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Can Adults with Mild Cognitive Impairment Build Cognitive Reserve and Learn Mindfulness Meditation? Qualitative Theme Analyses from a Small Pilot Study

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Abstract.
Background/Objective: High levels of chronic stress negatively impact the hippocampus and are associated with increased incidence of mild cognitive impairment (MCI) and Alzheimer's disease. While mindfulness meditation may mitigate the effects of chronic stress, it is uncertain if adults with MCI have the capacity to learn mindfulness meditation.
Methods: 14 adults with MCI were randomized 2:1 to Mindfulness Based Stress Reduction (MBSR) or a wait-list control group. We conducted qualitative interviews with those who completed MBSR. Transcribed interviews were: a) coded using an emergent themes inductive approach informed by grounded theory; b) rated 0–10, with higher scores reflecting greater perceived benefit from, and understanding of, mindfulness meditation. Ratings were correlated with daily home practice times and baseline level of cognitive function.

[1]Cathy Kerr unexpectedly passed away prior to this publication. This work could not have been completed without her effort and inspiration, and this manuscript is published in her honor.

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Results: Seven themes emerged from the interviews: positive perceptions of class; development of mindfulness skills, including meta-cognition; importance of the group experience; enhanced well-being; shift in MCI perspective; decreased stress reactivity and increased relaxation; improvement in interpersonal skills. Ratings of perceived benefit and understanding ranged from 2–10 (mean = 7) and of 0–9.5 (mean = 6), respectively. Many participants experienced substantial benefit/understanding, some had moderate, and a few had minimal benefit/understanding. Understanding the key concepts of mindfulness was highly positively correlated with ≥20 minutes/day of home practice ($r = 0.90$) but not with baseline cognitive function ($r = 0.13$).
Conclusions: Most adults with MCI were able to learn mindfulness meditation and had improved MCI acceptance, self-efficacy, and social engagement. Cognitive reserve may be enhanced through a mindfulness meditation program even in patients with MCI.

Keywords: Alzheimer's disease, meditation, mild cognitive impairment, mindfulness, randomized clinical trial, yoga

INTRODUCTION

Up to 20% of adults with mild cognitive impairment (MCI) may progress to dementia each year [1]. Currently, no standard therapy exists to prevent or delay progression from MCI to Alzheimer's disease (AD). Such an intervention would have tremendous impact on patients, families, and the economic burden of the disease. While pharmacologic interventions have been unsuccessful, non-pharmacologic interventions, such as aerobic exercise, have demonstrated promise in improving cognition and increasing the volume of the hippocampus, the key brain region that preferentially atrophies in early AD [2–4]. The mechanism mediating these changes is not well-understood, but modifications in vascular disease burden and/or the stress-reducing component of exercise may play a role [5]. Chronic stress negatively impacts the hippocampus, and high levels of chronic stress are associated with an increased incidence of MCI and AD [6–8]. Adults who are prone to high levels of psychological distress (as determined by items from the neuroticism subscale of the Neo-Five Factor Inventory) are more likely to develop dementia [9]. Animal research demonstrates that high levels of cortisol (the "stress hormone") can damage the hippocampus [10], a key structure involved in memory processing that atrophies with AD. Thus, other stress-reducing interventions, such as meditation and yoga, might be helpful for adults with MCI.

Mindfulness based stress reduction (MBSR) is a widely tested and standardized eight-week mind-body intervention created by Dr. Jon Kabat-Zinn at the University of Massachusetts Medical School [11]. This course teaches mindfulness meditation and yoga, which have been shown to decrease perceived stress [12] and cortisol levels [13] and improve overall well-being [14]. Previous studies have shown that the hippocampus is selectively activated during meditation [15–17], and experienced meditators have larger volumes and gray matter concentration in their hippocampi compared to matched controls [18]. In addition, research has shown that an eight-week MBSR class may increase gray matter density in the hippocampi of adults [19]. MBSR is thus a stress-reducing intervention that impacts the hippocampus and could potentially interrupt the progression of MCI through these effects. The period of time when an individual has MCI is transient and offers a rare window of opportunity prior to the development of dementia; finding an intervention that could help patients at this point of time could be invaluable. Since adults with MCI still have brain plasticity [20], we hypothesized that adults with MCI would be able to learn and benefit from mindfulness meditation and yoga. If MBSR is determined to be helpful for adults with MCI, it could be easily used and recommended as a standardized intervention in the treatment of MCI.

We conducted a pilot randomized controlled trial of MBSR in adults with MCI to assess intervention feasibility, obtain preliminary data, and assess for trends on whether teaching mindfulness meditation to those with high susceptibility of developing dementia (e.g., those with MCI) could affect the progression to dementia and positively impact well-being. We previously reported data from this randomized pilot controlled pilot trial demonstrating that adults with MCI can safely participate in and adhere to a MBSR program [21]. Mean class attendance was 7.9 out of 9, and mean daily home practice was 26 ± 20 min. There were no adverse events reported related to the study protocol. There were trends for improvements on measures of cognition (Alzheimer Disease Assessment Scale Cognitive Subscale, ADAS-Cog) and well-being (i.e., Resilience Scale, Perceived Stress Scale, Quality of Life-Alzheimer's Disease, Herth Hope Index, and Life-Orientation Test-Revised). After the intervention, those who had participated in MBSR had trends of less bilateral hippocampal

volume atrophy and increased functional connectivity between the posterior cingulate cortex and bilateral medial prefrontal cortex and left hippocampus compared to controls [22]. These results suggest that MBSR may have a positive impact on the regions of the brain most related to MCI and AD. This pilot study was not powered to fully assess cognitive outcomes and changes in well-being.

