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IMOVE: Protocol for a randomized, controlled 2x2 factorial trial of improvisational movement and social engagement interventions in older adults with early Alzheimer's disease

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ABSTRACT

Background: In addition to cognitive impairment, people with Alzheimer's disease (PWAD) experience neuropsychiatric symptoms (e.g., apathy, depression), altered gait, and poor balance that further diminish their quality of life (QoL). Here, we describe a unique, randomized, controlled trial to test the hypothesis that both movement and social engagement aspects of a group dance intervention alter the connectivity of key brain networks involved in motor and social-emotional functioning and lead to improved QoL in PWAD.
Methods: IMOVE (NCT03333837) was a single-center, randomized, controlled 2x2 factorial trial that assigned PWAD/caregiver dyads to one of 4 study conditions (Movement Group, Movement Alone, Social Group, or Usual Care control). The Movement Group participated in twice-weekly group improvisational dance (IMPROVment® Method) classes for 12 weeks. The Movement Alone intervention captured the same dance movement and auditory stimuli as the group class without social interaction, and the Social Group used improvisational party games to recapitulate the fun and playfulness of the Movement Group without the movement. The primary outcome was change in QoL among PWAD. Key secondary outcomes were functional brain network measures assessed using graph-theory analysis of resting-state functional magnetic resonance imaging scans, as well as neuropsychiatric symptoms, gait, and balance.
Results: A total of 111 dyads were randomized; 89 completed the study, despite interruption and modification of the protocol due to COVID-19 restrictions (see companion paper by Fanning et al.). The data are being analyzed and will be submitted for publication in 2023.

1. Introduction

Dementia is a progressive decline in cognition that impairs a person's ability to perform activities of daily living. Alzheimer's disease (AD) is the most common cause of dementia, and accounts for an estimated 60%–80% of cases [1]. In addition to memory loss, confusion, and difficulty completing familiar tasks, people with Alzheimer's disease (PWAD) and related dementias experience neuropsychiatric symptoms (i.e., apathy, depression, anxiety, agitation, aggression) [1–3], altered gait, and poor balance [4–6] that impair quality of life (QoL) [7–11] and increase medical costs [12–16]. Caregivers (CGs) of people with dementia are twice as likely to report substantial emotional, financial and physical difficulties than CGs for older people with other needs [17]. Notably, the severity of neuropsychiatric symptoms and functional disability in PWAD and related dementias is positively associated with burden and healthcare utilization among CGs [18–22].

Neurodegeneration causes the changes in behavior and cognition associated with AD. Graph theory-based analysis of resting-state functional MRI (fMRI) has shown that AD, even at very early stages [23], induces changes in the organization and connectivity of functional brain networks (reviewed by Dennis and Thompson [24]). Among older adults

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Abbreviations

AD	Alzheimer's disease
CG	Caregiver
DMN	Default Mode Network
E_{Glob}	Global Efficiency
E_{Loc}	Local Efficiency
FAB	Fullerton Advanced Balance Scale
MA	Movement Alone
fMRI	functional Magnetic Resonance Imaging
MCI	Mild Cognitive Impairment
MG	Movement Group
NPI-Q	Neuropsychiatric Inventory Questionnaire
PWAD	Person/people with Alzheimer's disease
QoL	Quality of Life
RCT	Randomized Controlled Trial
ROI	Region of Interest
SEM	Structural Equation Modeling
SG	Social Group
SI	Scaled Inclusivity
SMC	Somatomotor Cortex
UC	Usual Care

with MCI, reduced connectivity between the sensorimotor and fronto-parietal networks was associated with slower gait [25]. Healthy older adults also show decreased global efficiency and modularity in brain regions associated with mobility and cognition [26–28]. Emerging evidence suggests that, similar to other movement and exercise interventions [29–32], dance may increase brain volumes [33,34], structural connectivity [35], brain-derived neurotrophic factor [33], and functional connectivity [36,37] in older adults.

There is mounting evidence that sensory and motor regions of the central nervous system are affected by the pathology of AD [38–40]; thus, interventions that target and support the sensorimotor system may enhance patient function as AD progresses or slow the progression of disability. Dance incorporates movement, social engagement, and cognitive stimulation and thus, may help maintain quality of life for older adults, including PWAD. Although the evidence base for dance movement is compromised by heterogeneity in dance interventions and outcomes across studies, several recent meta-analyses of randomized, controlled trials (RCTs) have shown that dance interventions improve cognition in older adults with MCI [41–44]. Fewer studies have assessed the impact of dance on neuropsychiatric and motor symptoms; however, a meta-analysis of 5 RCTs [45] showed that dance interventions improved depressive symptoms in older adults with MCI and dementia. In a meta-analysis of 8 RCTs [43], cognitive benefits of dance interventions in older adults with MCI were accompanied by significant improvements in physical function and QoL. Finally, Ghadiri et al. [46] recently showed that a 10-week Iranian dance intervention improved gait parameters in older women with dementia.

Unlike many other forms of dance, improvisational dance is not learned by repetition and reinforcement of specific steps. Improvisational dance utilizes verbal auditory cueing to convey ideas that elicit novel movement from class participants. Because the cues do not prescribe specific movements, improvisation allows movers to make empowering choices within a structured environment of select constraints [47,48]. Improvisational dance may or may not be rhythmically synchronized with music and is particularly well-suited for PWAD because it 1) does not rely heavily on memory; 2) can be seamlessly adapted to sitting, standing, or moving around the room; 3) is cognitively challenging; and 4) fosters a social, playful atmosphere.

