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Meditation and Music Improve Memory and Cognitive Function in Adults with Subjective Cognitive Decline: A Pilot Randomized Controlled Trial

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Abstract.
Background: While effective therapies for preventing or slowing cognitive decline in at-risk populations remain elusive, evidence suggests mind-body interventions may hold promise.
Objectives: In this study, we assessed the effects of Kirtan Kriya meditation (KK) and music listening (ML) on cognitive outcomes in adults experiencing subjective cognitive decline (SCD), a strong predictor of Alzheimer's disease.
Methods: Sixty participants with SCD were randomized to a KK or ML program and asked to practice 12 minutes/day for 3 months, then at their discretion for the ensuing 3 months. At baseline, 3 months, and 6 months we measured memory and cognitive functioning [Memory Functioning Questionnaire (MFQ), Trail-making Test (TMT-A/B), and Digit-Symbol Substitution Test (DSST)].
Results: The 6-month study was completed by 53 participants (88%). Participants performed an average of 93% (91% KK, 94% ML) of sessions in the first 3 months, and 71% (68% KK, 74% ML) during the 3-month, practice-optional, follow-up period. Both groups showed marked and significant improvements at 3 months in memory and cognitive performance (MFQ, DSST, TMT-A/B; p's ≤ 0.04). At 6 months, overall gains were maintained or improved (p's ≤ 0.006), with effect sizes ranging from medium (DSST, ML group) to large (DSST, KK group; TMT-A/B, MFQ). Changes were unrelated to treatment expectancies and did not differ by age, gender, baseline cognition scores, or other factors.
Conclusions: Findings of this preliminary randomized controlled trial suggest practice of meditation or ML can significantly enhance both subjective memory function and objective cognitive performance in adults with SCD, and may offer promise for improving outcomes in this population.

Keywords: Alzheimer's disease, cognitive impairment, early memory loss, memory

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INTRODUCTION

Alzheimer's disease (AD), a progressive neurodegenerative disorder resulting in a loss of reasoning, memory, language, and ultimately, basic self-care skills, is a leading cause of death in the US, affecting at least 5.3 million Americans at an estimated annual cost of $226 billion for those over 65 [1]. The development of AD is generally insidious, with onset of clinical signs preceded years earlier by perceived and/or objective cognitive decline [2]. Longitudinal studies have linked subjective cognitive decline (SCD) to accelerated deterioration in cognitive function [3], an up to 4.5-fold increased risk for progression to mild cognitive impairment (MCI) [4, 5], and a 2- to 6.5-fold increased risk for AD [6, 7] after adjustment for demographics, depression, APOE4 status, and other risk factors. Recent prospective research has likewise shown SCD in clinically normal elders to remain strongly associated with cognitive performance even after adjustment for AD biomarkers, including amyloid-β [8]. The annual conversion rate from SCD to MCI or dementia in otherwise healthy individuals has been estimated to be 7–10% [9–11]. Notably, in one longitudinal study of 2,415 German elders [6], progression from SCD to MCI was shown to carry a 20- to 60-fold increased risk for the development of AD dementia, highlighting the importance of early intervention.

While cognitive function is in the normal range in those with SCD [12], a number of population-based studies have shown significant decrements in cognitive performance in adults with SCD relative to those without memory complaints [13, 14]. SCD has also been characterized by increased amyloid-β deposition and other pathological changes of the brain associated with AD [15–19], elevated levels of cerebrospinal fluid markers of AD [19, 20], reductions in hippocampal and grey matter volume [14, 21, 22], and increased white matter lesions [23]. Neuropathological changes consistent with AD have likewise been associated with SCD at autopsy even in those who were not diagnosed with cognitive impairment [24, 25]. Moreover, longitudinal studies of cognitively normal older adults have demonstrated not only that SCD is strongly associated with episodic memory-related hippocampal atrophy, a hallmark of AD [26], but that these neurodegenerative changes can precede the development of SCD by years [27, 28] and may help explain the subtle decline in objective cognitive performance recently shown to predate incident SCD [3]. These findings suggest that SCD may be a sensitive early clinical marker for AD.

To date, there are no approved treatments for early memory loss [29]. Nonetheless, this preclinical or prodromal period, when the burden of neurodegenerative changes is still relatively low, may represent a crucial therapeutic window for addressing cognitive decline and associated neuropathogenic changes. There is mounting evidence that mind-body therapies such as meditation and music-based interventions, including simple, passive (receptive) music listening, may offer promising treatment options. A growing body of literature suggests that both meditation practice and listening to familiar and/or relaxing classical music can improve neurostructural and neurophysiologic profiles, and may enhance memory and cognitive performance in both healthy and clinical populations, including those with and at risk for cognitive impairment [30–38]. For example, recent prospective controlled studies in older adults with and without dementia suggest meditation may induce beneficial structural and functional changes, including increased grey matter volume, grey matter density, and functional connectivity [38, 39], as well as enhanced oxygenation and glucose utilization in brain regions involved in cognitive processing, memory consolidation, and attention [38, 40]. Similarly, findings from preliminary randomized controlled trials (RCTs) in these populations suggest that meditation may also improve certain domains of cognition, including attention, executive function, memory, and processing speed [34–36, 40].