We also conducted qualitative interviews of the nine individuals who completed the MBSR intervention to explore further areas not captured in our standardized assessments. Qualitative research is a powerful complement to quantitative methodology that allows researchers to explore complex phenomena to gain a better understanding of the meaning of findings [23, 24]. The recent burgeoning of the scientific exploration of mind-body interventions has led many researchers to use qualitative research to elucidate mechanisms and perceived benefits [25–28]. As these interventions are complex, qualitative methods can help researchers appreciate nuances that may be challenging to assess with current quantitative instruments. Analyses of the interviews from this study provide rich insights into participant perceptions and overall impressions about safety, feasibility, benefits and challenges of a mindfulness intervention in adults with MCI while also directly addressing this important question: do adults with MCI still have the capacity to build cognitive reserve through mindfulness meditation?

MATERIALS AND METHODS

Study population

We recruited 14 participants from Beth Israel Deaconess Medical Center's (BIDMC) Cognitive Neurology Unit from 2010-2011. We identified potential participants through online medical record review, screening of clinic appointment logs, direct physician referrals, and flyers. BIDMC human subjects review board approved this study and each participant signed written informed consent. This study was registered with the NIH clinical trials database (Clinicaltrials.gov, NCT01605448).

Participants

We based inclusion and exclusion criteria on the previously established research operational definition of MCI [29] and the entry criteria for the Alzheimer's Disease Neuroimaging Initiative (ADNI) [30]. Inclusion criteria were: adults 55–90 years old with MCI, determined by a neurologist through a neurological history/physical exam (R.E. Wells) and neuropsychological testing (J. Wolkin) and defined as: 1) memory complaint, corroborated by an informant; 2) abnormal cognitive function documented by neuropsychological test performance $\leq$1.5 standard deviation below normative controls (Wechsler Memory scale IV, Logical Memory subtest); 3) normal general cognitive function; 4) Mini-Mental Status Exam (MMSE) score of >24 of 30; 5) no/minimal impairment in activities of daily living; 6) not sufficiently impaired, cognitively or functionally, to meet the National Institute of Neurological and Communicative Disease and Stroke/Alzheimer's Disease and Related Disorders Association criteria for AD; 7) Clinical Dementia Rating (CDR) total score of 0.5, with at least 0.5 on memory subscale. Exclusion criteria were: any history of brain lesions or major head trauma (e.g., MRI/CT scan within 24 months without such); depression (Hamilton Depression Rating Scale score >12), actively practicing meditation/yoga or having taken a recent class; and inability to have an MRI (typical MRI exclusions applied).

Study design

Telephone screens were conducted using the Modified Telephone Interview for Cognitive Status (mTICS) [31], and those scoring 19–38 were then evaluated by a neurologist (R.E. Wells) in-person for inclusion. Participants were randomized 2:1 to either MBSR or usual care. Participants randomized to usual care were offered MBSR at the conclusion of the study (e.g., wait-list control group). The intervention was run over two cohorts. To generate treatment assignment, we used permuted block randomization with randomly varying block size.

Study visits occurred with each participant at baseline and at eight weeks. At both study visits, participants underwent a battery of neuropsychological measures of cognition and standardized well-being questionnaires. At the eight-week study visit, we performed semi-structured interviews with the participants randomized to MBSR to explore further areas not captured in our standardized quantitative measures. Participants were queried about their experiences with MBSR, such as positive and negative aspects, benefits, obstacles, expectations, and changes they experienced as a result of their participation. Participants were also asked to assess class logistics, safety, and whether they would recommend

the program to others (See the Supplementary Material for the full Interview Guide). A study investigator trained in qualitative interviewing techniques conducted the audiotaped interviews that were then transcribed verbatim.

MBSR intervention

The class was the standard MBSR program; no modifications for adults with MCI were made. Participants met as a group with the instructor (R. Wall) weekly for eight (two-hour) sessions, plus one "mindfulness retreat day" (approximately 6 hours) between sessions six and seven. Mindfulness (nonjudgmental moment-to-moment awareness) was cultivated through meditation, body scan (sequential attention to parts of the body), and mindful movement (bodily awareness during simple Hatha yoga postures). Chairs were provided for seated exercises; mats were provided for movement exercises. In addition to learning the mindfulness practice, participants were given the opportunity to share their experiences of the practice of mindfulness with others in the group. The instructor provided information about stress and stress relief. Participants were given readings and weekly assignments of ways to incorporate mindfulness into their daily lives so that routine activities could become a meditative practice (e.g., brushing teeth, taking a shower, washing dishes, etc.). Participants were all given the same standard guided audio recordings and encouraged to practice at home for 30 min per day at least five additional days per week. During the intervention, a member of the research team called each participant weekly to encourage class attendance, home practice, and to address any issues. Given the pilot nature of this study and the uncertainty of whether patients with MCI would be able to independently engage in the intervention, each MBSR participant was given the option of inviting a family member or close friend to the classes to facilitate full participation. Of the nine participants who completed the MBSR course, three had a friend/spouse join them for some of the classes. One spouse attended all classes, one spouse attended some of one class, and one friend came to a few classes. The classes were held at BIDMC.

