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Preventing Loss of Independence through Exercise (PLIÉ): A Pilot Trial in Older Adults with Subjective Memory Decline and Mild Cognitive Impairment

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Abstract.

Background: Preventing Loss of Independence through Exercise (PLIÉ) is a group movement program initially developed for people with mild-to-moderate dementia that integrates principles from several well-established traditions to specifically address the needs of people with cognitive impairment.

Objective: To investigate whether PLIÉ would benefit cognitive and behavioral outcomes and functional brain connectivity in older adults with milder forms of cognitive impairment.

Methods: Participants (≥ 55 y) with subjective memory decline (SMD) or mild cognitive impairment (MCI) were assessed with tests of cognitive and physical function, self-report questionnaires, and resting state functional magnetic resonance imaging (rs-fMRI) on a 3 Tesla scanner before and after participating in twice weekly PLIÉ classes for 12 weeks at the San Francisco Veterans Affairs Medical Center.

Results: Eighteen participants completed the pre-post intervention pilot trial. We observed significant improvements on the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog; effect size 0.34, $p = 0.002$) and enhanced functional connections between the medial prefrontal cortex (mPFC) and other nodes of the default mode network (DMN) after PLIÉ. Improvements (i.e., lower scores) on ADAS-cog were significantly correlated with enhanced functional connectivity between the mPFC and left lateral parietal cortex (Spearman's $\rho = -0.74$, $p = 0.001$) and between the mPFC and right hippocampus (Spearman's $\rho = -0.83$, $p = 0.001$). After completing PLIÉ, participants reported significant reductions in feelings of social isolation and improvements in well-being and interoceptive self-regulation.

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Conclusion: These preliminary findings of post-PLIÉ improvements in DMN functional connectivity, cognition, interoceptive self-regulation, well-being and reduced feelings of social isolation warrant larger randomized, controlled trials of PLIÉ in older adults with SMD and MCI.

Keywords: Aging, cognitive dysfunction, exercise therapy, memory disorders, mild cognitive impairment, mind-body therapies, self-report

INTRODUCTION

The prevalence of Alzheimer's disease and related dementias (ADRD) has become a growing burden to individuals, families, and society. In the absence of efficacious pharmacological treatments that prevent, slow, or reverse cognitive decline associated with ADRD [1], it is important to investigate alternative forms of treatment. At the 2009 Summit on Integrative Medicine and the Health of the Public, the Institute of Medicine called for an integrative approach to health care, including a "seamless integration of resources to empower individuals to improve their health" [2]. We reflected this approach when we developed Preventing Loss of Independence through Exercise (PLIÉ), a group movement program that integrates principles from several well-established traditions including Feldenkrais Method[®], Rosen Method, Tai Chi, and yoga, with elements from occupational therapy, physical therapy, and dance movement therapy.

PLIÉ is specifically designed to address the needs of people with cognitive impairment. The seven Guiding Principles of the program are: 1) repetition with variation (to promote procedural learning while maintaining engagement); 2) progressive, functional movement (to support basic functional movements such as standing safely from a seated position); 3) slow pace and step-by-step instruction (to enable participants to participate fully, experience feelings of success, and minimize cognitive demands); 4) participant-centered goal orientation (a goals assessment is performed at the beginning of the program, and instructors tailor content to address the personal interests and goals of participants); 5) body awareness, mindfulness and breathing (to bring non-judgmental awareness to the body in the present moment); 6) social interaction (participants sit in a circle, and many movements involve reaching across the circle to touch hands or elbows, or standing in a circle holding hands and moving together to facilitate social connection); and 7) positive emotions (participants are encouraged to move in ways that feel good, personally meaningful music is incorporated, and all

classes end with sharing of appreciations and things that bring joy) [3, 4]. Consistent with the relationship-centered approach of integrative medicine [5], PLIÉ instructors are taught to incorporate these guiding principles in a flexible manner based on participants' in-the-moment needs and experiences, rather than having a scripted "package of care."

In a previous pilot study [4], we showed that PLIÉ produced potentially clinically meaningful (≥ 0.25 SDs) improvements on the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog), Short Physical Performance Battery (SPPB), and Quality of Life Scale in Alzheimer's Disease (QOL-AD) in 12 patients with mild-to-moderate dementia. We also qualitatively analyzed the PLIÉ class videos and fieldnotes of the PLIÉ instructors [3]. Although not statistically significant, the combined quantitative and qualitative findings suggested that PLIÉ had potentially clinically meaningful changes. Because we did not have an opportunity to investigate the neural mechanisms underlying PLIÉ's effect in our prior work [4], one goal of this study was to examine PLIÉ's effect on brain function with resting-state functional magnetic resonance imaging (rs-fMRI).

PLIÉ was originally developed for people with dementia. However, research suggests that pharmacotherapy may be more effective if initiated earlier in the course of ADRD before neural damage has occurred [6]. While there has been no comparable research examining the impact of complementary and integrative therapies at different stages of ADRD, there is evidence that mind-body interventions can improve cognition and everyday functioning in older adults with mild cognitive impairment (MCI) [7–9]. Therefore, a second goal of this study was to investigate whether PLIÉ would similarly benefit people with milder forms of cognitive impairment. Because people with milder forms of cognitive impairment have less neurodegeneration than people with dementia, we posited that PLIÉ may have a greater likelihood of slowing cognitive decline in individuals with SMD and MCI than in people with dementia.

MCI is generally regarded as a transitory stage of cognitive decline between normal aging and dementia

[10], although not every patient with MCI will progress to dementia [11]. There is also suggestive evidence that subjective reports of memory decline may be an important risk factor for future dementia or worsening of cognitive dysfunction [12], though psychological conditions such as anxiety, depression, and histrionic personality may also play a role in memory impairment [13]. We examined whether PLIÉ, which targets abilities that are relatively well-maintained in people with dementia (e.g., procedural memory, mindful body awareness, positive emotions, social connection) while minimizing cognitive demands, would also benefit people with MCI and subjective memory decline (SMD). Because MCI and SMD are different diagnoses, combining the two might increase the heterogeneity of the study sample. However, not everyone who experiences memory difficulties sees a neurologist for a formal diagnosis. Therefore, we felt that including individuals with SMD makes findings of the study more generalizable.

