MEDEX PROTOCOL

Remediating Age Related Cognitive Decline in Older Adults

a. Study Overview:

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), which are key to participating and engaging in meaningful daily activities. These cognitive losses match age-related changes in brain structure, such as volume loss, and function, including reduced functional connections within cognitive circuits.

We need interventions that remediate age-related cognitive decline. The brain retains the potential for neuroplasticity in old age, 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).

Stress and (in) activity are key predictors of decline, putatively via neuroendocrine, immune, metabolic, and neurotrophin changes that are targets for intervention. **Therefore, two promising interventions are <u>Mindfulness-Based Stress Reduction (MBSR) and exercise</u>.**

In this study, we will examine the effects of four interventions on age-related cognitive decline in healthy older adults: Mindfulness Based Stress Reduction (MBSR) psychotherapy, multi-component intensity-based exercise, and their combination, compared to a discussion group. 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. It is widely available, acceptable to older people, and carries minimal risk of side effects or adverse events. Exercise – specifically, intense, multi-component exercise – also appears to affect brain structure and function and improve cognitive performance.

Accordingly, we will enroll approximately 450 and randomize approximately 300 non-demented healthy adults aged 65 to 84 to one of four conditions: MBSR alone, exercise alone, MBSR + exercise, or a health education discussion group control condition. The study will consist of an approximately 10-week acute intervention phase with weekly visits followed by an approximately 15-month maintenance phase with monthly visits for MBSR and health education participants. It will consist of an approximately 6-month acute intervention phase with weekly visits followed by an approximately 12-month maintenance phase with weekly visits for exercise participants. MBSR and exercise interventions will incorporate additional prompts, for example, surveys via a tablet device, 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.

A subset of up to 15 individuals, including staff, ages 18-84, will be enrolled in the study and undergo some study procedures in order to perform cross-validation of machines, procedures, etc. at each study site. This subset will be recruited from study staff, volunteers familiar with the study (e.g. staff from other study sites), etc. This subset will not be identical to the participants who will be randomized (e.g.

will not have cognitive impairment, etc.), but will be screened for the same safety criteria prior to undergoing procedures. These individuals will not participate in the study interventions.

b. Subject Recruitment and Retention:

Study staff will partner with several care networks, including Washington University clinics in primary and specialty medical care and geriatric medicine, the Washington University Physician Network, and referrals from local practitioners and the BJC Medical Group.

Of the 9,500 participants currently enrolled in the Volunteers for Health Research registry, providing opportunity for wide-based screening of self-nominated volunteers to potentially identify and contact, and Washington University Alzheimer's Disease Research Center, providing access to older adults within the Clinical Dementia Rating 0 (no dementia) cohort (N=420) who have also been typed for Alzheimer's biomarkers, we believe a sufficient number of participants are available to reach our recruitment goals. Washington University Public Affairs will engage local media for messaging the study, using newspaper or radio advertising. Our prior geriatric clinical trials have been able to recruit in the hundreds despite much more narrow inclusion criteria by these wide-based screening methods. Based on our experience, we expect participants to be approximately 60-70% female, and approximately 25% minorities, with the St. Louis site enrolling approximately 20% African Americans and the San Diego site recruiting approximately 30% Latinos and others.

In addition, referrals from Dr. Lenze's clinic practice, community psychiatrists, the Volunteer for Health registry detailed in the study overview, the ADRC, and the Advanced Depression Options and Neurostimulation (ADDON) Clinic at WUSM will serve as additional sources of referrals.

Finally, recruitment procedures will include IRB-approved media advertisements, presentations to groups of elderly people and their families, referrals by word of mouth, and letters announcing the study to former research participants.

c. Consent:

All study procedures will comply with the Washington University IRB informed consent standards. All research team members involved in the design and conduct of this project maintain the required education on the protection of human research participants. All procedures to recruit participants for the protocol and obtain their informed consent will be supervised by the PIs. A detailed description of the research project will be relayed to all prospective participants. It will include the risks of participation, assurance of confidentiality, and the knowledge that their freedom to refuse participation or to withdraw from the project will not affect the treatment they are eligible to receive outside of the study. After all study related procedures, risks, and benefits are explained and discussed, potential participants will be asked to sign an informed consent document and will be enrolled.

d. Inclusion/Exclusion Criteria:

Inclusion criteria:

-Community-living men and women age 65 to 84.
-Self-reported cognitive complaints that are a normal part of aging.
-No current meditation practice nor prior training in it.
-Sedentary (per PI discretion).

