mar-Apr 2013;54(2):158-64. doi:10.1016/j.psym.2012.04.007

44. Carlson LE, Speca M, Faris P, Patel KD. One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. *Brain Behav Immun*. Nov 2007;21(8):1038-49. doi:10.1016/j.bbi.2007.04.002
45. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients. *Psychoneuroendocrinology*. May 2004;29(4):448-74.
46. Lengacher CA, Kip KE, Barta M, et al. A pilot study evaluating the effect of mindfulness-based stress reduction on psychological status, physical status, salivary cortisol, and interleukin-6 among advanced-stage cancer patients and their caregivers. *J Holist Nurs*. Sep 2012;30(3):170-85. doi:10.1177/0898010111435949
47. Matousek RH, Pruessner JC, Dobkin PL. Changes in the cortisol awakening response (CAR) following participation in mindfulness-based stress reduction in women who completed treatment for breast cancer. *Complement Ther Clin Pract*. May 2011;17(2):65-70. doi:10.1016/j.ctcp.2010.10.005
48. Nyklicek I, Mommersteeg PM, Van Beugen S, Ramakers C, Van Boxtel GJ. Mindfulness-based stress reduction and physiological activity during acute stress: a randomized controlled trial. *Health Psychol*. Oct 2013;32(10):1110-3. doi:10.1037/a0032200
49. Yau JL, Seckl JR. Local amplification of glucocorticoids in the aging brain and impaired spatial memory. *Front Aging Neurosci*. 2012;4:24. doi:10.3389/fnagi.2012.00024
50. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocr Rev*. Aug 1986;7(3):284-301.
51. Mayer JL, Klumpers L, Maslam S, de Kloet ER, Joels M, Lucassen PJ. Brief treatment with the glucocorticoid receptor antagonist mifepristone normalises the corticosterone-induced reduction of adult hippocampal neurogenesis. Comparative Study
Research Support, Non-U.S. Gov't. *J neuroendocrinol*. Aug 2006;18(8):629-31. doi:10.1111/j.1365-2826.2006.01455.x
52. Oomen CA, Mayer JL, de Kloet ER, Joels M, Lucassen PJ. Brief treatment with the glucocorticoid receptor antagonist mifepristone normalizes the reduction in neurogenesis after chronic stress. Research Support, Non-U.S. Gov't. *Eur J Neurosci*. Dec 2007;26(12):3395-401. doi:10.1111/j.1460-9568.2007.05972.x
53. Kramer AF, Hahn S, Cohen NJ, et al. Ageing, fitness and neurocognitive function. Clinical Trial
Letter Randomized Controlled Trial. *Nature*. Jul 29 1999;400(6743):418-9. doi:10.1038/22682
54. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *J Gerontol A Biol Sci Med Sci*. Nov 2006;61(11):1166-70.
55. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. Feb 15 2011;108(7):3017-22. doi:10.1073/pnas.1015950108
56. Voss MW, Erickson KI, Prakash RS, et al. Neurobiological markers of exercise-related brain plasticity in older adults. *Brain Behav Immun*. Feb 2013;28:90-9. doi:10.1016/j.bbi.2012.10.021
57. Gomez-Pinilla F, Hillman C. The influence of exercise on cognitive abilities. *Compr Physiol*. Jan 2013;3(1):403-28. doi:10.1002/cphy.c110063
58. Dishman RK, Berthoud HR, Booth FW, et al. Neurobiology of exercise. *Obesity (Silver Spring)*. Mar 2006;14(3):345-56. doi:14/3/345 [pii]10.1038/oby.2006.46 [doi]
59. Izumi Y, Yamada KA, Matsukawa M, Zorumski CF. Effects of insulin on long-term potentiation in hippocampal slices from diabetic rats. *Diabetologia*. Jul 2003;46(7):1007-12. doi:10.1007/s00125-003-1144-2
60. Voss MW, Vivar C, Kramer AF, van Praag H. Bridging animal and human models of exercise-induced brain plasticity. Research Support, N.I.H., Extramural Research Support, N.I.H., Intramural Research Support, Non-U.S. Gov't. *Trends Cogn Sci*. Oct 2013;17(10):525-44. doi:10.1016/j.tics.2013.08.001
61. Creer DJ, Romberg C, Saksida LM, van Praag H, Bussey TJ. Running enhances spatial pattern separation in mice. *Proc Natl Acad Sci U S A*. Feb 2 2010;107(5):2367-72. doi:10.1073/pnas.0911725107
62. Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience*. 2004;124(1):71-9. doi:10.1016/j.neuroscience.2003.09.029
63. van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci*. Sep 21 2005;25(38):8680-5. doi:10.1523/jneurosci.1731-05.2005

64. Clark PJ, Brzezinska WJ, Thomas MW, Ryzhenko NA, Toshkov SA, Rhodes JS. Intact neurogenesis is required for benefits of exercise on spatial memory but not motor performance or contextual fear conditioning in C57BL/6J mice. *Neuroscience*. Sep 9 2008;155(4):1048-58. doi:10.1016/j.neuroscience.2008.06.051
65. Butters MA, Bhalla RK, Andreescu C, et al. Changes in neuropsychological functioning following treatment for late-life generalised anxiety disorder. *Br J Psychiatry*. Sep 2011;199:211-8. doi:10.1192/bjp.bp.110.090217
66. DeLuca AK, Lenze EJ, Mulsant BH, et al. Comorbid anxiety disorder in late life depression: association with memory decline over four years. *Int J Geriatr Psychiatry*. Sep 2005;20(9):848-54. doi:10.1002/gps.1366
67. Karp J, Butters M, Begley A, Miller M, Lenze E. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in mid-life and older adults. *J Clin Psychiatry*. In Press;
68. Lenze E, Hershey T, Newcomer JW, et al. Antiglucocorticoid therapy for older adults with anxiety and co-occurring cognitive dysfunction: results from a pilot study with mifepristone. *Int J Geriatr Psychiatry*. In Press;
69. Lenze EJ, Dew MA, Mazumdar S, et al. Combined pharmacotherapy and psychotherapy as maintenance treatment for late-life depression: effects on social adjustment. *Am J Psychiatry*. Mar 2002;159(3):466-8.