Extrapolating from our prior work on PLIÉ in people with dementia [4], we hypothesized that 12 weeks of PLIÉ would improve cognition in individuals with MCI and SMD. Based on neuroimaging findings from other mind-body [14, 15] and physical exercise [16] interventions in healthy older adults and individuals with MCI, we hypothesized that 12 weeks of PLIÉ would improve functional connectivity within the default mode network (DMN), a set of brain regions that are more active at rest in the “default” state [17–19]. DMN connectivity has been proposed to be a potentially useful noninvasive biomarker for assessing an intervention’s impact in adults with mild AD [20] because the DMN involves the same brain areas affected by cerebral atrophy, reduced metabolism, and amyloid in early AD [21].

METHODS

The study was approved by the institutional review boards at the University of California, San Francisco (UCSF), the San Francisco Veterans Affairs Medical Center (SFVAMC), and the Human-Subject Research Protection Organization at the Department of Defense. The study was designed as a single-arm, proof of concept, pre-post pilot trial and was registered with clinicaltrials.gov (NCT03526146). Data were collected at the SFVAMC from December 2018 to March 2020.

Participants

Study participants were recruited from August 2018 to December 2019 using online advertisements, flyers posted in the general community, and direct mail to MCI patients at the SFVAMC and UCSF. All participants provided informed consent and were paid for participation (up to \$100 for completion of all study procedures).

Inclusion criteria were: 1) age ≥ 55 years; 2) diagnosis of MCI by a neurologist or primary care physician OR self-reporting of noticeable memory decline over the past year combined with objective cognitive impairment, as indicated by Montreal Cognitive Assessment (MoCA) [22] scores of 26 or lower; 3) English fluency; 4) ambulatory (e.g., able to take 2 steps without cane or walker); 5) willingness and ability to undergo 3 Tesla magnetic resonance imaging (MRI); 6) willingness and ability to participate in twice weekly hour-long PLIÉ classes at the San Francisco VA Medical Center for 12 weeks; and 7) living in the community in a private home or apartment.

Exclusion criteria were: 1) behavioral or physical issues that would be disruptive or dangerous to self or others (e.g., active psychosis, drug abuse, severe behavioral issues) in the group class setting; 2) physical or mental health condition that would make participation in group class difficult (e.g., severe physical limitations, limited life expectancy); 3) contraindications to safely undergoing MRI scan (e.g., claustrophobia severe enough to prevent MRI examination, presence of ferromagnetic objects in the body that would interfere with MRI examination and/or cause a safety risk such as pace makers, implanted stimulators, pumps, etc.); 4) history of structural brain lesions or stroke temporally related to the onset or worsening of cognitive impairment; 5) plans to travel or move during the study period that would result in missing a substantial number of the PLIÉ classes; 6) plans to start/change any psychotropic medication, including start dementia medication (e.g., cholinesterase inhibitor or memantine) during study period; 7) current participation in another research study; 8) evidence of dementia (e.g., MoCA score < 18).

Eighteen participants completed the pre- and post-intervention assessments and the 12-week intervention. Of the 18 study completers, five had MCI diagnoses while 13 had SMD with no formal MCI diagnosis. We administered the MoCA to 12 of the 13 study completers with SMD at baseline to confirm memory impairment (i.e., MoCA < 26) and absence

of dementia (MoCA > 17). One participant with SMD was enrolled prior to the modification of our study protocol to include the MoCA. However, her baseline ADAS-cog score, 18.7, suggested cognitive impairment without dementia. The MoCA score of another participant with SMD was only recorded as being within the inclusion range (≤ 26 but > 18) without noting the actual value. However, his baseline ADAS-cog score, 10.7, was also suggestive of cognitive impairment without dementia.

Intervention

Details of the PLIÉ intervention have been described elsewhere [3, 4]. Briefly, two PLIÉ classes were conducted each week for 12 weeks. Every class began with greetings and a brief check-in to ensure that everyone felt welcomed and acknowledged. During this portion of class, participants had an opportunity to interact with each other as a group. Next participants, seated in a circle facing each other, engaged in mindful body awareness exercises that involved massaging or tapping all major body parts and breathing exercises. The goal was to bring participants into awareness of their bodies and breathing in the present moment, and to create a calming ritual that is repeated at the beginning and end of each class. Participants then engaged in a series of seated and/or standing exercises that focused on increasing capacity to perform movements needed for daily function, such as increasing range of motion, transitioning smoothly from sitting to standing, and balancing while standing and moving. The movement sequences built slowly in complexity over the course of the program and progressed from more seated movements at the beginning of the program to more standing movements later in the program. The exact proportion of sitting to standing exercises varied depending on the functional ability of individuals in the class. Some of the movements were designed for self-to-self interaction while others were designed for self-to-other interactions. The instructors also facilitated social interaction between the participants and directed the participants to engage with each other through the movements. Mindful, seated rest periods were integrated throughout the program. Occasionally, personally meaningful music was included in parts of the classes. Each class ended with breathing exercises and an invitation for participants to share what made them feel grateful, appreciative, or happy. The goal of this was to facilitate positive feelings of social connection and to provide participants with

another opportunity to interact as a group. The hour-long PLIÉ classes were held twice weekly over 12 weeks at the SFVAMC. All of the PLIÉ classes were led by a team of two instructors so that the participants could easily see one of the two instructors while sitting in a circle. The instructors compiled a log of the exercises performed at each class. The PLIÉ class logs were presented and discussed at weekly team meetings.

PLIÉ instructors

The same two PLIÉ instructors taught three groups of PLIÉ participants from March 2019 to February 2020. The maximum number of participants per class was ten, although class size varied from class to class depending on attendance. The senior PLIÉ instructor (JAL) has been leading PLIÉ classes and training PLIÉ instructors for 10 years. She is certified in the Feldenkrais Method® of Somatic Education in the US and Europe and has had a private somatic practice for 17 years. She also has experience in teaching movement in both one-on-one and in group formats to senior citizens and non-ambulatory adults with cerebral palsy and other complex cognitive, orthopedic and neurological issues. The assistant PLIÉ instructor (AL) had a 200-hour yoga teacher training certification and a Master of Science in behavioral health.

