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Meditation's impact on default mode network and hippocampus in mild cognitive impairment: A pilot study

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HIGHLIGHTS

- We conducted a randomized trial of meditation for mild cognitive impairment (MCI).
- Meditation may increase functional connectivity in the default mode network in MCI.
- Mediation may reduce hippocampal volume atrophy in MCI.
- Meditation may have a positive impact on brain regions most related to dementia.
- Further research with larger sample sizes and longer-follow-up are needed.

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ABSTRACT

Those with high baseline stress levels are more likely to develop mild cognitive impairment (MCI) and Alzheimer's Disease (AD). While meditation may reduce stress and alter the hippocampus and default mode network (DMN), little is known about its impact in these populations. Our objective was to conduct a "proof of concept" trial to determine whether Mindfulness Based Stress Reduction (MBSR) would improve DMN connectivity and reduce hippocampal atrophy among adults with MCI. 14 adults with MCI were randomized to MBSR vs. usual care and underwent resting state fMRI at baseline and follow-up. Seed based functional connectivity was applied using posterior cingulate cortex as seed. Brain morphometry analyses were performed using FreeSurfer. The results showed that after the intervention, MBSR participants had increased functional connectivity between the posterior cingulate cortex and bilateral medial prefrontal cortex and left hippocampus compared to controls. In addition, MBSR participants had trends of less bilateral hippocampal volume atrophy than control participants. These preliminary results indicate that in adults with MCI, MBSR may have a positive impact on the regions of the brain most related to MCI and AD. Further research with larger sample sizes and longer-follow-up are needed to further investigate the results from this pilot study.

1. Introduction

Over 50% of those with mild cognitive impairment (MCI), a transitional state between normal aging and dementia, will develop dementia within five years [9]. Despite the clinical and public health significance of MCI, there are no known therapies preventing progression to dementia.

In older adults, high levels of perceived stress are associated with a higher risk of developing MCI and AD [33,34]. Meditation has been shown to decrease perceived stress, cortisol levels and improves well-being [11,22]. Mindfulness Based Stress Reduction

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's Disease; DMN, default mode network; MBSR, Mindfulness Based Stress Reduction; MPFC, medial prefrontal cortex; PCC, posterior cingulate; BIDMC, Beth Israel Deaconess Medical Center; ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subscale; MMSE, Mini-Mental Status Exam; CDR, Clinical Dementia Rating; ROI, region of interest.

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(MBSR) is a standardized, widely tested mind/body intervention (>100 published trials) that teaches mindfulness meditation and yoga [18]. Cross-sectional studies show meditators have more hippocampal gray matter concentration [15] and volumes [24] than controls and the hippocampus is selectively activated during meditation [23]. A recent longitudinal study showed that after MBSR, participants had increased hippocampal gray matter density compared to before [14]. The hippocampus, a critical site of episodic memory, progressively atrophies from normal aging to MCI to AD [12]. The default mode network (DMN), a set of brain regions that are more active at rest in the "default" state (e.g. medial prefrontal cortex [MPFC], posterior cingulate cortex [PCC], hippocampus, and lateral/inferior parietal cortex), may also be especially impacted by meditation [3,8,16,19,27]. The DMN involves the same areas affected by cerebral atrophy, reduced metabolism, and amyloid in early AD/MCI [4]. DMN connectivity may be a noninvasive biomarker useful for assessing an intervention's impact in adults with MCI [10].

Could meditation improve the functional connectivity of the DMN and reduce the rate of hippocampal atrophy in adults with MCI? In this context, we conducted a pilot randomized controlled trial in adults with MCI to test our hypotheses that MBSR would (1) increase regional functional connectivity in the areas of the DMN, specifically the MPFC, hippocampus, and PCC; (2) slow the rate of hippocampal atrophy.

2. Methods

2.1. Study population

We recruited 14 participants from 2010 to 2011 from Beth Israel Deaconess Medical Center's (BIDMC) Cognitive Neurology Unit. The study was approved by BIDMC's human subjects review board and registered with the NIH clinical trials database (Clinicaltrials.gov), NCT01605448. Inclusion criteria (based on the Alzheimer's Disease Neuroimaging Initiative criteria [1] and the research operational definition of MCI [12]): adults 55–90 years with MCI determined by a neurologist through history, physical, and neuropsychological testing (including Wechsler Memory scale IV, Mini-Mental Status Exam, Clinical Dementia Rating). Exclusion criteria: actively practicing meditation/yoga; any history of brain lesions or major head trauma.