Analyses

Participant baseline characteristics and results from the assessment of safety, feasibility, neuropsychological assessments, questionnaires, and fMRI data are reported elsewhere [21, 22]. The transcribed qualitative interviews were coded using an emergent themes inductive approach informed by grounded theory [32]. Two coders (R.E. Wells and M.L. Dossett) independently identified passages in the transcripts that represented common themes or content categories related to participant experiences with the MBSR intervention. An iterative process ensued over several meetings to discuss and resolve the major themes with the two coders and an expert in qualitative assessment (C.E. Kerr). The coders took individual notes that were reviewed collectively during this process. Once the final themes were determined, each interview was coded again for the presence/absence of each theme and key passages that reflected the themes were identified. The number of interviews coded with each theme was determined and labeled as "frequency." Data were analyzed and presented descriptively according to content categories. One final review of all the interviews was completed by one of the coders (R.E. Wells) to classify participants' responses to questions about class logistics of the MBSR program (e.g., challenges/dislikes, perspectives on class duration/frequency and safety, plans to continue practicing MBSR, and likelihood of recommending to others).

To assess the effect of the intervention on each participant, both coders also independently rated each interview on a 0–10 scale for both perceived benefit of the intervention and for perceived understanding of the intervention. Higher scores reflect a greater perceived understanding of, and benefit from, the intervention. The two coders discussed their separate ratings for each participant, and each coder then decided on a final rating for each participant. The two coders' separate ratings were then averaged for a final score for each participant. The interview ratings were correlated with daily home practice times and baseline level of cognitive function (using the baseline ADAS-cog) using Pearson correlations. The practice times were also categorized by <20 min/day versus ≥ 20 min/day and correlated with the ratings of perceived benefit and understanding of mindfulness. All analyses were performed on an intention-to-treat basis and all rating analyses were conducted using Excel 2016.

RESULTS

Of the nine participants who completed the MBSR course and qualitative interviews, the mean age was

73 (SD = 8) years, and Mini-Mental Status Exam score was 27 (SD = 2). Six women and three men participated, three had high school education and six had college or more education. All were white and non-Hispanic.

Seven themes emerged from the qualitative interviews, and each theme was reported by at least five of the nine participants (Table 1). The themes, ordered from most to least frequent, included: 1) **positive perceptions of class, 9/9** (i.e., enjoyed class/appreciated & surprised by benefits, sad class over, recognition of time/discipline required for participation, plans to continue what learned), 2) **development of mindfulness skills, 8/9,** (i.e. body/breath awareness, improved attention/concentration, increased awareness of environment/beauty, development of meta-cognition); 3) **importance of the group experience**, **8/9** (i.e., benefited from knowing others with a similar condition, most enjoyed the comradery although one did not feel comfortable in the group, helpful to observe others' experience with meditation), 4), **enhanced well-being 8/9** (i.e., improved well-being/mood, improved self-confidence, greater self-compassion, and improved motivation to engage in activities); 5) **shift in perspective about MCI 7/9** (i.e., improved acceptance and awareness of condition, improved self-efficacy despite MCI, improved hope/expectation, perceived memory benefit or no benefit); 6) **decreased stress reactivity and increased relaxation 7/9** (i.e., improved ability to relax, decreased physiological reactivity to stress, decreased rumination); and 7) **improvement in interpersonal skills 5/9** (i.e., kinder/more appreciative of others, recognized/appreciated importance of social connections).

The 0–10 ratings by the coders of the **perceived benefit** of the intervention ranged from 2–10, with an average score of 7 and a median of 7.5 (Table 2). The 0–10 ratings by the coders of the **perceived understanding** of the intervention ranged from 0–9.5, with an average score of 6 and a median of 5.5. The inter-rater reliability was 100% concordant within three points. Based on the average score, participants were categorized into those who appeared to attain substantial benefit or understanding (mean ratings of $\geq$7–10) versus moderate (mean ratings of 4–6) versus minimal (mean ratings of 0–3). About half of the participants had substantial benefit or understanding ($n = 5$ and 4, respectively), some had moderate benefit or understanding ($n = 3$ and 3, respectively), and few demonstrated little-to-no benefit or understanding ($n = 1$ and 2, respectively) (Table 2).

The coders' ratings of perceived benefit and perceived understanding were highly positively correlated with home practice time ($r = 0.71$ and 0.70, respectively) but not with baseline cognition (ADAS-cog $r = 0.23$ and 0.13, respectively). Those who practiced at home 20 or more minutes per day were highly positively correlated with those who benefited from and understood the key concepts of mindfulness compared to those who practiced less than 20 min per day ($r = 0.83$ and 0.90, respectively).

Many participants found the intervention beneficial and enjoyable, as evidenced by their comments, such as "I enjoyed it so much I wish it would go on forever" and "I think you're making history here." (Table 1). Participants were specifically queried about any challenges, obstacles, or dislikes that they experienced. When asked about negatives, one-third of the participants specifically commented that they did not have any negatives to report. Four participants commented that time and discipline were challenging aspects of the program. Several participants individually had challenges that were not reported by others, such as: one participant felt the yoga was too hard; another participant felt (s)he wasn't "getting it;" and another participant commented on both not understanding the purpose of every activity and on the practice being one of personal preference. One participant had several dislikes/challenges, including the repetitiveness of the instructions during class, the yoga seeming too easy, and the meditation seeming too hard.