Exclusion criteria:

-Known diagnosis of dementia, mild cognitive impairment, other clinical neurodegenerative illness (e.g., Parkinson's disease, cerebrovascular disease), psychotic disorder, or any unstable psychiatric condition.
-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 would interfere with the assessments, such as taking medications for diabetes or ferromagnetic metal/bridgework that would interfere with MRI signal.
-IQ <70 as estimated by the Wechsler Test of Adult Reading
-Sensory impairment (language, hearing, or visual) that would prevent participation.
-Substance abuse within 6 months that would affect their participation per PI discretion
-Concurrent cognitive training, such as brain-training software, or other interventions expected to affect neuroplasticity.
-Medications that interfere with measurements, including cancer chemotherapy, glucocorticoids, and interferon.
-Inability to cooperate with protocol.

e. Rationale for Inclusion & Exclusion:

This study requires the safe evaluation of exercises and mindfulness training on cognitive remediation in older adults. Accordingly, it is important that subjects who participate in this study have no current or recent unstable medical or psychiatric conditions that would increase their risk. To this end, subjects will be carefully screened to exclude those individuals who have any medical conditions that would increase their risk, affect their ability to complete the study procedures, or any subclinical symptomatology at the discretion of the PI. Per PI discretion, participants that have a history of substance abuse will be excluded due to the impact on cognition.

f. 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 up to 20 participants 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 half day retreat. Participants will continue attending monthly classes as part of the maintenance phase after the ten-week acute intervention period. 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* as a companion guide. Participants get daily at-home assignments with recordings of meditative practices. Subjects may be asked to track their daily practice on an electronic data collection device (tablet or personal device via status/post through REDCap) or by paper and pencil. We will ask if they are adhering to their home practice and intervene with prompts and counseling for those not keeping up with their home practice. Subjects will be asked to practice MBSR at home, with the goal of working up to 1 hour of practice per day.

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. It consists of classes twice weekly, building up to 1.5-hour, 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. Participants will continue attending once per week supervised exercise sessions as part of the maintenance phase after a 6-month acute intervention period. 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 and have been shown to improve cognitive function in older adults. Participants will complete 1 repetition max measurements (1RMs), determining the maximum amount of weight they can lift in one repetition at baseline, 6 months, and 18 months. Participants will record physiological and exercise information obtained during in-person exercise classes, such as heart rate, blood pressure, minutes of aerobic activity, etc.

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 with the goal of achieving a heart rate between 70 and 85% peak.
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 will gradually increase the volume and intensity with a goal of 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 120 minutes of home exercise each week. The aerobic component will consist of walking, using exercise DVDs, and/or other aerobic activities; additionally, participants will be given a rotation of exercise activities for strength and balance-training exercises practiced in class that can be done safely at home. Subjects may be asked to track their daily practice on an electronic data collection device (tablet or personal device via status/post through REDCap) or by paper and pencil. We will ask if they are adhering to their home exercise 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 in the acute phase. During the maintenance phase participants will come in monthly to receive MBSR (after initial MBSR course) and weekly to exercise classes (after 6 month acute phase). 120 minutes of at-home exercise each week as well as daily, at-home mindfulness practice of up to 1 hour will be assigned and may be asked to be tracked via the tablet, personal device, or paper and pencil.

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). We use *Living a Healthy Life with Chronic Conditions: Self-Management of Heart Disease, Arthritis, Diabetes, Depression, Asthma, Bronchitis, Emphysema and Other Physical and Mental Health Conditions* Workbook as a companion guide. 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 (with a regular 2.5 hour class replacing the half day retreat). In our RCT of MBSR in older adults, participants found Health Education credible (high scores on a credibility and expectations for improvement scale) 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.

g. Screening Process:

Screening Process (including baseline assessments)

After providing Informed Consent and signing a written informed consent document approved by WUSM HRPO, participants will begin the screening process to assess eligibility for the study. The screening process involves a series of in-person visits, conducted over the course of approximately 4 visits. Each visit will last approximately 2-4 hours. They may occur in any order. Participants may be ineligible if they are deemed at risk for study participation based on any of these measures. Screening visits will include all of the following measures and assessments. They will be conducted in-person with study staff in our research lab suite or at facilities on the Washington University/Barnes-Jewish Medical Center campus. If specific assessments cannot be completed prior to randomization, a participant may still be eligible to proceed per PI discretion.

