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A randomized controlled trial of Kundalini yoga in mild cognitive impairment

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ABSTRACT

Background: Global population aging will result in increasing rates of cognitive decline and dementia. Thus, effective, low-cost, and low side-effect interventions for the treatment and prevention of cognitive decline are urgently needed. Our study is the first to investigate the effects of Kundalini yoga (KY) training on mild cognitive impairment (MCI).

Methods: Older participants (≥55 years of age) with MCI were randomized to either a 12-week KY intervention or memory enhancement training (MET; gold-standard, active control). Cognitive (i.e. memory and executive functioning) and mood (i.e. depression, apathy, and resilience) assessments were administered at baseline, 12 weeks and 24 weeks.

Results: At baseline, 81 participants had no significant baseline group differences in clinical or demographic characteristics. At 12 weeks and 24 weeks, both KY and MET groups showed significant improvement in memory; however, only KY showed significant improvement in executive functioning. Only the KY group showed significant improvement in depressive symptoms and resilience at week 12.

Conclusion: KY group showed short- and long-term improvements in executive functioning as compared to MET, and broader effects on depressed mood and resilience. This observation should be confirmed in future clinical trials of yoga intervention for treatment and prevention of cognitive decline (NCT01983930).

Key words: Kundalini yoga, Kirtan Kriya, memory enhancement training, cognition, mild cognitive impairment, mood, resilience

Introduction

Global population is aging rapidly with the estimated rise to over 2 billion people age ≥60 years by 2050 (UN, 2013) – this will logically lead to increasing rates of cognitive decline. Current data suggest that mild cognitive impairment (MCI) ranges between 10% and 20% in samples of older adults (Petersen, 2004). MCI may lead to more serious cognitive issues, including Alzheimer's disease and related dementias' (Petersen, 2004). Thus, innovative and cost-effective treatments are urgently needed for treatment and prevention of cognitive decline, and these types of interventions would be useful if they have practical benefits, including minimal invasiveness, low dependency, and low-risk of interactions with prescription medications.

Mind–body practices including yoga and meditation are increasingly shown to be effective for the treatment of age-related cognitive issues (Lavretsky, 2009). For example, a recent study by Gothe *et al.* (2014) compared the effects of a yoga intervention versus a stretching–strengthening program over eight weeks in 118 community-dwelling older

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adults, and found significantly improved cognition (i.e. executive function, working memory and efficiency of mental-set shifting, and flexibility) for the yoga group participants compared with the control group. Several reviews of yoga and meditation studies in both healthy and clinical samples, expert meditators and novices, using neural and other physiological measures, suggest that engagement in mind–body practices (including Mindfulness Based Stress Reduction, Vipassana, Kundalini yoga (KY), and Tai Chi) result in improved cognitive function, as well as mood and stress (Lavretsky, 2009; Shahidi *et al.*, 2011; Abbott and Lavretsky, 2013). However, many of these studies did not apply rigorous randomized controlled trial (RCT) design.

One type of meditation from a standard KY practice, Kirtan Kriya (KK), has been studied previously in older adults and caregivers (Black *et al.*, 2013; Lavretsky *et al.*, 2013; Khalsa, 2015; Innes *et al.*, 2016a; 2016b). This yoga practice has existed for hundreds of years. KK was used as a homework exercise and includes chanting the mantra sounds, Saa Taa Naa Maa along with repetitive finger movements, or mudras, and visualizations (mudras). KK is designed to be balancing and uplifting. The sounds come from the mantra "Sat Nam," which means "my true essence." This secular practice can be adapted to several lengths (e.g. for 11 or 32 minutes). It has been shown to be effective in increasing cognitive and emotional functioning (e.g. less depression, anxiety and stress, and improved mood, sleep, cognition, attention, memory, and resiliency) in dementia caregivers and individuals with cognitive impairment (Black *et al.*, 2013; Lavretsky *et al.*, 2013). Our recent pilot study demonstrated similar response to KY and memory enhancement training (MET) with respect to improved mood and cognition, with some differences in changes in brain connectivity associated with performance on verbal memory tests (Eyre *et al.*, 2016).

The inclusion of a gold standard intervention for cognitive training is important to compare with mind–body interventions. MET is considered a "gold-standard" technique for enhancing cognitive functioning. The goal of MET is to optimize cognitive functioning to support individuals with life functioning and quality of life (Flak *et al.*, 2014). There is evidence suggesting that MET promotes significant improvements in cognitive performance, memory, and quality of life in studies with healthy, older, and individuals with cognitive issues (Jean *et al.*, 2010; Simon *et al.*, 2012). Thus, MET provides a rigorous control for KY meditation and may shed light on the specific benefits afforded by each practice, especially related to memory and cognitive functioning. To our knowledge, yoga has never been compared to MET in a direct head-to-head comparative clinical trial.

This study is the first RCT to investigate the effects of KY training on MCI. Participants were randomized to either a 12-week KY intervention or MET (gold-standard, active control). Cognitive (i.e. memory and executive functioning) and mood (i.e. depression, apathy, and resilience) assessments were administered at baseline, 12 weeks and 24 weeks post-intervention. We hypothesized that (1) both KY and MET would result in improved memory, but KY would result in broader improvements in both memory and executive function, mood, and resilience compared to MET at 12 weeks; and (2) KY intervention will result in sustained improvement in cognition, mood, and resilience compared to MET at 24 weeks.

Methods

Study procedures

All participants were recruited via advertisements from UCLA outpatient clinics and the UCLA Longevity Center Program, and from the community to participate in the "Memory Training Versus Yogic Meditation Training in Older Adults with Subjective Memory Complaints and MCI" study at UCLA from 2013 to 2015 (NCT01983930). This study was approved by the UCLA Institutional Review Board. All participants underwent IRB-approved informed consent procedures prior to enrolling in the study.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) age ≥ 55 years; (2) subjective memory complaints; (3) Clinical Dementia Rating (CDR) scale score of 0.5 (Hughes *et al.*, 1982); (4) sufficient English proficiency at the 8th grade level or higher as determined by the word reading subtest of the Wide Range Achievement Test-4 (Wilkinson, 2006) to participate in MET; (5) capacity to provide informed consent.

Exclusion criteria included the following: (1) current or past Axis I psychiatric disorders, or recent unstable medical or neurological disorders; (2) any disabilities preventing participation in the MET or KY conditions (e.g. severe visual or hearing impairment); (3) insufficient English proficiency; (4) a diagnosis of dementia per the DSM-5; (5) Mini Mental Health Examination (Folstein *et al.*, 1975) score of 24 or below; (6) use of psychoactive medications; (7) participation in a psychotherapy that involves cognitive training;

and (8) participants with prior or current training in yoga.

Screening procedures

At baseline, participants underwent a screen including the following: (1) an interview by a trained study staff to identify physical and cognitive symptoms; (2) a standard battery of hematologic studies; (3) neurological examination (i.e. the Unified Parkinsons Disease Rating Scale (Fahn, 1987); (4) select memory tests (i.e. the Fluid Object Memory Evaluation (Fuld *et al.*, 1990); and (5) a neuropsychiatric evaluation (Structured Clinical Interview for DSM Disorders) (First *et al.*, February 1996); (6) medical comorbidity was assessed with the Cerebrovascular Risk Factor Prediction Chart (Truelsen *et al.*, 1994); the Cumulative Illness Rating Scale-Geriatric (Fahn, 1987; American Heart Association, 1990; Miller *et al.*, 1992; Endicott *et al.*, 1993; Ware *et al.*, 1994); (7) mood assessments included the Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1982).

Outcome measures

Participants were assessed at screening and baseline (pre-treatment) and at 12 weeks (post-treatment), and re-assessed at 24-week follow-up. The above-mentioned mood measures and adverse events were assessed every 2 weeks for the first 12 weeks of the study, and then monthly until 24-week follow-up. At baseline (pre-intervention), participants were administered an extensive test battery assessing demographic, cognitive, and clinical variables. The same battery of tests was repeated at 12 and 24 week post-intervention.

Primary outcome measures were cognitive and included memory and executive functioning. Verbal memory was measured with the following: (1) the Hopkins Verbal Learning Test (HVLT) (total and delayed recall scores) (Shapiro *et al.*, 1999), (2) the Wechsler Memory Scale (WMS-IV). Visual-spatial skills and visual memory were assessed using the Rey Osterrieth (Rey-O) test 3- (immediate) and 30-minute (delayed) recall (Shin *et al.*, 2006). Individual executive functions were assessed using (1) the Trail Making Test part B (Reitan, 1958) to measure cognitive flexibility, (2) the Stroop Word-Color Test (Golden, 1975) to assess response inhibition and the Animal Naming Test (Sager *et al.*, 2006) as a measure of semantic fluency.

