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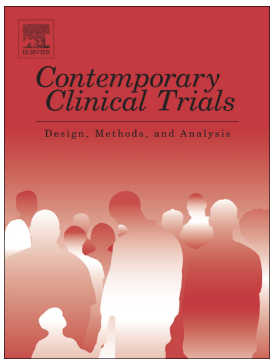

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Multi-domain Online Therapeutic Investigation Of Neurocognition (MOTION) – A randomized comparative-effectiveness study of two remotely delivered mind-body interventions for older adults with cognitive decline.

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ABSTRACT

Background: Research suggest that mind-body movement programs have beneficial effects on cognitive outcomes for older adults with cognitive decline. However, few studies have directly compared specific approaches to mind-body movement or studied the impact of remote program delivery.

Methods: In a 3-arm randomized controlled trial (RCT) for older adults with cognitive impairment, we are comparing a multidomain mind-body program that emphasizes movement, body awareness, personal meaningfulness, and social connection, and a traditional Chinese mind-body exercise (Tai Chi) to a health and wellness education control condition. All 3 interventions are delivered remotely two times per week (onehour per session) for 12 weeks. The two active interventions are live-streamed. Outcomes are assessed prior to, after, and 6-months after the interventions. The co-primary outcomes are changes on the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) and brain functional connectivity in the Default Mode Network (DMN). Secondary outcomes include measures of specific cognitive domains (e.g., executive function, attention), mobility, and self-report measures of general well-being, quality of life, social engagement, self- and attention-regulation.

Conclusion: This RCT will directly compare the effects of two mind-body movement programs versus an education control delivered remotely over 12 weeks on cognitive, neuroimaging, and participant-reported outcomes. If successful, these programs may provide scalable strategies for slowing cognitive decline, which could potentially delay dementia onset in some individuals.

Trial registration ID: NCT05217849

Keywords:

aging, cognitive dysfunction, exercise therapy, memory disorders, mild cognitive impairment, subjective memory decline, mind-body therapies

INTRODUCTION

Background and Rationale:

The number of people with Alzheimer's disease (AD) and AD-related dementias (AD/ADRD) in the United States are projected to double from nearly 7 million to 14 million by 2060[1] and from 57 million worldwide to over 150 million by 2050.[2] Dementia symptoms develop gradually, over years to decades. Mild cognitive impairment (MCI) is considered an intermediate stage between normal aging and dementia, and a risk factor for progression to dementia.[3] Subjective memory decline (SMD) is also considered a risk factor for dementia.[3] While there is currently no cure for dementia, research suggests that up to 40% of AD/ADRD cases may be attributable to modifiable risks, and that even small reductions in risks have the potential to prevent millions of cases over the next several decades.[4,5]

Cross-sectional[6] and longitudinal[7] observational studies, randomized controlled trials (RCTs),[8-11] systematic reviews and meta-analyses[12,13] have identified exercise as a promising non-pharmacological option for preventing cognitive decline and for improving quality of life in older adults with cognitive impairment.[14] Although there is extensive evidence

that aerobic exercise has a wide range of beneficial effects on brain health,[15] most older adults are unable to meet the Surgeon General guidelines of 150 minutes of moderate to vigorous activity per week,[16] often due to physical limitations and/or comorbid health conditions. Thus, there is growing interest in non-aerobic exercise activities for supporting brain health in older adults.

There is suggestive evidence that mind-body exercises outperform conventional physical exercise and health education for regulating mood and depression, which are crucial risk factors that contribute to cognitive decline in older adults with MCI.[17] Indeed, research suggests that Tai Chi, an ancient Chinese mind-body practice, may be superior to strength training and aerobics for improving balance, flexibility, and cognition,[18,19] including in older adults with cognitive impairment.[20] We reported that 16 weeks of treatment with escitalopram together with Tai Chi was more effective for reducing depression symptoms and helping older adults with MCI and depression achieve remission compared to 16 weeks of escitalopram and health education.[21] In another study, we found that Tai Chi improved general health and increased in functional connectivity in multiple brain regions, including the default mode network (DMN), with older adults with MCI and depression.[22,23] The DMN is a group of brain regions that shows synchronized activity patterns when the brain is at rest and decreased activity when the brain is engaged in the external environment.[24] Decreased functional connectivity in the DMN has been reported in patients with AD and MCI.[25]