Exclusionary Questions-

Questions about medical and mental health history, medications, and extracurricular activities will be asked. Subjects may be asked to sign a release of information to obtain copies of their medical records to review for inclusion/exclusion criteria. We will perform a brief physical examination to evaluate general medical health. Participants will complete the WTAR as an estimate of IQ. Those with a standard score less than 70 will not be eligible for the study. Questionnaires assessing mood and substance abuse will be administered. Per PI discretion, participants will be ineligible if they present with substance abuse that would affect their participation.

Treadmill Tests with EKG-

A maximal treadmill or bicycle test and EKG will be conducted at screening to check for cardiac stability. We will also use the screening test to determine resting and maximal/peak heart rate for calculation of a safe and optimal aerobic exercise prescription. A submaximal treadmill or bicycle test will subsequently be done after 6 months of treatment as an outcome measure. An EKG will be performed at 6 months as necessary. An IV draw line may be placed prior to beginning the treadmill test. For safety reasons it will be left in place during the visit but will be removed before leaving.

Subjects will begin walking on the treadmill or pedaling on the bike at a slow speed. The speed will start at a warm up speed and increase slightly to a constant speed for the remainder of the test. The grade of

the treadmill or resistance on the bicycle will increase gradually throughout the test. The test is complete when a subject feels they can no longer continue or until it is no longer deemed safe for the patient to continue. Pulse and blood pressure will be monitored during the test. Participants will remain in the laboratory for a minimum of 15 minutes after finishing their exercise test. They will have their blood pressure measured just before leaving the lab. They will be asked to remain in the lab until their BP has returned to its pre-exercise value (within 10 and 5 Torr for systolic and diastolic, respectively). All parts of this procedure may take up to 2 hours to complete.

Strength, Mobility, Behavioral/Functional Assessments-

Subjects will undergo a variety of assessments at screener, after 6 months, and after 18 months of treatment. They will perform strength, mobility, and balance related tasks, such as: a grip strength test, arm length measurement, the Short Physical performance Battery (SPPB), including several measures of balance, three short (25-30') walking tests, be asked to stand and sit multiple times from a chair, etc. Subjects will hold positions as long as they can up to 20 seconds for balance measures. The walking test and chair stands will be timed. All balance testing will be measured using BtrackS balance tracking system, a computerized force plate that will provide a more objective and detailed assessment of balance than administrator observation alone. These tasks will take a total of about 20 minutes.

fsOGTT and Blood tests-

fsOGTT and/or blood tests will be done at screening/baseline, after 6 months, and after 18 months of treatment. After an approximately 10 to 12-hour overnight fast (except for water), an IV line will be inserted for blood sampling by the CRU nursing personnel. Subjects will be supine and one hand may be kept in a box thermostatically warmed to 50C to arterialize the blood samples, which will be drawn from an indwelling needle in that hand or forearm. Subjects then undergo a 15 to 30-minute period of habituation. Fasting blood samples and a blood DNA sample (one sample only) will be collected after the habituation period for baseline, 6, and 18 month timepoints. After all fasting blood samples are collected at baseline and 6 months, blood samples will be obtained immediately before and at 10, 20, 30, 60, 90, and 120 minutes after ingesting a 75g oral glucose load. Subjects will be given a meal once the IV has been removed. Approximately 270ml or less of blood will be obtained from each subject during the course of the study (approximately 90ml during each fsOGTT visit at baseline and 6 month, and less at 18 month).

Study staff will be administer other study related assessments during this test or immediately before or after, including interview questions about mental health, personality, and ability to solve problems related to everyday tasks (e.g. OTDL).