Participants were also queried about class logistics, specifically the class length (two hours each) and duration (eight-weekly classes), safety of the exercises, whether they were planning on continuing mindfulness practice, and whether they would recommend the program to others. Seven of the nine participants felt that the two-hour class duration was appropriate; interestingly, one commented that sometimes the classes felt too long, and another commented on wanting longer classes. Seven of the nine participants felt that the eight weekly classes were the right length; in fact, one even commented "I don't know how you could do less." Two participants commented that they wanted more time, with one stating "I enjoyed it so much I wish it would go on forever. I really mean it, I'm going to miss this ...I should think eight weeks is minimum." Eight of the nine participants thought that all the class activities were safe to perform. One participant had difficulty with the floor exercises due to discomfort and suggested having more instructions

Table 1
Themes, Descriptions, and Quotations from Qualitative Interviews

Theme (Frequency*)	Finding Specific to MCI or New/Important Finding in MCI	Description of Thematic Concepts and Sample Quotations
Positive Perceptions of Class (9/9)		**Enjoyed the class/appreciated the benefits** • "The program has benefitted me enormously." • "It's been a godsend for me." • "I think very positive of this whole experience." • "I think this was a wonderful experience." • "I've been to dancing before and it was good, but nothing compared to this." • "I was just grateful for [this opportunity]: I think it has helped me a lot and I really do appreciate it." • "I think you're making history here. People will be able to take care of themselves better and be more responsible for their care." **Surprised by benefits** • "When the doctor had recommended it to me I was saying, 'I don't really need this, I can conquer this myself.' . . . . [But] I did go and now I would recommend it to anyone. I was afraid of it, I didn't really understand really what mindfulness was. I was saying 'I don't think this is really good for me. I am 62 years old' but it's the best thing I ever took." • "I never realized how much it was going to help me." **Sad class over** • "I enjoyed it so much I wish it would go on forever. I really mean it, I'm going to miss this." **Recognition of time/discipline required for participation** • "Whatever is required you have to put in your time in order to get results" **Plans to continue what learned** • "I think it will be a cold day in hell when I quit [the mindfulness practice]." • "It was a great experience for me. It will just never go away. I will be doing some of this and I think I will be doing more of it down the road."
Development of Mindfulness Skills (8/9)	✓	**Body/breath awareness** • "I'm more aware of my body, breathing, and relaxation." • "I'll tell you how [this class] affected me: I realized I had a body. You go through life and you don't realize you have your chest and your knees and you don't really think about those things. This sort of made you very aware of the various parts of your body." • "At first some of the exercises were things I hadn't normally done. Now I love them. We learned to listen to our bodies and then we only did what our bodies would let us do. Maybe the next week we could do a little bit more." **Improved attention/concentration** • "I think it's made me try to concentrate more on what I do and remember. I think that's a big benefit to me."

		Increased awareness of environment/beauty • "I'm more sensitive to the beauty of the world around me. It's beginning to expand so that things that I was put off by, or repelled by, I sort of am now amused by . . . .I like the sense of amusement and I like the sense of beauty, the physical beauty of the world around is just incredible." • "I think I have a much happier view of life. I was looking at an insect . . . and I was just taken with the elegance of it . . . the incredible complexity in that tiny creature . . . I appreciate it." • "Be happy with what you have, and I think I have learned that." **Development of meta-cognition: ability to think about thinking** • "Before, I used to beat myself up, 'Why am I thinking this?' Now I can just say, 'I'm just thinking.' You can see me lighten up over that one." • "Our mind does wander in so many different ways depending on what's going on in your life. Now I can just say 'I'm just thinking."'
Importance of the Group Experience (8/9)	✓	**Benefited from knowing others with a similar condition** • "It's nice to know everyone else [in the group] is in the same boat." • "I think it was helpful to just know you're not alone." • "I think it was very positive . . . you are able to see that you're not alone, there are other people that have the same [memory] problems, and not that makes you feel better, but you realize that it just happens. Unfortunately I'm one of the *x* number of people that [memory loss] happens to. It doesn't happen to everybody." • "You realize that you're not the only one who has some of your problems." • "It's opened up my thinking that I don't stand alone . . . I'm one of the many." **Most enjoyed the comradery** • "I feel that there was some comradery as we went along and then I couldn't wait to get here." **One did not feel comfortable in group** • "I was just a misfit for that group . . . it would appear, with the members of that group, they have age or memory difficulties that I don't think I have...I felt that I was not part of that group." **Helpful to observe others' experience with meditation** • "I think the technique I could have absorbed one on one with a guru. I think it went better because I could observe other people and their responses and . . . you learn from that."
Enhanced Well-being (8/9)		**Improved well-being/mood** • "I just feel better. I'm not doomed forever. I think I'm going to be okay." • "I've been more upbeat." • "I feel more buoyant." • "I'm more of a happy camper." • "I feel like I'm just calmer." • "I feel so much happier because I think it's helped me. I just feel good. Even my husband says he can't believe the difference in me." **Improved self-confidence** • "This helped me feel a little better inwardly as a person." **Greater self-compassion**

(*Continued*)

Table 1
(*Continued*)