The IMPROVment™ method (https://improvment.wfu.edu/) is a group-based, improvisational dance intervention grounded in 4 principles: non-judgment, non-competitiveness, curiosity, and playfulness. In a previous study, this method improved balance and mobility in people with Parkinson's disease, and markedly changed functional brain network architecture in the one participant scanned [49]. Ongoing community classes as well as the largest support group for people with Parkinson's disease in Forsyth County, North Carolina, USA arose from this study, demonstrating the establishment of meaningful social connections among participants. Additionally, a pilot study evaluated the feasibility and potential benefits of IMPROVment classes (twice weekly for 8 weeks) versus usual care in people with MCI or early-stage dementia and their CGs [50]. The intervention arm (n = 5 dyads) demonstrated 96% class attendance, and qualitative feedback suggested that participants felt socially connected to the group. QoL and balance were improved from baseline in the intervention arm, whereas worsening of both parameters was observed in usual care controls. Neuroimaging analyses revealed improvements in several brain network characteristics among participants in the intervention arm, but not in the usual care arm. These included global efficiency and modularity, two metrics that are reduced with age and pathology [24,51,52].

Results of the pilot study described above informed the design of IMOVE, a study designed to test the hypothesis that both movement and social engagement alter the connectivity of key brain networks involved in motor and social-emotional functioning and lead to improved QoL in PWAD.

2. Methods

2.1. Design and ethics

IMOVE (NCT03333837) is a single-center, randomized, controlled 2x2 factorial trial (Fig. 1) designed to test the separate and combined effects of social engagement and dance movement on QoL in PWAD [53]. The factorial design follows current strategy developed for assessing effects of multi-component interventions. As our focus is on the individual effect of social engagement and dance, and their additive effect, the factorial design preserves power, which is a function of the overall sample size, not individual cell size. The protocol was reviewed and approved by Wake Forest School of Medicine (WFSM) Institutional Review Board. All PWAD and CGs provided their written informed consent to participate.

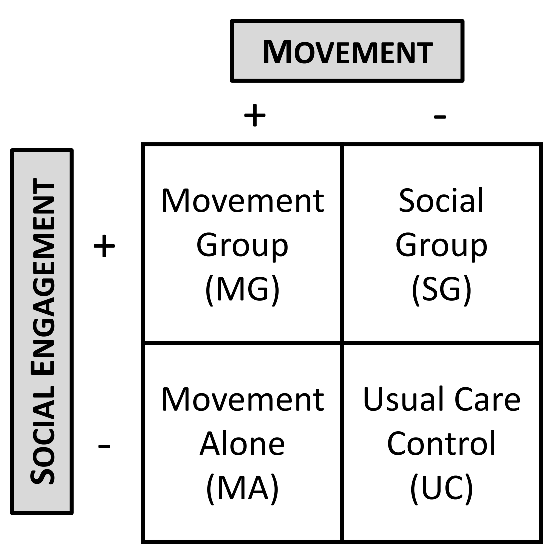

Fig. 1. Intervention arms of the IMOVE trial testing separate and combined effects of movement and social engagement.

2.2. Recruitment

Participant dyads (i.e., one PWAD and one CG) were recruited through the WFSM Kulynych Memory Assessment Clinic (MAC) and the WFSM Alzheimer's Disease Research Center (ADRC) after their routine evaluation and diagnostic classification. The assessments in these two settings, described in more detail below, are highly overlapping and ensured consistency in adjudication of cognitive status. Participants could be referred from other clinics as long as the adjudication procedure was similar to that used in the MAC or ADRC and a cognitive battery, bloodwork, exam by a physician, and neuroimaging were performed. Additional participants recruited from the community followed similar procedures and were cognitively adjudicated through the ADRC.

2.3. Adjudication of cognitive status

Cognitive evaluation included a neuropsychological test battery, functional status questionnaires completed by a proxy, and a history and physical by a board-certified geriatrician. In the MAC and ADRC, patients without recent imaging or blood work to rule out reversible causes of cognitive impairment received standard blood assays and an MRI (or CT scan if MRI was contraindicated). After reviewing all data and in consultation with the diagnostic team, dementia experts assigned a diagnosis of AD, other forms of dementia, MCI, or normal cognition using Alzheimer's Association/National Institute on Aging criteria [54]. The cognitive test battery included tests of naming, word fluency, working and episodic verbal and visual memory, and global cognition. Depression and other psychiatric symptoms, functional independence, and CG assessment of cognitive and physical function were also assessed via interviews and questionnaires. Participants were required to have a Mini Mental State Exam (MMSE) score $\geq$15 to participate.

2.4. Eligibility

2.4.1. People with AD

Participants were 60–85 year-old English speakers who were adjudicated as having MCI or early-stage dementia of the predominantly AD, vascular, or mixed AD/vascular type within 1 year of beginning the study. PWAD were required to have an eligible CG and be able to undergo MRI. PWAD were excluded from participation if they had other causes of dementia, such as Lewy body, frontotemporal, or Parkinsonian dementia; had any major medical problem that could reasonably affect cognitive or brain imaging measures used to determine eligibility or outcomes, or severely impact attendance (e.g., current cancer treatment); had other neurological diseases, such as amyotrophic lateral sclerosis, Parkinson disease, or multiple sclerosis; were taking medication (e.g., benzodiazepines) that could negatively influence safety during intervention sessions; had current drug or alcohol use/dependence that, in the opinion of the investigator, would interfere with adherence to study requirements; had any reason for which the study doctor or personal physician felt that the intervention was contraindicated; had planned extensive travel during the study period; were enrolled in another interventional study within 3 months prior to beginning this study; or were unwilling to provide consent or assent for study participation. PWAD who had suffered a cortical stroke, had current stroke symptoms, or who had stroke deemed exclusionary by the study physician were excluded. PWAD with subcortical stroke that was resolved or asymptomatic could be included if found to be appropriate by the study physician.