DEXA-

Body composition will be assessed at screening/baseline, after 6 months, and after 18 months of treatment. Total body fat and total fat-free mass will be determined by DEXA (GE Lunar (iDXA)). Appendicular skeletal muscle mass will be estimated from these data as described and validated by Heymsfield et al. The error of regional fat free mass determination by this technique, as compared with computerized tomography, is less than 5%.

Neuroimaging-

Neuroimaging will be done at screening/baseline, after 6 months, and after 18 months of treatment. Subjects will receive a head MRI (approximately 1 hour).

MRI Methods

Overview – We will use resting-state functional connectivity (fMRI) to define functional connectivity between various regions within established cortical neural networks. Participants who pass MRI screening will undergo an MRI scan. All MRI examinations will be done on Siemens 3T Trio Scanner (Erlangen, Germany) at Washington University.

Anatomical (Structural) MRI – Anatomic (structural) MRI will be obtained using standard imaging. All imaging will include both anatomic (structural) and functional (fMRI) MRI. The anatomic MRI obtained at baseline will be reviewed for incidental findings. The PI will share any significant findings on the MRI that may affect the participant's health with the participant. With the participant's consent, we will also share the findings with their physician or health clinic, to facilitate a health care evaluation.

Resting-State Functional MRI – A gradient recalled echo-planar sequence (EPI) [Repetition time [TR]=2200ms, echo time [TE]=27ms, flip angle=90°, 4x4x4 mm voxels] is used to capture images of blood oxygenation level-dependent (BOLD) contrast responses while participants are awake in the scanner performing no task (eyes open, no music, head phones in place). EPI images of the whole brain are volume acquisitions across 36 axial slices. Four EPI runs, lasting 8 minutes 15 second search, will be used to record resting state, spontaneous brain activity.

Sensory Testing-

A brief battery of vision and hearing tests imposing minimal burden will be administered. This includes a computerized visual acuity test, a contrast vision eye chart test, and the Ishihara color vision test. Each of these tests will require participants to read letters or numbers presented through electronic and paper eye charts. Participants will be instructed to use glasses or corrective lenses during these assessments. Words in Noise, a hearing test that is part of the NIH Toolbox, will also be administered. Participants will wear headphones and repeat words recited to them by a computerized voice.

Neuropsychological Testing-

Neuropsychological testing will occur at screening/baseline, and after 3, 6, and 18 months of treatment. Subjects will undergo an approximately 2 – 2.5 hour computerized and paper/pencil neuropsych battery. Subjects will sit at a computer terminal where different images will be presented on the screen. These could be numbers, letters, words, sentences, or pictures (faces, parts of the body, locations, tools). They will respond by pressing a button, reading aloud what they see on the screen, or picking from among a group of answers. Subjects will also listen to computerized recordings and verbal lists of information and be asked to repeat the information back to study staff.

Behavioral Measures-

Subjects will complete self-report behavioral measures: Cognitive and Affective Mindfulness Scale-Revised (CAMS-R), Falls Self-Efficacy Scale International (FES-I), NIH Patient-Reported Outcome Measurement Information System (PROMIS) questionnaires (Anxiety, Depression, Sleep, Satisfaction with Social Roles and Activities, Ability to Participate in Social Roles), NIH Quality of Life Outcomes in Neurological Disorders (Neuro-QOL) questionnaires (Cognitive Function, Positive Affect and Well-Being), 3-D Wisdom Scale (3DWS), Connor Davidson Resilience Scale (CDRS), Lifetime Orientation Test – Revised (LOT-R), Santa Clara Brief Compassion Scale (SCBCS), and a Self-Related Successful Aging Question.

At Home Tasks-

The following procedures will be completed at home during the screening process. Study staff will review each task in-person before subjects are asked to complete them at home. Staff will be available for questions at any time.

Tablets: Participants will be asked to answer questions for approximately 10 days on an EMA (Ecological Momentary Assessment) collection device that the study will either provide to them (tablet) or on their personal device using an application (app), status/post, created through REDCap. EMA queries about present moment experience in real time multiple times throughout the day. In our recent NCCIH-funded grant (previously NCCAM), we developed an application that allows tablets to be used as EMA data-capture devices. Participants will be asked questions about their emotions 3 times a day. Questions will take no longer than 15 minutes total per day. Participants are instructed not to answer questions during unsafe times (i.e. while driving). Participants will be instructed on how to download status/post to their personal device if they choose to use the application to answer the questions. If provided a tablet, participants will return the tablet at an upcoming visit upon completion of the 10 days. Participants will answer EMA items on a device at 3 timepoints during the study (screening/baseline, 6 months, and 18 months). During the study interventions, participants may also answer study related questions (e.g. time spent practicing, etc.) or receive information (e.g. intervention prompts, etc.) on a tablet or, if they choose, on their own personal device.