Because various exercises may confer different benefits,[14] we developed an integrative mind-body group movement program for older adults with cognitive impairment that integrated 'best elements' from conventional and complementary/alternative exercise

approaches.[26,27] We called the program Preventing Loss of Independence through Exercise (PLIÉ), which targets abilities and neural mechanisms that are relatively well-preserved in people with memory loss, such as the ability to learn new movements sequences through repetition (i.e., procedural memory[28]), while helping participants to connect with others in meaningful ways and to experience positive emotions.[26,27,29] PLIÉ was developed using an inductive or "bottom up" approach where we engaged front-line practitioners from a variety of movement modalities, including physical and occupational therapy, dance movement therapy, Tai Chi, yoga, Feldenkrais and Rosen methods. We convened a day-long meeting in which representatives from all groups shared strategies for optimally engaging older adults with dementia. Later, we distilled these strategies into guiding principles and a program structure that we piloted tested and refined over time.[26,27] The result was an integrative group program that teaches basic movements necessary for daily life (e.g., transitioning between sitting and standing), helps participants to improve their focus and attention through mindful body awareness, and increases well-being through social and emotional connection with others. Our studies show that PLIÉ has a wide range of physical, cognitive, social and emotional benefits in persons with dementia whether they participant in the program by themselves[26,27,29] or with care partners.[30,31] In older adults with MCI/SCD, 12-weeks of PLIÉ increases DMN[32] functional connectivity and this increased connectivity is significantly correlated with improvements in cognition, well-being, stress management, and decreases in feelings of social isolation.[33] We developed and tested an online, livestreamed version of PLIÉ that we called Moving Together. Similar to PLIÉ, our research suggests Moving Together significantly improves quality of life in

participants with cognitive impairment and helps their care partners to better manage stress.[34,35]

The purpose of this manuscript is to describe the study protocol for the Multi-domain Online Therapeutic Investigation Of Neurocognition (MOTION) trial. The primary aim of the trial is to test the efficacy of Moving Together (MT) and Tai Chi Chih (TCC), a version of Tai Chi without the martial arts components,[36] versus an attention control condition for reducing cognitive symptomology and enhancing functional connectivity in the DMN in older adults with MCI or SMD. We chose to study MT and TCC because of promising results in our previous studies,[21-23,26,27,29] and because of the need for additional rigorous research on mind-body interventions given their growing popularity among older adults.

The COVID pandemic highlighted the importance of programs that have "wide reach" for older adults with cognitive impairment. Therefore, we chose to deliver the interventions via a livestreaming format to enhance the scalability of available resource, and to address the growing demand for effective interventions that reduce dementia risk.

METHODS

Trial Design

MOTION is a two-site (San Francisco VA Health Care System, SFVAHCS, and University of California, Los Angeles, UCLA), exploratory RCT for older adults with MCI and SMD, defined as self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.[37] Participants are randomly assigned to receive livestreamed MT, livestreamed TCC, or asynchronous online Health and Wellness Education

(HWE) in a 1:1:1 ratio (see Fig. 1). The study protocol, consent forms, outcome measures, and recruitment materials are approved by the institutional review board (IRB) at the University of California, San Francisco (UCSF), which serves as the IRB of record for both sites. The study is also approved by the San Francisco VA Research and Development Committee and Department of Defense Human Research Protection Office.