Secondary outcomes measures included mood assessments with the GDS (Yesavage *et al.*, 1982), a self-assessment scale often used in geriatric depression trials. We also measured commonly present symptoms of apathy or amotivation by using the Apathy Evaluation Scale (AES) (Marin *et al.*, 1991). Psychological resilience to stress as a target for the mind–body interventions was measured by using the Connor-Davidson Resilience scale (Connor and Davidson, 2003).

Side effects were monitored at each visit using the UKU Side Effect Rating Scale (Lingjaerde *et al.*, 1987). Anticipation of the outcomes was assessed at baseline on the Likert scale of 1–10 (range 1 (dissatisfied) to 10 (completely satisfied), and satisfaction with the outcomes was also assessed on the scale of 1–10 (range 1 (dissatisfied) to 10 (completely satisfied), at weeks 6 and 12. In addition, number of classes attended was monitored for each participant.

Randomization and blinding procedures

After all baseline test results were reviewed and eligibility criteria were confirmed, participants were randomized to either MET or KY groups using a computer-generated random assignment scheme, which assigns participants in a 1:1 ratio to each group in the blocks of 8–10 subjects. All groups were called "wellness and mental stimulation" groups. All behavioral raters, the principal investigator, all statisticians and data managers were blind to the group assignment, and participants were asked not to disclose their group assignment to the raters. No unblinding occurred in the process of assessment.

Yoga training program

The KY group engaged in a 60-minute KY class per week, and a daily 12-minute KK meditation and homework assignment. Each 60-minute KY was conducted by the same instructor and followed the following structure: (1) tuning in (5 minutes); (2) warm up (12 minutes); (3) breath techniques "Pranayama" (12 minutes); (4) KK (12 minutes); (5) meditation (15 minutes); (6) rest "Shavasana" and closing (min). Standardized handouts and CDs were given to participants for their 12-minute home practice of KK meditation, which includes repetitive finger movements (or mudras), as well as chanting of the mantra "Saa, Taa, Naa, Maa," meaning "Birth, Life, Death, and Rebirth," first chanted aloud, then in a whisper, and silently for the total of 11 minutes followed by a final 1 minute of deep breathing relaxation accompanied by the visualization of light.

Memory enhancement training program

MET was developed by researchers within the UCLA Longevity Center. It involves a scripted curriculum for trainers and a companion workbook for participants. The standard detailed protocol for the MET program is based on evidence-based techniques that use verbal and visual association strategies and practical strategies for memory (Verhaeghen *et al.*, 1992; Gross and Rebok, 2011). MET is manualized and includes several components, including the following: (1) education about memory; (2) pre-training for memory strategies (i.e. "pre-training"); (3) instruction in specific memory strategies; (4) home practice with logs to track activity; (5) addressing non-cognitive factors, such as self-confidence, anxiety, and negative expectations; and (6) small (i.e. about 10 persons) group sessions. Each weekly session is organized in the same way; trainers (1) document the number of participants attending the session, collect homework completion logs and assess engagement in alternative treatments; (2) review the previous session's homework to reinforce techniques; (3) teach new techniques, reviews, and conduct in-class exercises; and (4) assign homework. Participants were expected to spend about 20 minutes on homework per day and document in their daily diaries. Each session is devoted to learning and practicing techniques, and 15 minutes are reserved for reviewing homework. Specific techniques taught include the following: visual associative strategies for learning faces and names (adapted from McCarty (1980)); verbal associative techniques (such as the use of stories) to remember lists; organizational strategies (categorizing items on a grocery list); learning memory habits to recall where one places items, what one has done in the recent past (e.g. locking doors, turning off appliances); and how to remember future tasks (i.e. appointments).

Statistical analyses

All data were entered into the database at the time of their collection and analyzed after completion of the trial. Patients in the treatment groups were compared using t-tests (for continuous variables) or χ^2 tests (for categorical variables) on all demographic and clinical measures at baseline to assess the success of the randomization procedures. Completers and dropouts in the two groups were compared using t-tests or χ^2 tests. All the outcome measures of interest are continuous and were analyzed using a mixed effects general linear model, as implemented in SAS PROC MIXED. The model included treatment group as the between-subject factor, time as the within-subject factor, and the interaction term between time and treatment group as a predictor. Age, sex, and education were used as covariates. *Post hoc* analyses determined the significance of specific pair-wise group differences and within-group changes. Effect sizes (ES; Cohen's d) for all outcome measures over time were estimated. The level of significance for outcomes was set at the α level of $p < 0.05$, two-tailed. We did not employ any correction procedures for multiple comparisons, since (1) all the analyses were hypothesis driven and (2) this is the first study comparing KY and MET to examine these measures – we are reporting the results of all analyses and conclusions are based on the pattern of results. This approach thus permits the discovery of important features of the study findings without the reduction of power that would result from correction.

Results

The CONSORT diagram for the study is shown in Figure 1. After screening 168 participants and in-person diagnostic testing, 85 individuals met criteria for in-person screening and 81 were enrolled into the study, with 79 individuals receiving the allocated intervention.

Table 1 shows the demographic characteristics of the two groups. There were 38 participants (25 women) in the KY group and 41 in the MET group (27 women). The groups did not differ by age, ethnicity, years of education, or BMI. The groups differed significantly in the performance on the Trails B time ($t = -1.98$, $df = 69$, $p = 0.05$) and the Stroop Word-Color ($t = 1.98$, $df = 69$, $p = 0.05$) tests. Baseline scores were used as covariates in all analyses.

At the end of the 12-week intervention, nine participants had dropped out from each of the two groups. Drop-out rate did not differ by group allocation. One participant in the yoga group discontinued due to dizziness. No other side effects occurred. We determined that completers and drop-outs in the two groups did not differ significantly in any of the baseline characteristics, except for educational level in the MET group. Completers in the MET group were significantly more educated (17.3 (3.5)) compared to dropouts (15.0 (1.5); $p = 0.02$). The groups did not differ on the number of classes attended (KY: 7.13 (4.35) vs. MET: 7.14 (4.18); $p = 1.0$). Further, satisfaction scores (Week 6 scores: KY: 8.3 (1.3) vs. MET 7.9 (2.3); $p = 0.4$; Week 12 scores: KY: 8.4 (1.8) vs. MET 7.8 (1.8); $p = 0.3$), and anticipation scores (Week 6 scores: KY: 7.9 (1.4) vs. MET 7.7 (2.4); $p = 0.7$; Week 12 scores: KY: 8.5 (1.9) vs. MET 7.8 (1.9); $p = 0.2$) also did not differ between the groups.

Analysis of change in memory over time

There were no between-group differences in memory changes with time; however, there were

Table 1. Demographic characteristics at baseline for KY and MET groups

VARIABLE	KY GROUP (N = 38)	MET GROUP (N = 41)	STATISTICS $t(77)/\chi^2$ (1)	P-VALUE
Sex				
Female	25 (65.8%)	27 (65.9%)	0.00	1
Male	13 (34.2%)	14 (34.1%)		
Race				
Caucasian	24 (63.2%)	30 (73.2%)	0.90	03
Non-Caucasian	14 (36.8%)	11 (26.8%)		
Age (years)	68.1 (8.7)	67.6 (8.0)	0.29	08
Education (years)	17.4 (3.4)	16.7 (3.3)	0.92	04
BMI	26.7 (4.9)	25.1 (4.7)	1.40	02

Figures indicate mean with standard deviation (SD) for the continuous and N (%) for the categorical variables; t(77) are presented for the continuous and χ^2 (1) for categorical measures.
MET = memory enhancement training; KY = Kundalini yoga.