70. Lenze EJ, Dixon D, Mantella RC, et al. Treatment-related alteration of cortisol predicts change in neuropsychological function during acute treatment of late-life anxiety disorder. *Int J Geriatr Psychiatry*. Jun 17 2011;doi:10.1002/gps.2732
71. Lenze EJ, Host HH, Hildebrand MW, et al. Enhanced medical rehabilitation increases therapy intensity and engagement and improves functional outcomes in postacute rehabilitation of older adults: a randomized-controlled trial. *J Am Med Dir Assoc*. Oct 2012;13(8):708-12. doi:10.1016/j.jamda.2012.06.014
72. Lenze EJ, Mantella RC, Shi P, et al. Elevated Cortisol in Older Adults With Generalized Anxiety Disorder Is Reduced by Treatment: A Placebo-Controlled Evaluation of Escitalopram. *Am J Geriatr Psychiatry*. Aug 11 2010;doi:10.1097/JGP.0b013e3181ec806c
73. Lenze EJ, Mulsant BH, Shear MK, et al. Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial. *Am J Psychiatry*. Jan 2005;162(1):146-50. doi:162/1/146 [pii]10.1176/appi.ajp.162.1.146
74. Lenze EJ, Rollman BL, Shear MK, et al. Escitalopram for older adults with Generalized Anxiety Disorder: a placebo-controlled trial. *JAMA*. 2009;301(3):296-303.
75. Reynolds CF, 3rd, Butters MA, Lopez O, et al. Maintenance Treatment of Depression in Old Age: A Randomized, Double-blind, Placebo-Controlled Evaluation of the Efficacy and Safety of Donepezil Combined With Antidepressant Pharmacotherapy. *Arch Gen Psychiatry*. Jan 2011;68(1):51-60. doi:10.1001/archgenpsychiatry.2010.184
76. Reynolds CF, 3rd, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med*. Mar 16 2006;354(11):1130-8. doi:354/11/1130 [pii]10.1056/NEJMoa052619
77. Wetherell JL, Petkus AJ, White KS, et al. Antidepressant medication augmented with cognitive-behavioral therapy for generalized anxiety disorder in older adults. *Am J Psychiatry*. Jul 1 2013;170(7):782-9. doi:10.1176/appi.ajp.2013.12081104
78. Whyte EM, Lenze EJ, Butters MA, et al. Acetylcholinesterase inhibitors for the treatment of post-stroke cognitive impairment in the medical rehabilitation setting. *Cerebrovasc Dis*. 2008;26:317-321.
79. Lenze E, Hickman S, Hershey T, et al. Mindfulness-Based Stress Reduction for older adults with worry symptoms and co-occurring cognitive dysfunction. *Int J Geriatr Psychiatry*. In Press;
80. Langer J, Weisman J, Rodebaugh TL, Binder E, Lenze E. Short-Term Affective Recovery from Hip Fracture Prospectively Predicts Depression and Physical Functioning. *Health Psychology*. In Press;
81. Wetherell JL, Gatz M, Craske MG. Treatment of generalized anxiety disorder in older adults. *J Consult Clin Psychol*. 2003;71:31-40.