Theme (Frequency*)	Finding Specific to MCI or New/Important Finding in MCI	Description of Thematic Concepts and Sample Quotations
		• "I guess I'm learning it's okay to have compassion for yourself."
		Improved motivation to engage in activities
		• "It got me to not sit around, just do things that I enjoy doing. It's so easy to get lazy."
		• "[This class] gets you to do things more than you would have done. You get very lazy when you get older. These types of things prevent you from getting completely lazy. You are sitting and talking to other people and exercising with other people and I think that's a plus."
Shift in Perspective about Mild Cognitive Impairment (MCI) (7/9)	✓	**Improved acceptance and awareness of condition**
		• "You realize that [memory loss] happens to most people as they grow older. Now it's just a matter of being more aware of what things I can do to just keep things going a little better and enjoying life a little more."
		• "I notice my friends around my age can cite their own examples of memory loss. On the other hand, the memory loss that I am experiencing is at a higher level than theirs and that's just the way it is."
		• "I've learned more about myself, but not necessarily good things. It's brought out more of the problems that maybe I never adjusted to or realized. My memory, whether it's always getting bad or whether it just started to get bad, it just seems to be getting worse. There is no sense in hiding it. I might as well understand what's happening and try to do whatever I can to not let it bother me, and to see if I can get things to go better."
		• "It's made me realize that I have a [memory] problem . . . I'm more aware of the problems where I might have in the past gone over it."
		Improved self-efficacy despite MCI
		• "I certainly can absorb a memory failure much better than I could have before."
		• "I'm more aware now of what I'm doing and trying to make sure that I write things down; if I have an appointment I'm more aware of that now."
		• "I think it's been a great tool for me to move forward and to know that I can take control of myself and my situation and that I can deal with the ins/outs of daily living. It's really a tool for wellness."
		Improved hope/expectation
		• "I think there is the hope you can manage your condition now."
		Noticed benefit to memory
		• "I can have a good conversation without losing every single word. There are still times I lose words, but not as often as I was. I think it's super."
		Noticed no improvement in memory
		• "If there is a benefit to my memory I am not very aware of it."

Decreased Stress Reactivity and Increased Relaxation (7/9)		**Improved ability to relax** • "Anytime I'm feeling a little extra stress, I go up and can do some breathing and I'm good to go." • "I keep saying to myself under stress now, 'just breathe.'" • "It's taught me how to relax." **Decreased physiological reactivity to stress** • "[I got lost driving to class one day] and I was able to calm myself down and . . . I was proud of myself for being able to do that because I used to feel my heart pumping all the time because I used to get so excited . . . [now] I can stop myself from getting exciting and I can just think about what I'm doing or what I have to do. It has really helped a lot." **Decreased rumination** • "I can calm myself down from obsessive thinking . . . the circular thinking that I would get into, [the class] has a powerful impact on that."
Improvement in Inter-personal Skills (5/9)	✓	**Kinder, more appreciative of others.** • "I don't interrupt people anymore. I will take what they say, breathe, then say here's my response." • "I think I am a lot kinder to people" • "Increasingly a sense of appreciation for people—I mean I like people, but it's different; I'm looking at people and the instinct to smile comes to me." **Recognizes importance of social connections.** • "I think it may have improved some of my social connections to people . . . I'm more thoughtful of people. I appreciate the personalities of people." • "I think . . . my sense of other people is stronger as I'm paying more attention to what their needs and desires may be . . . I feel better about that, the way I interact with people." • "My daughter and I had a bad fall out a while back. After taking this mindfulness class, I found myself calling her and crying and saying, 'I want you, I need you.' She felt the same way about me, but both of us were so stubborn that we wouldn't get together. I feel that I am a kinder person from it. I appreciate people more than take them for granted." • "One of the things I got out of the class, I realize I wasn't talking as often as I should with some of my friends and I enjoyed speaking with the people here . . . I called up some friends of mine I haven't called in a good amount of time. We have had some very good conversations . . . I think that's good."

*Frequency, number of interviews coded with this theme (out of 9 total interviews).

Table 2
Coders' Ratings of Participants Perceived Benefits and Perceived Understanding of the Intervention

Participant	Average Perceived Benefit Score	Average Perceived Understanding Score
A	10	9.5
B	9.5	9.5
C	9.5	8
D	8	9
E	7.5	5.5
F	6.5	5.5
G	5	3.5
H	5	3
I	2	0
Legend	Range (from 0–10)	Interpretation
	7–10	Substantial benefit/understanding
	4–6	Moderate benefit/understanding
	0–3	Little benefit/understanding

regarding safety. One participant also commented that learning mindfulness helped them understand their limits with regard to safety, specifically, "I don't push my body to get my leg up higher, I don't think it's about that. It's about being safe, you get to know your body and take it to your own limit." Eight of the nine participants planned to continue the mindfulness practice, and one commented that "I think it would be a cold day in hell when I quit." Eight of the nine participants would recommend the program to others, with one stating, "I think everybody should be in the program" and another stating "I would recommend it to anyone in the same situation as I am in." The one that was not planning on continuing the practice acknowledged the benefit of the program but felt like "a misfit for that group ... I felt that I was not part of that group." Interestingly, one of the participants specifically appreciated having the MBSR course in the hospital, as "it's nice to have a wellness program in an illness setting (hospital)."

DISCUSSION

The qualitative interviews revealed new and important findings specific to MCI, including the development of mindfulness skills, importance of the group experience, and improvement in interpersonal skills. While the MBSR class was not developed or structured to directly address MCI, most participants commented on improved awareness, acceptance, and self-efficacy despite their condition, valuable outcomes as patients with MCI have a rare window of opportunity to address many end-of-life issues with autonomy before further disease progression. However, patients with MCI are often reluctant to accept the MCI diagnosis, making it challenging to move forward with decisions about the future [33]. As intended and seen in prior research [12, 34], MBSR decreased stress reactivity and improved relaxation for most participants. In the process, many participants noticed improvement in overall health and feelings of well-being. The integrity and effectiveness of the intervention was demonstrated by the themes, specific comments, and the coders' ratings. Those adults who practiced more had higher scores on the coders' qualitative interview ratings of perceived benefit and understanding of the intervention, and their ratings were not correlated with their baseline cognition. Those who practiced $\geq$20 min/day were most likely to have understood the underlying concepts of mindfulness.