2.4.2. Caregivers

Eligible CGs were individuals who spent $\geq$10 h per week with a PWAD and were willing to regularly accompany the PWAD to intervention sessions and actively participate. A CG was required to be present at each intervention session and study visit. In acknowledgement of the complex caregiving situations experienced by many families experiencing dementia, different CGs could accompany the PWAD to intervention sessions, e.g., if the primary caregiver had a conflict, a regular secondary caregiver could accompany the PWAD. CGs were excluded for unwillingness to provide consent for study participation; any major medical problem that could reasonably affect ability to attend study and intervention visits; taking medication that could negatively influence safety during the intervention sessions; current drug or alcohol use/dependence that, in the opinion of the investigator, would interfere with adherence to study requirements; or extensive travel planned during the study period without availability of an alternate CG.

2.5. Procedures

2.5.1. Randomization

After completion of baseline assessments, participants were randomized to one of 4 study conditions (Movement Group [MG], Movement Alone [MA], Social Group [SG], or Usual Care [UC]) through a computerized randomization scheme. Randomization codes were generated and maintained by the study statistician. Because recruitment occurred in waves, randomization was performed in blocks of 16 dyads (4 per arm) that each corresponded with a wave of data collection. We anticipated that sex-balance of PWAD participants would be achieved, as it was in the pilot, because although women are more likely to be diagnosed with dementia, they are also more likely to be CGs. However, if gender balance of PWAD was not achieved in any wave, gender blocking could be employed in the next wave.

2.5.2. Blinding

Study staff who administered testing during study visits were blinded to the randomization scheme. Therefore, group assignment was not known during screening, baseline, or follow-up assessments. One primary study staff member was unblinded after baseline visits for the purposes of notifying participants of their study arm, coordinating intervention visits as needed, and making reminder calls. All other study staff remained blinded to perform follow-up testing visits. Intervention staff were not blinded to study group assignments but did not perform any research assessments on participants. Participants were instructed not to mention their study group to staff performing assessments. The principal investigator and biostatistician were blinded until database lock.

2.5.3. Non-imaging assessments

The schedule of PWAD baseline and follow-up assessments is summarized in Table 1, and assessments are described below The primary outcome, QoL in PWAD, was assessed using the Quality of Life AD (QOL-AD) [55,56], a 13-item scale designed to assess quality of life in people with dementia that is validated for use in people with a Mini Mental State Exam score as low as 10.

Secondary outcomes focused on the two hypothesized global mechanisms of change: physical and emotional well-being. Physical function was assessed using: 1) the Expanded Short Physical Performance Battery (eSPPB) [57], a global mobility assessment that includes brief assessments of gait speed, lower body strength and balance with a 4 m walk, a 4 m narrow walk, time to rise from a chair 5 times, and time to stand in different standing balance postures, including standing on one leg; 2) Timed Up and Go (TUG) [58], which measures the time for a participant to rise from a chair, walk 3 m, turn, walk back to the chair, and sit; 3) Postural sway (or stability) was evaluated with center-of-Pressure (COP) trajectory data collected at 100 Hz using an Advanced Mechanical Technology Incorporated (AMTI) AccuSway biomechanics force platform for ten 30 s trials, five completed with a foam mat [59–64]; and 4) the Fullerton Advanced Balance Scale (FAB) [65], which measures balance using 10 different performance-based tests. Mood was assessed using: 1) self-report by the PWAD on the 15-item Geriatric Depression Scale [66], 2) Geriatric Anxiety Scale [67], and 3) Apathy Evaluation Scale [68]; and 4) through caregiver report of symptoms using the

Table 1
Schedule of PWAD procedures and assessments.

Procedure/Assessment	Source Data Type	Baseline Visit 1 Within 14 weeks of intervention start	Baseline Visit 2 Within 6 wks of intervention start	Follow-up Visit 1 0–7 days after intervention completion	Follow-up Visit 2 1–21 days after intervention completion
Apathy Evaluation Scale[b]	Paper		X	X	
Blood draw – biomarkers[c]	Lab Report	X		X	
Consent	Paper	X			
Contact form	Paper	X			
Demographics	Paper	X			
Expanded Short Physical Performance Battery[b]	Paper	X			X
Falls Efficacy Scale[b]	Paper		X	X	
Fullerton Advanced Balance Scale[b]	Paper	X		X	
Gait Variability[b]	Electronic	X			X
Geriatric Anxiety Scale[b]	Paper		X	X	
Geriatric Depression Scale[b]	Paper		X	X	
Medical history/Medications	Paper	X			
Montreal Cognitive Assessment[c]	Paper	X			X
Magnetic resonance imaging	Electronic		X	X	
Multisensory Reaction Time[c]	Electronic		X		X
Neuropsychiatric Inventory Questionnaire[b]	Paper		X	X	
Philadelphia Mindfulness Scale[c]	Paper	X			X
Postural sway[b]	Electronic	X			X
Quality of Life-AD[a]	Paper	X		X	
Repeatable Battery for the Assessment of Neuropsychological Status[c]	Paper		X		X
Study expectations	Paper	X			
Timed Up and Go[b]	Paper	X			X
Unusual Uses Task[c]	Paper		X		X

[a] Primary outcome.
[b] Secondary outcomes.
[c] Exploratory outcomes.

Neuropsychiatric Inventory Questionnaire (NPI-Q) [69], a questionnaire where the CG rated the frequency, severity, and distress of symptoms in the PWAD across 12 domains.

Tertiary or exploratory outcomes included a test of divergent thinking, the Unusual Uses Task, to assess whether participating in weekly classes that encouraged creative thinking altered divergent thinking [70,71]; the Philadelphia Mindfulness Scale [72,73]; a brief test of multisensory reaction times [74]; and a blood draw to assess biomarkers of stress (allostatic load) [75]. To control for any potential relationships between study interventions and cognition, an abbreviated cognitive battery, the Repeatable Battery for Neuropsychological Status [76] was administered at baseline and follow-up. Change in cognition was not a prespecified outcome as it was not expected to change with such a short duration of observation. Standard demographic and health variables collected for statistical adjustment, anticipated questions, or exploration of alternate hypotheses for PWAD included demographic characteristics, self-reported medical history, body-mass index, and blood pressure.