PLIÉ instructor training and fidelity assessment

All PLIÉ instructors are experienced in teaching mind-body movement (e.g., Feldenkrais, Yoga) to groups, and then receive in-depth training in PLIÉ that consists of a minimum of 6 months of observation, mentorship, and supervision with a lead PLIÉ Instructor. In addition to learning specific movements and body awareness exercises, PLIÉ instructors are taught to engage participants in the group experience and to foster relationships and social connections among group members. Interpersonal connections and group cohesion are developed from the beginning with participants introducing themselves, with the instructors modeling for members acknowledgment of individuals' contributions, including interactive movements that involve others, and inviting sharing of experiences and appreciations, especially at the end of each PLIÉ session. The PLIÉ Instructors strive to create a safe, convivial, learning environment through their embodiment of PLIÉ principles such as communication in non-critical ways, encouraging change through discovery or guidance rather than

correction, creating an exploratory, playful environment, and offering and modeling a welcoming, caring, interpersonal, shared learning experience. Fidelity to the program was assessed by 1) having PLIÉ instructors provide a descriptive summary and complete a detailed checklist of movements taught after each class; and 2) having one of the PLIÉ creators (DB, WM, MC) attend one class per month and complete a fidelity checklist to ensure adherence to the guiding principles.

Measures

Participants were assessed prior to (baseline) and after (post-treatment) completing 12-weeks of PLIÉ (24 classes). The primary neuroimaging outcome was functional connectivity in DMN. The secondary imaging outcomes were total and hippocampal subfield volumes.

To be consistent with our prior work, the primary behavioral outcome was cognition, assessed with the ADAS-cog [23]. Secondary behavioral outcome measures included the SPPB [24], Geriatric Depression Scale [25], QOL-AD [26], and self-reported measures of interoceptive self-regulation (i.e., ability to regulate distress by attention to body sensations) and interoceptive attention (i.e., ability to sustain and control attention to body sensations). Interoceptive self-regulation and attention were assessed with portions of the Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2) [27]. To avoid overburdening study participants with the entire 37-item MAIA-2 scale, we focused on two interoceptive measures that had previously been shown to respond to mindfulness interventions [28]. Self-regulation in particular has been shown to be a key element of psychological health and a main aspect at the mind-body interface that improves with approaches aiming to foster mindful bodily awareness [29]. Other secondary outcome measures included the PROMIS Social Isolation measure [30] and the Neuro-QoL [31], which was used to assess feelings of well-being and lower extremity function. Because the PROMIS Social Isolation and Neuro-QoL were added later to the study, we only have these measures for 12 of the 18 completers.

Image acquisition

Imaging data was acquired on a Siemens Skyra 3-Tesla scanner at the SFVAMC. Participants' heads were positioned comfortably within a 32-channel

head coil, and head motion was minimized with firm cushions. During the resting-state functional MRI (rs-fMRI) scans, participants were instructed to close their eyes and to remain awake. The rs-fMRI images were acquired for 8 minutes and 12 seconds with an echo-planar imaging (EPI) sequence using the following parameters: 180 time points, repetition time: 3 s; echo time: 30 ms; flip angle: 80° acquisition matrix: 64 × 64; number of slices = 48; slice thickness = 3.3 mm, spatial resolution = 3.3 × 3.3 × 3.3 mm³. We also acquired anatomic images (3-dimensional MPRAGE) with the following parameters: repetition time: 2.5 s; echo time: 2.98 ms; inversion time: 1100 ms, 1.0 × 1.0 × 1.0 mm³ resolution; acquisition matrix 256 × 256 with 1 mm thick contiguous slices) for co-registration with the rs-fMRI data and quantification of total and hippocampal subfield volumes. Arterial spin labeled magnetic resonance imaging (MRI) was also acquired; however, this report will focus on PLIÉ's effect on DMN functional connectivity and hippocampal subfield volumes.

Image preprocessing

The rs-fMRI data were preprocessed using the CONN toolbox [32] (version 19c) running on MATLAB version 2014a (MathWorks, Inc., Natick, MA, USA). Slice timing was corrected based on slice order. Using the SPM software platform, fMRI data were realigned and normalized in accordance with the standard Montreal Neurological Institute (MNI) template. The ART scrubbing procedure (http://www.nitrc.org/projects/artifact_detect/) was applied to handle image artifacts due to head movement. Next, fMRI data were bandpass filtered at 0.008–0.09 Hz, and discerned from the signal contributions from cerebrospinal fluid, brain white matter, and micro head movement (six parameters). Finally, a Gaussian filter kernel (full width at half maximum = 8 mm) was applied to spatially smooth all functional images.

Image analysis

We used the CONN toolbox [32] to analyze functional connectivity, utilizing the DMN regions of interest (ROIs) defined a priori within the CONN toolbox. These include the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and lateral parietal (LP) regions bilateral. Although the a priori CONN DMN ROIs does not include the hippocampus

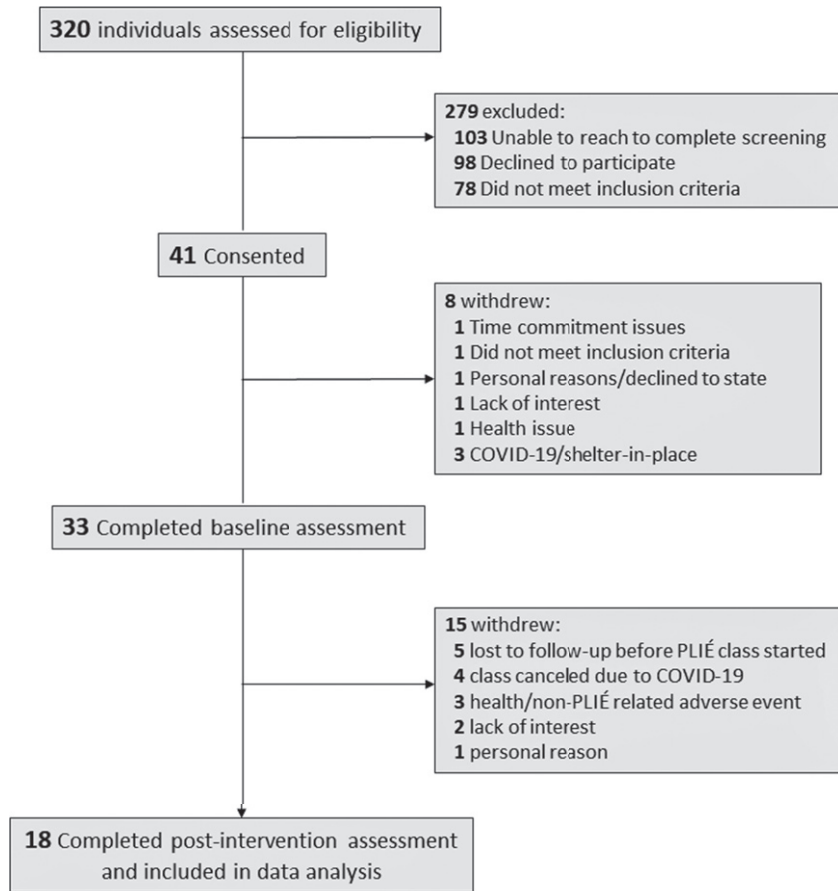


Fig. 1. Flow diagram of participants through trial.