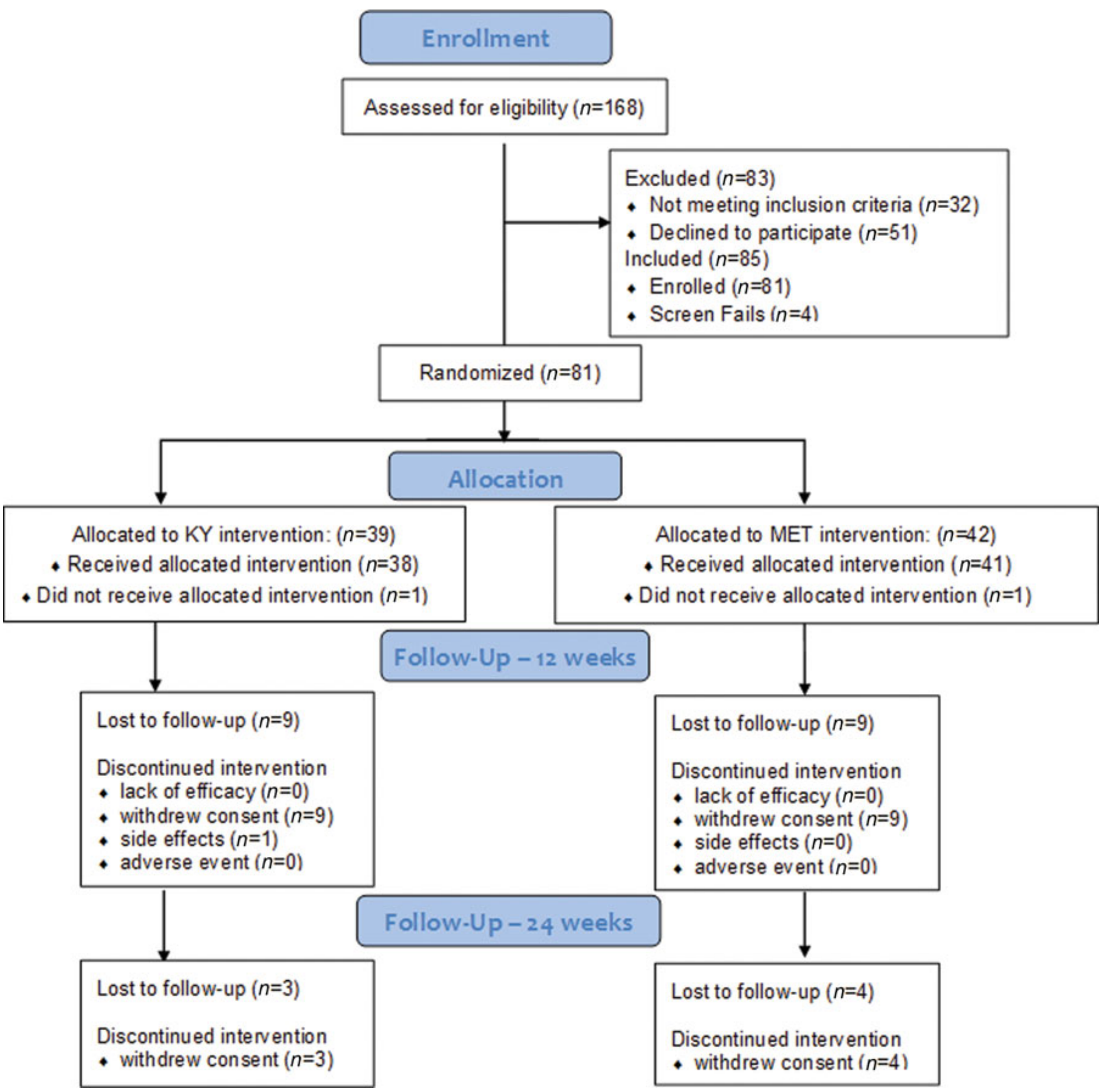

Figure 1. (Colour online) CONSORT flow diagram.

Table 2. Cognitive measures in the Kundalini yoga and memory enhancement groups

Measures	KY group Baseline mean (SD)	KY group 12-weeks mean (SD)	KY group 24-weeks mean (SD)	KY within-group analysis 12-weeks baseline t, df = 74 (p-value), ES*	KY within-group analysis 24 weeks-baseline t, df = 74 (p-value), ES*
Memory					
HVLT total	25.76 (6.20)	27.14 (6.75)	28.81 (6.52)	1.53 (0.13), 0.28	2.75 (0.01), 0.54
HVLT delayed	9.03 (2.70)	9.48 (1.86)	9.73 (2.22)	1.30 (0.20), 0.24	1.54 (0.13), 0.30
WMS Imm recall	17.19 (9.53)	22.28 (8.15)	23.35 (7.81)	5.21 (<0.0001), 0.95	5.00 (<0.0001), 0.98
WMS delayed recall	5.22 (2.88)	6.72 (1.85)	7.58 (4.30)	5.24 (<0.0001), 0.96	3.32 (0.001), 0.65
Rey-O 3-min	16.01 (5.93)	18.90 (6.85)	18.77 (8.48)	2.96 (0.004), 0.54	1.98 (0.05), 0.39
Rey-O 30-min	16.71 (6.36)	19.10 (7.65)	20.31 (7.11)	2.64 (0.01), 0.48	3.81 (0.0003), 0.75
Executive function					
Trails B (sec)	112.26 (60.09)	96.28 (41.25)	89.45 (40.39)	– 2.52 (0.01), −0.46	– 3.80 (0.0003), −0.75
Stroop Word-Color	37.41 (11.62)	42.90 (12.02)	43.12 (12.99)	3.88 (0.0002), 0.71	3.06 (0.003), 0.60
Animals	18.79 (5.05)	20.69 (4.83)	21.15 (4.98)	2.26 (0.03), 0.41	2.75 (0.01), 0.54

Measures	MET group Baseline mean (SD)	MET group 12-Weeks mean (SD)	MET group 24-Weeks mean (SD)	MET within-group analysis	
Memory					
HVLT total	26.02 (5.42)	28.90 (4.19)	27.96 (5.44)	2.94 (0.004), 0.54	1.74 (0.09), 0.35
HVLT delayed	8.93 (2.26)	9.93 (2.08)	9.60 (2.74)	2.54 (0.01), 0.46	1.82 (0.07), 0.36
WMS Imm recall	18.27 (7.90)	24.00 (6.49)	24.72 (5.62)	5.82 (<0.0001), 1.06	5.59 (<0.0001), 1.18
WMS delayed recall	6.27 (2.39)	7.27 (1.17)	7.36 (1.47)	3.22 (0.002), 0.59	1.68 (0.10), 0.34
Rey-O 3-min	16.80 (5.29)	21.22 (6.76)	22.63 (7.19)	3.92 (0.0002), 0.72	4.12 (0.0001), 0.82
Rey-O 30-min	16.69 (5.34)	20.88 (7.38)	23.60 (6.92)	3.53 (0.001), 0.64	6.50 (<0.0001), 0.76
Executive function					
Trails B (sec)	89.25 (35.74)	89.89 (34.17)	83.99 (29.77)	0.15 (0.88), 0.03	– 1.35 (0.18), −0.27
Stroop Word-Color	43.22 (13.02)	44.30 (11.67)	42.92 (14.46)	0.73 (0.46), 0.13	0.00 (1.0), 0.00
Animals	19.95 (4.09)	20.17 (5.02)	20.19 (5.18)	0.48 (0.63), 0.09	0.96 (0.34), 0.19

HVLT Total = Hopkins Verbal Learning Test Total Recall; HVLT Delayed = Hopkins Verbal Learning Test Delayed Recall; WMS Imm recall = Wechsler Memory Scale-III Verbal Paired Associate test Immediate Recall; WMS Delayed recall = Wechsler Memory Scale-III Verbal Paired Associate test Delayed Recall; Rey-O = Rey-Osterrieth complex figure test; Trails B = Trail Making Test B; KY = Kundalini yoga.
*ES = estimated effect size (Cohen's d).

several significant within-group changes for both KY and MET (see Table 2). At 12 weeks, both the KY and MET groups showed significant within-group improvements in immediate and delayed recall verbal memory (WMS Logical Memory; ES (KY) = 0.95, 0.96; ES (MET) = 1.06, 0.59) and visual memory (Rey-O; ES (KY) = 0.54, 0.48; ES (MET) = 0.64, 0.72). Only the MET group showed significant improvement in verbal memory (HVLT; ES (MET) = 0.54, 0.46). The change in HVLT scores over time is shown in Figure 2.

At 24 weeks, significant within-group improvements were noted for both the KY and MET groups in WMS Logical Memory immediate recall (ES (KY) = 0.98; ES (MET) = 1.18) and on the Rey-O 3-minute (ES (KY) = 0.39; ES (MET) = 0.82) and 30-minute visual memory (ES (KY) = 0.75; ES (MET) = 0.76). However, only the KY group showed sustained significant

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Table 3. Mood measures in the KY and MET groups

MEASURES	KY GROUP BASELINE MEAN (SD)	12-WEEKS MEAN (SD)	24-WEEKS MEAN (SD)	KY WITHIN-GROUP ANALYSIS 12-WEEKS BASELINE t, df = 74 (p-VALUE), ES	24 WEEKS-BASELINE t, df = 74 (p-VALUE), ES
GDS	7.70 (6.57)	4.48 (4.66)	5.23 (5.47)	− 3.37 (0.001), −0.62	− 2.73 (0.01), −0.54
AES	43.89 (7.98)	48.41 (6.80)	46.69 (6.72)	2.84 (0.01), 0.52	1.76 (0.08), 0.35
CDRISC	75.08 (13.66)	78.41 (10.56)	78.12 (10.51)	2.18 (0.03), 0.40	1.49 (0.14), 0.29
MEASURES	MET GROUP BASELINE MEAN (SD)	12-WEEKS MEAN (SD)	24-WEEKS MEAN (SD)	MET WITHIN-GROUP ANALYSIS	
GDS	6.51 (5.28)	4.53 (3.51)	4.60 (4.18)	− 1.60 (0.11), −0.30	− 0.91 (0.36), 0.18
AES	42.17 (6.54)	49.93 (8.98)	49.50 (11.11)	4.90 (<0.0001), 0.89	4.34 (<0.0001), 0.87
CDRISC	72.29 (14.38)	74.1 (14.90)	72.84 (13.36)	1.03 (0.31), 0.19	0.08 (0.93), 0.02

GDS = geriatric depression scale; AES = apathy evaluation scale; CDRISC = Connor–Davidson resilience scale; KY = Kundalini yoga.