Likewise, exposure to music has been shown in experimental models to promote positive effects on the brain, including increased neurogenesis, enhanced synaptic plasticity, and beneficial changes in neurotropin and neurotransmitter (e.g., dopamine) levels [41, 42]. Findings from recent human studies suggest listening to classical and/or familiar music may also increase grey and white matter volume in cortical and subcortical brain areas involved in cognitive processing, enhance functional connectivity of these regions, and modulate activity in brain structures implicated in emotional regulation and reward, behavioral responses, working memory and attention [30, 31, 43]. Findings from recent pilot research [32], including a Finnish RCT of caregiver-dementia patient dyads [44] suggest a simple music listening program may lead to improvements in certain critical domains of memory and cognitive functioning as well.

However, despite the apparent promise of these low cost, non-invasive therapies, rigorous controlled trials remain sparse, and none has to date examined the possible value of meditation or music listening for improving multiple domains of cognition in adults with subjective memory loss. Based in part on encouraging findings from pilot work by our group and others [45–47], this parallel-arm, RCT compared the effects of two 12-week mind-body programs, music listening (ML) and Kirtan Kriya meditation (KK), a beginner multimodal meditation practice, on memory and cognitive function in older adults with SCD.

MATERIALS AND METHODS

Participant eligibility criteria, trial design, and study procedures are described in detail elsewhere [48] and are outlined briefly below. The study was approved by the West Virginia University Institutional Review Board.

Study participants

Independently living older adults with early memory loss were recruited for the study, using intranet and email advertising as well as brochures and flyers placed in community, health care, and workplace settings. Major study inclusion criteria were as follows: English-speaking adults at least 50 years of age with either a) physician confirmed diagnosis of MCI; or b) SCD as defined by meeting six criteria consistent with expert reviews and prospective studies available at the time [6, 10, 12, 49]. These included: 1) presence of subjective cognitive deficits within the past 6 months; 2) frequency of memory problems at least once/week; 3) able to give an example in which memory/cognitive problems occur in everyday life; 4) belief that one's cognitive capacities have declined in comparison with 5 or 10 years previously; 5) absence of overt cognitive deficits or dementia diagnosis; and 6) expressed worry regarding memory problems, a factor shown to further increase risk of progression to MCI and AD [3, 10]. Excluded from the study were those who: 1) practiced meditation or other relaxation techniques within the past year; 2) recently (within the last 6 weeks) changed dosage of cholinesterase inhibitors [e.g., donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon)] or psychotropic medication (e.g., tricyclics, SSRIs, MAOIs, anti-panic or anti-anxiety agents); 3) had a history of psychotic or schizophrenic episodes, major neurologic diagnosis (Parkinson's, stroke, brain injury, epilepsy) or other condition that might impair cognition or confound assessments [e.g., cardiovascular event within the past 6 months (myocardial infarction, unstable angina, hospitalization for congestive heart failure, bypass surgery or angioplasty (coronary or carotid), transient ischemic attack)]; 4) had received chemotherapy treatment within the past 10 years; or 5) recently (within the last 3 months) experienced serious physical trauma or received a diagnosis of a serious chronic health condition requiring medical treatment and monitoring (e.g., uncontrolled hypertension, serious endocrine or pulmonary disorder, renal disease, active cancer treatment). Study buddies willing to attend all assessment visits were required for those with MCI and encouraged for those with SCD who were concerned about their ability to fully understand the consent process or complete the questionnaires.

Assessments

After providing written informed consent, participants completed the baseline assessment; we gathered information on medical history, current medication and supplement use, lifestyle and anthropometric characteristics, and demographic factors. We evaluated memory and cognitive function using three well-established, validated instruments, including measures of memory function (Memory Functioning Questionnaire (MFQ) [50]), executive function (Trail Making Test Parts A and B (TMT) [51]), and psychomotor speed, attention, and working memory (the 90-second Wechsler Digit-Symbol Substitution Test (DSST) [52]). The MFQ is a 64-item self-report questionnaire scored on a 7-point Likert scale, with higher scores indicating better memory functioning; the four subscales include: General Frequency of Forgetting, Seriousness of Forgetting, Retrospective Functioning, and Mnemonics Usage. MFQ scores have been inversely associated with brain amyloid burden in cognitively normal older adults [15–17], and shown to differentiate non-cognitively impaired adults from those with SCD [53], suggesting that the MFQ may offer a useful measure for detecting preclinical AD. The TMT, a sensitive measure of cognitive functioning [54] is a two-part paper-and-pencil test: the TMT-A, in which numbers (1–25) are connected in an ascending order (1–2–3;...); and the TMT-B which requires connecting numbers (1–13) and letters (A–L) alternately (1-A-2-B...). Scores reflect the number of seconds

required to complete each part. While both parts are designed to measure attention and information processing speed, the TMT-B also measures additional domains of executive function, including cognitive flexibility and working memory [54]. In a recent longitudinal study of memory clinic patients with SCD, worse TMT-B scores independently predicted subsequent conversion to MCI or AD [55]; likewise, TMT-B was found to be the best single predictor for dementia in a prospective study of Swedish MCI patients [56]. Finally, the DSST is a timed test in which participants are asked to translate numbers into symbols, following a key which is visible throughout the test. One point is scored for each correctly drawn symbol completed within 90 seconds. These assessments were repeated at 3 months, and again at 6 months (3 months post-intervention).