82. Wetherell JL, Sorrell JT, Thorp SR, Patterson TL. Psychological interventions for late-life anxiety: a review and early lessons from the CALM study. *J Geriatr Psychiatry Neurol*. Jun 2005;18(2):72-82. doi:18/2/72 [pii] 10.1177/0891988705276058
83. Wetherell JL, Stoddard JA, White KS, et al. Augmenting antidepressant medication with modular CBT for geriatric generalized anxiety disorder: a pilot study. *Int J Geriatr Psychiatry*. Sep 27 2010;doi:10.1002/gps.2619
84. Wetherell JL, Ayers CR, Sorrell JT, et al. Modular psychotherapy for anxiety in older primary care patients. *Am J Geriatr Psychiatry*. Jun 2009;17(6):483-92. doi:10.1097/JGP.0b013e3181a31fb5 00019442-200906000-00007 [pii]

85. Andreescu C, Lenze EJ, Mulsant BH, et al. High worry severity is associated with poorer acute and maintenance efficacy of antidepressants in late-life depression. *Depress Anxiety*. 2009;26(3):266-72. doi:10.1002/da.20544 [doi]
86. Kraemer HC, Giese-Davis J, Yutsis M, et al. Design decisions to optimize reliability of daytime cortisol slopes in an older population. *Am J Geriatr Psychiatry*. Apr 2006;14(4):325-33. doi:14/4/325 [pii] 10.1097/01.JGP.0000201816.26786.5b
87. Beluche I, Carriere I, Ritchie K, Ancelin ML. A prospective study of diurnal cortisol and cognitive function in community-dwelling elderly people. *Psychol Med*. Jun 2010;40(6):1039-49. doi:10.1017/s0033291709991103
88. Comijs HC, Gerritsen L, Penninx BW, Bremmer MA, Deeg DJ, Geerlings MI. The association between serum cortisol and cognitive decline in older persons. *Am J Geriatr Psychiatry*. Jan 2010;18(1):42-50. doi:10.1097/JGP.0b013e3181b970ae
89. Ferrari E, Magri F. Role of neuroendocrine pathways in cognitive decline during aging. Review. *Ageing research reviews*. Jul 2008;7(3):225-33. doi:10.1016/j.arr.2008.07.001
90. Fiocco AJ, Wan N, Weekes N, Pim H, Lupien SJ. Diurnal cycle of salivary cortisol in older adult men and women with subjective complaints of memory deficits and/or depressive symptoms: relation to cognitive functioning. *Stress*. Sep 2006;9(3):143-52. doi:U177M33285M47350 [pii]10.1080/10253890600965674
91. Gerritsen L, Comijs HC, Deeg DJ, Penninx BW, Geerlings MI. Salivary cortisol, APOE-varepsilon4 allele and cognitive decline in a prospective study of older persons. *Neurobiol Aging*. Oct 29 2009;doi:S0197-4580(09)00313-3 [pii]10.1016/j.neurobiolaging.2009.09.007
92. Heffelfinger AK, Newcomer JW. Glucocorticoid effects on memory function over the human life span. *Dev Psychopathol*. Summer 2001;13(3):491-513.
93. Karlamangla AS, Singer BH, Chodosh J, McEwen BS, Seeman TE. Urinary cortisol excretion as a predictor of incident cognitive impairment. *Neurobiol Aging*. Dec 2005;26 Suppl 1:80-4. doi:S0197-4580(05)00305-2 [pii] 10.1016/j.neurobiolaging.2005.09.037 [doi]
94. Lee BK, Glass TA, McAtee MJ, et al. Associations of salivary cortisol with cognitive function in the Baltimore memory study. *Arch Gen Psychiatry*. Jul 2007;64(7):810-8. doi:64/7/810 [pii] 10.1001/archpsyc.64.7.810
95. Li G, Cherrier MM, Tsuang DW, et al. Salivary cortisol and memory function in human aging. *Neurobiol Aging*. Nov 2006;27(11):1705-14. doi:S0197-4580(05)00307-6 [pii]10.1016/j.neurobiolaging.2005.09.031
96. Lind K, Edman A, Nordlund A, Olsson T, Wallin A. Increased saliva cortisol awakening response in patients with mild cognitive impairment. *Dement Geriatr Cogn Disord*. 2007;24(5):389-95. doi:000109938 [pii] 10.1159/000109938
97. Lupien S, Lecours AR, Lussier I, Schwartz G, Nair NP, Meaney MJ. Basal cortisol levels and cognitive deficits in human aging. *J Neurosci*. May 1994;14(5 Pt 1):2893-903.
98. Lupien SJ, Nair NP, Briere S, et al. Increased cortisol levels and impaired cognition in human aging: implication for depression and dementia in later life. *Rev Neurosci*. 1999;10(2):117-39.
99. Rosnick CB, Rawson KS, Butters MA, Lenze EJ. Association of cortisol with neuropsychological assessment in older adults with generalized anxiety disorder. *Aging Ment Health*. 2013;17(4):432-40. doi:10.1080/13607863.2012.761673
100. Wolf OT, Convit A, Thorn E, de Leon MJ. Salivary cortisol day profiles in elderly with mild cognitive impairment. *Psychoneuroendocrinology*. Oct 2002;27(7):777-89. doi:S0306453001000798 [pii]
101. Rogers RD, Monsell S. Costs of a predictible switch between simple cognitive tasks. *Journal of experimental psychology: General*. 1995;124(2):207.
102. Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J. 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia*. Jun 1997;35(6):747-58.
103. Gallegos AM, Hoerger M, Talbot NL, et al. Toward Identifying the Effects of the Specific Components of Mindfulness-Based Stress Reduction on Biologic and Emotional Outcomes Among Older Adults. *Journal of alternative and complementary medicine*. Feb 5 2013;doi:10.1089/acm.2012.0028
104. Moynihan JA, Chapman BP, Klorman R, et al. Mindfulness-based stress reduction for older adults: effects on executive function, frontal alpha asymmetry and immune function. *Neuropsychobiology*. 2013;68(1):34-43. doi:10.1159/000350949

105. Jha AP, Krompinger J, Baime MJ. Mindfulness training modifies subsystems of attention. *Cogn Affect Behav Neurosci*. Jun 2007;7(2):109-19.