(HP), we also performed seed to voxel analyses to probe functional connectivity between the HP and other nodes of the DMN. For individual analyses, we calculated Pearson's correlation coefficients between the time-course of activation within the DMN ROIs, the HP and the time-courses of all other voxels. This generated a seed-to-voxel connectivity matrix where positive correlation coefficients indicated positive functional connectivity and negative correlation coefficients showed negative functional connectivity. First-level correlations were then Fisher-transformed and subjected to second-level tests of ROI-to-ROI connectivity within the CONN DMN ROIs and HP to examine treatment effects (baseline > post-PLIÉ and post-PLIÉ > base). Clusters were defined by applying a high t -threshold of $p < 0.001$ (uncorrected) to individual voxels. For the extracted clusters, the threshold was $p < 0.05$. The false discovery rate (FDR) was used to correct the results. Independent tables of connectivity were obtained with the CONN DMN ROIs and

hippocampus as targets. The following parameters were computed for each ROI pair: T -value, as well as uncorrected and corrected (FDR) p -values. Only pairs with $p < 0.05$ FDR corrected were accepted, which resulted in a minimum T -value of 2.90. Resting-state fMRI data from one participant was excluded from analysis due to excessive motion artifact at the baseline assessment. Additionally, we extracted first-level connectivity values from the DMN and hippocampal ROIs to examine the relationship between connectivity and performance on the ADAS-cog by using Spearman's correlation analyses in SPSS.

FreeSurfer [33] version 6.0 and FreeSurfer's longitudinal stream [34] were used to process the structural MR images and to extract hippocampal subfield volumes. The FreeSurfer version 6.0 hippocampal segmentation algorithm predicts the location of hippocampal subregions by using a probabilistic atlas built from a combination of manual delineations

of the hippocampal formation from 15 ultra-high-resolution ($120\ \mu\text{m}^3$), *ex vivo* MRI scans showing definitive borders and manual annotations of surrounding subcortical structures from an independent dataset of 39 *in vivo* 1-mm T1 MRI scans. We visually checked for overestimation or underestimation of GM/WM matter boundaries and to identify brain areas erroneously excluded during skull stripping. We also checked that the hippocampal subregion masks were well positioned. For the current study, we focused on volumes of CA1, CA2/3, CA4, dentate gyrus, subiculum, and presubiculum. Total hippocampal volume was derived by summing the subregions and the tail of the hippocampus. Volumes of the left and right total hippocampus and hippocampal subregions were combined.

Statistical analysis

Statistical Analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp). Descriptive statistics were summarized by presenting the number and percentage for categorical variables and mean and standard deviation (SD) for continuous variables. Shapiro-Wilks testing indicated that many of the behavioral outcome measures were non-normally distributed. Therefore, pre- to post-treatment effects on behavioral measures were evaluated with the Wilcoxon signed-rank test. Because Shapiro-Wilks tests indicated that total hippocampal and hippocampal subfield volumes were normally distributed, paired *t*-tests were used to evaluate pre- to post-treatment effects on hippocampal volumes. Within-group effect sizes were calculated by subtracting pre-PLIÉ from post-PLIÉ values and dividing by the baseline SD.

This pilot trial was designed as a “proof of concept” study to generate hypotheses to be tested in future, fully powered trials. According to the Oxford English Dictionary, “proof of concept” is a phrase attributable to “evidence, usually deriving from an experiment or pilot project, demonstrating that a design concept, business idea, etc., is feasible.” For this reason, we did not adjust for multiple comparisons. However, we included *p*-values to indicate the likelihood that the results for any single test are due to chance. To examine the relationship between the ADAS-cog scores and the strength of the connections between DMN ROIs, we extracted first-level connectivity values from the DMN ROIs and subjected these to Spearman’s correlation analyses in SPSS.

RESULTS

Figure 1 presents the Consolidated Standards of Reporting Trials (CONSORT) flow. Table 1 summarizes the demographic and clinical characteristics of the participants. Forty-one participants were consented for the study and 33 participants completed baseline (pre-PLIÉ) assessments. There were no significant demographic differences between participants who did and did not complete the baseline assessment.

Treatment attrition

Eighteen of the 33 participants who completed baseline assessments also completed the intervention and post-PLIÉ assessments. These participants attended an average of 20 ± 3 PLIÉ classes (range 14–24). Five participants dropped out after the baseline assessment and did not attend any PLIÉ classes. Six participants dropped out during the intervention, three for non-PLIÉ related health emergencies, three for other/personal reasons (e.g., lack of interest in the intervention or inability to commit to study schedule). Four participants were enrolled in a PLIÉ group that was subsequently canceled due to COVID-19. There were no significant demographic differences between the 18 study completers and the participants who did not complete the intervention. Five of the 18 study completers had MCI diagnoses, 13 had SMD.

Primary outcome measures

12-week change in ADAS-cog

Figure 2 summarizes the overall ADAS-cog score and scores of the objective (i.e., subject completed) ADAS-cog subcomponents at baseline and post-PLIÉ. On average, study completers showed a 2.8 ± 3.0 point improvement on the overall ADAS-cog score after the intervention (pre-post PLIÉ effect size [ES]: 0.34, $p = 0.002$). *Post-hoc* examination of the objective ADAS-cog subcomponents revealed significant improvements on verbal episodic memory (i.e., immediate and delayed word recall).