Assessments of CGs were performed for the purpose of adjusting for certain variables if needed that might influence PWAD QoL. Caregiver assessments were similar to PWAD assessments and were administered as summarized in Supplementary Table S1. Measures administered to CGs that were not administered to PWAD included: 1) the NEO Five Factor Inventory [77], because previous work suggests that CG personality may influence caregiver reports of neuropsychiatric symptoms and burden [78] and 2) the Zarit Caregiver Burden Scale [79], a 21-item self-report scale where caregivers rate items describing frequency of burdensome or stressful situations. CGs did not undergo MRI.

2.5.4. Neuroimaging

PWAD completed 1-h MRI scans at baseline and follow-up. These included T1-weighted structural images, fMRI images, and images needed for potential alternate hypotheses (e.g., FLAIR images to assess white matter hyperintensity burden, related to slower gait speed in aging [80]). All MRI images were acquired on a 3 T (3 T) Siemens Skyra scanner with a 32-channel headcoil.

Acquisition. A high resolution T1-weighted image was collected using a 3D volumetric MPRAGE-GRAPPA sequence (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, FOV = 256 mm, number of slices = 192, voxel size = 1.0 × 1.0 × 1.0 mm, scan duration = 312 s). Whole-brain blood oxygenation level-dependent (BOLD) imaging was acquired during resting state, where participants are asked to view a cross in the middle of a screen with eyes open (TR = 2000 ms, TE = 25 ms, FOV = 256 mm number of images = 190, voxel size = 4.0 × 4.0 × 4.0 mm, scan duration = 380 s, acquired anterior-to-posterior) [81]. A 14 s reverse-encoded BOLD scan was acquired for distortion correction using the same parameters, but acquired in the posterior-to-anterior direction. A T2-FLAIR SPACE image was acquired for the estimation of WMH (TR = 5000 ms, TE = 383 ms, FOV = 256 mm, number of slices = 192, voxel size = 1.0 × 1.0 × 1.0 mm, scan duration = 417 s).

Preprocessing. High resolution T1-weighted anatomical were spatially normalized to the MNI template using ANTs [82]. To ensure an accurate whole-brain mask prior to spatial normalization using ANTs, images were segmented using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and a whole-brain mask was created for each participant using both white and grey matter segments. Whole-brain mask images were manually inspected and cleaned to remove excess parenchymal tissue using MRIcron (https://www.nitrc.org/projects/mricron) to create a final whole-brain mask.

BOLD fMRI images were preprocessed using SPM, FSL, and warping parameters from ANTs implemented in an automated pipeline run through Matlab (The MathWorks, Natick, MA, USA). The first 10 vol were dropped to allow for signal stabilization and the 'topup' procedure in FSL was used for distortion correction. SPM12 was used to complete slice time correction and realignment of functional images. The transformation derived from ANTs was applied to warp BOLD images to MNI space. Motion scrubbing [83] and a band-pass filter (0.009–0.08 Hz) to account for low-frequency drift and physiologic noise were applied.

Finally, the data were adjusted for head motion and non-neural signal using 6 rigid-body motion parameters generated during realignment and average signal from white matter and CSF.

Brain Network Generation. The preprocessed fMRI data were used to create a network, or graph, for each individual using all the voxels within the grey matter segmentation mask [84]. Nodes in the graph were defined as individual voxels. The presence of a connection (edge) between two nodes (i and j) was determined by 1) completing a voxel-wise time series regression analysis to generate a whole-brain functional connectivity matrix for all node pairs; 2) thresholding the correlation matrix to create a binarized adjacency matrix (A_{ij}) where a value of 1 indicated the presence of an edge and a value of 0 indicated no edge. In order to ensure comparable edge density across participants, a sparsity threshold was calculated using ($S = \log(N)/\log(K)$), where N is the number of nodes and K is the average degree (i.e., number of edges per node in the network). Only positive edges were retained in the final matrix. Functional network variables of interest are described in section 2.9.2.

Regions of interest (ROIs). Regional changes in whole brain metrics and community analyses were performed on two *a priori* ROIs: the somatomotor cortex (SMC) and default mode network (DMN). The SMC is involved in motor planning and execution and the DMN has been implicated in mood disorders [85] and AD [86]. ROIs were generated using resting-state brain networks from independent data in 22 normal young adults from a prior study [87].

Neuroimaging outcomes included functional brain network measures assessed with graph-theory analysis [88] of resting-state fMRI scans (Table 2). Path length is the number of edges that must be crossed to get from one node to another. Longer path length in people with AD has been associated with slower cognitive performance, beta amyloid deposition, and depression [89–91]. Global Efficiency (E_{Glob}) reflects the efficiency with which information from one node can move through the network [92]. Decreased E_{Glob} has been associated with aging, cognitive impairment, and depression [26,91]. Local Efficiency (E_{Loc}) is related to clustering, and reflects the efficiency with which information from one node is propagated to its neighbors [92] and has been reported to change with cognitive impairment and depression [91]. We computed modularity (Q) [93,94], to assess community structure strength in the brain networks using the "Louvain" algorithm [95]. Our work has demonstrated decreased modularity associated with decreased physical function [28], and others have shown that cognitive impairment and AD are associated with alterations in modularity [23,90]. Consistency of community structure across individuals was measured within ROIs using Scaled Inclusivity (SI) [96]. SI values range from 0 to 1 where high SI indicates that a particular network community is consistently observed within the group [97]. Reduced consistency of SMC community structure has been observed in older adults with poor mobility function compared with young adults [28].

Table 2
Secondary outcomes.