106. Mrazek MD, Franklin MS, Phillips DT, Baird B, Schooler JW. Mindfulness training improves working memory capacity and GRE performance while reducing mind wandering. *Psychol Sci*. May 2013;24(5):776-81. doi:10.1177/0956797612459659
107. Brefczynski-Lewis JA, Lutz A, Schaefer HS, Levinson DB, Davidson RJ. Neural correlates of attentional expertise in long-term meditation practitioners. *Proc Natl Acad Sci U S A*. Jul 3 2007;104(27):11483-8. doi:0606552104 [pii]10.1073/pnas.0606552104 [doi]
108. Lutz A, Brefczynski-Lewis J, Johnstone T, Davidson RJ. Regulation of the neural circuitry of emotion by compassion meditation: effects of meditative expertise. *PLoS One*. 2008;3(3):e1897. doi:10.1371/journal.pone.0001897
109. Miller DI, Taler V, Davidson PS, Messier C. Measuring the impact of exercise on cognitive aging: methodological issues. *Neurobiol Aging*. Mar 2012;33(3):622 e29-43. doi:10.1016/j.neurobiolaging.2011.02.020
110. Shah K, Stufflebam A, Hilton TN, Sinacore DR, Klein S, Villareal DT. Diet and exercise interventions reduce intrahepatic fat content and improve insulin sensitivity in obese older adults. Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *Obesity*. Dec 2009;17(12):2162-8. doi:10.1038/oby.2009.126
111. Villareal DT, Miller BV, 3rd, Banks M, Fontana L, Sinacore DR, Klein S. Effect of lifestyle intervention on metabolic coronary heart disease risk factors in obese older adults. Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *Am J Clin Nutr*. Dec 2006;84(6):1317-23.
112. Weiss EP, Racette SB, Villareal DT, et al. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. Randomized Controlled Trial Research Support, N.I.H., Extramural. *The American journal of clinical nutrition*. Nov 2006;84(5):1033-42.
113. Bugg JM, Head D. Exercise moderates age-related atrophy of the medial temporal lobe. *Neurobiol Aging*. Mar 2011;32(3):506-14. doi:10.1016/j.neurobiolaging.2009.03.008
114. Bugg JM, Shah K, Villareal DT, Head D. Cognitive and neural correlates of aerobic fitness in obese older adults. Research Support, N.I.H., Extramural. *Experimental aging research*. 2012;38(2):131-45. doi:10.1080/0361073X.2012.659995
115. Gordon BA, Rykhlevskaia EI, Brumback CR, et al. Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. Comparative Study Research Support, N.I.H., Extramural. *Psychophysiology*. Sep 2008;45(5):825-38. doi:10.1111/j.1469-8986.2008.00676.x
116. Erickson KI, Miller DL, Roecklein KA. The aging hippocampus: interactions between exercise, depression, and BDNF. *Neuroscientist*. Feb 2012;18(1):82-97. doi:10.1177/1073858410397054
117. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci*. Nov 2004;20(10):2580-90. doi:10.1111/j.1460-9568.2004.03720.x
118. Head D, Bugg JM, Goate AM, et al. Exercise Engagement as a Moderator of the Effects of APOE Genotype on Amyloid Deposition. *Arch Neurol*. May 2012;69(5):636-43. doi:10.1001/archneurol.2011.845
119. Villareal DT, Chode S, Parimi N, et al. Weight loss, exercise, or both and physical function in obese older adults. *N Engl J Med*. Mar 31 2011;364(13):1218-29. doi:10.1056/NEJMoa1008234
120. Galvin JE, Roe CM, Coats MA, Morris JC. Patient's rating of cognitive ability: using the AD8, a brief informant interview, as a self-rating tool to detect dementia. *Arch Neurol*. May 2007;64(5):725-30. doi:64/5/725 [pii]10.1001/archneur.64.5.725
121. Wechsler D. *Wechsler Test of Adult Reading: WTAR*. Psychological Corp.; 2001.
122. Vos SJ, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol*. Oct 2013;12(10):957-65. doi:10.1016/s1474-4422(13)70194-7
123. Jack CR, Jr., Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann Neurol*. Jun 2012;71(6):765-75. doi:10.1002/ana.22628
124. Arcury TA, Grzywacz JG, Neiberg RH, et al. Daily Use of Complementary and Other Therapies for Symptoms Among Older Adults: Study Design and Illustrative Results. *J Aging Health*. Oct 11 2010;doi:0898264310385115 [pii]10.1177/0898264310385115

125. Grzywacz JG, Suerken CK, Quandt SA, Bell RA, Lang W, Arcury TA. Older adults' use of complementary and alternative medicine for mental health: findings from the 2002 National Health Interview Survey. Research Support, N.I.H., Extramural. *J Altern Complement Med*. Jun 2006;12(5):467-73. doi:10.1089/acm.2006.12.467
126. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res*. Mar 1992;41(3):237-48.
127. First M, Spitzer R, Gibbon M, Williams J. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)*. American Psychiatric Press; 1997.
128. Carmody J, Baer RA. How long does a mindfulness-based stress reduction program need to be? A review of class contact hours and effect sizes for psychological distress. *J Clin Psychol*. Jun 2009;65(6):627-38. doi:10.1002/jclp.20555 [doi]
129. Stahl B, Goldstein E. *A Mindfulness-Based Stress Reduction Workbook*. New Harbinger Pubns Inc; 2010.
130. Nichols JF, Hitzelberger LM, Sherman JG, Patterson P. Effects of resistance training on muscular strength and functional abilities of community-dwelling older adults. *J Aging Phys Act*. 1995;3(3):238-250.
131. Nichols JF, Omizo DK, Peterson KK, Nelson KP. Efficacy of heavy-resistance training for active women over sixty: muscular strength, body composition, and program adherence. *J Am Geriatr Soc*. Mar 1993;41(3):205-10.