To assess *expectation of benefit,* participants completed the 6-item Credibility/Expectancy Questionnaire (CEQ) [57] following their first intervention practice session. To allow tracking of adherence, participants completed daily home practice logs which were collected at the follow-up assessment visits. At each follow-up visit, participants also recorded any changes in medication and/or supplement use and in exercise routines using a form specifically designed for this purpose. In addition, participants were asked to complete a 3- and 6-month study evaluation questionnaire adapted from that used in our previous studies [45, 58]. This survey included a single 5-point Likert scale item to assess change in concerns regarding memory. All participant assessments and entry of outcomes data were performed by research staff blinded to participant treatment assignment.

Randomization and treatment allocation

Eligible participants were randomized to one of two treatment groups described below, in a 1 : 1 ratio using a randomly varying block randomization method to ensure equal distribution between groups [59]. Following baseline assessment, the consenting team member, who had no advance knowledge of the statistician-prepared group allocation schedule, gave the next sequentially numbered, sealed opaque envelope containing the treatment assignment to the participant.

Interventions

Following randomization, participants received one-on-one training in their assigned relaxation practice (see below). The 30–45-minute onsite training was delivered by a trainer familiar with both study programs and experienced in teaching a range of mind-body skills. In addition, each participant received a program CD and a short reference guide, along with a portable CD player for home use. Participants were instructed to engage in their assigned practice while seated comfortably with eyes closed, for 12 minutes daily for 12 weeks (84 practice sessions total) and to record every practice session daily on the home practice log, along with any comments. The trainer called each participant within the first week of the intervention to provide additional instruction as needed, and remained available thereafter to clarify any additional issues that arose in the course of the intervention. During the 3-month, practice-optional post-intervention period, participants were likewise asked to record any practice on their daily log sheets.

Kirtan Kriya meditation program

KK is a multisensory practice that engages several areas of the brain, yet is easy to learn and practice. The meditation includes a kirtan (repeated singing of the 'Sa-Ta-Na-Ma' mantra), a mudra or physical/motor component (touching each fingertip to the thumb in sequence with the chant), and a visualization component (imagining the sound energy entering the crown of the head and exiting between the eyebrows in an 'L'). The meditation CD contained a user-friendly introductory track with detailed instructions regarding the KK practice and five 12-minute meditation tracks, including three guided sessions.

Music listening program

The ML CD contained 12 minutes of relaxing instrumental music from each of 6 classical composers. Participants were instructed to sample each composer at least once during the 12 weeks, but were otherwise left to listen to whichever composer they chose on a daily basis.

Analysis

Data analysis was performed using IBM SPSS, Version 23. Baseline differences between the intervention groups and between dropouts and non-dropouts were assessed using chi-square (for categorical variables), independent samples *t*-tests

(for normally distributed continuous variables), or Mann-Whitney U tests (for ordinal or continuous variables with evidence of skewing); a p value of ≥ 0.1 was used for determining baseline differences. Potential differences between treatment groups were analyzed using chi-square for retention, and one-way ANOVA for treatment expectancies and adherence. In preliminary assessments, within-group changes over time at 3 and 6 months were assessed using ANCOVA with age and baseline scores as covariates; age-adjusted between-group differences in treatment outcomes were assessed using Repeated Measures ANOVA. In our intention-to-treat (ITT) analyses, we used the SPSS multiple imputation function (10 iterations) to replace missing data [60]. Effect sizes were calculated using Cohen's d. As this was a pilot feasibility study, alpha was set at 0.05. Bivariate and age-adjusted correlations were performed using Pearson's r. Variables with a non-normal distribution were log-transformed prior to analysis.

To evaluate the robustness of our findings, we performed additional analyses restricted to those most at risk for cognitive decline, including participants: age $\geq$60 years; with SCD onset within the last 5 years; with at least 2 AD risk factors; and with poorer baseline scores on the MFQ (<75th centile) and the TMT-B ($\geq$88 seconds, a cut-off shown to predict subsequent cognitive decline and dementia in a recent study of memory clinic patients with MCI) [56]. We also evaluated the potential modifying influence of age ($\geq$60 versus <60 years), history of depression/anxiety, use of medications linked to memory change, baseline cognition scores (<50th versus $\geq$50th centile) and obesity. To assess the potential influence of medication change, we conducted additional analyses, both adjusting for this factor statistically and excluding those reporting change in medication.

RESULTS

A total of sixty eligible adults, all with SCD, were enrolled in the study. Enrolled participants ranged in age from 50–84 years old (mean (M) = 60.6, SE = 1.0). The majority of participants were female (85%) and non-Hispanic white (93%) (Table 1). Baseline MFQ scores averaged 246.1 ± 2.9, with 42% of participants scoring 88 or above in their baseline TMT-B. Participants reported experiencing memory problems for an average of approximately 3 years ($M = 35.42 \pm 4.2$ months). Prevalence of additional modifiable AD risk factors was also high. Ninety-four percent of participants reported at least one, and 66% reported 2 or more metabolic/vascular risk factors for AD; overall, prevalence of measured AD risk factors averaged 2.8 ± 0.2 in this sample of older adults (Table 1).