Hypothesis	Secondary Outcome
Improved gait and balance are potential mechanisms by which dance may improve QoL in PWAD.	Fullerton Advanced Balance Scale Postural sway Gait speed and variability Expanded Short Physical Performance Battery
Improvement in neuropsychiatric symptoms, particularly apathy and depression, is a potential mechanism by which dance may improve QoL in PWAD.	Neuropsychiatric Inventory Questionnaire (NPI-Q) Geriatric Depression Scale and Geriatric Anxiety Scale Apathy Evaluation Scale
Gait/balance and neuropsychiatric improvements due to dance are accompanied by changes in brain function as assessed by graph theory-derived measures of network structure calculated on resting state fMRI images.	Global efficiency (E_{Glob}) Local efficiency (E_{Loc}) Community structure (SI)

fMRI = functional magnetic resonance imaging; PWAD = people/person with Alzheimer's disease; QoL = quality of life; SI = scaled inclusivity.

2.6. Interventions

2.6.1. Class themes and structure

Protocolization of the study interventions will be more fully described in a forthcoming publication by Soriano et al. Six themes were created to distinguish teaching methodologies and to provide structure for the 12-week intervention. Each theme was explored for 2 weeks (4 classes), with each class and theme gaining in complexity as the 2 weeks progressed. The themes were loosely inspired by Rudolph Laban's Movement Analysis system which was developed to describe human movement [98], and included: isolation, which we defined as moving one or more body parts independently; shape, which focused on creating shapes or images with the body; time, which had to do with the amount of time that one takes to complete a movement or the rhythm used or a particular relationship with a piece of music; flow, which we defined as ongoingness; space/direction which was about connecting the body to the space around it and the pathways one takes through space; and effort, which was the quality with which a dancer moves their body. Once the exercises were organized into themes, an exercise order was created, and classes could be taught by any trained IMPROVment instructor.

Improvisation was the element that spanned all 3 intervention arms of the study. Thus, the same 6 themes were a guiding force in development of the SG arm. Common party games such as Hangman, Boggle, and Pictionary were modified to adhere to these themes and to include improvisation as described in a forthcoming publication by Soriano et al. Games were also modified to reduce individual competitiveness, to be easy and fun to learn, and to work in a group environment.

Group interventions were initiated in waves as described in section 2.5.1. All three intervention arms (MG, MA, SG) met for 1-h sessions twice weekly for 12 weeks (for a total of 24 sessions). Participants had the option to complete the 24 sessions within 13 weeks to allow make-up days for missed classes. Attendance was documented at each session.

All interventions took place in spaces that were safe, well-lit, had convenient parking, and were accessible for a range of mobility and included a local dance studio, two different churches, and a community center. For dance interventions, spaces were free from obstacles, had a sturdy chair with no arms available to each PWAD, and were equipped with a means for playing music or recordings of dance instructors. The primary dance PI (Soriano) or an instructor trained by her conducted all group interventions, both movement and social, to control for factors related to instructor personality across study arms.

2.6.2. Movement Group (MG)

The IMPROVment method and theory were described previously [49,50]. Briefly, this improvisational dance method is grounded in 4 principles that shape the tone of the class and result in a sense of social belonging: non-judgment, non-competitiveness, curiosity, and playfulness. Active imagination, variability, and pacing are integral components of the method. The instructor provides verbal cues that activate the imagination (e.g., moving in a windstorm, arriving at the beach) and may demonstrate an optional response, but asks participants to respond with their own gestural inventions. Variability is accomplished by presenting new prompts or adding complexity to a specific exercise. Some cues require dual- or multi-tasking (e.g., direct traffic with the right side of the body and pick apples with the left). Cues are often delivered one after another, preventing participants from defaulting to habitual responses or being limited by self-perceptions of their capabilities. Participants cannot rely on copying another, memory, or anticipation to address the motor problem presented. There is little time to change one's mind, become embarrassed, or be dissatisfied with the choice made. Thus, the method builds on the idea that daily living requires flexible, adaptive responses to real-life challenges.

Classes were structured in 4 phases: (1) group warm-up in chairs positioned in a circle, (2) standing barre or back of the chair with solo and responsive exercises, (3) moving as a group through free space (with and without a partner), and (4) recuperation and rest. All exercises could be adapted for sitting, and the choice to stand or walk was always determined by the participant. Similar exercises could appear within each phase (seated/standing/walking), creating a progression of motor skills, but the class series did not build incrementally. The recuperation phase involved movements that were slower, simpler, and often more familiar (e.g., seated hamstring stretch). To track fidelity to the protocol, instructors noted any exercises that were missed at the conclusion of each intervention.

2.6.3. Movement Alone (MA)

The MA intervention was designed to capture the same dance movement and auditory stimuli as the group class without social interaction. Recordings of the dance instructors, including the same range of prompts presented to group classes, were played. This ensured participants heard comparable music and received comparable verbal auditory cues to prompt dance movements that those in the MG arm heard, but without interacting with other people. Participants were asked to follow the same schedule as participants in the MG arm and completed two 1-h dance sessions each week. The MA intervention took place at the same locations as the MG and SG study arms. MA participants were met at the site by study staff, who checked them in, organized the music and recordings, and were present outside the room while the participant danced for safety. A sample of each participant's individual dances session was video recorded for the purpose of confirming movement fidelity versus the MG intervention.

2.6.4. Social Group (SG)

In the pilot study, the individual item on the QOL-AD that increased most in PWAD who participated in the MG intervention was 'Ability to do things for fun'. Therefore, the SG intervention consisted of improvisational party games to foster curiosity and playfulness, use imagery, and encourage non-judgment. Games included 'Balderdash', 'Wise and Otherwise', 'Pictionary', and 'Tell Me A Story' cards. As mentioned above, the games were organized around the same themes as the movement exercises and were designed to follow the same core components as the MG (active imagination, pacing, variability, and non-judgement, non-competitiveness, curiosity, playfulness). Multiple games were played within each session to incorporate pacing and variability.