132. Villareal DT, Banks M, Sinacore DR, Siener C, Klein S. Effect of weight loss and exercise on frailty in obese older adults. Randomized Controlled Trial Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't. *Arch Intern Med*. Apr 24 2006;166(8):860-6. doi:10.1001/archinte.166.8.860
133. American College of Sports Medicine Position Stand. Exercise and physical activity for older adults. Review. *Med Sci Sports Exerc*. Jun 1998;30(6):992-1008.
134. Roberts CK, Little JP, Thyfault JP. Modification of insulin sensitivity and glycemic control by activity and exercise. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *Med Sci Sports Exerc*. Oct 2013;45(10):1868-77. doi:10.1249/MSS.0b013e318295cdbb
135. Chang YK, Pan CY, Chen FT, Tsai CL, Huang CC. Effect of resistance-exercise training on cognitive function in healthy older adults: a review. Review. *J Aging Phys Act*. Oct 2012;20(4):497-517.
136. MacCoon DG, Imel ZE, Rosenkranz MA, et al. The validation of an active control intervention for Mindfulness Based Stress Reduction (MBSR). Randomized Controlled Trial Research Support, N.I.H., Extramural
Validation Studies. *Behaviour Research and Therapy*. Jan 2012;50(1):3-12. doi:10.1016/j.brat.2011.10.011
137. Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *J Behav Ther Exp Psychiatry*. 1972;3(4):257-260.
138. Kabat-Zinn J. *Wherever you go, there you are: Mindfulness meditation in everyday life*. Hyperion Books; 1994.
139. Gershon RC, Cella D, Fox NA, Havlik RJ, Hendrie HC, Wagster MV. Assessment of neurological and behavioural function: the NIH Toolbox. Letter. *Lancet Neurol*. Feb 2010;9(2):138-9. doi:10.1016/S1474-4422(09)70335-7
140. Newcomer JW, Selke G, Melson AK, et al. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch Gen Psychiatry*. Jun 1999;56(6):527-33.
141. Balota DA, Tse CS, Hutchison KA, Spieler DH, Duchek JM, Morris JC. Predicting conversion to dementia of the Alzheimer's type in a healthy control sample: the power of errors in Stroop color naming. Research Support, N.I.H., Extramural. *Psychology and Aging*. Mar 2010;25(1):208-18. doi:10.1037/a0017474
142. Smallwood J, Davies JB, Heim D, et al. Subjective experience and the attentional lapse: task engagement and disengagement during sustained attention. *Conscious Cogn*. Dec 2004;13(4):657-90. doi:10.1016/j.concog.2004.06.003
143. Mantella RC, Butters MA, Amico JA, et al. Salivary cortisol is associated with diagnosis and severity of late-life generalized anxiety disorder. *Psychoneuroendocrinology*. Jul 2008;33(6):773-81. doi:S0306-4530(08)00066-8 [pii]10.1016/j.psyneuen.2008.03.002
144. Erickson KI, Kim JS, Suever BL, Voss MW, Francis BM, Kramer AF. Genetic Contributions to Age-Related Decline in Executive Function: A 10-Year Longitudinal Study of COMT and BDNF Polymorphisms. *Front Hum Neurosci*. 2008;2:11. doi:10.3389/neuro.09.011.2008
145. Hashimoto R, Moriguchi Y, Yamashita F, et al. Dose-dependent effect of the Val66Met polymorphism of the brain-derived neurotrophic factor gene on memory-related hippocampal activity. *Neurosci Res*. Aug 2008;61(4):360-7. doi:10.1016/j.neures.2008.04.003
146. Karnik MS, Wang L, Barch DM, Morris JC, Csernansky JG. BDNF polymorphism rs6265 and hippocampal structure and memory performance in healthy control subjects. *Psychiatry Res*. Jul 30 2010;178(2):425-9. doi:10.1016/j.psychres.2009.09.008

147. Ray S, Britschgi M, Herbert C, et al. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *Nat Med*. Nov 2007;13(11):1359-62. doi:10.1038/nm1653
148. Thompson PD, Buchner D, Piña IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation*. 2003;107(24):3109-3116.
149. Taylor DL, Nichols JF, Pakiz B, Bardwell WA, Flatt SW, Rock CL. Relationships between cardiorespiratory fitness, physical activity, and psychosocial variables in overweight and obese breast cancer survivors. *Int J Behav Med*. Dec 2010;17(4):264-70. doi:10.1007/s12529-010-9076-y
150. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. Mar 1994;49(2):M85-94.