The participants' comments and ratings show that most of the adults with MCI in this study were able to learn the key tenants of mindfulness, demonstrating that the memory impairment in MCI is not prohibitive of learning such skills. The fundamental elements of mindfulness [11] were seen in the comments and themes of the participants. Further, the qualitative ratings of perceived benefit and understanding of the intervention were not correlated with baseline cognition, suggesting that the level of cognitive decline seen in MCI may not influence one's ability to learn skills in a mindfulness intervention. Several participants even reported enhanced "meta-cognition" (awareness of one's own mental processes) [35], an interesting finding that demonstrates that adults with MCI can develop such a highly skilled level of self-awareness. Meta-cognition requires significant executive processing to be able to reflect on one's own cognitive processes.

Although mindfulness meditation can be independently learned and practiced, MBSR is conducted in a group experience. The perceived benefits and importance of the group experience was one of the major themes that emerged. While group classes are known to provide meaningful group support benefits [36, 37], they may be especially helpful for adults with MCI. The group process was helpful for the comradery that developed, the opportunity to connect and communicate with peers in a meaningful way, and the appreciation they had for knowing that others had a similar condition. The group effects may also have synergized with the intervention delivered,

as participants found value in observing that others with MCI could successfully learn to do mindfulness meditation and underscores the importance of group programs for patients with MCI. One participant even commented that, "I think the technique I could have absorbed one on one with a guru. I think it went better because I could observe other people and their responses and ... you learn from that." The study was run over two cohorts, and participants from both cohorts commented on the importance of the group experience, demonstrating that the positive group experience was not likely due to cohesion of a particular group of individuals, but rather an experience typical of any MBSR course.

Another interesting and unexpected finding was the impact the intervention had on interpersonal skills. Mindfulness meditation is often thought of as a very personal practice, but the interviews revealed that many participants used the skills to appreciate and become more mindful of their relationships with others. Several even commented on improving previously damaged relationships. Although to our knowledge, this finding has not been previously reported following MBSR, increased interpersonal skills with meditation practice and yoga have been described [38, 39]. Interpersonal skills and social connections are very important in patients with MCI and may affect disease progression. A recent study demonstrated that adults with MCI have weaker social networks than those without cognitive impairment, and social networks are a significant mediator of the relationship between MCI and mood problems [40]. Further, social engagement may be a protective factor against the development of dementia, as those with more social activity are less likely to develop dementia [41–43]. Communication skills can be damaged by the process of memory loss in MCI; as a result patients may decrease their interactions with others. For example, one participant specifically commented, "Before the trial, [it was] very frustrating. I knew I was getting more quiet amongst friends, I go to talk then I couldn't remember—I wasn't retaining conversations. I go to use words then couldn't find the words that I wanted." This process of losing verbal communication may inherently lead to fewer social interactions. MBSR may improve social cognition and ultimately boost this cognitive domain.

The non-significant trends of improvements in the quantitative measures of well-being were in the areas of resilience, perceived stress, quality of life, hope, and generalized optimism [21] and match themes and examples that emerged from the qualitative interviews, such as enhanced well-being, mood, self-confidence, hope, ability to relax, kindness, and decreased stress reactivity and rumination. Throughout the interviews, there was a strong sense of appreciation, both for the course and for the new skills. In addition to improving one's outlook on life, it is possible that MBSR may indirectly increases one's sense of gratitude. Gratitude is strongly related to well-being and can have positive health benefits [44, 45]. Lovingkindness (metta) meditation, which focuses on gratitude, was briefly discussed in this MBSR program but was not a focus of the program.

This study excluded those with a clinical diagnosis of depression, was not powered to find changes on measures of depression and anxiety, and did not observe changes on measures of depression and anxiety with the Center of Epidemiology Depression Scale or the State/Trait Anxiety Inventory [21]. Yet interestingly, one of the main themes that emerged from the qualitative interviews was perceived improvements in mood and overall well-being. Many patients with MCI have concurrent neuropsychiatric symptoms such as depression and anxiety [46, 47], and it is unclear if these symptoms serve as the earliest manifestations of the disease or if the MCI diagnosis makes one more vulnerable to such symptoms. Regardless, in a study of over 1,800 patients with MCI, baseline levels of depression were associated with increased incidence of dementia and AD [48]. Neuropsychiatric symptoms and poor psychological well-being are also associated with AD pathology, including cerebral amyloid deposition [49, 50], APOE $\varepsilon 4$ [51, 52], and AD cerebrospinal fluid markers [53]. Targeting neuropsychiatric symptoms in adults with MCI may delay the transition to dementia [54], a key treatment focus at this time given limited treatment options to prevent progression. MBSR may improve the psychological health of patients with MCI and be an effective way to target this issue. As one cognitive neurologist who referred patients to this trial stated, "MCI patients all seem to have anxiety and stress; some may be contributing to their memory problems, others have it because of the diagnosis. Most patients are reluctant to see psychiatry, so this is a good way to get around that."

The improved functional connectivity in the default mode network that occurred with this intervention (as reported elsewhere [22]) may mediate the improvements in emotional well-being and the development of meta-cognition as seen by participants' comments and themes from the interviews. It is possible that fMRI is sensitive enough to pick up these

changes that participants describe, but the small sample size limited the power to detect these differences in the neuropsychological measures and standardized questionnaires assessing well-being. Prior research has shown that connectivity changes are related to cognition in adults with AD [55]. The development of breath awareness that participants reported (as a component of mindfulness skills, Table 1) is an important finding that may play a role in the development of emotion regulation. Prior research has demonstrated that mindful attention to breath may help develop amygdala-dorsal prefrontal cortex integration, promoting a neural pathway for emotional regulation with mindfulness practice [56]. Further, the hippocampus, which atrophies with MCI/AD, plays an important role in the neurobiology of exercise [4] and meditation [57], and breath plays a role in both these activities. Future research is important to evaluate the hippocampus' role in breath awareness for adults learning to meditate.