2.6.5. Usual care (UC)

The UC control arm captured the condition of no added social contact and no added dance movement. Participants randomized to the UC arm were asked to continue their current disease management and lifestyle for 12 weeks. Participants were called monthly and reminded by phone to maintain their usual lifestyle. Because the condition of not receiving an intervention can have ethical implications and reduce retention rates, UC participants were invited to join a weekly community improvisational dance class after they completed the study or to join MG classes if space allowed.

2.7. Monitoring of health status

All participants were required to notify study staff of any major changes in their lifestyle or health status that might affect study outcomes or their safety during participation. In addition, changes in health status, medications, or lifestyle were solicited by study staff via phone once monthly. Participants were specifically asked about falls. Solicited and unsolicited reports of health events were documented. A participant was asked to discontinue the intervention if they had any change in health status that met exclusion criteria or if the intervention or testing was judged by study staff, the participant, study physician, or personal physician to put the participant at risk.

2.8. Handling of adverse events

An adverse event was defined as any untoward medical occurrence in a subject during participation in the clinical study, regardless of relationship to participation. Anticipated adverse events in the MG and MA arms included falling, tripping, and muscle soreness. If a participant fell during the intervention 2 or more times during the 12-week period, the option to stand or walk would be removed, and they would be asked to remain seated for the remainder of the sessions. However, no participants fell during intervention. If participants tripped, the instructions were modified as necessary to prevent further tripping. Movement intensity could be reduced if needed to prevent further muscle soreness in affected participants. Study safety was reviewed at least monthly and adverse events were reported biannually to the Data Safety and Monitoring Board.

2.9. Statistical analyses

2.9.1. General design issues

The study uses a full-factorial design to test the main effects of movement and social engagement and their possible synergistic effect. Suppose Y represents the primary outcome of interest post-intervention, and $Y^{(BL)}$ the outcome at baseline. The following ANOVA model forms the basis of the power calculations and subsequent analyses:

$$Y_{ijk} = \mu + \beta_1 X_i + \beta_2 Z_j + \beta_3 (XZ)_{ij} + \beta_4 Y_{ijk}^{(BL)} + \varepsilon_{ijk} \quad \text{Equation 1}$$

where *X represents* the movement component, μ represents the mean, Z represents the social component, and (*XZ*) represents the interaction between X and Z, and ε represents random error, with, $i, j = 1{,}2$, and $k = 1{,}.{,}n$, where n is the sample size. Equation (1) decomposes the response (QoL-AD) into the sum of effect of the variables and controls for value pre-intervention.

2.9.2. Data analysis

Analysis of Aim 1: Determine the independent effects of social engagement and dance movement on QoL in people with dementia by assessing the main effects of social engagement and movement. We will use analysis of variance (Equation (1)) to assess the main effects of social engagement and movement on QoL. Effect coding for the X, Y variables will be used so that the coefficients β_1 and β_2 in Equation (1) can be directly tested and interpreted respectively as half the main effects of the movement and the social components. The null hypothesis is that there will be no main effect. Statistically, we will test the following two hypotheses: H_0: $\beta 1 = 0$; $\beta 2 = 0$ at the level of $\alpha = 0.05$. Following common practice, we will not adjust for covariates in testing main effects unless severe imbalances occurs in cell distributions of demographic variables including gender and age. The synergistic effects of the movement and social engagement will be evaluated by testing the hypothesis: H_0: $\beta_3 = 0$.

Analysis of Aim 2: Assess potential mechanistic links between functional neuroimaging metrics, behavioral outcomes, and overall QoL scores using structural equation modeling in all groups combined. Longitudinal structural equation modeling (SEM) will be used to assess Aim 2 using the path diagram in Fig. 2 (note that Fig. 2 represents a cross-sectional "slice" of the overall longitudinal model of 3 time points). With the Markov assumption such that a measure at a previous time point has a direct effect on the same measure at current time point, we will analyze the data such that QoL will be the observed outcome variable. Movement is hypothesized to exert effects on QoL through changes in somatomotor brain networks, a latent variable comprised of multiple graph theory-derived measures of connectivity in the somatomotor ROI defined in section 2.5.4, including E_{Glob}, E_{Loc}, and