With the exception of prevalence of obesity, which was marginally lower in the KK than in the ML group, the two groups were similar overall in demographics, lifestyle factors, medical history, and in baseline measures of memory and cognitive functioning (Tables 1 and 2). Baseline scores on measures of cognition and memory were correlated with age (r's ≥ 0.3, p's ≤ 0.02), but were not significantly related to other demographic characteristics, lifestyle factors, obesity, or number of metabolic or other modifiable risk factors. Likewise, baseline scores did not differ by history of depression or anxiety, high cholesterol, hypertension, cancer or other chronic conditions, or by use of medications commonly linked to memory changes. Reported change in medication at the follow-up assessment was also similar between groups ($p \geq 0.4$). At 3 months, a total of six participants (3 KK, 3 ML), reported a change in medication, including antidepressant ($n = 2$), analgesic ($n = 2$), steroid ($n = 1$), and muscle relaxant ($n = 1$). At the 6-month assessment, four participants reported a change in medication (1 KK, 3 ML), including antidepressant ($n = 2$), analgesic ($n = 1$), and statin medication ($n = 1$).

All participants received the intervention to which they were allocated. Attrition rates were low, with 92% of participants (27/30 KK, 28/30 ML) completing the 12-week program, and 88% (26/30 KK, 27/30 ML) completing the full 6-month study. Completers were similar to non-completers in all baseline characteristics (p's ≥ 0.3).

Program adherence was high; participants completed an average of 93% (91% KK, 94% ML) of sessions in the first 12 weeks, and 71% (68% KK, 74% ML) of sessions during the 3-month, practice-optional follow-up period. There were no between-group differences in either retention or adherence at any time point (p's ≥ 0.4), or in any domain of treatment expectancy (all p's ≥ 0.2). In addition, treatment expectancy scores were not correlated, at any time point, with change over time in any outcome measured (p's ≥ 0.1). No adverse events were reported by any participant.

Table 1
Participant baseline characteristics: Pilot feasibility RCT of a 12-week Kirtan Kriya meditation (KK) versus a 12-week music listening (ML) program in 60 adults with subjective cognitive decline

	Overall ($n=60$)		KK ($n=30$)		ML ($n=30$)		p
	n	%	*n*	%	*n*	%	
Demographic characteristics							
Age (range 50–84 years)							
Mean age ± SE	*60.58 ± 1.01*		*60.93 ± 1.56*		*60.23 ± 1.32*		*0.73*
Female Gender	51	85.00%	26	86.67%	25	83.33%	0.71
Race/Ethnicity: Non-Hispanic White	56	93.33%	27	90.00%	29	96.67%	0.25
Education							0.17
12 years or less	10	16.67%	3	10.00%	7	23.33%	
≥12 years	50	83.33%	27	90.00%	23	76.67%	
Employment status							0.65
Employed full or part time	44	73.33%	23	76.67%	21	70.00%	
Retired/Homemaker/Other	16	26.67%	7	23.33%	9	30.00%	
Marital status							0.65
Married/co-habiting	39	65.00%	19	63.33%	20	66.67%	
Divorced/widowed/separated/single	21	35.00%	11	36.67%	10	33.33%	
Lifestyle and health-related factors							
Smoking status							0.78
Never smoked	38	63.33%	19	63.33%	19	63.33%	
Former smoker	19	31.67%	10	33.33%	9	30.00%	
Current smoker	3	5.00%	1	3.33%	2	6.67%	
Caffeinated beverage consumption							
Mean oz consumed/day±SE	*21.92 ± 4.15*		*22.34 ± 7.07*		*21.51 ± 3.19*		*0.85*
Physical activity							0.95
None	15	25.00%	8	26.67%	7	23.33%	
Mean minutes/week±SE	*111.64 ± 14.61*		*107.89 ± 15.89*		*115.78 ± 24.82*		*0.44*
Body mass index (BMI)							
Obese (BMI ≥30)	29	48.33%	11	36.67%	18	60.00%	0.07
Mean ± SE	*29.94 ± 0.94*		*29.17 ± 1.16*		*31.33 ± 1.34*		*0.23*
History of diagnosed:							
Diabetes	9	15.00%	4	13.33%	5	16.67%	0.72
Hypertension	19	31.67%	8	26.67%	11	36.67%	0.41
High cholesterol	35	58.33%	19	63.33%	16	53.33%	0.43
Depression	23	38.33%	13	43.33%	10	33.33%	0.43
Anxiety	17	28.33%	9	30.00%	8	26.67%	0.77
Number of cardiometabolic AD risk factors* *Mean ± SE*	*1.83 ± 0.16*		*1.77 ± 0.23*		*1.90 ± 0.22*		*0.68*
Total number of major modifiable risk factors for AD** *Mean ± SE*	*2.82 ± 0.19*		*2.70 ± 0.29*		*2.93 ± 0.24*		*0.54*
Number of medications (regular use)[-t]							*0.71*
None	32	53.33%	16	53.33%	16	53.33%	
One	14	23.33%	6	20.00%	8	26.67%	
Two or more	14	23.33%	8	26.67%	6	20.00%	
History of hormone replacement therapy[-t-t]	19	37.25%	8	30.77%	11	44.00%	0.61

*Including diabetes, hypertension, high cholesterol, obesity (BMI ≥30), cardiovascular disease. **Also including history of depression or anxiety disorder, current smoking, and lack of physical activity. [-t]Including those commonly linked to memory changes: Statins, narcotic analgesics, steroids, benzodiazepines, beta blockers, antihistamines, anticonvulsants, tricyclic and other non-SSRI/SNRI antidepressants. [-t-t]Percentages calculated in women only.