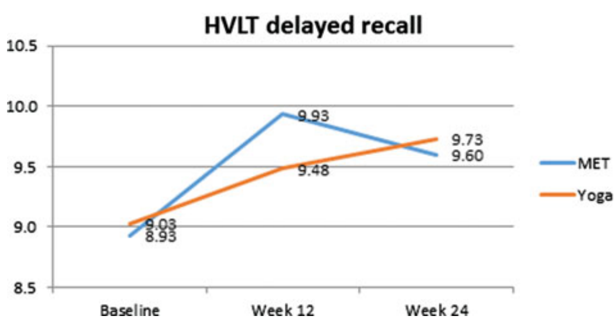

Figure 2. (Colour online) HVLT delayed recall scores in Kundalini yoga and memory enhancement training.

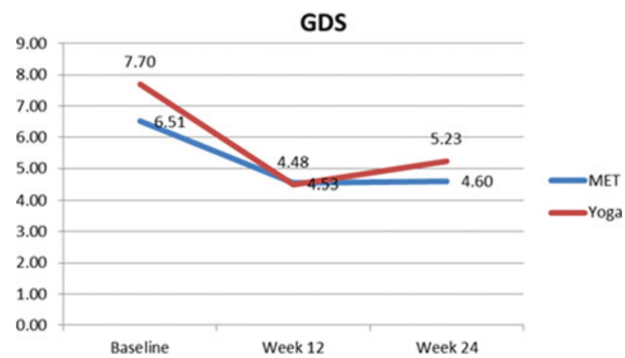

Figure 3. (Colour online) GDS scores in Kundalini yoga and memory enhancement training.

improvements on other measures, including WMS Logical Memory delayed recall (ES (KY) = 0.65) and HVLT total (ES (KY) = 0.54).

Analysis of change in executive functioning over time

The two intervention groups differed significantly ($F(2,74) = 3.24$, $p = 0.04$) in their change in Trails B scores both at 12 weeks ($t(74) = 2.27$, $p = 0.03$; effect size, ES= −0.46) and at 24 weeks ($t(74) = 2.16$, $p = 0.03$; ES = −0.75) follow-up post-intervention, favoring the KY group. While change in no other executive functioning scores reached significance for the between-group comparisons, there were several significant within group changes for KY, as shown in Table 2.

Only the KY group showed significant improvement in Stroop Word-Color Task (ES (KY) = 0.71), Trails B (ES (KY)= −0.46) and Animals (ES (KY) = 0.41)) at week 12. Further, only the KY group showed sustained significant improvements on Stroop Color-Word (ES (KY) = 0.60), Trails B (ES (KY) = −0.75) and Animal Naming (ES (KY) = 0.54) at 24 weeks.

Analysis of mood, apathy, and resilience over time

Significant within-group improvements were obtained for both the KY and MET groups in apathy (AES: ES (KY) = 0.52; ES (MET) = 0.89) at 12 weeks. Only the KY group showed significant improvements in depression ratings (GDS: ES (KY) = −0.62) and resilience (CDRISC: ES (KY) = 0.40) at 12 weeks. At 24-weeks post-intervention, the MET group showed sustained significant improvement in apathy (ES (MET) = 0.87), and the KY group showed sustained significant improvement in depression (ES (KY) = −0.54). No between-group comparisons reached statistical significance. Changes in GDS and CD-RISC scores over time are seen in Figures 3 and 4 and Table 3.

Discussion

This is the first RCT to explore the effects of KY in comparison to MET in an MCI cohort.

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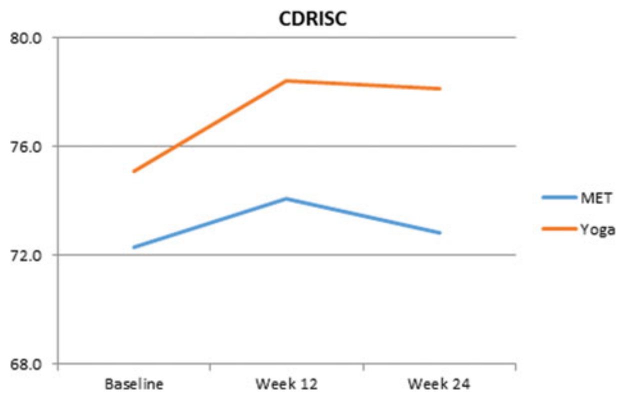

Figure 4. (Colour online) CD-RISC scores in Kundalini yoga and memory enhancement training.

In summary, the study found that KY had similar effects of memory, with additional beneficial effects on executive functioning and mood symptoms. These findings were consistent with our hypotheses.

There is a relative dearth of studies examining yoga and its effects on memory enhancement (Marciniak *et al.*, 2014). We are not aware of previous studies exploring KY yoga in MCI patients. One main study of which we are aware explores the effects of yoga and exercise in 135 healthy men and women aged 65–85 years (Oken *et al.*, 2006). In this study, participants were exposed to 6 months of Hatha yoga classes, walking classes, or wait-list control; participants were screened with a variety of mood and cognition tests (e.g. Stroop test). Interestingly, after the intervention, there were no effects from either of the active interventions on any of the cognitive and alertness outcome measures. The yoga intervention produced improvements in physical measures (e.g. timed 1-legged standing, forward flexibility), as well as a number of quality-of-life measures related to sense of well-being and energy and fatigue compared to controls. Interesting, a previous pilot study on KK meditation demonstrated activation of the brain areas associated with attention and exclusive functions (frontal area, cingulate cortex), which takes places during the meditation (Newberg *et al.*, 2010).

We explain the "brain-fitness" effects of KY on multiple domains and on executive functions by the multi-component training using KY classes, and encapsulated KK meditation. We attribute the cognitive improvement in memory and executive function to the "brain fitness effect" of the daily "mind exercise" with the use of the alternating components of the chanting mantra meditation (KK) with mudras and visualization that may strengthen specific verbal and visual skills, and enhance global awareness and attention, as well as weekly KY classes that also represent multi-component exercise with additional stress-reducing effect. This is consistent with the recent neural evidence showing that KY is associated with enhanced neural activity and structural changes in brain circuits associated with executive function (Marciniak *et al.*, 2014). These findings are also consistent with our recently published report documenting increased connectivity in the language network on fMRI in association with performance on verbal memory resulting from KY+KK intervention compared to MET control group (Eyre *et al.*, 2016). Collectively, results from the present study and previous neuroimaging studies published by our group suggest that KY can increase "brain fitness" with increased connectivity and improved cognitive performance on the tests of memory and executive function, along with improvement in mood, apathy, and psychological resilience, and these effects may be sustained over time, beyond those offered by MET.

Yoga interventions have shown promise in addressing depressive symptoms in older adults. Prior review of published RCTs of yoga for depression in adults revealed that while all trials found benefit trial methodologies have generally been weak with lack of blinding, short duration of the intervention, variable outcome measures, limited information about participants, randomization procedures, compliance, and dropout rates (Pilkington *et al.*, 2005). Comparative studies of yoga have likewise been limited, with one trial demonstrating that yoga may provide benefit as an augmentation strategy for antidepressant treatment (Janakiramaiah *et al.*, 2000). Yoga is commonly used in combination with other treatments for depression, anxiety, and stress-related disorders. Data on use of yoga for anxiety and depression in older adults are more limited; however, one significant study of 69 older adults in India did compare the impact of yoga to Ayurveda or a wait-list control condition on sleep and depressive symptoms (Krishnamurthy and Telles, 2007). Participants in the yoga group practiced physical postures, relaxation techniques, regulated breathing, devotional songs, and attended lectures for more than 7 h a week during the course of the 6-month trial. Practice of yoga significantly impacted quality of sleep and level of depressive symptoms when compared to the two control conditions, neither of which demonstrated significant effects. In particular, depressive symptoms, as measured by the short form of the *GDS*, decreased in the yoga group from a baseline average of 10.6–8.1 by 3 months and 6.7 by 6 months. The average time to fall asleep decreased in the yoga group by 10 minutes, while total number of hours

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slept increased by 60 minutes, and resulted in a greater feeling of being rested after 6 months. A recent study by Shahidi *et al.* (2011) compared the effectiveness of laughter yoga, group exercise therapy, and control in decreasing depression in older adult women (60–80 years). In this study, 70 depressed women were chosen if their GDS was >10. This study went for 10 sessions and found a significant improvement in depression score with both yoga and group exercise therapy as compared with control.