Accelerometry: Participants will be given a wrist-worn device, called an actigraph, used to measure activity and sleep. Actigraphy data will be collected by having the patient wear the device approximately 24-hours per day (the devices are not waterproof and will not be worn during any water activities) for approximately 10 days. Participants will return the device at a future visit. If there was a problem collecting actigraphy data during the initial wear, participants may be asked to wear the device for approximately another 10 days. Participants will be asked to wear the actigraph at 3 timepoints during the study (screening/baseline, 6 months, and 18 months) following the timelines described. Participants may also be asked to wear the device at stress tests during testing at the research facility. Only movement data, and no GPS or other identifying information, will be collected via the actigraphy device.

Salivary Cortisol: Participants will collect salivary cortisol at home 3-times a day (waking, 30 minutes later, and at bedtime) over a three-day period at screening/baseline, after 6 months, and after 18 months of treatment. They will be provided with instructions for collecting their saliva using cotton swabs. Kits will be sent home with participants and will be returned to study staff once all samples have been collected. If there was a problem collecting samples during the initial collection, participants may be asked to re-collect the needed timepoints again.

h. Randomization:

After the screening process and baseline data has been collected, subjects will be randomly assigned to receive one of the 4 treatment groups: Mindfulness-Based Stress Reduction (MBSR) only, Exercise only, MBSR plus Exercise, or the health education group called Living a Healthy Lifestyle.

Mindfulness Based Stress Reduction (MBSR) Only-

If subjects are randomized to the MBSR only group, their participation will last approximately 20 months. For the first 8-weeks of participation, this group will meet weekly for approximately 2.5-hours and will be led by trained clinicians. In addition to the 8 weeks, there is an orientation meeting and a one-day (about 4 hours) retreat included, totaling 10 weekly classes. In the MBSR classes, subjects will learn about mindfulness or being present in the moment. This will include various practices designed to reduce stress, such as meditation and gentle movement, and they will be asked to practice some of these exercises at home up to 1 hour per day. After completing the first 10-weeks of the study, subjects will come in for monthly visits.

Exercise Only-

If subjects are randomized to the Exercise only group, participation will last a total of approximately 20 months. For the first 6-months of participation, this group will meet approximately 2-times per week, working up to 1.5 hour visits. After the first 6 months participation in classes will taper to weekly visits. Subjects will also be given exercises to do at home that will last the entire 20 months of participation. These classes will be directed and supervised by trained exercise instructors. Each session will consist of aerobic exercises and resistance training to improve fitness and overall health. Subjects will also do exercises to help improve balance, mobility, and flexibility. Subjects will be asked to exercise at home up to 120 minutes per week.

MBSR plus Exercise Group-

If subjects are randomized to this group, participation will last a total of approximately 20 months. Subjects will come in for MBSR sessions as described above for 2.5-hours weekly for 10-weeks, and exercise up to 1.5-hours 2-times each week for 6 months, then monthly for MBSR classes and weekly for exercise classed for the remainder of the study. Subjects will also be asked to practice at home.

Living a Healthy Life group (Health Education)-

If subjects are randomized to the Living a Healthy Life group, their participation will last a total of approximately 20 months. For the first 10-weeks, this group will meet weekly for approximately 2.5-hours. It matches MBSR in time and number of sessions (with a regular 2.5 hour class replacing the half day retreat). Subjects will discuss health topics relevant to them and their peers. Subjects will learn skills to manage health problems that are associated with many illnesses and skills to promote healthy living. After completing the first 10-weeks of the study, subjects will come in for monthly visits.