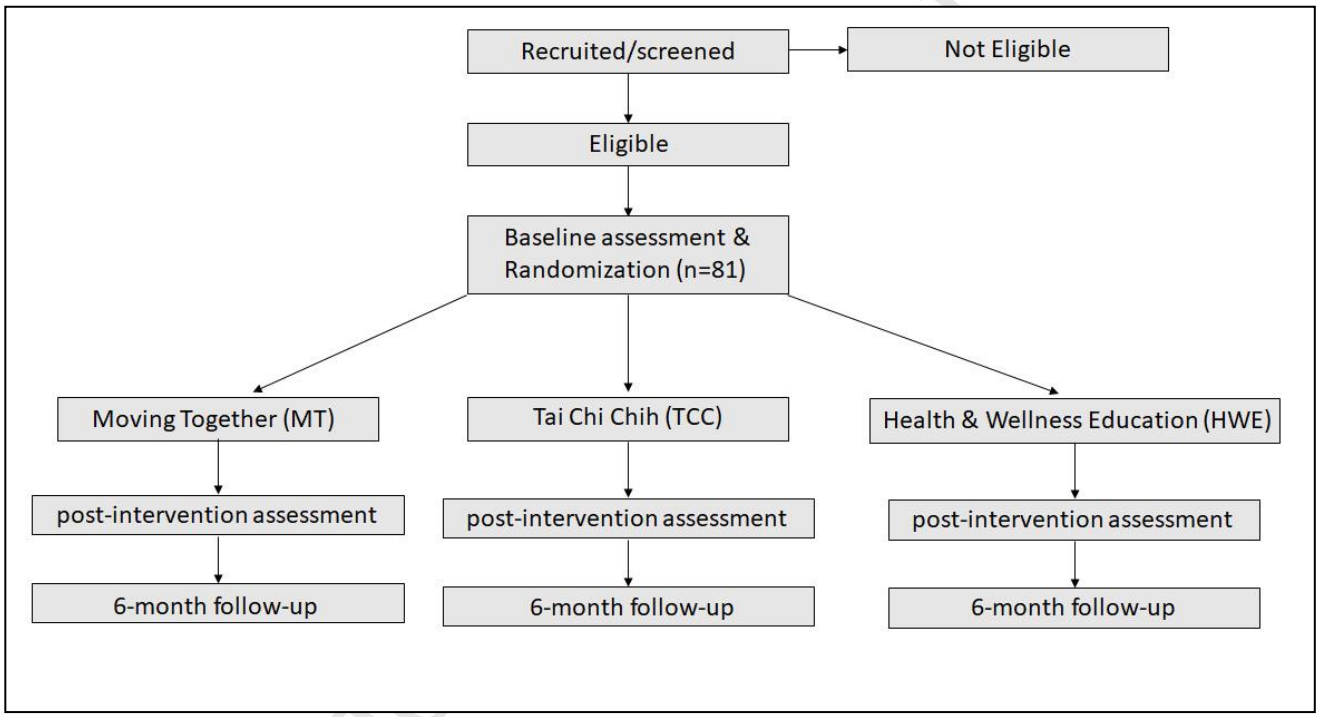

Figure 1. Study design

Eligibility Criteria

Participants are recruited from the community in the San Francisco Bay Area and the Greater Los Angeles Metropolitan Area. Inclusion criteria are age $\geq$ 55 years, a diagnosis of MCI by a neurologist or primary care physician OR subjective memory decline together with objective cognitive impairment, as indicated by Montreal Cognitive Assessment[38] (MoCA) scores of 26 or lower. The subjective memory decline must be unrelated to an acute event,

such as a stroke or traumatic brain injury (TBI).[37] Other inclusion criteria include: English fluency, access to highspeed internet at home, willingness to travel to either SFVAHCS or UCLA for in-person assessments, and capacity to provide informed consent.

Exclusion criteria are bipolar disorder, psychosis, current alcohol or substance dependence, recent unstable medical or neurological disorders, disabilities preventing participation in MT or TCC (e.g., primarily use wheelchair, severe visual or hearing impairment that would limit ability to follow instructor's on screen instructions), insufficient English proficiency, limited life expectancy (i.e., enrolled in hospice, metastatic cancer), plan to travel for > 1 week during 12-week intervention period, diagnosis of dementia or MoCA score suggestive of dementia (i.e., MoCA <18),[39] starting dementia medication (e.g., cholinesterase inhibitor or memantine) or psychoactive medication in past 3 months or plans to start/change dementia or psychoactive medication during study period, current participation in another study or interventions, contraindications to magnetic resonance imaging (MRI), including claustrophobia severe enough to prevent MRI examination, presence of ferrometallic objects in the body that would interfere with MRI examination and/or cause a safety risk (e.g., pacemakers) and prior or current training in PLIÉ/MT, TCC or another mind-body movement practices. For example, having a regular yoga practice is exclusionary, but having a sitting meditation practice that does not involve body movement is not exclusionary. Table 1 summarizes the key eligibility criteria.

Table 1. Key eligibility criteria

Key inclusion criteria:
• Age $\geq$ 55 years • Diagnosis of mild cognitive impairment (MCI) or self-reported subjective memory decline (SMD) not secondary to an acute event (e.g., stroke or TBI)

- Montreal Cognitive Assessment (MoCA) score 18 to 26
- English language fluency
- Access to high-speed, wireless internet connection

Key exclusion criteria:

- Bipolar disorder
- Psychosis
- Dementia (MoCA score < 18)
- Current alcohol or substance dependence
- Started/changed dementia or psychotropic medication within past 3 months
- Contraindications for MRI
- Severe visual or auditory impairment
- Existing regular mind-body practice that involves mindful movements

Interventions

Table 2 summarizes the key components of the three online interventions.