Overall, our pilot study provides novel and promising observations of cognitive benefits of yoga compared to the "gold standard" memory enhancement. However, because of its pilot nature, the study may not be powered to detect differences on multiple cognitive domains. Additionally, we do not have long-term follow-up, which means we are unable to explore cognitive decline toward dementia. A considerable number of eligible participants declined to participate, with the most cited reasons being logistic issues, such as the frequency of visits, and duration of the trial. However, a key point of our study was the high satisfaction with the intervention, which led to minimal dropout once the participants were enrolled. We are not able to separate the difference in the impact of multiple components of the KY and KK practice. Future research may attempt to separate the components of KK meditation to examine which specific activity (chanting, hand mudras, and visualization of light) promotes the enhancements reported in the present study as well as previous studies. Moreover, future studies may also separate the weekly class component and the at-home daily meditation practice to examine the effects of social interaction, class engagement, and yoga exercises. It is also possible that some of the maintenance effects were due to homework practice of KY and MET. Thus, future research may aim to investigate maintenance effects beyond 6 months and with more thorough investigation of program adherence.

Conclusion

This is the first RCT to compare KY effects on cognition and mood compared to gold standard, active control MET, for individuals with MCI. Both groups demonstrated improvement in verbal and visual memory. The KY group showed broader effect on executive functioning, depressed mood, and resilience with greater and sustained improvement in mood, compared to MET. These encouraging effects of yoga intervention should be further addressed in future longitudinal clinical trials directed at prevention of cognitive decline that will integrate the use of biomarkers of treatment response to shed light on the underlying mechanisms of response to the interventions.

Conflict of interest

None.

Description of authors' roles

HY, NSC, HL, LE, KVD were all involved in the collection of data. HE, HY, AL, PP, NSC, PS, KN, BB, DK, BA, LE, KVD, and HL were all involved in the analysis of data, interpretation, drafting and completion of the manuscript. All authors approved the final manuscript.

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Impact of Yoga Versus Memory Enhancement Training on Hippocampal Connectivity in Older Women at Risk for Alzheimer's Disease

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Abstract.
Background: Yoga may be an ideal early intervention for those with modifiable risk factors for Alzheimer's disease (AD) development.
Objective: To examine the effects of Kundalini yoga (KY) training versus memory enhancement training (MET) on the resting-state connectivity of hippocampal subregions in women with subjective memory decline and cardiovascular risk factors for AD.
Methods: Participants comprised women with subjective memory decline and cardiovascular risk factors who participated in a parent randomized controlled trial (NCT03503669) of 12-weeks of KY versus MET and completed pre- and post-intervention resting-state magnetic resonance imaging scans (yoga: $n = 11$, age $= 61.45 \pm 6.58$ years; MET: $n = 11$, age $= 64.55 \pm 6.41$ years). Group differences in parcellated (Cole-anticevic atlas) hippocampal connectivity changes (post- minus pre-intervention) were evaluated by partial least squares analysis, controlling for age. Correlations between hippocampal connectivity and perceived stress and frequency of forgetting (assessed by questionnaires) were also evaluated.
Results: A left anterior hippocampal subregion assigned to the default mode network (DMN) in the Cole-anticevic atlas showed greater increases in connectivity with largely ventral visual stream regions with KY than with MET ($p < 0.001$), which showed associations with lower stress ($p < 0.05$). Several posterior hippocampal subregions assigned to sensory-based networks in the Cole-anticevic atlas showed greater increases in connectivity with regions largely in the DMN and frontoparietal network with MET than with KY ($p < 0.001$), which showed associations with lower frequency of forgetting ($p < 0.05$).

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Conclusion: KY training may better target stress-related hippocampal connectivity, whereas MET may better target hippocampal sensory-integration supporting better memory reliability, in women with subjective memory decline and cardiovascular risk factors.

Keywords: Alzheimer's disease, cardiovascular, hippocampus, memory, resting-state, yoga

INTRODUCTION

Early preventive interventions that focus on modifiable risk factors may delay the onset of the symptoms of Alzheimer's disease (AD), an irreversible neurodegenerative disease, in high-risk populations [1–3]. Known modifiable risk factors include cardiovascular factors such as obesity, high blood pressure, and high cholesterol; non-modifiable risk factors include female sex, *APOE* E4, and family history of cardiovascular disease [4–9]. Yoga has known beneficial effects on cardiovascular functioning, including blood pressure and cardiorespiratory fitness [10–12]. Additionally, neuroimaging studies suggest that yoga has neuroprotective effects. In particular, yoga training and regular practice show positive effects on the volume of the hippocampus, a region implicated in subjective memory decline and AD [13–19]. Furthermore, yoga has been shown to be safe and have positive effects on cognitive functioning in older individuals, including those with mild cognitive impairment or early-stage dementia [20–23]. Thus, yoga may be an ideal early intervention for those with modifiable risk factors for AD development.

Kundalini yoga (KY) is a form of yoga that combines movement and meditation, with a greater focus on breathing, mantra recitation, and mental visualization compared to that in other common yoga practices (e.g., hatha), which mostly focus on postures. This combination of greater focus on breathing and mental engagement with less and more gentle movement renders KY an ideal form of yoga for older adults. Kirtan Kriya (KK) is a brief yogic meditation in the KY tradition that has been shown to improve perceived stress, psychological well-being, quality of life, and mood in individuals with subjective cognitive decline [24]. We previously reported beneficial effects of KY combined with an at-home KK practice (KY+KK) on depression, resilience, and executive functioning in a randomized controlled trial (RCT) in older adults with mild cognitive impairment [25–27]. Further, our recent RCT of KY+KK versus memory enhancement training (MET) suggested a more robust neuroprotective effect on right hippocampal volume with KY+KK than with MET in older women with subjective memory decline and cardiovascular risk factors. As resting-state connectivity of the hippocampus may be more sensitive to cognitive changes than hippocampal volumes [13], an analysis of hippocampal resting-state connectivity may further elucidate the neuroprotective effects of KY+KK. Additionally, hippocampal subregions are differentially involved in memory functions [28]. Therefore, we investigated the effect of yoga (KY+KK) versus MET on parcellated hippocampal resting-state connectivity in women with subjective cognitive decline and cardiovascular risk factors for AD. We hypothesized greater increases in hippocampal connectivity with regions implicated in memory decline with KY+KK than with MET.

MATERIALS AND METHODS

Participants

Participants comprised women with subjective memory decline and cardiovascular risk factors who participated in a parent randomized controlled trial (RCT; NCT03503669) of yoga (KY+KK) versus MET. Among the 63 participants (yoga: $n = 26$; MET: $n = 37$) who completed the parent RCT, a subsample (yoga: $n = 11$, mean age ± standard deviation [SD] = 61.45 ± 6.58 years; MET: $n = 11$, mean age ± SD = 64.55 ± 6.41 years) completed resting-state magnetic resonance imaging (rsMRI) at baseline and 12 weeks of follow up (Table 1). Patients with a self-reported decline in memory function during the previous year, one or more cardiovascular risk factors, and sufficient English proficiency and mental capacity to provide informed consent and actively participate in the study were included. Cardiovascular risk factors included an atherosclerotic cardiovascular disease risk score within the 7.5th percentile on the Cerebrovascular Risk Factor Prediction Chart, atherosclerotic findings on hematologic testing, myocardial infarction (at least 6 months prior), diabetes, and current pharmacological treatment for

Table 1
Demographic and baseline clinical data

	Yoga ($n = 11$)	MET ($n = 11$)	p
Age (y)	62.0 (53–59)	64 (54–76)	0.26
Education (y)	16.0 (13–18)	16.0 (13–18)	0.73
Race, n (%)			
White	7 (64)	6 (55)	1.00†
Asian	3 (27)	2 (18)	
Black	0 (0)	2 (18)	
Hispanic	0 (0)	1 (9)	
Other	1 (9)	0 (0)	
Homework (d/wk)	4.8 (1.8–6.9)	5.0 (2.6–6.3)	0.89
Anxiety (HAMA)	4.5 (2–10)	4.0 (1–14)	0.52
Depression (BDI)	7.5 (1–16)	6.0 (3–21)	1.00
Frequency of forgetting (MFQ1)	4.25 (2.3–5.8)	4.75 (3.3–5.9)	0.22
Seriousness of forgetting (MFQ2)	3.6 (2.4–6.4)	4.1 (2.3–6.0)	0.29
Perceived stress (PSS)‡	22 (20–30)	21 (15–26)	0.75

Data are presented as median (range), unless otherwise indicated. p-values were determined by the Kruskal-Wallis test, unless otherwise indicated. †Fischer's exact test for white vs non-white. ‡One participant in the yoga group had missing PSS data. HAMA, Hamilton Anxiety Rating Scale; BDI, Beck Depression Inventory; MET, memory enhancement training; MFQ1, Memory Function Questionnaire Factor 1; MFQ2, Memory Function Questionnaire Factor 2; PSS, Perceived Stress Scale.

blood pressure or hyperlipidemia. Exclusion criteria were as follows: history of a psychiatric or neurological disorder; surgery within the 3 months prior; disabilities such as severe visual or hearing impairments; dementia; current participation in cognitive training in a therapeutic setting; current psychoactive medication use; prior experience with KY or KK; myocardial infarction within 6 months; and MRI-incompatible implants or other imaging contraindications.