Change in measures of memory and cognition over time

At 3 months, participants in both the KK and ML groups showed significant improvements relative to baseline in measures of both memory and cognitive functioning, including the MFQ total score (p's ≤ 0.004), the DSST (p's ≤ 0.04), and the TMT-A and B (p's ≤ 0.05); changes in the MFQ included improvements in three of the four subscales as well (Table 3). In addition, the percentage of participants scoring in the at-risk range on the TMT-B declined significantly over time (p's ≤ 0.02); of the 24 participants with low TMT-B scores at baseline, only 7 (2 KK, 5 ML) remained in the at-risk range at 6 months. As indicated in Table 3, overall effect sizes varied from small (DSST) to large (MFQ, TMT-B). These improvements were maintained or

Table 2
Participant baseline scores on memory and cognitive function tests and average reported duration of memory concerns

	KK (N = 30) *Mean (SE)*	ML (N = 30) *Mean (SE)*	*P*
Memory Functioning Questionnaire			
Total (range 64–448)	241.83 (9.92)	253.43 (10.07)	0.31
Frequency of Forgetting (range 33–231)	138.50 (5.43)	146.77 (5.26)	0.28
Seriousness of Forgetting (range 18–126)	64.83 (3.83)	73.87 (4.30)	0.15
Retrospective Memory Functioning (range 5–35)	11.70 (0.63)	11.64 (0.62)	0.82
Mnemonic Use (range 9–56)	21.92 (1.60)	21.48 (1.92)	0.35
90 Second Digit Symbol Substitution Test	50.57 (1.74)	50.20 (1.83)	0.89
Trail-making Test (TMT)			
TMT-A	33.76 (1.08)	34.63 (2.18)	0.73
TMT-B	85.54 (7.14)	90.59 (7.64)	0.53
TMT-B ≥88 seconds: N (%)	13 (43.33%)	12 (40.00%)	0.79
Months Experiencing Memory Problems (range 5 to 180 months, median = 24 months)	36.30 ± 7.08	34.18 ± 4.47	0.80

further strengthened at 3-months post-intervention, with participants in both groups showing significant improvements relative to baseline in all measures of cognitive performance (p's ≤ 0.006), as well as overall memory functioning and two MFQ subscales (Frequency of Forgetfulness and Retrospective Memory Functioning) (p's ≤ 0.006). There were no significant between-group differences in measures of memory or cognition at either 3 or 6 months (p's > 0.1). Similarly, the two groups did not differ in reported concerns regarding their memory at the completion of the 6-month study; 57% of participants assigned to the KK group versus 54% of those in the ML program indicated they were less or much less concerned about their memory than when they started.

Repeated ITT analyses yielded similar results. Findings were not modified by gender, age, obesity, history of depression/anxiety, number of AD risk factors, or baseline performance on memory or cognition tests. Neither excluding those who had changed medications, nor adjusting for medication change in the models appreciably altered the findings. Improvements in the DSST at 3-months post-intervention were significantly related to practice adherence ($r = 0.3$, $p < 0.03$), an association that was more pronounced in the KK than the ML group ($r = 0.5$, $p < 0.005$ versus 0.1, $p = 0.3$, respectively). Adherence was not significantly associated with other measures of memory or cognition, although associations were in the expected direction.

Relationships between change over time in both subjective and performance-based measures are given in Table 4. Reduced memory concerns at 6 months were strongly related to certain improvements in the MFQ at both time points, including the Frequency of Forgetfulness at 3 months ($r = 0.5$, $p < 0.001$), and, at 6 months, the MFQ total score ($r = 0.5$, $p < 0.001$) and two subscales (Frequency of Forgetfulness ($r = 0.5$ and Seriousness of Forgetting, $r = 0.4$, p's < 0.01). Regarding the relation of the MFQ to cognitive performance measures, improvements in the MFQ were significantly related only to those in the DSST at 3 months ($r = 0.3$, $p \leq 0.05$ for the MFQ total at 3 months and 6 months). In contrast, reported memory concerns at study conclusion were not related to scores on objective performance-based measures at any time point (p's > 0.1). Beneficial changes in DSST scores at 6 months were significantly associated with improvement in TMTA scores at both 3 months and 6 months ($r = 0.3$, $p = 0.02$ and $r = 0.4$, $p = 0.009$, respectively). Additional adjustment for age and education did not appreciably alter these findings.

DISCUSSION

In this RCT of adults with SCD, both the KK and ML groups showed significant improvements in subjective measures of memory function and objective measures of attention, processing speed, and executive function at 3 months, with effect sizes primarily in the moderate to large range. These gains were sustained or further strengthened at 3-months post-intervention, with participants in both groups showing significant improvements relative to baseline in all measures of cognitive performance, as well as in multiple domains of memory functioning. At study completion, over 55% of participants reported a reduction in memory concerns relative to baseline, a factor linked to significantly increased risk for accelerated cognitive decline and conversion to MCI and AD [3, 10, 61].