12-week change in DMN functional connectivity

After 12 weeks of PLIÉ, the connections between nodes of the DMN got stronger (pre-PLIÉ: $F_{2,15} = 33.63$, $p_{\text{FDR}} = 0.00002$, post-PLIÉ: $F_{2,15} = 55.73$, $p_{\text{FDR}} = 0.000002$). Table 2 summarizes the change in the strength of the connections between nodes of the DMN pre- and post-PLIÉ. At baseline,

Table 1
Sociodemographic Characteristics of Study Completers

	Screened for eligibility ¹	Completed Screening	Enrolled in Study	Completed Study
N	320	139	41	18
Sex, no. (%)				
Male	232 (73%)	85 (61%)	26 (63%)	11 (61%)
Female	88 (28%)	54 (39%)	15 (37%)	7 (39%)
MCI diagnosis, no. (%)	–	40 (29%)	10 (24%)	5 (28%)
SMD, no. (%)	–	87 (63%)	31 (76%)	13 (72%)
Age, mean (SD)	–	72.0 (11.0)	73.1 (9.8)	75.6 (9.1)
Education, mean (SD), y	–	15.7 (2.8)	15.5 (2.1)	14.8 (2.5)
Race, no. (%)				
Caucasian	–	99 (71%)	31 (76%)	16 (89%)
Asian/Pacific Islander	–	10 (7%)	4 (10%)	2 (11%)
Hispanic or Latino	–	14 (10%)	1 (2%)	1 (6%)
African American	–	18 (13%)	5 (12%)	0 (0%)
Other	–	16 (12%)	4 (10%)	2 (11%)
Marital status, no. (%)				
Single	–	25 (18%)	7 (17%)	4 (22%)
Married/partnered	–	62 (45%)	20 (49%)	9 (50%)
Divorced	–	29 (21%)	6 (15%)	1 (6%)
Widowed	–	23 (17%)	8 (20%)	4 (22%)
Veterans, no. (%)	–	68 (49%)	22 (54%)	9 (50%)
MCI diagnosis, no. (%)	–	51 (37%)	16 (39%)	5 (28%)
TBI history ² , no. (%)	–	51 (37%)	16 (39%)	3 (17%)
Baseline MoCA, mean (SD) ²	–	–	24.0 (1.9) ³	24.2 (2.0) ⁴

SD, standard deviation; MCI, mild cognitive impairment; SMD, subjective memory decline; TBI, traumatic brain injury; MoCA, Montreal Cognitive Assessment ¹181 individuals did not complete the telephone eligibility screening either because they were not interested in or were ineligible for the study. Thus, there is no demographic information about these individuals other than their sex. ²determined by Ohio State University Traumatic Brain Injury (OSU-TBI) Identification Method. ³data unavailable for 1 participant with SMD; the scores of the other 5 SMD participants were only recorded as being in the inclusion range (≤ 26 and > 18). ⁴data unavailable for 1 participant; the score for the other participant was recorded only as being in the inclusion range.

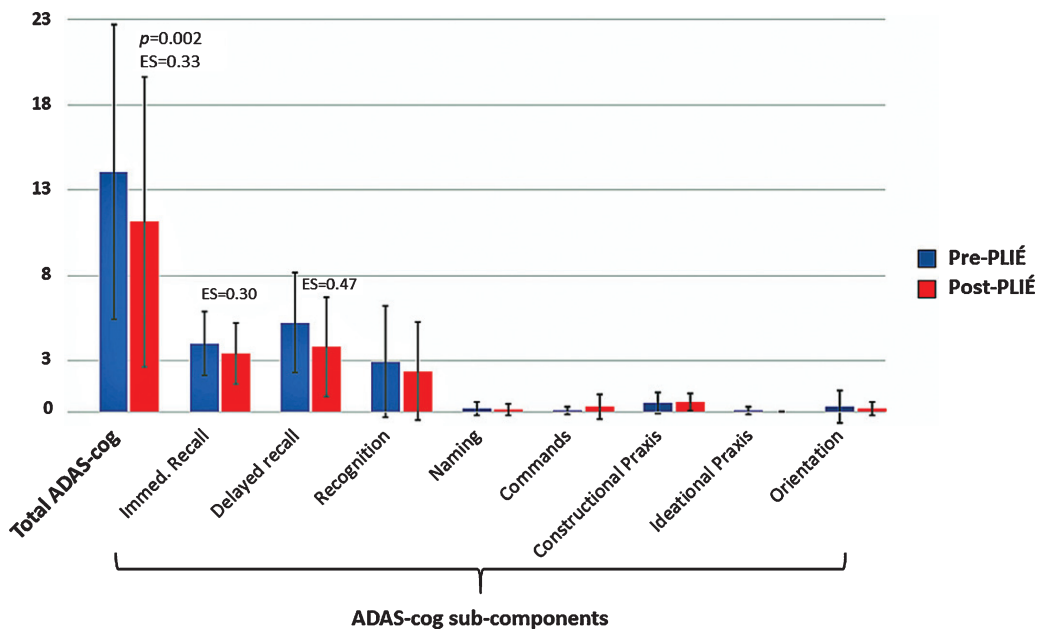


Fig. 2. Total ADAS-cog scores and ADAS-cog sub-components at pre- (blue) and post- (red) PLIÉ in the 18 study completers.

the mPFC was not functionally connected with other nodes of the DMN. However, after 12 weeks of PLIÉ,

the mPFC was functionally connected with the PCC, left LP and right HP nodes of the DMN (see Fig. 3).

Table 2
Strength of functional connectivity within DMN nodes pre- and post-PLIÉ

Connection	Pre-PLIÉ		Post-PLIÉ	
	<i>t</i> (16)	<i>p</i> _{FDR}	<i>t</i> (16)	<i>p</i> _{FDR}
1. RHP & LHP	8.54	0.000001	8.22	0.000002
2. RLP & LLP	7.44	0.000007	10.46	<0.000001
3. PCC & RLP	6.03	0.000004	7.18	0.000001
4. PCC & LLP	6.50	0.000002	8.15	0.000001
5. PCC & LHP	3.56	0.004	–	–
6. mPFC & PCC	–	–	2.26	0.06
7. mMPFC & LLP	–	–	3.21	0.005
8. mPFC & RHP	–	–	3.09	0.02

R, right; L, left; H, hippocampus; LP, lateral parietal; PCC, posterior cingulate cortex; mPFC, medial prefrontal cortex.

Post-PLIÉ, the strength of the connection between the mPFC and right HP and between the mPFC and left LP were significantly correlated with better performance (i.e., lower scores) on the ADAS-cog (see Fig. 4) as well as verbal memory subscores of the ADAS-cog.

Secondary outcome measures

Table 3 summarizes secondary behavioral and imaging outcome measures pre- and post-PLIÉ. After 12 weeks of PLIÉ, there were significant improvements on self-reported measures of interoceptive self-regulation ($ES = -0.72$, $p = 0.005$), feelings of social isolation ($ES = 0.70$, $p = 0.02$), and well-being ($ES = -0.56$, $p = 0.03$). There were also trends of improvement in physical function, quality of life, interoceptive attention regulation and larger total hippocampal CA4 and dentate gyrus volumes after 12 weeks of PLIÉ.