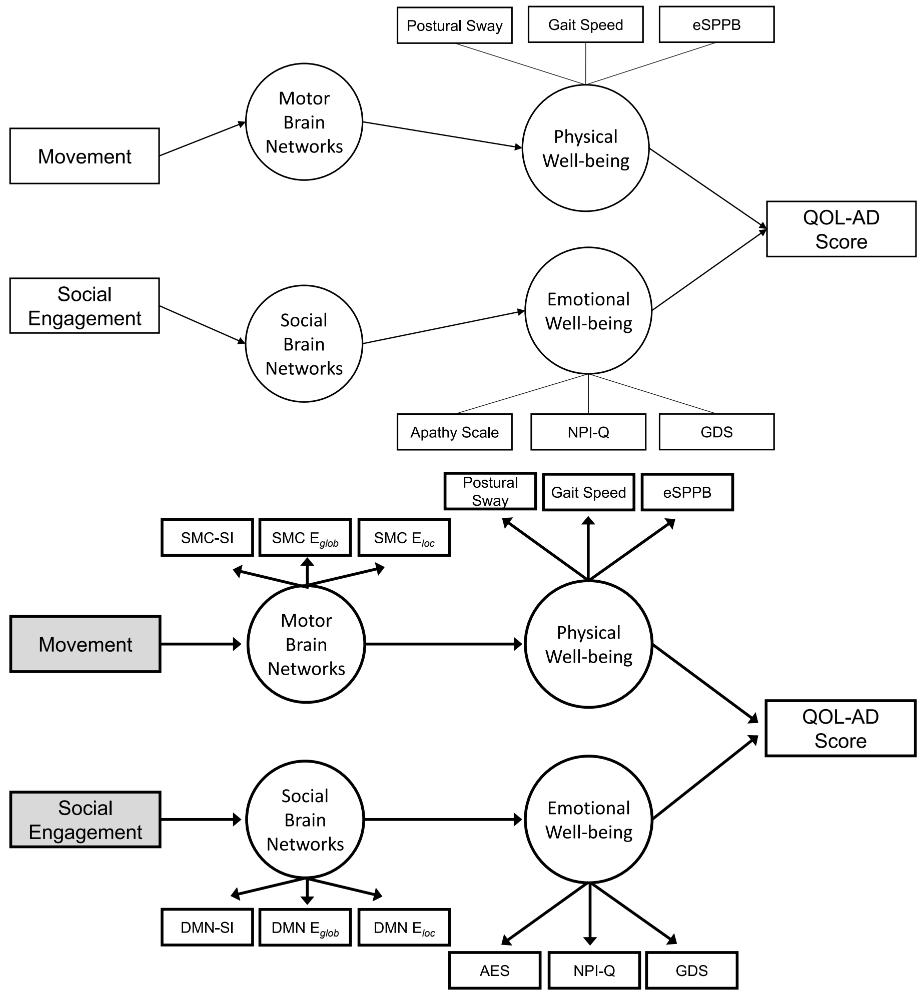

Fig. 2. Path diagram for proposed SEM analysis. Grey shaded squares represent components of the intervention hypothesized to be generating an effect. Circles represent latent variables in the model. Boxes connected to circles with an arrow to represent observed variables used to create latent variables. Solid lines represent hypothesized effects. AES = Apathy Evaluation Scale; DMN = default mode network; E_{glob} = global efficiency; E_{loc} = local efficiency; GDS = Geriatric Depression Scale; GAS = Geriatric Anxiety Scale; NPI-Q= Neuropsychiatric Inventory Questionnaire; SEM = structural equation modeling; SMC = somatomotor cortex; SI = scaled inclusivity.

modularity. Changes in somatomotor network structure are hypothesized to result in improved gait (a latent variable comprised of gait speed, gait variability, and stride length derived from the instrumented mat) and balance (a latent variable including balance measured with the FAB, balance confidence measured with the Falls Efficacy International Scale, and postural sway measured with the force plate). Social engagement was hypothesized to alter connectivity in the default mode network, modeled using multiple graph theory-derived measures of connectivity in the DMN ROI, including E_{Glob}, E_{Loc}, path length, and degree. Altered DMN connectivity was hypothesized to result in decreased neuropsychiatric symptoms and increased QoL. SEM analysis [99] will proceed in several stages. First, confirmatory factor analytic models will be fitted to the stated indicators for individual latent variables. We will examine goodness-of-fit indexes to determine the appropriate measurement models and refine the measures if necessary. Second, we will assess the consistency between the structural model and the data. Structural connections that are not significant will be deleted and will be reported, and alternative hypotheses will be tested. This iterative process will result in a final structural model that offers insight into the mechanism through which improvisational dancing affects overall well-being in the population of PWAD. SEM analysis will be conducted using Mplus v7.4.

2.9.3. Sample size

Our pilot data showed a difference of 1.4 on the QOL-AD between the UC control and dance group [50]. Although the pilot did not test separate effects of social engagement and dance movement and was an 8-week rather than a 12-week intervention, the pilot data suggested the amount of change we could expect. For power calculations, we used a conservative estimate of effect size of 0.55 per main effect. The power of the study using a sample size of 30 per cell in the 2x2 factorial design (total N = 120) is approximately 85%. If due to attrition the sample size dropped to N = 100, then power would be reduced to 78%. The power analysis assumed a 2-sided test at $\alpha = 0.05$, and the calculation was conducted using the SAS macro FactorialPowerPlan [100]. We collected follow-up data on all participants to the best of our ability for the purpose of completing an intent-to-treat analysis.

3. Results

Participant flow is summarized in Fig. 3. Of 1194 dyads telephone screened, 101 were randomized. A total of 54 dyads had completed study interventions when in-person interventions ceased due to COVID-19 restrictions (March 2020). Interventions were suspended until the protocols for the MG, MA, and SG groups could be modified for virtual delivery. We adopted an engineering-inspired, rapid refinement model to identify and rectify weak points in our remote intervention protocols