Moving Together (MT) is a gentle, group movement program designed for people with cognitive impairment.[26,27] Developed as an extension of the in-person PLIÉ program, MT is designed to be livestreamed online. MT integrates elements from traditional movement approaches (e.g., physical and recreational therapy) with specific mind-body techniques to train procedural ('muscle') memory for basic functional movements (e.g., transitioning safely between sitting and standing, and balancing while standing and walking), increase mindful-body awareness, and facilitate social connection. The active MT exercise sequence consists of a structured format that is repeated at every class to promote procedural learning. Each class begins with greetings and body awareness (e.g., massaging and tapping body parts) and breathing exercises (10 minutes). The MT movement sequences were developed and refined over previous studies and are designed to be repetitive and build slowly in functional complexity over the course of the program based on the ability levels and needs of the group (45 minutes). All movements are performed slowly and purposefully, so that persons with cognitive impairment can follow and participate successfully. Resting,

breathing and mindful body awareness exercises are incorporated throughout to provide breaks and bring focus to and acceptance of the present moment. Personally meaningful music is incorporated to engage feelings of enjoyment and well-being. Each class ends with a return to body awareness exercises and awareness of breath, and participants are invited to share appreciations of things in their lives that give them joy or gratitude to support social connection (5 minutes). Instructors also incorporate weekly themes to support participant learning of the underlying principles for the program. Weekly themes include: Sense & Breathe; Enjoy & Explore; Go Slow; Music; Repetition Builds 'Muscle' Memory; Patience, Respect & Dignity; Social Engagement & Emotional Connection; Community; Known Your Goals; The Power of Touch; Learning How to Learn; and Commencement and New Beginnings. The MT classes are taught by a trained MT instructor and livestreamed synchronously via high-speed internet for one hour, two days per week for 12 weeks.

Tai Chi Chih (TCC) is form of Tai Chi that has fewer moves and does not include the martial arts component of Tai Chi. The standard protocol is adapted from "Tai-Chi-Chih! Joy Through Movement,"[36] which we have used previously in other studies.[22,23] TCC employs "meditation through movement" as a means of helping older adults cope with fatigue, perceived physical limitations, and negative emotional states. Like the MT format, TCC classes begin with 10 minutes of greetings and warm-up exercises (e.g., stretching, breathing), followed by 45 minutes of TCC, and 5 minutes of cool down. During the active TCC section and over the course of the training, participants learn to perform 20 movements including: Rocking Motion, Bird Flaps its Wings, Around the Platter, Around the Platter variation, Bass Drum, Daughter on the Mountaintop, Daughter in the Valley, Carry the Ball to the Side, Push Pull, Pulling in Energy,

Pulling Taffy, Pulling Taffy-Anchor, Pulling Taffy-Wrist Circles, Pulling Taffy-Perpetual Motion, Working the Pulley, Light at the Top of the Head, Joyous Breath, Passing Clouds, Six Healing Sounds, and Cosmic Consciousness Pose. The TCC protocol is designed to be easy to learn, performed standing or sitting, and appropriate for older adults who are not otherwise able to adhere to physical exercise.[40] The TCC sessions are taught by a certified TCC instructor and livestreamed synchronously via high-speed internet for one hour, two days per week for 12 weeks.

To facilitate participation, MT and TCC participants are encouraged to connect their devices to larger screens (e.g., smart TVs) so they can better view the instructors. Study staff are on hand to provide technical support throughout the 12-week intervention period. Participants without the necessary equipment to access the online classes are loaned devices or peripheral accessories for the duration of the trial.

Health and Wellness Education (HWE) serves as an active control for nonspecific treatment elements such as attention to health that pose rival explanations for the effectiveness of MT and TCC. The HWE protocol is adapted from the in-person attention control curriculum that we used in previous studies.[22,23] The HWE curriculum consists of didactic videos on topics related to health and wellness, tailored to older adults, from University of California Television (UCTV), a media outlet featuring programming through UC. We also received permission from TEDTalk to use lectures by UCSF professors. The HWE curriculum did not undergo formal validity testing. However, we reviewed each video to ensure that it did not include activities emphasized in MT or TCC.

HWE participants are instructed to watch the pre-recorded HWE videos on a web-

based platform (i.e., Edpuzzle) at a specific time twice a week during the intervention. Any HWE participant who misses a class can request access to view the missed video asynchronously. Table 2 summarizes the key components of each intervention.