DISCUSSION

This proof-of-concept trial examined the effects of a novel group movement intervention (i.e., PLIÉ) that integrates principles from several well-established traditions on cognitive and brain function in a group of older adults who did not meet criteria for dementia but were experiencing symptoms of cognitive decline. Consistent with our hypothesis, cognition in individuals with SMD (72% of the study sample) and MCI (28% of the study sample) did show an improvement after 12 weeks of PLIÉ as measured by the ADAS-cog. Although it has been proposed that the ADAS-cog may have limitations in more mildly impaired individuals, who tend to have scores close to the ceiling [35], we observed improvements

in this study. This suggests that the ADAS-cog may have value in older adults with SMD and MCI. This finding adds to our previous work [4] and suggest that older adults with milder forms of cognitive impairment may also benefit from PLIÉ. Consistent with our hypothesis that 12 weeks of PLIÉ would improve DMN functional connectivity, we found increased functional connectivity after 12-weeks of PLIÉ that was correlated with better ADAS-cog scores. This finding is in line with other studies that have reported associations between increased DMN functional connectivity and better cognitive function [36–39].

The DMN is a network of interconnected brain regions that shows synchronized activity when the brain is at-rest and decreased activity when the subject is engaged in external tasks [17, 40]. Nodes of the DMN include the mPFC, PCC, LP, and medial temporal lobe structures including the HP [41, 42]. Consistent with reports that aging disrupts connectivity between the anterior and posterior nodes of the DMN [37, 43–46], we observed that the mPFC was not functionally connected with other nodes of the DMN at baseline in our participants, who were, on average, 76 years old. However, after 12 weeks of PLIÉ, the mPFC showed higher functional connectivity with the PCC, right HP, and left LP nodes of the DMN. Moreover, the strength of the connection between the mPFC and the right HP and between the mPFC and left LP were significantly correlated with ADAS-cog total and memory subscores post-PLIÉ. This is reminiscent of other studies that have reported significant relationships between connectivity of anterior to posterior nodes of the DMN and memory performance [46].

Our findings are also consistent with previous reports of increased DMN functional connectivity [47] and hippocampal networks [48] after aerobic training in healthy older adults and of improved cognition in individuals with MCI [49–52]. In a study that examined the effects of 12 weeks of aerobic walking exercise on DMN functional connectivity in older adults with MCI, Chirles et al. [16] reported increased functional connectivity between the PCC/precuneus and other DMN regions, including the left inferior parietal lobe. We also observed increased connectivity between the PCC and bilateral LP after 12 weeks of PLIÉ. Our results suggest that movement exercises that are not aerobic per se, but which focus on training procedural memory for basic functional movements and are designed to increase mindful body awareness and facilitate social connection provide (core

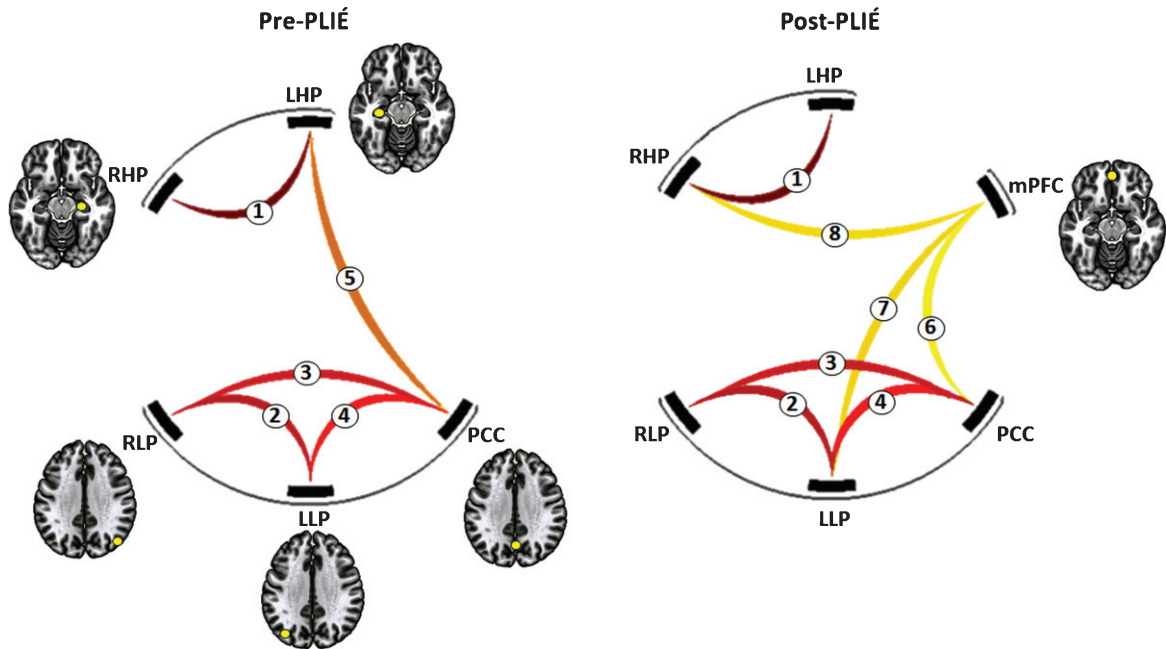


Fig. 3. Change in default mode network (DMN) connectivity before and after PLIÉ. The numbers on the connections correspond to numbers denoting the connections in Table 2. RHP, right hippocampus; LHP, left hippocampus; RLP, right lateral parietal; LLP, left lateral parietal; PCC, posterior cingulate cortex; mPFC, medial prefrontal cortex.

Table 3

Correlation (Spearman's ρ) between strength of DMN functional connectivity (β) and ADAS-cog total and memory subcomponent scores

Connection	ADAS-cog		Immediate Recall		Delayed Recall	
	Pre-PLIÉ	Post-PLIÉ	Pre-PLIÉ	Post-PLIÉ	Pre-PLIÉ	Post-PLIÉ
1. RHP & LHP	-0.03	-0.19	0.20	-0.04	-0.09	-0.22
2. RLP & LLP	-0.02	-0.24	0.13	-0.04	0.06	-0.11
3. PCC & RLP	0.42	0.24	0.44	0.36	0.38	0.29
4. PCC & LLP	0.22	-0.36	0.17	-0.18	0.34	-0.30
5. PCC & LHP	0.01	-0.13	-0.02	-0.13	-0.03	0.01
6. mPFC & PCC	-0.21	-0.25	-0.06	-0.22	-0.09	-0.26
7. mPFC & LLP	0.08	-0.74 ^a	-0.14	-0.72 ^a	-0.02	-0.69 ^b
8. mPFC & RHP	-0.29	-0.83 ^c	-0.30	-0.84 ^d	-0.16	-0.80 ^e

R, right; L, left; H, hippocampus; LP, lateral parietal; PCC, posterior cingulate cortex; mPFC, medial prefrontal cortex ^a $p=0.001$, ^b $p=0.002$, ^c $p=0.00004$, ^d $p=0.00003$, ^e $p=0.0001$.

principles of PLIÉ), also benefit individuals with SMD and MCI.