The study was approved by the UCLA Institutional Review Board, and written informed consent was obtained from all participants.

Study design

The study methodology is depicted in Fig. 1. Participants were randomized (1:1) to undergo yoga (KY+KK) training or MET for 12 weeks. Classes (60 min/week) were held in person, in groups of 6–10 participants, and were supplemented by daily homework/practice assignments. Participants were required to attend at least 10 classes and not participant in any other mind-body practices. Adherence to at-home assignments was monitored by self-report at each class.

In the yoga group, classes were led by a certified KY instructor under the following protocol: tuning in (5 min); warm up (15 min); breathing techniques (i.e., Pranayama, 15 min); KK (12 min); final resting pose (i.e., Savasana, 10 min); and closing (3 min). In addition, participants received a CD with 12 min of KK for daily home practice. During KK, participants sat with their eyes closed and feet flat on the floor, visualized a beam of white light entering the center of the top of the head and exiting the middle of the forehead (i.e., the third eye), and chanted while touching the thumb of each hand to the other fingers sequentially as follows: "Saa" (i.e., birth; thumb to second finger), "Taa" (i.e., life; thumb to middle finger), "Naa" (i.e., death; thumb to ring finger), and "Maa" (i.e. rebirth; thumb to fifth finger). Five rounds were completed, with the

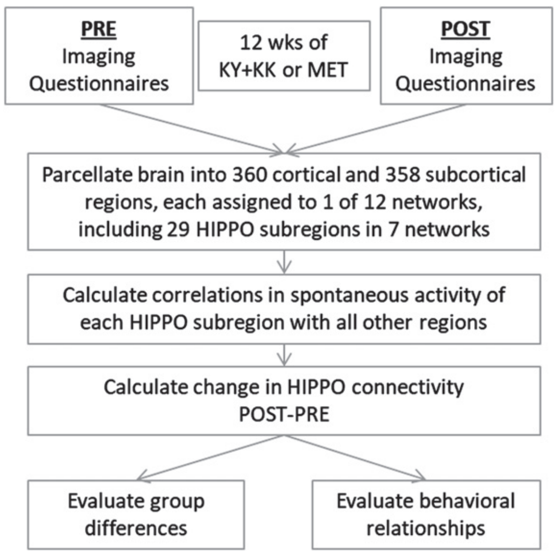

Fig. 1. Flowchart of the study methodology.

first and fifth chanted out loud, second and fourth whispered, and the third thought silently, followed by a 1-min closing comprising energetic integration and meditation.

In the MET group, classes were led by a qualified memory training instructor and focused on teaching memory strategies using a scripted curriculum and companion workbook developed by researchers at the UCLA Longevity Center. Each class included a review of completed homework (15 min), and an introduction to new techniques, review of previous techniques, and group exercises (45 min). Participants were instructed to spend approximately 20 min daily on assigned homework. Specific techniques taught in the MET group include verbal associative techniques to remember lists (e.g., building a story around a list), organizational strategies (e.g., categorizing items on a grocery list), visual associative strategies to remember faces and names (adapted from [29]), strategies for remembering where an item was placed and recent activities (e.g., locking doors), and strategies for remembering future tasks (e.g., appointments).

Additional details regarding the randomization and protocols can be found in our previous publication [19].

Questionnaires

Participants completed questionnaires, including the Perceived Stress Scale (PSS) [30], Memory Function Questionnaire (MFQ) [31], Hamilton Anxiety Rating Scale [32], and Beck Depression Inventory [33], pre-intervention and post-intervention (at baseline and the 3-month follow up, respectively). The MFQ assesses subjective memory functioning and includes 4 components. In the present study, we focused on the first factor, namely the frequency of forgetting (MFQ1), which has been shown to more robustly reflect AD pathology than other MFQ components [34]; higher scores indicate better functioning. The PSS is a 10-item questionnaire that assesses feelings of stress during the prior month; higher scores indicate more perceived stress.

Neuroimaging

MRI-eligible participants underwent scanning at baseline (pre-intervention) and the 3-month follow up (post-intervention). High-resolution T1-weighted (multi-echo MPRAGE) and T2-weighted MR images and resting-state BOLD images were collected using a Prisma-fit system (Siemens, Erlangen, Germany) with a 32-channel head coil. Multi-echo MPRAGE scans were acquired with the following parameters: isotropic 0.8-mm^3 voxels; 208 slices; TR: 2500 ms; TE: 1.81, 3.6, 5.39, and 7.18 ms; TI: 1000 ms; FOV: 256 mm; matrix size: 256×256 mm; and flip angle: 8 degrees. T2-weighted scans were acquired with the following parameters: isotropic 0.8-mm^3 voxels; 208 slices; TR: 3200 ms; TE: 564 ms; FOV: 256 mm; matrix size: 256×256 mm; and flip angle: 120 degrees. Resting-state scans (eyes open, with a fixation cross) were collected in both anterior-posterior and posterior-anterior directions (6.4 min each; total scan time, 12.8 min) with the following parameters: isotropic 2.0-mm^3 voxels; 72 slices; TR: 800 ms; TE: 37.0 ms; FOV: 208 mm; matrix size: 208×208 mm; and flip angle: 52 degrees. Fieldmaps were acquired in both anterior-posterior and posterior-anterior directions before resting-state scans.

Imaging data were pre-processed with the minimal Human Connectome Project (HCP) pipeline, including structural preprocessing of the T1-weighted and T2-weighted images by PreFreeSurfer, FreeSurfer, and PostFreeSurfer and functional preprocessing of the BOLD images by fMRIVolume and fMRISurface, followed by denoising using multi-run ICA-FIX [35–39].

Denoised and normalized resting-state images were parcellated according to the Cole-Anticevic Brain Network Parcellation (CAB-NP) atlas [40]. This atlas extends the HCPMMP atlas by including a fine-grained parcellation of subcortical regions. The CAB-NP atlas comprises 360 cortical and 358 subcortical parcels, with each parcel assigned to one of 12 major networks (specifically, the default mode network [DMN], auditory network [AN], frontoparietal network [FPN], language network, dorsal attention network, cingulo-opercular network, somatomotor network [SMN], posterior multimodal network [PMM], ventral multimodal network, primary visual network, and secondary visual network) [40]. The CAB-NP atlas includes 29 hippocampal parcels (17 and 12 in the left and right hemispheres, respectively), with 4 assigned to the DMN, 6 each assigned to the AN and SMN, 1 assigned to the FPN, 2 each assigned to the ventral multimodal and primary visual networks, and 8 assigned to the secondary visual network, which is consistent with the many roles of the hippocampus in

Table 2
Change in clinical scores

	Yoga		MET		p for group difference
	Change	p	Change	p	
HAMA	–3.10 (2.89)	**0.02**	0.0 (5.88)	0.99	0.06
BDI	–3.40 (4.12)	**0.02**	–1.27 (5.44)	0.60	0.20
MFQ1	0.73 (1.02)	0.06	0.003 (0.39)	0.98	0.20
MFQ2	0.51 (1.53)	0.32	–0.47 (1.08)	0.52	0.12
PSS	1.20 (9.74)	1.0	0.27 (4.92)	0.71	0.67

HAMA, Hamilton Anxiety Rating Scale; BDI, Beck Depression Inventory; MET, memory enhancement training; MFQ1 Memory Function Questionnaire Factor 1 (frequency of forgetting); MFQ2, Memory Function Questionnaire Factor 2 (seriousness of forgetting); PSS, Perceived Stress Scale.

learning and memory, spatial navigation, sensory integration, and emotion processing. For each participant, normalized (Fisher's z-transformed) pairwise correlations between each hippocampal parcel timeseries and the timeserieses of all remaining parcels were computed, creating 29 hippocampal subregion connectivity maps for each scan (pre- and post-intervention). The change in connectivity for each hippocampal subregion was calculated by subtracting the post-intervention map from pre-the intervention map.