151. Shannon BJ, Dosenbach RA, Su Y, et al. Morning-evening variation in human brain metabolism and memory circuits. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *J Neurophysiol*. Mar 2013;109(5):1444-56. doi:10.1152/jn.00651.2012
152. White N, Roddey C, Shankaranarayanan A, et al. PROMO: Real-time prospective motion correction in MRI using image-based tracking. Research Support, N.I.H., Extramural. *Magn Reson Med*. Jan 2010;63(1):91-105. doi:10.1002/mrm.22176
153. Fischl B. FreeSurfer. *Neuroimage*. Aug 15 2012;62(2):774-81. doi:10.1016/j.neuroimage.2012.01.021
154. Braver TS, Paxton JL, Locke HS, Barch DM. Flexible neural mechanisms of cognitive control within human prefrontal cortex. *Proc Natl Acad Sci U S A*. May 5 2009;106(18):7351-6. doi:10.1073/pnas.0808187106
155. Barch DM, D'Angelo G, Pieper C, et al. Cognitive improvement following treatment in late-life depression: relationship to vascular risk and age of onset. *Am J Geriatr Psychiatry*. Aug 2012;20(8):682-90. doi:10.1097/JGP.0b013e318246b6cb
156. Pfefferbaum A, Adalsteinsson E, Sullivan EV. Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. *Neuroimage*. Jul 1 2005;26(3):891-9. doi:S1053-8119(05)00143-6 [pii] 10.1016/j.neuroimage.2005.02.034
157. Patriat R, Molloy EK, Meier TB, et al. The effect of resting condition on resting-state fMRI reliability and consistency: a comparison between resting with eyes open, closed, and fixated. *Neuroimage*. Sep 2013;78:463-73. doi:10.1016/j.neuroimage.2013.04.013
158. Birn RM, Molloy EK, Patriat R, et al. The effect of scan length on the reliability of resting-state fMRI connectivity estimates. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *Neuroimage*. Dec 2013;83:550-8. doi:10.1016/j.neuroimage.2013.05.099
159. Cole MW, Yarkoni T, Repovs G, Anticevic A, Braver TS. Global connectivity of prefrontal cortex predicts cognitive control and intelligence. *J Neurosci*. Jun 27 2012;32(26):8988-99. doi:10.1523/jneurosci.0536-12.2012
160. Song M, Zhou Y, Li J, et al. Brain spontaneous functional connectivity and intelligence. *Neuroimage*. Jul 1 2008;41(3):1168-76. doi:10.1016/j.neuroimage.2008.02.036
161. Stevens AA, Tappon SC, Garg A, Fair DA. Functional brain network modularity captures inter- and intra-individual variation in working memory capacity. *PLoS One*. 2012;7(1):e30468. doi:10.1371/journal.pone.0030468
162. van den Heuvel MP, Stam CJ, Kahn RS, Hulshoff Pol HE. Efficiency of functional brain networks and intellectual performance. *J Neurosci*. Jun 10 2009;29(23):7619-24. doi:10.1523/jneurosci.1443-09.2009
163. Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Competition between functional brain networks mediates behavioral variability. *Neuroimage*. Jan 1 2008;39(1):527-37. doi:10.1016/j.neuroimage.2007.08.008
164. Park J, Park DC, Polk TA. Parietal functional connectivity in numerical cognition. *Cereb Cortex*. Sep 2013;23(9):2127-35. doi:10.1093/cercor/bhs193
165. Jancke L, Langer N, Hanggi J. Diminished whole-brain but enhanced peri-sylvian connectivity in absolute pitch musicians. *J Cogn Neurosci*. Jun 2012;24(6):1447-61. doi:10.1162/jocn_a_00227
166. Koyama MS, Di Martino A, Zuo XN, et al. Resting-state functional connectivity indexes reading competence in children and adults. *J Neurosci*. Jun 8 2011;31(23):8617-24. doi:10.1523/jneurosci.4865-10.2011

167. Koyama MS, Di Martino A, Kelly C, et al. Cortical signatures of dyslexia and remediation: an intrinsic functional connectivity approach. *PLoS One*. 2013;8(2):e55454. doi:10.1371/journal.pone.0055454
168. Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M. Learning sculpts the spontaneous activity of the resting human brain. *Proc Natl Acad Sci U S A*. Oct 13 2009;106(41):17558-63. doi:10.1073/pnas.0902455106
169. Mackey AP, Miller Singley AT, Bunge SA. Intensive reasoning training alters patterns of brain connectivity at rest. *J Neurosci*. Mar 13 2013;33(11):4796-803. doi:10.1523/jneurosci.4141-12.2013
170. Voss MW, Prakash RS, Erickson KI, et al. Effects of training strategies implemented in a complex videogame on functional connectivity of attentional networks. *Neuroimage*. Jan 2 2012;59(1):138-48. doi:10.1016/j.neuroimage.2011.03.052
171. Putcha D, Brickhouse M, O'Keefe K, et al. Hippocampal hyperactivation associated with cortical thinning in Alzheimer's disease signature regions in non-demented elderly adults. *J Neurosci*. Nov 30 2011;31(48):17680-8. doi:10.1523/jneurosci.4740-11.2011
172. Dickerson BC, Wolk DA. MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. *Neurology*. Jan 10 2012;78(2):84-90. doi:10.1212/WNL.0b013e31823efc6c
173. Dickerson BC, Salat DH, Greve DN, et al. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology*. Aug 9 2005;65(3):404-11. doi:10.1212/01.wnl.0000171450.97464.49
174. O'Brien JL, O'Keefe KM, LaViolette PS, et al. Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. *Neurology*. Jun 15 2010;74(24):1969-76. doi:10.1212/WNL.0b013e3181e3966e