Table 2. Key elements of the three interventions

	Moving Together (MT)	**Tai Chi Chih (TCC)**	**Health & Wellness Education (HWE)**
Frequency	• 1 hr, 2 days/wk	• 1 hr, 2 days/wk	• 1 hr, 2 days/wk
Duration	• 24 hrs over 12 wks	• 24 hrs over 12 wks	• 24 hrs over 12 wks
Format	• Virtual group • Semi-structured	• Virtual group • Structured	• Asynchronous • Structured
Content Cognitive Engagement	• Attend to instructor • Learn & recall new movements • Being flexible	• Attend to instructor • Learn & recall new movements • Being flexible	• Attend to lecturer • Learn new information
Physical Engagement	• Progressive, functional movements	• 20 specific movements	• No movement
Psychosocial Engagement	• Social interaction with instructor and others in group encouraged	• Social interaction with instructor and others in group allowed but not encouraged	• No social interaction (but there was one video on benefits of socialization)
Mindfulness	• Moving with breath and mindfulness • Body awareness	• Moving with breath and mindfulness • Body awareness	• No focus on breath, mindfulness, or body awareness
Positive Emotions	• Focused on positive emotions	• Not focused on positive emotions	• Not focused on positive emotions (but there was one video on science of happiness)
Repetition	• Movements repeat with variations	• Movements repeat without variations	• No repetition
Participant-centeredness	• Participant-centered goal orientation	• Participant-centered pace	• Not participant centered
Pacing	• Slow pace • Step-by-step instructions	• Slow pace • Step-by-step instructions	• Self-paced

Interventions Safety

The MT and TCC movements are designed to be gentle and to meet older adults at their current functional levels. Movements in both programs build slowly in complexity and intensity

over the course of the 12-week program. The MT and TCC instructors are taught to carefully watch participants for signs of pain or discomfort during class, and to modify movements as needed to protect against injury. Risks of injury in the programs is further minimized by asking participants about previous injuries before they begin the program and making needed adjustments.

Adverse events that occur during the MT, TCC, and HWE sessions, or associated with assessment are recorded. In case of any serious adverse event, the trial shall be paused, and effective treatment measures taken.

Intervention fidelity

After each class, the MT and TCC instructors record exercises taught and observations of participants' experiences and reactions to the program, both positive and negative, using a standardized checklist specifying critical and minimum components of each intervention. Safety issues are addressed by instructors for any movements, postures or other elements that require special attention to reduce risk of injury. Weekly intervention team meetings are held to review progress and discuss and troubleshoot any challenges that arise during the classes. The MT and TCC group sessions are recorded and stored on a secure server. A random 10% of the class recordings are reviewed for adherence to the protocol by study investigators using a standardized checklist of specific movement sequences and intervention elements.

Adherence

Study staff track participants' class attendance and level of engagement. To help participants adhere to the interventions, we send reminder emails prior to the class start time and call participants if they have not logged on when expected or appear to have technical difficulties during class. For participants in the MT and TCC groups, the instructors greet and communicate with each participant when they log onto the sessions to reinforce self-efficacy and adherence. For participants in the HWE group, we use Edpuzzle to track attendance and level of engagement (i.e., how much of the video's contents participants view, how many quiz questions participants answered correctly, participants' feedback about the video's content).

After completing the 12-week interventions, participants in the MT and TCC groups have access to a private YouTube channel with a video of their instructor performing the moves and sequence taught during the intervention. This is meant to facilitate participants' ability to continue practicing MT or TCC after the 12-week intervention if they wish. Participants' use of the practice videos is monitored through REDCap: They must provide their study ID number to view the MT or TCC practice video embedded in a survey link. Although this method allows us to track who has logged onto the practice videos, it does not capture how long participants view the video after accessing the web page. HWE participants have access to a private YouTube channel with a library of all the videos that they viewed over the past 12 weeks.

Blinding

Given the nature of the intervention, blinding of study participants is not possible. Participants are informed that the study is examining the effects of three different online wellness interventions for improving physical and cognitive function, and brain connectivity.

Participants in the HWE group are not informed that it is the attention control condition. Study staff who administer the assessments and conduct analyses will be blind to group assignments. Intervention and technical support staff will not be blinded to group assignments.

Outcomes

Table 3. Components of the mind-body interventions, outcomes, and specific outcome measures

Component	Outcomes	Specific outcome measures
COGNITIVE ENGAGEMENT Attend to instructor; learn and recall new movements; being flexible	General cognition	ADAS-cog[41] DMN[42] functional connectivity
	Executive function/attention	Trail Making Test[43] D-KEFS color-word interference test[44] Verbal fluency RBANS[45] Coding Frontal executive network[46] Salience network[46]
	Verbal learning and memory	RBANS[45] Story Memory Test
PHYSICAL ENGAGEMENT Sit and standing exercises; move to rhythm; moving with breath; breathing deeply and with mindfulness	Lower body strength, balance	Timed Up and Go[47] test Cognitive Dual Walking Task[48]
PSYCHOSOCIAL ENGAGEMENT Social interactions with instructor and other participants in group	Emotional well-being	PROMIS-29[49] Neuro-QoL[50]
Building social network	Social support; loneliness	PROMIS Social Isolation[51]
Mindful engagement with body and movement	Mindfulness; interoception	Freiburg Mindfulness Index[52] Multidimensional Assessment of Interoceptive Awareness, version 2[53] Body Experience Questionnaire[54]
Taking on new challenges, mastering new skills over time	Interest in life; emotional well-being	Neuro-QoL[50]