Statistical analysis

Group differences in demographic and baseline clinical characteristics were evaluated using the non-parametric Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. Statistical analyses were performed using SPSS version 26 (IBM Corp. Albany, NY).

Group differences in hippocampal subregion connectivity changes with intervention were evaluated by non-rotated partial least squares analysis [41], implemented in Matlab using plscmd scripts, with and boot-strap estimation (5000 samples) (https://www.rotman-baycrest.on.ca). p-values <0.001 were considered significant.

To aid in the interpretation of the group difference, relationships between post-intervention hippocampal subregion connectivity and the MFQ1 and PSS were tested by Spearman partial correlational analysis across both groups (controlling for age) for those connections showing significance on the abovementioned partial least squares analysis. As one participant in the yoga group had missing MFQ/PSS post-intervention data, the correlational analysis was performed on 21 participants. p-values <0.05 were considered significant.

RESULTS

Demographic and clinical data

Baseline demographics and clinical data are summarized in Table 1. There were no significant differences between groups in baseline demographic and clinical characteristics. Additionally, there was no significant difference between groups in homework compliance (average number of days per week). As previously reported, while none of the changes in the clinical scores (BDI, HAMA, PSS, and MFQ1 MFQ2) were significantly different between groups, anxiety and depression scores improved significantly in the yoga group, but not in the MET group; changes in other scores did not reach significance (Table 2) [19].

Hippocampal subregion connectivity changes

Four hippocampal subregions showed significant differences in connectivity changes between the two groups ($p < 0.001$) (Fig. 2b). Specifically, an anterior hippocampal subregion assigned to the DMN (centered at –10 –8 –21) showed significantly greater connectivity increases with 12 brain regions, including visual system regions (right V2, V8, fusiform face complex, and V4t) and a posterior hippocampal subregion (centered at –23 –40 0), in the yoga group than in the MET group ($p < 0.001$; Fig. 3a).

In addition, one posterior hippocampal subregion assigned to the AN (centered at –25 –32 –12) and two posterior hippocampal assigned to the SMN (centered at –23 –40 0 and 21 –40 2) showed significantly greater connectivity increases with 13, 28, and 49 brain regions, respectively, in the MET group than in the yoga group ($p < 0.001$; Fig. 3b). These regions were concentrated in the DMN and FPN.

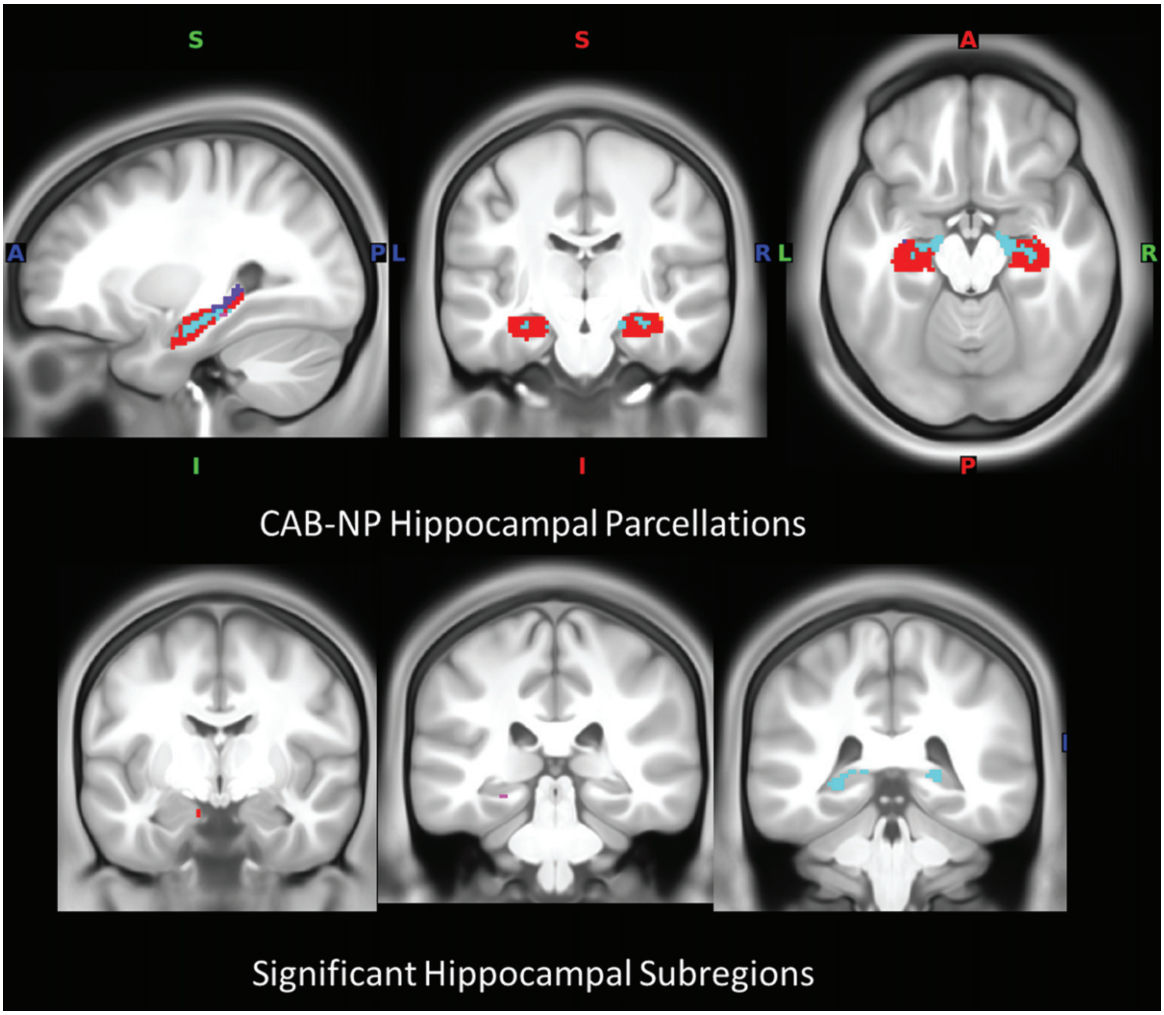

Fig. 2. Hippocampal subregions. a) Hippocampal parcellations in the CAB-NP atlas color-coded according to assigned network (note: not all parcellations are visible). b) Location of hippocampal subregions with significance in the connectivity analysis. Red, default mode network; magenta, auditory network; cyan, somatomotor network; blue, primary visual network; CAB-NP, Cole-Anticevic brain network parcellation.

Associations between post-intervention hippocampal subregion connectivity and perceived stress/memory functioning

Among the 12 connections showing greater increases in the yoga group than in the MET group, 3 (involving connectivity between the left anterior DMN hippocampal subregion and the right V8, medial temporal area, and V4t) were significantly and negatively correlated with the post-intervention PSS score ($p < 0.05$; Fig. 2a) There were no significant correlations with the post-intervention MFQ1 score.

Among the 90 connections showing greater increases in the MET group than in the yoga group, 15 were significantly and positively correlated with the post-intervention MFQ1 score (i.e., better functioning in terms of the frequency of forgetting), mainly involving connectivity between the right posterior hippocampal subregion assigned to the SMN and regions in the DMN ($p < 0.05$; Fig. 2b). There were no significant correlations with the post-intervention PSS score.