Tablet and Email Surveys After Randomization-

Participants may be asked to answer study related questions or receive information on a tablet or their personal device during the study interventions. Participants may be provided with a tablet to take home or given the choice to download the application to receive these questions or prompts. They may also be asked to record daily home practice on the tablet device or their personal device. In the rare case that a participant is unable to use the tablet, they will be allowed to record the data using paper surveys. Emails may be sent acquiring information about health and habits since enrolling in the study, for example, falls or breaks in at-home practice.

i. Follow-up Assessments: 3-month, 6-month, and 18-month visits:

If specific assessments cannot be completed during follow-up visits, a participant may still be eligible to proceed per PI discretion.

After approximately 3-months participants will return to complete the neuropsychological testing battery and behavioral measures. This visit will last approximately 2-3 hours.

After 6-months and 18-months of participation, participants will repeat similar measures completed at screening/baseline visits. These follow up visits may be split into approximately 4 visits lasting approximately 2 – 4 hours each. Measures will include: treadmill or bicycle test (EKG as needed), strength, mobility, and balance assessments, an fsOGTT and/or blood draws, DEXA scan, MRI, sensory testing (18 month only), neuropsychological testing, and behavioral surveys. Subjects will also be asked to answer EMA questions via an electronic device for approximately 10 days, wear an actigraph for approximately 10 days, and collect saliva for 3 days.

j. Schedule and Description of Study Assessments:

General Measures-

Contact/Screening Log - This form will be completed to enhance the ability to contact participants throughout the study and to collect demographic information. This form includes: name, address, phone number including alternate, email, DOB, age, ethnicity, race, gender, referral location and source, and eligibility status.

Screening Assessments-

Prior to conducting any of the planned experimental conditions, all subjects will be screened for the presence of listed exclusions and will be assessed to rule out the presence of medical conditions or medications that would be a contraindication to participation in this study.

Holistic Practices – The Holistic Practices questionnaire assesses subjects for any current participation in practices similar to MBSR. Subjects participating in these types of practices will be excluded.

Medical History Questionnaire – All subjects will complete a medical history questionnaire during the screening visit. Those who present with conditions that may interact negatively with any intervention condition or study assessments will be excluded.

Medication Questionnaire – All subjects will inform study staff of current medications during the screening process. Those who are taking medications that may interact negatively with any intervention condition or study assessments will be excluded.

Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) – The PAR-Q+ is a series of questions completed during the phone screen to assess whether subjects will need to provide further approval from their medical doctor prior to participating in the study. Based on the results of the questionnaire subjects will be reviewed by the study team and will provide medical clearance from their doctor as needed.

Wechsler Test of Adult Reading (WTAR) – The WTAR is used to gain an estimate of IQ. Participants read words from a page and are scored on correct pronunciation. Those with a standard score less than 70 will not be eligible for the study.

Study Assessments-

3-D Wisdom Scale (3DWS) – The 3DWS is a brief 12 item self-report measure of subjective wisdom. This measure will be completed at all timepoints.

Arm Length – Arm length will be measured one time on all participants going forward and on participants who are already currently enrolled in the study. Arm length is used to more accurately process accelerometry data. This measure poses no safety risk to participants.

Cognitive and Affective Mindfulness Scale-Revised (CAMS-R) – The CAMS-R is a brief 12 item self-report measure of mindfulness with items written in everyday language. This measure will be complete at all timepoints.

Connor Davidson Resilience Scale (CDRS) – The CDRS is a brief 10 item self-report measure of subjective resilience. This measure will be completed at all timepoints.

Credibility and Expectations Questionnaire (CEI) – Once subjects are assigned to their respective intervention they will be assessed for subjective beliefs that the intervention is credible. Subjects will also indicate their expectations that the assigned intervention will improve their condition (i.e. cognition). This measure is administered only after the first class.

Cumulative Illness Rating Scale for Geriatrics (CIRS-G) - Medical history and current medications will be assessed at screening/baseline and study PIs will use this information to score a CIRS-G at screening/baseline only. This is a score of overall health.

Early Trauma Inventory Self Report (ETISR) – An instrument for the assessment of physical, emotional, and sexual abuse, as well as general traumas, which measures frequency, onset, emotional impact, and other variables. It will be administered one time.