175. Chhatwal JP, Sperling RA. Functional MRI of mnemonic networks across the spectrum of normal aging, mild cognitive impairment, and Alzheimer's disease. *J Alzheimers Dis*. 2012;31 Suppl 3:S155-67. doi:10.3233/jad-2012-120730
176. Mevel K, Chetelat G, Eustache F, Desgranges B. The default mode network in healthy aging and Alzheimer's disease. *Int J Alzheimers Dis*. 2011;2011:535816. doi:10.4061/2011/535816
177. Mulder ER, de Jong RA, Knol DL, et al. Hippocampal volume change measurement: Quantitative assessment of the reproducibility of expert manual outlining and the automated methods FreeSurfer and FIRST. *Neuroimage*. Feb 9 2014;doi:10.1016/j.neuroimage.2014.01.058
178. Jiang J, Sachdev P, Lipnicki DM, et al. A longitudinal study of brain atrophy over two years in community-dwelling older individuals. *Neuroimage*. Feb 1 2014;86:203-11. doi:10.1016/j.neuroimage.2013.08.022
179. Schmand B, Rienstra A, Tamminga H, et al. Responsiveness of Magnetic Resonance Imaging and Neuropsychological Assessment in Memory Clinic Patients. *J Alzheimers Dis*. Jan 28 2014;doi:10.3233/jad-131484
180. Jovicich J, Marizzoni M, Sala-Llonch R, et al. Brain morphometry reproducibility in multi-center 3T MRI studies: a comparison of cross-sectional and longitudinal segmentations. *Neuroimage*. Dec 2013;83:472-84. doi:10.1016/j.neuroimage.2013.05.007
181. Braun U, Plichta MM, Esslinger C, et al. Test-retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. *Neuroimage*. Jan 16 2012;59(2):1404-12. doi:10.1016/j.neuroimage.2011.08.044
182. Guo CC, Kurth F, Zhou J, et al. One-year test-retest reliability of intrinsic connectivity network fMRI in older adults. Research Support, Non-U.S. Gov't. *Neuroimage*. Jul 16 2012;61(4):1471-83. doi:10.1016/j.neuroimage.2012.03.027
183. Zuo XN, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP. Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. *Neuroimage*. Feb 1 2010;49(3):2163-77. doi:10.1016/j.neuroimage.2009.10.080
184. Feldman G, Hayes A, Kumar S, Greeson J, Laurenceau JP. Mindfulness and emotion regulation: The development and initial validation of the Cognitive and Affective Mindfulness Scale-Revised (CMS-R). *J PSychopathol Behav Assess*. 2007;29(3):177-190.
185. Diehl M, Marsiske M, Horgas AL, Rosenberg A, Saczynski JS, Willis SL. The Revised Observed Tasks of Daily Living: A Performance-Based Assessment of Everyday Problem Solving in Older Adults. *J Appl Gerontol*. 2005;24(3):211-230. doi:10.1177/0733464804273772
186. Collins RL, Kashdan TB, Gollnisch G. The feasibility of using cellular phones to collect ecological momentary assessment data: Application to alcohol consumption. *Exp Clin Psychopharmacol*. 2003;11(1):73.
187. Cain AE, Depp CA, Jeste DV. Ecological momentary assessment in aging research: A critical review. *J Psychiatr Res*. 2009;43(11):987-996.

188. Slater CH, Bick D. Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation. *JAMA*. 1994;271(17):1377.
189. Goyal M, Singh S, Sibinga EM, et al. Meditation Programs for Psychological Stress and Well-being: A Systematic Review and Meta-analysis. *JAMA Intern Med*. Jan 6 2014;doi:10.1001/jamainternmed.2013.13018
190. Orsillo SM. *Acceptance and mindfulness-based approaches to anxiety: Conceptualization and treatment*. Springer Verlag; 2005.
191. Bishop SR, Lau M, Shapiro S, et al. Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice*. 2004;11(3):230-241.
192. Lau MA, Bishop SR, Segal ZV, et al. The Toronto Mindfulness Scale: development and validation. *J Clin Psychol*. Dec 2006;62(12):1445-67. doi:10.1002/jclp.20326
193. Baer RA, Walsh E, Lykins ELB. Assessment of mindfulness. *Clinical handbook of mindfulness*. 2009:153-168.
194. Axelson DA, Bertocci MA, Lewin DS, et al. Measuring mood and complex behavior in natural environments: use of ecological momentary assessment in pediatric affective disorders. *J Child Adolesc Psychopharmacol*. Fall 2003;13(3):253-66. doi:10.1089/104454603322572589 [doi]
195. Moskowitz DS, Young SN. Ecological momentary assessment: what it is and why it is a method of the future in clinical psychopharmacology. *J Psychiatry Neurosci*. Jan 2006;31(1):13-20.
196. Granholm E, Loh C, Swendsen J. Feasibility and validity of computerized ecological momentary assessment in schizophrenia. *Schizophr Bull*. May 2008;34(3):507-14. doi:sbm113 [pii]
10.1093/schbul/sbm113
197. Johnson EI, Grondin O, Barrault M, et al. Computerized ambulatory monitoring in psychiatry: a multi-site collaborative study of acceptability, compliance, and reactivity. *Int J Methods Psychiatr Res*. 2009;18(1):48-57. doi:10.1002/mpr.276
198. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol*. 2008;4:1-32.
199. Trull TJ, Ebner-Priemer UW. Using experience sampling methods/ecological momentary assessment (ESM/EMA) in clinical assessment and clinical research: introduction to the special section. *Psychol Assess*. Dec 2009;21(4):457-62. doi:2009-22537-001 [pii]10.1037/a0017653
200. Ebner-Priemer UW, Trull TJ. Ambulatory assessment: An innovative and promising approach for clinical psychology. *European Psychologist*. 2009;14(2):109.