DISCUSSION

The present study found differential changes in the resting-state connectivity of hippocampal subregions under two training conditions, one directly targeting memory strategies (MET) and one combining yoga

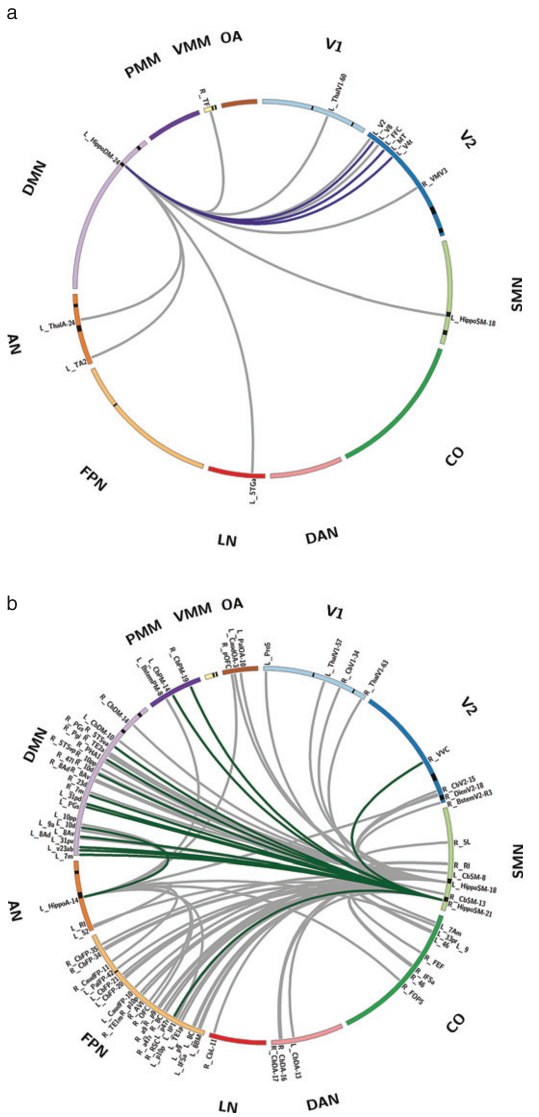

Fig. 3. Hippocampal subregion connectivity differentially impacted by KY+KK and MET intervention, and behavioral relationships. a) Hippocampal subregion connectivity showing a greater increase with KY+KK than with MET. b) Hippocampal subregion connectivity showing a greater increase with MET than with KY+KK. Lines between regions indicate a significant group difference in the change in connectivity (post-invervention – pre-intervention). Colored lines represent connections with a significant relationship to behavioral scores across both groups (dark purple, PSS; dark green, MFQ1). Hippocampal subregions are indicated by a black band in the ideogram, and the CAB-NP atlas name is shown for all significant connections. Significant connections are also listed in Supplementary Table 1. V1, primary visual; V2, secondary visual; CO, cingulo-opercular; DMN, default mode network; FPN, frontoparietal network; PMM, posterior multimodal; SMN, somatosensory network; DAN, dorsal attention network; OA, orbito-affective; VMM, ventral multimodal; LN, language network; AN, auditory network; CAB-NP, Cole-Anticevic brain network parcellation; KY+KK, Kundalini yoga combined with Kirtan Kriya; MFQ1, Memory Function Questionnaire Factor 1; PSS, Perceived Stress Scale.

classes and at-home yogic meditation (KY+KK), in women with subjective memory decline and cardiovascular risk factors. A fine-grained analysis was performed, using 29 hippocampal subregions assigned to 7 major resting-state networks in the CAB-NP atlas. While the yoga group showed greater connectivity increases involving an anterior hippocampal subregion assigned to the DMN, the MET group showed greater widespread connectivity increases involving posterior hippocampal subregions assigned to sensory-based networks; specifically, the SMN and AN. Further, connections more robustly impacted by yoga than by MET showed associations with lower perceived stress; specifically, greater connectivity between the anterior hippocampal subregion assigned to the DMN and regions in the visual system was associated with lower PSS scores. In contrast, connections more robustly impacted by MET than by yoga showed associations with better memory functioning; specifically, greater connectivity between the right posterior hippocampal subregion assigned to the SMN and regions mainly in the DMN was associated with higher MFQ1 scores (indicating less frequency of forgetting). These results partially support our hypothesis of greater hippocampal increases with memory-related regions with yoga than with MET, as discussed below.

Although the DMN is best known as involved in self-referential processing, including autobiographical processes, it is associated many functions such as semantic processing, mental simulation and future planning, and social cognition [42–46]. The core brain regions of the DMN traditionally comprise the medial prefrontal, posterior cingulate, and inferior parietal cortices, and hippocampus [47]. However, the CAP-NB atlas refines the subcortical contribution to the DMN, as well as other resting-state networks, based on multimodal information, assigning 4 of 29 hippocampal subregions to the DMN [40]. The DMN and hippocampus have both been implicated in cognitive decline and AD. For example, previous studies have shown that the severity of subjective memory AD progression severity is associated with decreased DMN functional connectivity, which may be preceded by reduced signal complexity in the DMN, especially in the hippocampus [13, 48–50]. Additionally, hippocampal volume reduction and hypoconnectivity are associated with subjective memory decline and AD [13, 14]. The two interventions may differentially address this hypoconnectivity and the course of memory decline.

KY+KK engages different senses simultaneously (visualization, vocalization, motor, and sensory stimulation), and the chanting component may modulate respiratory muscles, lung volume, and cardiovascular and autonomic nervous system functions [51]. Further, KK has been shown to improve perceived stress [24]. Consistent with this, KY+KK training preferentially increased connectivity of the anterior hippocampal subregion assigned to the DMN with visual system regions, including several stress-sensitive connections. Stress, particularly persistent stress, is known to impair hippocampal-dependent memory and spatial navigation functioning [52] and alters the functional modular organization of the brain towards less coupling between the hippocampus and visual (occipital) regions [53]. Additionally, decoupling between the DMN and visual system is associated with mind-wandering, which interferes with reading comprehension and memory for text [54, 55]. Further, hippocampal-fusiform coupling is important to memory consolidation of faces and recall performance [56, 57]. Thus, KY+KK training may better target hippocampal subregion connectivity impacted by stress, which may aid in processing information, including facial information, into memory. However, at the group level, there was no significant net change in the PSS score (Table 2). KY+KK may improve stress-impacted hippocampal connectivity in a subset of women with subjective memory decline and cardiovascular risk factors. Further studies with larger sample sizes are needed to characterize those who would benefit most from KY+KK.

KY+KK training also impacted anterior-posterior hippocampal subregion connectivity to a greater extent than MET. In a previous imaging study, lower resting-state connectivity between the anterior and posterior hippocampi was associated with a decline in episodic memory function over a period of 2 years [58]. As the anterior and posterior hippocampi differentially contribute to complementary memory functions (the anterior hippocampus is more related to encoding, response to novelty, and global information, while the posterior hippocampus is more related to retrieval and detailed information), greater connectivity between anterior and posterior hippocampi may create a more integrated representation of an event, improving memory for the event [58–61]. Thus, the observed greater increased connectivity between anterior and posterior hippocampal subregions with KY+KK training than with MET may suggest superior long-term neuroprotective benefits in terms of vulnerable hippocampal connections critical to episodic memory with KY+KK training. Further studies with longer follow up are needed.

The MET protocol was derived from evidence-based techniques that use verbal and visual association, as well as practical strategies for memory learning [62, 63]. We found more widespread connectivity increases with MET than with KY+KK training, which involved hippocampal subregions assigned to sensory-based networks (i.e., AN and SMN). The hippocampus must integrate information from different sensory modalities to adapt to the changing environment, as a component in its role in learning and memory [64]. The various mnemonic strategies in MET, including verbal, visual, and spatial associative techniques, generally aim to enhance multimodal sensory integration into memory processes. Thus, MET may show superiority to KY+KK in terms of hippocampal sensory-integration important to memory. Consistent with this, increased connectivity between the right posterior hippocampal subregion assigned to the SMN and 15 regions in the DMN, PMM, and FPN (involved in working memory and other cognitive functions) was significantly correlated with improvement in the MFQ1 score (i.e., reduction in the frequency of forgetting). However, at the group level, there was no significant net change in the MFQ1 score (Table 2). MET may improve hippocampal connectivity along with memory function in a subset of women with subjective memory decline and cardiovascular risk factors. Further studies with larger sample sizes are needed to characterize those who would benefit most from MET.

The present study has several limitations to acknowledge. The sample size was small because some patients who enrolled in the RCT were unable to participate in the neuroimaging component due to contraindications (e.g., implants); additionally, some participants dropped out of the parent study and did not complete follow-up scanning. While we used non-parametric statistical methods that are robust to smaller sample sizes, additional effects may have been masked by these sample-size limitations. Additionally, as a non-treatment/waiting-list group was not included in the study design, whether the observed connectivity changes differ from the naturalistic course is unclear. Future large-scale studies that include a placebo group/control arm are necessary to further clarify the beneficial effects of KY+KK and MET on hippocampal connectivity and memory.

Conclusions

KY+KK training may better target hippocampal subregion connectivity impacted by stress and associated with long-term episodic memory decline, whereas MET may better target hippocampal sensory-integration supporting better memory reliability, in women with subjective memory decline and cardiovascular risk factors. These results add to the literature on the benefits of yoga for brain health and further indicate yoga as a promising practice for older women with increased AD risk, especially those with greater perceived stress.

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CONFLICT OF INTEREST

Dharma S. Khalsa is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review.

All other authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article and/or its supplementary material.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-221159.

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