Table 3
Change over time in memory and cognitive functioning in older adults with subjective cognitive decline randomized to a 12 week Kirtan Kriya meditation program or a 12-week music listening program

Outcome Measures*	Change from Baseline (KK Meditation)						Change from Baseline (Music Listening)					
	3 months (Mean ± SE)	*p*	ES	6 months (Mean ± SE)	*p*	ES	3 months (Mean ± SE)	*P*	ES	6 months (Mean ± SE)	*p*	ES
Perceived Memory Function												
Memory Functioning Questionnaire												
Total	29.35 (8.44)	0.002	0.8	29.84 (7.82)	0.0008	0.7	25.71 (8.18)	0.004	0.5	31.67 (10.65)	0.006	0.7
Frequency of Forgetfulness	22.62 (5.68)	0.001	0.8	25.24 (5.60)	0.00003	1.0	14.07 (4.86)	0.007	0.5	17.59 (5.84)	0.006	0.6
Seriousness of Forgetting	6.81 (3.08)	0.04	0.4	3.42 (3.28)	0.31	0.2	9.32 (3.44)	0.01	0.4	7.26 (4.75)	0.14	0.3
Retrospective Memory Functioning	1.92 (0.65)	0.006	0.6	3.42 (0.67)	0.00003	1.0	2.57 (1.02)	0.02	0.8	4.22 (0.87)	0.00005	1.2
Mnemonic Use	–2.00 (0.14)	0.22	–0.2	–1.50 (1.07)	0.17	0.2	–0.25 (1.55)	0.87	0.0	2.59 (1.31)	0.06	0.3
Executive Function, Information Processing/ Psychomotor Speed, Attention, Working Memory												
Digit Symbol Substitution Test	2.08 (0.97)	0.04	0.2	5.15 (0.92)	0.000008	0.6	3.07 (0.94)	0.003	0.3	4.48 (0.93)	0.00006	0.4
Trail-making Test[-t]												
TMT-A	–2.84 (1.78)	0.05	0.3	–6.32 (1.64)	0.0008	0.8	–5.00 (2.31)	0.04	0.5	–5.93 (1.90)	0.004	0.7
TMT-B	–13.62 (6.27)	0.04	0.7	–21.35 (6.05)	0.00165	1.0	–19.43 (6.06)	0.003	0.9	–22.30 (5.93)	0.001	1.0
% Change in no. of participants with poor TMT-B scores[-t]	–46.8%	0.005		–82.3%	0.004		–46.4%	0.02		–53.7%	0.008	
Memory Concerns at 6 Months (%)[-t-t]				(%)						(%)		
More concerned				0.00%						7.69%		
Same amount of concern				43.48%						38.46%		
Less/Much less concerned				56.52%						53.85%		

*No significant between group differences at 3 or 6 months (p's > 0.05); [-t] Baseline score ≥88 seconds; [-t-t]Calculated from participant responses to the 5-point Likert scale question 'How concerned are you about your memory compared to when you began the study?'; ES, effect size; SE, Standard error.

Table 4
Correlations between change over time in measures of subjective memory function (MFQ, reported memory concerns at 6 months) and performance based measures of cognition (TMT-A, TMT-B, and DSST)

Change from Baseline	Change over time at 3 months								Change over time at 6 months								
	MFQ Total	MFQ Retro Mem	MFQ Forget	MFQ Seriousness	MFQ Mnemonic	TMT-A	TMT-B	DSST	MFQ Total	MFQ Retro Mem	MFQ Forget	MFQ Seriousness	MFQ Mnemonic	TMT-A	TMT-B	DSST	Memory concerns
At 3 months																	
MFQ																	
Total MFQ		0.48^{++}	0.72^{++}	0.78^{++}	0.37^{+}			0.27*	0.69^{++}	0.31^{**}	0.72^{++}	0.42^{**}	0.28*				
Retrospective Memory	0.48^{++}		0.31*	0.31*					0.36**	0.38**	0.31*	0.27*					
Freq Forgetfulness	0.72^{++}	0.31*		0.46^{++}				0.24(*)	0.91^{++}	0.35*	1.00^{++}	0.56^{++}					0.50^{++}
Seriousness of Forgetting	0.78^{++}	0.31*	0.46^{++}		0.25(*)				0.49^{++}	0.23(*)	0.45^{+}	0.42**					
Mnemonic use	0.37^{+}			0.25(*)									0.63^{++}				
TMT-A																–0.32*	
TMT-B															0.59^{++}		
DSST	0.27*	*0.24(*)*							0.33*	0.25(*)	0.25 (*)	0.31*				0.48^{++}	
At 6 months																	
MFQ																	
Total MFQ	0.69^{++}	0.36^{**}	0.91^{++}	0.49^{++}				0.29*		0.44^{++}	0.91^{++}	0.83^{++}	0.31*				0.47^{++}
Retrospective Memory	0.31^{**}	0.38**	0.35*	0.23(*)					0.44^{++}		0.35**	0.27 (*)					
Freq Forgetfulness	0.72^{++}	0.31*	1.00^{++}	0.45^{+}					0.91^{++}	0.35**		0.56^{++}					0.51^{++}
Seriousness of Forgetting	0.42**	0.27*	0.56^{++}	0.42**				0.22*	0.83^{++}	0.27 (*)	0.56^{++}						0.40**
Mnemonic use	0.28*				0.63^{++}				0.31*								
TMT-A																–0.36**	
TMT-B							0.59^{++}					0.23(*)					
DSST						–0.33*		0.48^{++}						–0.36**			
Memory concerns at 6 months			0.50^{++}						0.47^{++}		0.51^{++}	0.40**					

(*) $p<0.1$, $^{*}P<0.05$, $^{**}p<0.01$, $^{+}p<0.001$, $^{++}P<0.0001$. Abbreviations: DSST = Digit Symbol Substitution Test; Freq = frequency; MFQ = Memory Functioning Questionnaire; TMT = Trail-making Test.