The effort required to complete this program was significant, as the baseline and follow-up evaluations each took over four hours, the intervention took 22 hours over eight weeks, and participants were asked to practice mindfulness skills at home for 30 min/day. A main goal of this study was to assess whether patients with MCI could complete such a rigorous and demanding program. As previously reported, mean class attendance was 7.9 out of 9, and mean daily home practice was 26 ± 20 min. There were no adverse events reported that were related to the study protocol [21]. The qualitative interviews further revealed that the participants thought the two-hour class duration was appropriate, the eight weekly classes were manageable, and the program was safe. In fact, most planned to continue their practice and would recommend the program to others. Several participants commented on the time, discipline, and effort required to fully participate and learn this new skillset. One of the key principles and tenets of MBSR is an emphasis on the importance of individual effort, motivation, and regular disciplined practice, so this is not specific to adults with MCI [58]. This may be one element of the program that helps build self-efficacy. Although other meditation programs may be shorter and potentially more feasible and accessible, the effort required for this program may have contributed to the benefits seen. One third of the participants commented that they had "nothing negative to report" about the study. A few commented on how the program was one of personal preference, and one specifically felt like it was not for him/her. Overall, the participants felt the program was feasible as designed, and they were able to successfully learn mindfulness. Although two participants commented on not always understanding the purpose of each activity, with one viewing yoga as challenging and the other viewing meditation as difficult, participants did not report feeling overwhelmed by learning this new skillset. Actually, no participant commented that MCI prohibited his/her ability to participate or learn. Future studies may consider adaptations such as providing more modifications to the movements in the yoga practice to make it more accessible and providing more explanation about the purpose of some practices.

The coders' quantitative ratings are a unique aspect of this qualitative study. The ratings were conducted to better understand how each participant related to the program based on the coders' interpretations of the participants' perceived understanding and benefit of the intervention. About half of the participants reported great benefit and understood the key concepts of mindfulness, some moderately benefited or understood the concepts, and a few had little to no benefit or understanding of the concepts. As expected, there was no discordance with benefit from the program and understanding of the key concepts of mindfulness (e.g., no one understood all the key concepts of mindfulness but did not benefit from the program, or vice-versa). In addition, it is critical to recognize that some individuals may not benefit or "get" the concepts of mindfulness at all, even after an 8-week MBSR program. Determining predictive factors that would identify responders versus non-responders is an important future research goal.

The interview ratings highly correlated with home practice time, suggesting a possible dose-response relationship. Further, the finding that those who practiced 20 min/day were most likely to have understood the key concepts of mindfulness suggests this may be a critical amount of time needed to achieve clinical significance, although prior research on this question is conflicting [59, 60]. On the other hand, the correlation between home practice time and coders' ratings could be explained by the reverse, such that those who enjoyed and perceived benefit from the program may have been more likely to practice at home.

The term "cognitive reserve" is typically used to reflect activities done early or mid-life that protect against dementia and prior to the development of cognitive impairment. However, this study suggests the possibility that cognition enhancing activities such as MBSR may raise the threshold for the further progres-

sion of cognitive decline. Through the development of mindfulness skills, improvement in interpersonal skills and social connectivity, enhanced well-being and self-efficacy, and decreased stress reactivity, cognitive reserve may be enhanced even in patients already expressing cognitive decline and with a diagnosis of MCI. This preliminary hypothesis needs to be borne out in additional studies with biomarkers and detailed neuropsychological tests to evaluate if cognitive reserve can in fact be developed even after the diagnosis of MCI. The interviews revealed that participants were cognitively stimulated and emotionally boosted, potentially increasing resilience. These results are consistent with prior research showing that adults with MCI still have brain plasticity [20], but the skills learned with mindfulness meditation may specifically build cognitive reserve [61] and enable participants to build resilience for the grim future they may face. In addition, an aspect of enhanced well-being that emerged from the interviews was an improved motivation for being engaged in a new activity and learning a new skill. As one participant described, "you get very lazy when you get older. These types of things prevent you from getting completely lazy." This effortful mobilization may be an important component of any intervention for adults with MCI and may also help boost cognitive reserve. Prior research has shown that cognitive activities are helpful for older adults [62, 63]. Successfully engaging in MBSR's active cognitive activities of daily meditation exercises and weekly classes may increase their self-efficacy for engaging in other cognitive activities.

Several recent reviews of meditation interventions (of either Kirtan Kriya Meditation or mindfulness-based programs) [64] and yoga interventions [65] report on 11 additional studies [66–78] that have demonstrated benefits in adults with subjective cognitive decline, MCI, and AD. Since these reviews, an additional study of tai chi in older adults at risk for cognitive decline has been published [79], along with mindfulness studies in adults with subjective cognitive decline [80, 81], MCI [82], and dementia [83, 84]. The study designs and outcomes from these studies are very heterogeneous, and most studies were small and considered pilot/feasibility (except for two studies with sample sizes over 110 [70, 79]). All studies, similar to our study, found that the practice of mindfulness was feasible in patients with cognitive decline. Participants randomized to these interventions showed some improvements in measures of cognition, specifically in executive function, attention, and verbal memory. Three of the studies with long-term follow-up of one-two years [70, 79, 82] found that the mindfulness interventions may help preserve global cognition, with one study showing that those who meditated more had greater improvements in cognitive function ($p < 0.05$) [82]. Emotional reactivity, psychological well-being, perceived stress, mood, quality of life, subjective sleep quality, and mindfulness were all measures that improved as well. Preliminary neuroimaging results suggest that mindfulness based interventions may increase percent volume of brain change [68], increase cerebral blood flow in prefrontal, superior frontal, and superior parietal cortices [71], and improve functional connectivity of the default mode network [85]. In addition, since our original publications reporting our results of MBSR in adults with MCI [21, 22], there has been significant interest in understanding the role mind-body programs play in adults with MCI, dementia, subjective cognitive decline, and in aging in general [61, 86–95]. A manual of a mindfulness program for adults with dementia has even been published [96].