201. Wenze SJ, Miller IW. Use of ecological momentary assessment in mood disorders research. *Clin Psychol Rev*. Aug 2010;30(6):794-804. doi:S0272-7358(10)00101-7 [pii]
10.1016/j.cpr.2010.06.007
202. Hedeker D, Mermelstein RJ, Berbaum ML, Campbell RT. Modeling mood variation associated with smoking: an application of a heterogeneous mixed-effects model for analysis of ecological momentary assessment (EMA) data. *Addiction*. Feb 2009;104(2):297-307. doi:10.1111/j.1360-0443.2008.02435.x
203. Sliwinski MJ, Almeida DM, Smyth J, Stawski RS. Intraindividual change and variability in daily stress processes: findings from two measurement-burst diary studies. *Psychol Aging*. Dec 2009;24(4):828-40. doi:10.1037/a0017925
204. Salthouse TA. Robust cognitive change. *J Int Neuropsychol Soc*. Jul 2012;18(4):749-56. doi:10.1017/s1355617712000380
205. Glover GH, Mueller BA, Turner JA, et al. Function biomedical informatics research network recommendations for prospective multicenter functional MRI studies. Multicenter Study
Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.
Review. *J Magn Reson Imaging*. Jul 2012;36(1):39-54. doi:10.1002/jmri.23572
206. Maikusa N, Yamashita F, Tanaka K, et al. Improved volumetric measurement of brain structure with a distortion correction procedure using an ADNI phantom. Research Support, Non-U.S. Gov't. *Med Phys*. Jun 2013;40(6):062303. doi:10.1118/1.4801913
207. Marcus DS, Harms MP, Snyder AZ, et al. Human Connectome Project informatics: quality control, database services, and data visualization. *Neuroimage*. Oct 15 2013;80:202-19. doi:10.1016/j.neuroimage.2013.05.077
208. Dziak JJ, Nahum-Shani I, Collins LM. Multilevel factorial experiments for developing behavioral interventions: power, sample size, and resource considerations. *Psychol Methods*. Jun 2012;17(2):153-75. doi:10.1037/a0026972
209. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomised controlled trials. *BMC Med Res Methodol*. Nov 24 2003;3:26. doi:10.1186/1471-2288-3-26

210. Cummings BJ, Uchida N, Tamaki SJ, et al. Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. *Proc Natl Acad Sci U S A*. Sep 27 2005;102(39):14069-74. doi:10.1073/pnas.0507063102
211. Poulsen S, Lunn S, Daniel SI, et al. A randomized controlled trial of psychoanalytic psychotherapy or cognitive-behavioral therapy for bulimia nervosa. *Am J Psychiatry*. Jan 1 2014;171(1):109-16. doi:10.1176/appi.ajp.2013.12121511
212. Keselman HJ, Algina J, Lix LM, Wilcox RR, Deering KN. A generally robust approach for testing hypotheses and setting confidence intervals for effect sizes. Research Support, Non-U.S. Gov't. *Psychological methods*. Jun 2008;13(2):110-29. doi:10.1037/1082-989X.13.2.110
213. Wilcox RR. *Introduction to robust estimation and hypothesis testing*. Academic Press; 2012.
214. Hayes AF, Preacher KJ. Statistical mediation analysis with a multicategorical independent variable. *Br J Math Stat Psychol*. Nov 5 2013;doi:10.1111/bmsp.12028
215. Brier MR, Thomas JB, Snyder AZ, et al. Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. Jun 27 2012;32(26):8890-9. doi:10.1523/JNEUROSCI.5698-11.2012
216. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *Neuroimage*. Jan 1 2014;84:320-41. doi:10.1016/j.neuroimage.2013.08.048
217. Fox MD, Zhang D, Snyder AZ, Raichle ME. The global signal and observed anticorrelated resting state brain networks. Research Support, N.I.H., Extramural. *J Neurophysiol*. Jun 2009;101(6):3270-83. doi:10.1152/jn.90777.2008
218. Hacker CD, Perlmutter JS, Criswell SR, Ances BM, Snyder AZ. Resting state functional connectivity of the striatum in Parkinson's disease. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. *Brain*. Dec 2012;135(Pt 12):3699-711. doi:10.1093/brain/aws281
219. Buckner RL, Head D, Parker J, et al. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage*. Oct 2004;23(2):724-38. doi:10.1016/j.neuroimage.2004.06.018
220. Mathalon DH, Sullivan EV, Rawles JM, Pfefferbaum A. Correction for head size in brain-imaging measurements. *Psychiatry Res*. Jun 1993;50(2):121-39.
221. Brown TT, Kuperman JM, Erhart M, et al. Prospective motion correction of high-resolution magnetic resonance imaging data in children. Research Support, N.I.H., Extramural. *Neuroimage*. Oct 15 2010;53(1):139-45. doi:10.1016/j.neuroimage.2010.06.017
222. Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. Jul 1 2006;31(3):968-80. doi:10.1016/j.neuroimage.2006.01.021
223. Fischl B, Salat DH, van der Kouwe AJ, et al. Sequence-independent segmentation of magnetic resonance images. *Neuroimage*. 2004;23 Suppl 1:S69-84. doi:10.1016/j.neuroimage.2004.07.016