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subtest; DMN, Default Mode Network; D-KEFS, Delis-Kaplan Executive Function System; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status, PROMIS, Patient Reported Outcomes Measurement Information System), QoL, Quality of Life

The primary and secondary outcomes were selected based on the hypothesized effects of the components of the mind-body interventions. Table 3 lists specific components that are targeted by the interventions and assessed by the specific outcome measures.

Primary Outcomes

The primary aim of the trial is to examine the effects of MT and TCC versus HWE for reducing cognitive symptomology following the 12-week trial and at the 6-month follow-up. Cognitive symptomology will be assessed with the Alzheimer's Disease Assessment Scale, cognitive subtest[41] (ADAS-cog), one of the most commonly used outcome measures in dementia drug treatment trials and a measure considered by the Food and Drug Administration for approval of dementia medications. We will examine change in ADAS-cog score from baseline to post-intervention and from baseline to the 6-month follow-up. A 3-point change on the ADAS-cog has been suggested to be an appropriate minimal clinically relevant change.[55] The primary imaging outcome is change in DMN[42] functional connectivity from baseline to post-intervention.

Secondary outcomes

We will explore the effects of MT and TCC on specific cognitive domains (executive function, attention, auditory memory, and processing speed), mobility, psychosocial measures (e.g., well-being, mindfulness, social isolation, self-regulation). The D-KEFS[44] – Color-Word Interference test will be used to assess attention, response inhibition, and the set-shifting aspect of executive function. The (phonemic) verbal fluency test[56] will be used to assess executive function. The Trail-Making Test[43] (TMT), part A will be used to assess attention and

processing speed; part B will be used to assess attention, processing speed, and the set-shifting aspect of executive function. The Repeatable Battery for the Assessment of Neuropsychological Status[45] (RBANS) Coding test will be used to assess attention and processing speed, and the RBANS[45] Story Memory test will be used to assess auditory learning and memory.

To assess the interventions' effects on physical function, and to probe possible cognitive-motor interactions,[57-59] we will use the Timed Up and Go[47] (TUG) test and Cognitive Dual Walking Task,[48] which have been widely used in previous research on Tai Chi[60] and mind-body exercises.[61,62] To assess the interventions' effects on psychosocial engagement, which has also been linked with cognition,[63] we will use the PROMIS-29,[49] Neuro-QoL,[50] PROMIS Social Isolation scale,[51] the Freiburg Mindfulness Index[52] (FMI), two sub-scales of the Multidimensional Assessment of Interoceptive Awareness, version 2[53] (MAIA-2) to assess interoceptive attention (i.e., ability to sustain and control attention to body sensations) and interoceptive self-regulation (i.e., ability to regulate distress by attention to body sensations), and 12 questions from the Body Experience Questionnaire[54] (BEQ) to access body awareness (e.g., perception of bodily states based on proprioceptive and interoceptive signals[64]). Tests of individual cognitive domains and the self-report questionnaires are administered at baseline, post-intervention, and at the 6-month follow-up.

Because previous studies have reported effects of mindfulness training[65] and Tai Chi[66] on functional connectivity in other intrinsic networks (e.g., salience[46] and frontal executive[46]), we will also explore resting state functional connectivity in these other intrinsic networks.

Participation Timeline

Table 4 summarizes the schedule of events in the trial. Screening for inclusion and exclusion criteria is performed over the telephone after verbal consent. Participants who pass the initial telephone screen are further screened with the Montreal Cognitive Assessment[38] (MoCA) remotely, which has demonstrated good validity relative to face-to-face administration[67] and has been validated in different populations.[68,69] Participants with MoCA scores between 18-26 are eligible for the study.

Participants will sign and receive a copy of the consent form along with a copy of the Bill of Rights for Research prior to beginning study procedures. The Test of Premorbid Functioning[70] (TOPF) is administered at baseline to obtain an estimate of participants' premorbid cognitive ability. Behavioral and self-report outcome measures are obtained in-person at baseline, post-intervention, and the 6-month follow-up. Neuroimaging outcomes measures are obtained at the baseline and post-intervention timepoints. Participants are compensated $50 for baseline procedures, $100 for post-intervention procedures, and $50 for the 6-month post-intervention follow-up procedures. Participants are also compensated for travel/parking costs at each assessment timepoint.