2.2. Study design

This study was a prospective, randomized controlled pilot clinical trial with participants randomized 2:1 to either MBSR or usual care (and then offered MBSR at study conclusion). We randomized our participants 2:1 into the intervention and control, respectively, as we wanted to increase our experience with participants undergoing the active intervention. We used permuted block randomization with randomly varying block size to generate treatment assignment.

2.3. MBSR intervention

The class met weekly 8× for 2 h, plus one "mindfulness retreat day." Mindfulness, defined as non-judgmental moment to moment awareness, was cultivated through sitting and walking meditation, body scan, and mindful movement (yoga). Home practice (30 min/day) was encouraged with standard guided audio recordings.

2.4. fMRI acquisition and analyses

Participants underwent an fMRI at baseline and 8 weeks using a 3 T Siemens whole body scanner with echo-planar imaging capability using a 32-channel radio-frequency head coil at the Martinos Center for Biomedical Imaging at Massachusetts General Hospital. During the resting state fMRI scan, subjects were asked to keep their eyes open and look at a darkened screen for 6 min. The scan acquisition included 47 slices with thickness of 3 mm, TR 3000 ms, TE 30 ms, a 3 mm × 3 mm in-plane spatial resolution, and FoV 216 mm. T1 weighted MPRAGE type structural images were acquired using the following parameters: voxel size 1.2 mm × 1.2 mm × 1.2 mm, TR 2.2 s, TE 1.54 ms, flip angle 7 degrees, slices 144, field of view: 230.

2.5. Seed-based functional connectivity analyses

Seed based functional connectivity analysis was performed using methods employed in previous functional connectivity studies [17,21,28] using the fcfast script developed by Randy Buckner's group at Athinoula A. Martinos Center for Biomedical Imaging. (http://cnlwiki.pbworks.com/w/page/13165363/One%20Step%20Funcitonal%20Connectivity%20Analysis%20Script). The PCC (peak at 8–56 30 with 3 mm radius) was used as seed because of its importance in the DMN. Seed coordinates were used in a previous study on exercise training in older adults [29]. In brief, functional data were preprocessed to decrease image artifacts, between-slice timing differences, and to eliminate differences in odd/even slice intensity. Data were then spatially smoothed using a Gaussian kernel of 6 mm full-width at half-maximum and temporally filtered (0.009 Hz < f < 0.08 Hz). Several spurious or nonspecific sources of variance were removed by regression of the following variables: (1) six movement parameters computed by rigid body translation and rotation during preprocessing, (2) mean whole brain signal, (3) mean brain signal within the lateral ventricles, and (4) the mean signal within a deep white matter region of interest (ROI). Temporally shifted versions of these waveforms were also removed by inclusion of the first temporal derivatives in the linear model.

A functional connectivity analysis produced coefficients for each previously defined seed-voxel correlation using Pearson correlation analysis. Fisher's r-to-z transformation was used to convert correlation maps into z maps. Random effect models were applied for second level analysis. A two sample t-test on the pre- vs. post-differences between the MBSR and control groups (MBSR [pre–post] – control [pre–post]) was calculated to explore the difference between the two groups. Based on our hypothesis, we defined our a priori regions of interest (ROI) as the MPFC and hippocampus. An initial threshold of $p < 0.005$ was applied in data analysis. To correct for multiple comparisons, Monte Carlo simulations with the program AlphaSim program in AFNI were applied for the priori ROI using a template based on Anatomical Automatic Labeling tool box. The results showed that a voxel-wise threshold $p < 0.005$ with 29 voxels has a corrected threshold of $p < 0.05$ at the cluster level for priori ROIs. A threshold of $p < 0.005$ uncorrected and $p < 0.05$ corrected (family-wise error, FWE) at the cluster level was used for non-ROI.

2.6. MRI volumetric analyses

To explore the potential treatment effect on changes in brain structures, we compared the bilateral hippocampi volume change (in mm^3) between the two groups after the intervention compared to baseline. Data analysis were applied using freesurfer (http://surfer.nmr.mgh.harvard.edu/). We used the automated procedure for labeling different brain structures, and getting their

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