To our knowledge, this is the first RCT designed to examine the effects of mind-body practices on memory and cognitive functioning in adults with SCD, and among the first to evaluate the possible benefits of any behavioral or lifestyle intervention in this population [62, 63]. Gains observed in this study are similar to or greater than those reported with conventional exercise [64, 65], tai chi [64, 66], cognitive training [67, 68], and multicomponent interventions [62, 69, 70] in older adults with and without cognitive impairment, including trials of physical activity and other programs of nine months or longer duration [64, 65, 67–70]. While studies regarding the effects of meditation or music listening on indices of cognition in populations with or at risk for cognitive impairment remain few [33, 36, 71], our findings are broadly consistent with those of a recent RCT of meditation in Chinese elders with sleep impairment [72]; pilot studies of KK meditation in depressed dementia caregivers [47], adults with memory loss [46], and caregiver-AD patient dyads [45]; and two RCTs of music-based interventions in Finnish and Taiwanese dementia patients [44, 73] including a study of adults with early dementia and their caregivers [44] that incorporated music listening at home. In contrast, other controlled trials of mindfulness meditation in generally healthy elders [74–76], MCI patients [77], dementia caregivers [78], and nursing home residents [79]; of therapist-delivered music programs in psychiatric inpatients with cognitive impairment [80] and Italian elders with memory loss [81]; and of passive music listening in Taiwanese AD patients [82] showed little or no improvement in cognitive indices. Reasons for the more limited effects of mindfulness, relative to those observed with KK, remain unclear. The apparent disparities in findings could reflect several factors including differences in target populations [74, 75], as well as in participant compliance [74, 75]. For example, in studies of cognitively and psychologically healthy populations [74, 75], ceiling effects may have hampered investigators' ability to detect improvements. Reduced participant adherence to practice, perhaps in part due to the higher time demands of the intervention, may also have contributed [45, 83], potentially helping to explain the attenuation of benefits over time observed in some studies [75, 84]. In addition, the inconsistency in findings may in part relate to the more active, multimodal nature of KK practice, which, as discussed briefly below, may further contribute to gains in cognitive functioning.

We found significant, although modest associations between changes in the MFQ, a measure of subjective memory loss, and both concomitant and prior improvement in the DSST, a performance-based measure of psychomotor speed, attention, and working memory. These findings support the validity of the MFQ, and suggest that reduction in memory concerns may in part reflect objective improvements in certain domains of cognition. While studies examining the relation between change over time in subjective and objective measures of cognition are sparse, our findings are consistent with those of some, but not all cross-sectional studies [85]; the former include a recent investigation in healthy elders, which reported a significant correlation between the MFQ and DSST [86]. Notably, associations have been stronger in better educated and non-depressed adults, and with measures of cognitive domains most affected in early stages of AD [85].

High practice adherence diminished our ability to detect effects of practice frequency on improvements in memory and cognitive functioning. However, we nonetheless noted significant correlations between mean practice frequency and improvement in the DSST, suggesting a possible dose-response relationship between practice and improvement in this objective measure of cognitive function.

Possible mechanisms of action

While mechanisms underlying the observed cognitive improvements with KK and ML are not yet well understood, these practices likely strengthen cognitive functioning via multiple pathways, as discussed in our companion paper regarding the effects of KK and ML on the psychosocial outcomes of this RCT [87]. For example, meditation and ML may improve cognitive function by reducing the neuropsychiatric impairment that commonly accompanies SCD, and which has been strongly linked to increased risk for subsequent cognitive decline, neurodegenerative changes, and progression to MCI and dementia [4, 5, 36, 88–90], a relationship that is likely bidirectional. As documented in our previous paper we observed significant, sustained improvements in mood, stress, sleep, well-being, and quality of life (mental health component) that were particularly pronounced in the KK group [87]. Positive changes in psychosocial status were directly correlated with gains in memory function, and, albeit more modestly, cognitive performance, suggesting a possible functional connection [87]. That gains in cognition were

comparable between groups despite greater improvements in psychosocial status with KK suggests that ML may improve cognitive function via other pathways, including those delineated below.

Meditation and ML may also improve cognition by promoting beneficial functional and structural changes in brain structures associated with cognitive processing, attention, memory, emotional regulation, and reward [31, 44, 91–94]. For example, emerging evidence suggests that both meditation and ML can induce favorable changes in central nervous system dopaminergic and other neurochemical systems [95, 96] and enhance autonomic regulation, in part by modulating activation of the sympathoadrenal system and HPA axis [30, 31, 36]. In addition, recent controlled trials of ML and meditation, including exploratory studies of KK [46, 97], suggest these practices can modulate activity, increase grey matter volume and/or density, and promote functional connectivity in multiple brain areas compromised in AD, including the hippocampus, prefrontal cortex, insula, amygdala, orbitofrontal cortex, and anterior cingulate gyrus [30, 31, 37, 38, 44, 46, 92, 94, 97–104].

Recent cross-sectional [105] and prospective studies [47, 105, 106] also suggest that meditation may protect against the deleterious effects of stress-induced cellular senescence on immune and neuronal function by promoting telomere maintenance, a factor implicated in cognitive decline and the development of MCI and dementia [107–109]. Similarly, recent pilot trials offer preliminary evidence that meditation [110–116] and music interventions [117, 118], including simple music listening [118] might also attenuate or reverse harmful alterations in specific gene expression pathways implicated in AD pathogenesis, including those regulating cellular aging, inflammation, oxidative stress, and other factors contributing to neuropathological changes and cognitive decline [119–125].