Ecological Momentary Assessment – Items will be taken from each of the following questionnaires and delivered to participants via an electronic device 3 times a day for approximately 10 days: CAMS-R, PROMIS Anxiety, Depression, and Sleep, and Neuro-QOL Positive Affect and Well-Being. Questions will take no longer than 15 minutes total per day. EMA collection will be done at screening/baseline, 6 months, and 18 months.

Exercise Intervention measures – Participants will complete 1 repetition maximum measurements (1RMs), determining the maximum amount of weight they can lift in one repetition at baseline, 6 months, and 18 months. Participants will record physiological and exercise information obtained during in-person exercise classes, such as heart rate, blood pressure, minutes of aerobic activity, etc.

External Intervention Questionnaire – Questionnaire designed to assess any use of study interventions techniques outside of the study protocol. This measure will be complete at all timepoints.

Falls Self-Efficacy Scale International (FES-I) – The FES-I is a brief 7 item self-report measure of fear of falling. This measure will be completed at all timepoints.

Grip Strength Test – Hand-grip dynamometry will be used to assess muscular strength of both hands at screening/baseline, 6 months, and 18 months. This measure is widely used in geriatric exercise research as a reliable, quick, and safe measure of strength that correlates well with whole body strength measures, and predicts frailty in older adults. This assessment requires no more than approximately 2 minutes to complete. Trials will be conducted on each hand.

Home Practice Log – Subjects will be asked to practice at home. Participants may use an electronic device to record practice time. In the rare case that a participant is unable to use an electronic device, they will be allowed to record the data using paper surveys.

International Personality Item Pool (IPIP) – A 120 item questionnaire used to the assess personality using the five factor model. We will use the 20-item version of this questionnaire. It will be administered one time.

Lifetime Orientation Test – Revised (LOT-R) – The LOT-R is a brief 6 item self-report measure of subjective dispositional optimism. This measure will be completed at all timepoints.

Maintenance Phase Practice log – During the maintenance phase, a REDCap survey may be emailed to participants in the MBSR, Exercise, or MBSR+Exercise conditions one time per month asking about any breaks in at-home practice over the last month. Staff may follow-up with any participants who have had breaks.

Medical Records Release – Subjects will complete a medical records release form at screening to allow study staff to communicate study results with the subjects medical care team as necessary and as requested by the subject.

Mini International Neuropsychiatric Interview (MINI) – The MINI was designated as a brief structured interview for the major Axis I psychiatric disorders in DM – IV and ICD. Study staff will complete selected modules with patients to determine any psychotic disorders or unstable psychiatric conditions that would exclude subjects from participation at screening only.

NIH Patient-Reported Outcome Measurement Information System (PROMIS) – NIH PROMIS measures will be completed by all study subjects at all timepoints to assess subjective emotional and

social functioning: PROMIS Anxiety, PROMIS Depression, PROMIS Sleep, PROMIS Satisfaction with Social Roles and Activities, and PROMIS Ability to Participate in Social Roles.

NIH Quality of Life Outcomes in Neurological Disorders (Neuro-QOL) – NIH Neuro-QOL measure will be completed by all study subjects as all timepoints to assess subjective emotional and social functioning: Neuro-QOL Cognitive Function, and Neuro-QOL Positive Affect and Well-Being.

Neuroimaging questionnaires – Several questionnaires will be administered in close proximity to the MRI scan, for example, pre- and post-scan questionnaires assessing activity prior to or during the scan (e.g. sleep).

Reported Falls Questionnaire – After randomization into a group, a REDCap survey may be emailed to participants one time per month asking about any falls over the last month. Staff may follow-up with any participants who experienced a fall.

Revised Observed Tasks of Daily Living (OTDL-R) – The OTDL-R is a performance-based test of everyday problem solving. Subjects will complete tasks assessing medication use (following medicine label directions, understanding an aspirin leaflet, and completing a patient record form); telephone use (finding and dialing a number from the yellow pages, finding and dialing a number from a directory of social service resources from the phone book, and using a rate discount chart from a phone book); and financial management (making change with coins and bills, balancing a checkbook, and paying a utility bill with a check and mailing it). The OTDL-R will be done at screening/baseline, 6 months, and 18 months. The OTDL-R has correlated significantly with age, education, self-rated health, a paper-and-pencil measure of everyday problem solving, and measures of basic cognitive functioning.