Table 4. Schedule of enrollment, intervention, and assessments

	STUDY PERIOD				
	Enrollment	Allocation	Post-allocation		
TIMEPOINT	$-t_1$	0	t_1- t_{12}	t_{13}	t_{36}
ENROLLMENT:					
Eligibility screen	X				
Demographic information	X				
Technology Screening	X				
Medical/Psych history	X				
MoCA	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					

Moving Together (MT)			X		
Tai Chi Chih (TCC)			X		
Health and Wellness Education (HWE)			X		
ASSESSMENTS:					
Goals Assessment		X[a]			
ToPF	X				
Study Outcome Measures					
3 T Imaging	X			X	
ADAS-cog	X			X	X
TUG	X			X	X
Dual Walking Task	X			X	X
Trail-Making Test	X			X	X
D-KEFS Color-Word Interference Test	X			X	X
FAS Verbal Fluency	X			X	X
RBANS Story Memory	X			X	X
RBANS symbol	X			X	X
Neuro-QOL Wellbeing	X			X	X
Neuro-QOL lower extremity function	X			X	X
Neuro-QOL Emotional and Behavioral Dyscontrol	X			X	X
Neuro-QOL Cognitive Function	X			X	X
Freiburg Mindfulness Index	X			X	X
PROMIS-29 v2	X			X	X
PROMIS Social Isolation	X			X	X
MAIA 2 (2 questions)	X			X	X
BEQ (12 questions)	X			X	X

Abbreviations: MoCA: Montreal Cognitive Assessment; TOPF: Test of Premorbid Function; ADAS-cog: Alzheimer's Association Assessment Scale, Cognitive subtest; TUG: Timed Up and Go; RBANS: Repeatable Battery for the Assessment of Neuropsychological Studies; QOL: Quality of Life; PROMIS: Patient-Reported Outcomes Measurement Information System; MAIA 2: Multidimensional Assessment of Interoceptive Awareness, version 2; BEQ: Body Experience Questionnaire

[a] MT arm only

Sample size and recruitment

We propose to enroll 81 participants from the San Francisco Bay Area and Greater Los Angeles community through listings on ClinicalTrials.gov, Alzheimer's Association TrialMatch, UCSF and UCLA clinical trial listings, and UCSF's Clinical and Translational Science Institute Participant Recruitment Program (UCSF CTSI PRP), which offers social media recruitment and electronic health record (EHR) recruitment. UCSF patients with International Classification of

Diseases (ICD) 10 codes indicative of MCI (i.e., G31.84) in their EHRs will be targeted for recruitment. We will also use VA Informatics and Computing Infrastructure and VA Corporate Data Warehouse to identify veterans at the San Francisco and Greater Los Angeles VAs with G31.84 ICD-10 codes in their EHRs for recruitment.

The clinical research coordinator at each site will enroll participants. After eligible participants complete baseline assessments, research staff will use an in-house covariate-adaptive randomization[71] program to allocate participants in a 1:1:1 ratio to MT, TCC, or HWE conditions based on age, sex, race (White vs. non-White) and baseline ADAS-cog score.

Data collection

Behavioral assessments and MRI scans are conducted in-person at the SFVAHCS and UCLA. High-resolution T1-weighted scans (isotropic 1.0 mm^3 voxels; 176 slices; TR: 2500 ms; TE: 2.9 ms; TI: 1070 ms; FOV: 256 mm; matrix size: 256×256 mm; and flip angle: 8°) and resting-state functional MRI scans (eyes open; two 6.4 min scans; isotropic 2.0-mm^3 voxels; 72 slices; TR: 820 ms; TE: 35.0 ms; FOV: 208 mm; matrix size: 208×208 mm; and flip angle: 52°) are acquired on a 3T Siemens Skyra at the SFVAHCS and a 3T Siemens Prisma Fit at UCLA with a 32-channel head coil. Self-report questionnaires are completed by participants online via REDCap, either at home or on a computer at the SFVAHCS or UCLA.

Statistical analysis plan

Based on our previous studies, we estimate an attrition rate of around 20%, and that we will have approximately 21-22 completers per arm for analyses. We estimated the total number

of participants needed to detect a range of effect sizes (ES) with 80% power using 2-sided 0.05-level tests, where ES = difference/SD. The observed correlations between repeated measures range from 0.7 to 0.9 based on our previous studies. Thus, the proposed sample size will provide us with adequate power to detect ES of 0.45 to 0.63, depending on the degree of correlation between repeated measures. In our pilot study of PLIÉ in older adults with MCI/SMD,[32] we found an ES of -0.34 in ADAS-cog scores.