Limitations and future directions

This study has several important limitations. The principal limitation is the small sample size, limiting the ability to assess the neuropsychological and well-being measures and compare the qualitative findings to the quantitative results. The small sample size also increases the possibility we did not reach full content saturation with the themes that emerged. The study was not racially, ethnically, or socioeconomically diverse, so results may not generalize to all patients with MCI. Two-thirds of the participants had college or more education, so the baseline level of cognitive reserve of most patients in this study may be higher than patients with lower educational attainment. In addition, the ability to dedicate the time for participation in the classes and home practice may not be feasible for those with different socioeconomic backgrounds. Larger, more diverse studies may help address these concerns and even provide the power to adjust for such potential confounders or assess their impact. While practicing 20 min/day resulted in a higher likelihood of perceived benefit and understanding, this may not be causal. Those who were experiencing the most benefit/understanding may have been more engaged in the MBSR program, resulting in them practicing more on a daily basis. Longitudinal dose-relationship

studies need to be conducted that experimentally manipulate duration of practice to assess for such causal findings. Long-term follow-up with biomarkers would also help assess the long-term impact of a program like MBSR on MCI disease progression. While this study demonstrated that patients with MCI may still have the cognitive resources to learn mindfulness meditation, it is unclear at what point in the disease process this ability may become impaired. Studying patients across the MCI-AD spectrum may help tease out when cognitive impairment becomes too significant to experience meaningful benefit. The qualitative interview process was semi-structured, with prompting by the interviewer with potentially leading questions that may have influenced some of the themes that emerged. Further, participants may have provided positive responses to the interviewers to please the team, leading to biased results. Having interviews conducted by non-team members could prevent the potential for such biased results with future studies. While the coders' expertise in mind-body interventions helped elucidate many nuanced findings from the interviews, additional findings may be present that were not addressed. For example, the coders did not examine the difference between the participants' conversations of mindfulness that were inwardly focused versus outwardly focused.

Participants self-selected to participate based on interest in the intervention and recommendation from others, so those engaged in this study may have had pre-conceived concept or expectation of benefit. While three of the nine participants had a friend or family member attend at least some of a class with the participant, which may have improved overall engagement in the MBSR program, this impact was not assessed and larger studies with more participants may help measure such impact. The study was also limited to participants available to complete the time-intensive MBSR program and able to commit to a once/week class at a certain day/time/location. Shorter meditation interventions (such as with Kirtan Kriya) have shown positive outcomes in quality of life and cognition in adults with subjective cognitive decline [80, 81]. Future studies could compare such shorter meditation interventions (such as with Kirtan Kriya meditation) to MBSR in adults with MCI to assess if shorter programs may provide the same benefits seen in this study. Given such limitations, many are looking for more time-efficient ways to learn mindfulness and ways to increase access. However, it is important to note that considerations to increase access (e.g., online programs, independent study, etc.) may not generate the benefits seen in this study, especially related to group benefit. Future studies using such methods may consider assessing for benefits of online social connectivity. The coders' ratings used in this study to assess participants' perceived benefit and understanding of the intervention offered a quantitative assessment of a qualitative measure, but qualitative data are not intended to be quantitative and so this data must be interpreted with caution. Further, the coders' ratings of perceived benefit and understanding of the intervention were conducted by external reviewers evaluating the participants' interview comments. Future studies could ask participants themselves to give their own ratings. Identifying factors that could help predict responders versus non-responders is critically important to help target those that may most benefit from such a program.

Conclusion

The global burden of dementia has doubled from 1990 to 2016 [97]. Until treatment options are found that can prevent progression, mindfulness meditation may help patients living with MCI. Significant research has demonstrated that mental activity, exercise, and social engagement may help decrease the risk of further cognitive decline in adults with MCI, and the most recent American Academy of Neurology guidelines recommend these modalities for treatment [98, 99]. MBSR may be an ideal program during this window of opportunity prior to potential progression to dementia because it incorporates aspects of each of these activities. MBSR includes exercise (yoga), mental activity (mindfulness meditation), and one of the themes that emerged from this research was that it also enhances social engagement. For patients who have few other options for improvement and may live in fear of progression to dementia, psychological well-being and quality of life are crucial yet often forgotten factors to address and treat. More research is needed to determine if MBSR could have further benefits in other realms of cognition, but until then, MBSR is a primarily safe, feasible, well-accepted intervention that may positively impact quality of life in adults with MCI such that they may better handle their diagnosis and improve their approach to their condition and to life. This study showed promising evidence that adults with MCI can learn to practice mindfulness meditation, and by doing so, it may boost their cognitive reserve. Additional research to further explore these findings in MBSR is critical with larger sample sizes,

and long-term follow-up with cognitive testing and biomarkers.

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SUPPLEMENTARY MATERIAL

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