Saliva Diary – Subjects will be provided with instructions for collecting saliva at home and a saliva diary to record date and time of day each saliva sample was collected, wake and sleep times, and additional information about the collection process. Salivary cortisol will be collected at screening/baseline, 6 months, and 18 months.

Santa Clara Brief Compassion Scale (SCBCS) – The SCBCS is a brief 5 item self-report measure of compassion and its relation to pro-social behaviors. This measure will be completed at all timepoints.

Self-Related Successful Aging Question – This question is a subjective report of successful aging. It will be asked at all timepoints.

Short Physical Performance Battery (SPPB) - The short physical performance battery (SPPB) measures gait speed, chair stand and balance. It is used as a tool for detecting disability and can aid in the monitoring of function in older adults. The SPPB will be done at screening/baseline, 6 months, and 18 months. All balance testing will be measured using BtrackS balance tracking system, a computerized force platform that will provide a more objective and detailed assessment of balance than administrator observation alone.

Substance Use – A questionnaire assessing recent substance use.

Neurpsychological Battery-

All neuropsychological testing will be done at all timepoints (unless otherwise noted).

Legacy Measures

Consonant-vowel odd-even switching task (CVOE) – E-Prime task, computerized
Sustained Attention Response Task (SART) – E-Prime task, computerized
Stroop Switch Keyboard Task – E-Prime task, computerized
Paragraph Recall – paper and pencil
List Recall – paper and pencil

NIH Toolbox Cognitive battery (computerized)

Oral Reading Recognition (screening/baseline only)
Picture Vocabulary
Flanker Inhibitory Control (screening/baseline only)
Dimensional Change Sort
List Sorting Working Memory
Picture Sequence Memory
Pattern Comparison Processing

NIH Toolbox Sensory measure (computerized)

Words in Noise – hearing test (screening/baseline and 18 month)

Additional Sensory measures

Electronic Visual Acuity task
Ishihara Color Vision test
Mars Contrast Sensitivity test

k. Focus Groups

A subset of 120 participants who are randomized will be offered the opportunity to participate in focus groups. The primary aim of the focus groups will be to use qualitative research methods (e.g. interview) to understand the feasibility and acceptability of the MEDEX study interventions and to improve trial conduct.

Among the topics that will be addressed are:
-Benefits of participating in the MEDEX study intervention they are in.
-Barriers and facilitators of participation in the MEDEX study intervention they are in.
-Recommendations for improvement and higher engagement in the intervention (What did you like, what would you change, etc.).
-Recommendations and personal strategies for maintenance.
-Feasibility of translating the MEDEX components into community settings and how what this would look like (several examples will be provided including: Self-management, Technology delivered interventions, Peer coach programs delivered by older adults, Open gym alternatives such as Fitness Zones in public parks, and supervised and guided programs and other community engagement opportunities such as the Y and OASIS).

Consent will be obtained prior to participating in the focus groups. Refreshments and $25 will be provided. See "Protocol Older Adults MEDEX study" for full details.

l. Data Management and Analysis:

The 2x2 factorial design is optimal for testing the effects of each intervention and for testing the combined and interactive effects. 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, 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. We also assess cognition at 3 months to provide an "acute" MBSR endpoint, consistent with literature comparing interventions with different time scales. Secondary outcomes test intervention effects on everyday cognition (Cognitive concerns and Executive function), activity performance (OTDL-R), 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. Therefore we will also use modern robust methods for between-group testing, as described by Wilcox. 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 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. 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 mm3 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. Quality control will be performed to ensure that the study objectives are not compromised by subject head motion. 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.

Functional connectivity changes: As per Brier and Power 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 that we expect to increase as a function of the interventions.

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. Primary visual cortex will be a comparison region. Volumes will be adjusted for estimated intracranial volume using covariance to adjust for body size differences. We will examine neuroanatomical changes based on longitudinal T1-weighted images acquired with real-time, or prospective, motion correction (PROMO) 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. Automated cortical and subcortical parcellations of the T1-weighted images will be obtained using the Freesurfer 5.3.0 image analysis suite; 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. Neuroanatomical labels are applied to each voxel based on a probabilistic atlas derived from a manually labeled training set that included older adults. 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. 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 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.