Meditation and ML may also influence cognitive function indirectly by promoting reductions in systemic inflammation, thought to play an important role in cognitive decline and AD pathogenesis [126]. Elevated systemic inflammation has been linked to both telomere degradation [127–129] and cerebral volume loss [126]. Similarly, longitudinal studies have consistently shown high blood levels of proinflammatory biomarkers, including interleukin-6, tumor necrosis factor-alpha, and high sensitivity C-reactive protein, to predict cognitive decline [126]. Elevated inflammatory markers are also strongly associated, in a bidirectional manner, to chronic psychological stress, mood disturbance, sleep loss, and other distressful states [130–136]. While studies remain sparse, and trials in adults with memory loss are lacking, emerging evidence from healthy [137–139] and stressed adults [140], lonely older adults [110], and cancer patients [141] suggests that meditation [140] and ML may reduce systemic inflammation.

Strengths and limitations

Strengths of this investigation include the rigorous study design and measurement of both subjective and objective cognitive performance. Participants were recruited from the community, potentially enhancing generalizability and applicability of our findings. Additional strengths include the excellent adherence and retention rates in both groups. Collection of data on treatment expectancy also allowed adjustment for potential placebo effects. In addition, both KK and ML have been shown to have positive effects on a range of health and psychosocial outcomes strongly related to cognitive functioning and predictive of cognitive decline [33, 36, 142, 143]. The two interventions were also well matched in terms of structure, delivery, and practice time, reducing potential bias related to differential dosing, staff attention, ease of access, social interaction, or other factors.

Our use of a questionnaire to ascertain presence of SCD that incorporated criteria based on prior expert reviews and longitudinal studies and including worries regarding one's memory problems, a factor shown to strengthen the link of SCD to incident MCI and AD [3, 6, 10, 61], aided in capturing those at risk for cognitive decline. Our participants were characterized by high prevalence of established AD risk factors, as well as mean MFQ baseline scores that were similar to those of persons with amnestic MCI [144], and considerably lower than values reported in community-based samples [145]. In addition, in over 40% of participants, TMT-B scores at baseline were in the range associated with a high risk for accelerated cognitive decline and progression to MCI and dementia [55, 56].

This preliminary trial has several limitations as well. Our study sample size was relatively small, and our study population comprised relatively young, well-educated, motivated volunteers with SCD, potentially restricting generalizability to other populations with preclinical memory loss. While we assessed memory and cognitive function, we did not conduct diagnostic evaluation of cognitive status in

our study sample; it is thus possible that participants included some individuals with undiagnosed MCI. In addition, we lacked information on brain or CSF biomarkers of AD, and were thus unable to assess the effects of KK or ML on these potential mechanisms of action, to evaluate the modifying influence of these factors, or to examine the relation of these biomarkers to memory and cognitive function.

Possible practice effects may have accounted for some of the improvement, although the relatively long interval between assessments renders this possibility less likely. As noted above, several trials of both meditation and other non-pharmacologic interventions, including RCTs in adults at risk for cognitive decline, noted little change in cognition. For example, several studies of conventional exercise [146–148], tai chi [149], and meditation-based programs [47, 74, 75] in healthy seniors [74, 146], senior facility residents [148], depressed dementia caregivers [47], and elders with or at risk for memory loss [147, 149] showed little or no change over time in the TMT among participants in the control group, with some noting worsening over time in this measure [75, 146, 147, 149]; several trials likewise reported minimal or no change even among participants assigned to the active intervention [74, 75, 147–149]. By contrast, we observed marked and significant improvement in multiple domains of memory and cognition, including the TMT. Nonetheless, given that we did not include a standard care control group, the possibility of practice effects cannot be ruled out. In addition, blinded treatment administration was not possible in this study, potentially biasing expectations of participants and raising the possibility of placebo effects. However, the expectancy scores of the two groups were similar and, most importantly, unrelated to either subjective memory function or objective cognitive performance, suggesting that expectations of treatment and associated placebo effects are unlikely to explain our findings.

Those with a history of anxiety or depression or currently taking medication for these disorders were not excluded from participation, which could in part explain the perceived declines in memory function in some participants. However, in this study, history of depression was unrelated to baseline cognitive scores; we also found no evidence for either a confounding or modifying effect of current antidepressant medication use or history of depression, suggesting these factors did not influence our findings. In addition, both depression and anxiety are strongly predictive of subsequent cognitive decline and dementia in formerly cognitively intact adults [90, 150, 151], arguing that depressed adults represent an at-risk group that should not be excluded from clinical trials of interventions designed to improve cognitive function [87]. In fact, at least two scales of AD risk for non-demented adults include depression [152].

Conclusions

Findings of this pilot RCT suggest that a simple program of daily KK meditation or ML can significantly enhance both subjective memory function and objective cognitive performance in older adults with SCD, with benefits sustained or improved at 6 months. Our success in enrolling participants with SCD, coupled with the excellent retention and adherence rates, and significant improvements observed, suggest that preclinical memory loss may represent an ideal target for therapeutic intervention in adults at risk for AD. Additional rigorous trials are needed to further evaluate the possible benefits of KK and ML for adults with preclinical memory loss, to ascertain the long term effects of these practices on cognitive health, and to explore potential mechanisms of action.

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