Prior to primary analyses, descriptive statistics and graphical summaries will be obtained for the primary outcomes to check for outliers and violations of model assumptions and to assess the need for transformations or non-parametric methods, and to examine longitudinal trajectories. Longitudinal analysis will rely on generalized linear mixed models (GLMMs), which account for correlations induced by repeated measurements within subjects, allow for both fixed and time-varying covariates and automatically handle missing data. Thus, GLMMs produce unbiased estimates as long as observations are missing at random. We will fit a single model using all time points for each outcome. Our specific aims and hypotheses correspond to specific contrasts within those models. Demographic variables will be compared by treatment group and examined in relation to outcome variables to identify appropriate covariates, if needed.

Our primary analysis will consist of a GLMM for ADAS-cog and a GLMM for DMN connectivity with treatment group effects and time main effects, along with two-way interactions of time and group. Based on our previous work[22,23,32] and the work of others,[18-20] we hypothesize that, compared to HWE, both MT and TCC will result in a greater reduction of ADAS-cog score after the 12-week trial, and this difference will be maintained at the 6-month follow-up. These four hypotheses are considered independent; therefore, we will not adjust for

multiple comparisons. We further hypothesize that compared to HWE, both MT and TCC will lead to increased functional connectivity within the DMN after the 12-week trial. These two hypotheses are considered independent; therefore, we will not adjust for multiple comparisons. Change in ADAS-cog and DMN connectivity will be treated as co-primary outcomes. We will carefully examine the effect size of each co-primary endpoint to ensure clinically meaningful treatment effects.

Exploratory analyses will include models of secondary outcomes that are conceptually similar to the models described above. We will also examine within-group comparisons of 12-week and 6-month behavioral outcomes to determine maintenance effects and any added benefits of extended practice after the active intervention is over. These exploratory analyses will be used for hypothesis-generation rather than hypothesis-testing. Interim analyses are not planned.

DISCUSSION

Innovative and effective approaches for boosting cognitive function will be critical if we wish to reduce the prevalence of AD/ADRD. Non-pharmacological mind-body interventions have the potential to improve outcomes across multiple domains for older adults with MCI and SMD.[72,73] Despite the increasing popularity of non-pharmacological interventions, there remain barriers to accessing these programs. Although some senior centers offer Tai Chi, PLIÉ and Moving Together are new interventions that are currently only available through research studies. Besides limited availability, transportation demands and distance to facilities that offer

in-person mind-body interventions, particularly for people in rural areas, can be obstacles to receiving these types of interventions.

This is the first study that will examine the efficacy of two mind-body interventions delivered via a livestreaming format for older adults with MCI and SMD. One benefit of virtual programs is it increases the potential for scalability. That is, online interventions can theoretically be delivered from anywhere to anywhere, reducing costs and taking advantage of an available resource to make the interventions more widely accessible. However, virtual programing also poses some challenges (e.g., need for access to adequate internet bandwidth and devices to facilitate full participation). These challenges could potentially exacerbate disparities for people with lower socioeconomic status and/or who live in rural locations with limited internet.

One limitation of this trial may be its relatively small sample size, which will only enable us to detect moderate to large effect sizes. If results of this trial are not statistically significant but suggest smaller effect sizes, a larger study may be necessary. The small sample size also will limit our ability to explore differences in effects based on other factors such as age, gender, or baseline cognitive status. Another limitation is that inclusion/exclusion criteria are designed to maximize internal validity, which may reduce generalizability. If these interventions are successful, additional studies with fewer eligibility restrictions will be worthwhile.

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Declaration of Competing Interest

DEB, MAC, and WEM are co-inventors of Preventing Loss of Independence through Exercise (PLIÉ) and have the potential to earn royalties. DEB and CB co-founded Together Senior Health. DEB, CB, and JAL are shareholders of Together Senior Health. CB and JAL are employees of Together Senior Health. The remaining authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

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Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Deborah E. Barnes, Margaret A. Chesney, and Wolf E. Mehling are co-inventors of Preventing Loss of Independence through Exercise (PLIÉ) and have the potential to earn royalties. Deborah E. Barnes and Cynthia Benjamin co-founded Together Senior Health. Deborah E. Barnes, Cynthia Benjamin, and Jennifer A. Lee are shareholders of Together Senior Health. , Cynthia Benjamin and Jennifer A. Lee are employees of Together Senior Health.

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