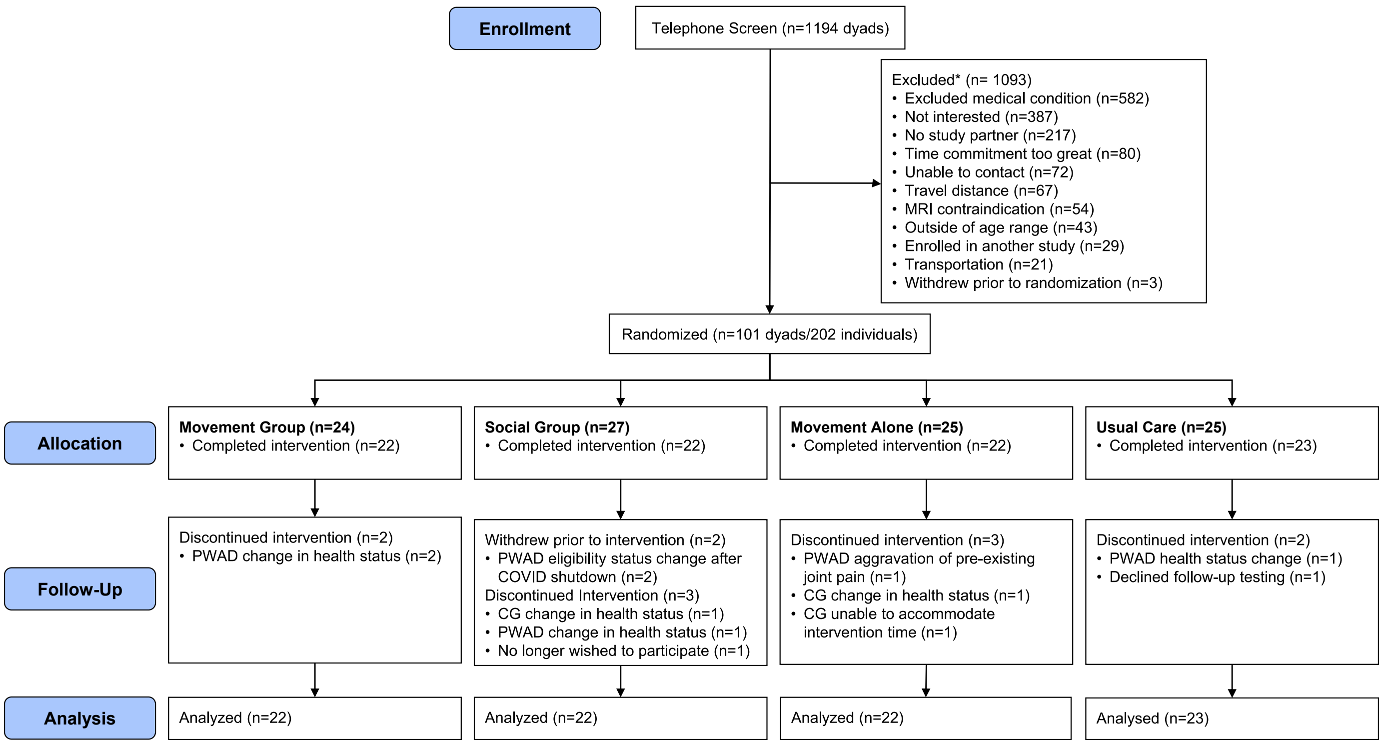

Fig. 3. IMOVE participant flow from enrollment to analysis. *Participants could meet more than one exclusion criterion. CG = caregiver; MRI = magnetic resonance imaging; PWAD = people with Alzheimer's disease.

until participants in each arm consistently reported high levels of engagement, social connection, and enjoyment. This iterative approach is described in a companion article to this publication (Fanning et al.). Interventions resumed virtually in November 2020. Of the 101 dyads enrolled, 89 completed their assigned interventions. Study data are being analyzed and results will be submitted for publication in 2023.

4. Discussion

The multimodal and integrated nature of dance does not easily conform to the constraints of traditional RCT design (e.g., blinding of researchers/participants, isolating variables, limiting cross-factorial influences). Studies capable of capturing the complexity of interpersonal interactions while determining physiological mechanisms and respecting the integrity of the dance form under investigation are challenging to design and execute. The IMOVE study is the product of a unique, highly innovative, and productive partnership [49,50] that combines expertise in dance and neuroscience. To our knowledge, there is no published mechanistic model to explain the effects of dance on QoL or secondary symptoms in PWAD. Furthermore, our 2x2 factorial design is the first to evaluate the independent and combined contributions of 2 key aspects of an arts-based intervention.

We hypothesize that both movement and social engagement alter the connectivity of key brain networks involved in motor and social-emotional functioning, and lead to improved QoL in PWAD. A better understanding of the physiological changes that occur during dance, and their links to improved QoL and symptom management, could facilitate identification of other interventions that may ameliorate secondary symptoms of AD. Such a model may also help to identify other patient populations that may benefit from dance or other art forms.

Several caveats and limitations of our work warrant mention. Inclusion criteria were based on cognitive adjudication by consensus through our ADRC. However, the time and financial constraints of the granting mechanism precluded biomarker assessment of AD status. The APOE allele is associated with increased risk for late-onset AD, and PWAD who have the APOE4 genotype may respond differently to physical activity interventions. Genotyping of PWAD was not performed due to budget limitations, but samples were collected and stored for potential future analyses. Second, because the study population was limited to patients with early AD and their CGs, the value of the intervention in patients with later-stage disease cannot be assumed based on our results. Third, the study was designed to evaluate the potential impact of a 12-week intervention in PWAD, and the duration of impact beyond completion was not assessed. Finally, the breadth of assessments employed reflects the fact that dance outcomes are different from aging outcomes and are not well-established. The assessment requirements were somewhat burdensome for PWAD, CGs, and study staff. As the secondary outcomes were set up for exploratory analysis for potential mechanistic pathways, they were not adjusted for multiple comparisons. The results of this study, when published, will strengthen the literature with respect to identification of endpoints that are sensitive to dance interventions and inform future designs.

Overall, this manuscript reports on an innovative trial design that uses current strategies for testing multicomponent interventions to study dance as an art form and lifestyle choice that may have specific benefits for brain and body health during aging. The scientific study of the health effects of participating in dance and other art forms is growing rapidly. This study design contributes to gaps in the literature on dance by applying a method of study design that helps move forward understanding of the core components of dance that could contribute to brain and body health. There is a clear need for larger studies that target health outcomes and use scientific design choices to help elucidate the 'medicine of dance' to help move this vibrant and rapidly growing field forward.

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Authors' contributions

Christina E. Hugenschmidt: Conceptualization, Methodology, Writing – Review and Editing, Visualization, Supervision, Funding Acquisition. Edward H. Ip: Methodology, Formal Analysis, Writing – Review and Editing. Jessie Laurita-Spanglet: Methodology. Phyllis Babcock: Project Administration, Investigation. Ashley R. Morgan: Project Administration, Data Curation, Investigation. Kamryn King: Methodology. Jason T. Fanning: Writing – Review and Editing. Jantira T. Thomas: Investigation, Resources. Christina T. Soriano: Conceptualization, Methodology, Writing – Review and Editing, Supervision, Funding Acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101073.

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