Our findings are also similar to those of a pilot study that examined the effects of mindfulness-based stress reduction (MBSR) versus usual care in individuals with MCI [14]. Although Wells and colleagues did not find significant improvements in ADAS-cog scores after 8 weeks of MBSR, they did report enhanced DMN connectivity between the PCC, mPFC, and HP after 8 weeks of MBSR compared to usual care [14]. We also observed trends of increased total hippocampal volume and increased

CA4/dentate gyrus volume post-PLIÉ. Notably, the subgranular zone of the dentate gyrus is one of the two areas in the adult brain where neurogenesis occurs [53]. Interestingly, Wells et al. also found trends of reduced hippocampal atrophy in the MSBR group. In addition to elements of physical exercise, PLIÉ includes mindful body movements and mindful breathing. Thus, our findings are in line with prior reports of increased hippocampal volume after physical exercise [54] and MBSR [55] interventions. PLIÉ and MSBR also share other common elements such as weekly time commitment

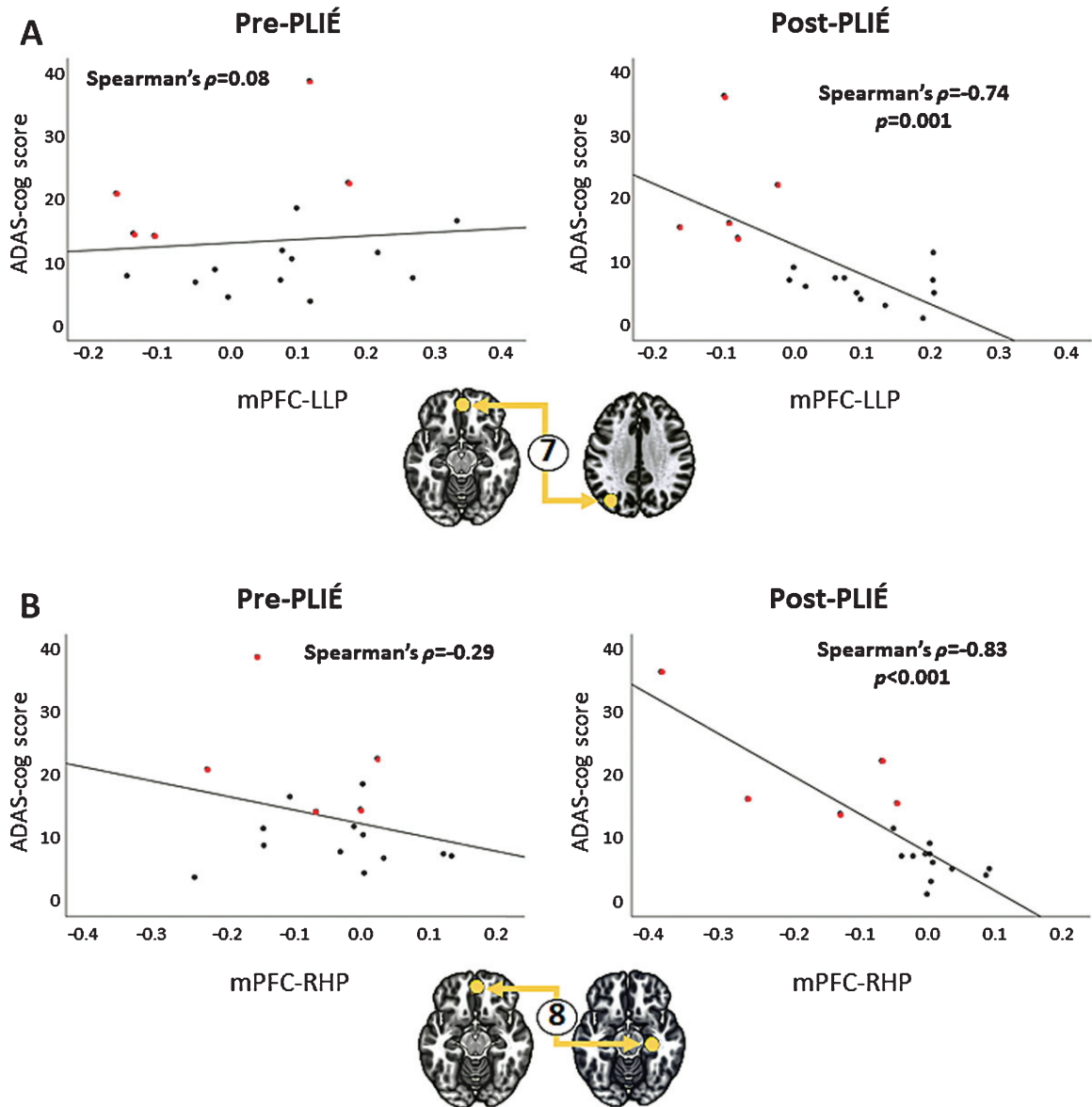


Fig. 4. Relationship between ADAS-cog scores and the strength of connection between the medial prefrontal cortex (mPFC) and (A) left lateral parietal cortex (LLP), connection #7 in Fig. 3, and (B) the right hippocampus (RHL), connection #8 in Fig. 3, after PLIÉ. Prior to PLIÉ, there were no significant correlations between ADAS-cog scores and the strength of these connections. Red circles represent participants with MCI.

and attention from and interactions with an instructor.

The mindful body movements and breathing that are part of PLIÉ draw on meditation practices such as a form of moving meditation called brain-wave vibration meditation, which was designed to help quiet the mind and to release negative emotions through performing rhythmic movements and focusing on bodily sensations [56]. In a study that examined DMN

functional connectivity, Jang et al. [56] reported that practitioners of brain-wave vibration meditation had increased functional connectivity within the DMN, particularly in the mPFC, compared to meditation-naïve control subjects.

PLIÉ also includes elements from yoga, the ancient mind-body practice that incorporates breathing, exercise, and meditation techniques. In a study with older adults with MCI, Eyre et al. [15] reported

Table 4
Pre- and Post-PLIÉ effects on secondary behavioral and imaging outcome measures

	Pre-PLIÉ (SD)	Post-PLIÉ (SD)	Effect size (95% CI)	<i>p</i>
<i>Behavioral Measures</i>				
MAIA-2 Self-regulation	3.3 (1.4)	4.1 (0.7)	-0.72 (-1.40, -1.07)	0.005 ^c
MAIA-2 Attention Regulation	3.1 (1.3)	3.6 (0.8)	-0.46 (-0.20, 1.25)	0.07 ^c
PROMIS Social Isolation ^{a,b}	9.6 (2.7)	7.9 (2.1)	0.70 (-0.12, 1.80)	0.02 ^c
NeuroQOL- Well Being ^a	34.7 (4.6)	37.2 (4.3)	-0.56 (-1.38, -0.68)	0.03 ^c
NeuroQOL- Lower Extremity Function ^a	38.0 (2.1)	37.2 (3.2)	0.30 (-0.51, 0.99)	0.13 ^c
SPPB	8.6 (2.1)	9.4 (2.3)	-0.36 (-1.02, -0.38)	0.06 ^c
QOL-AD	35.6 (6.0)	37.2 (6.2)	-0.26 (-0.92, -0.18)	0.08 ^c
GDS ^b	3.8 (2.5)	3.1 (2.8)	0.26 (-0.39, 0.85)	0.11 ^c
<i>Total and Hippocampal subfield volume (mm³)</i>				
Total Hippocampus	6321.71 (1197.06)	6369.19 (1234.85)	-0.04 (-0.69, 0.26)	0.07 ^d
CA1	1177.54 (251.78)	1187.58 (255.87)	-0.04 (-0.69, 0.26)	0.14
CA3	379.06 (87.45)	382.36 (91.43)	-0.04 (-0.69, 0.26)	0.25
CA4	492.44 (116.66)	497.41 (121.69)	-0.04 (-0.70, 0.25)	0.08 ^d
Dentate Gyrus	548.36 (125.28)	554.73 (130.50)	-0.05 (-0.70, 0.24)	0.05 ^d
Presubiculum	547.82 (106.35)	552.83 (111.61)	-0.05 (-0.70, 0.24)	0.32
Subsiculum	768.15 (161.03)	774.69 (159.14)	-0.04 (-0.69, 0.25)	0.23

MAIA-2, Multidimensional Assessment of Interoceptive Awareness 2, SPPB, Short Physical Performance Battery; QOL-AD, Quality of Life Alzheimer's Disease; GDS, Geriatric Depression Scale ^aData available for 12 participants because measure was not implemented in first PLIÉ group ^blower score = better outcome ^c*p*-value calculated using Wilcoxon signed-rank test ^d*p*-value calculated from paired *t*-test.

that yoga and a memory enhancement training program both improved verbal memory performance in participants with MCI. Furthermore, the improvements in verbal memory scores were correlated with increased functional connectivity between the DMN and frontal medial cortex after yoga and memory training. Although both memory training and yoga enhanced memory performance, Eyre et al. [57] found that only the yoga intervention also improved executive function, depressive symptoms, and resilience in older adults with MCI. The measure of "resilience" assessed by Eyre et al. [57] may be viewed as a measure of the ability to cope with stress, which is somewhat similar to the self-regulation measure that we examined with the MAIA-2 questionnaire [27]. A sample item of the MAIA-2 self-regulation scale is "When I feel overwhelmed, I can find a calm place inside." Notably, there were significant post-PLIÉ improvements on the MAIA-2 measure of interoceptive self-regulation, as well as significant post-PLIÉ reductions in feelings of social isolation (PROMIS), and enhanced feelings of well-being (NeuroQOL). All of these may be construed as improved mood/reduced depression post-PLIÉ.

Although we hypothesized that PLIÉ may have a greater likelihood of slowing cognitive decline in individuals with less neurodegeneration (e.g., people with SMD and MCI) than people with dementia, our prior studies suggest that PLIÉ has beneficial effects in people at all stages of cognitive

decline/neurodegeneration. Specifically, we have found that PLIÉ improves quality of life in people with dementia [4, 58, 59], and we have successfully delivered PLIÉ to individuals with dementia in multiple settings (e.g., adult day centers, community settings, nursing homes). PLIÉ is highly flexible and may be adapted to suit the needs of participants with different levels of cognitive and functional impairment.

This pilot trial had some limitations that should be noted. First, we did not have an active control group. Therefore, we cannot rule out the possibility that practice, context, or placebo effects may have contributed to the behavioral findings and self-report measures. However, it is more difficult to argue that the post-PLIÉ changes we observed on DMN functional connectivity and the trends of post-PLIÉ increases in hippocampal volume can be attributed to practice or placebo effects. Second, because the study only had one arm, the assessors were unblinded, which may have led to potential biases. A third limitation is that we performed numerous statistical tests without adjusting for multiple comparisons; therefore, there is a potential of false positives. The reason why we did not adjust for multiple comparison was because this was meant to be an initial, exploratory proof-of concept trial to generate hypotheses for future, fully powered trials. Therefore, we followed the general recommendations for exploratory pilot studies [60]. Another limitation is that with only 18 completers, these findings are preliminary and need

confirmation through larger, controlled studies. Also, because only 18 of the 33 enrolled participants who completed baseline assessments, completed the intervention and the post-intervention assessments, it is conceivable that the study completers represent a self-selected group of individuals who noticed the benefits of PLIÉ and followed through with the program. Five participants who dropped out after completing the baseline assessment never attended any PLIÉ class. It is possible these five individuals were dissuaded by the commute to and from the SFVAMC, where the PLIÉ classes were held, unable/unwilling to commit to attending classes twice a week for 12 weeks, or only took part in baseline procedures for the \$50 payment. Because these five participants never attended any PLIÉ classes, it is difficult to construe their dropping out as a reflection of the intervention. Three participants dropped out because of unanticipated medical emergencies. Only three participants dropped out after attending at least one PLIÉ class because they did not like the intervention or because of time commitment issues. When considered in this context, the dropout rate is comparable with many other intervention trials. A final limitation of the study is we did not follow-up with the study completers to investigate how long the benefits of PLIÉ can be maintained. These limitations notwithstanding, results from this proof-of-concept pilot trial provide preliminary evidence that PLIÉ may improve cognitive function, increase self-regulation, and reduce social isolation in people with MCI and SMD, and that the neurological mechanism of action may be increased DMN connectivity. Fully powered trials of PLIÉ are warranted to test this hypothesis.

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