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Research report

Potential benefits of mindfulness-based interventions in mild cognitive impairment and Alzheimer's disease: An interdisciplinary perspective

Eddy Larouche[a,b], Carol Hudon[a,b], Sonia Goulet[a,b,*]

[a] École de psychologie, Université Laval, 2325, rue des Bibliothèques, Québec, QC, Canada G1V 0A6
[b] Centre de recherche de l'Institut universitaire en santé mentale de Québec (CRIUSMQ), 2601, de la Canardière (F-2400), Québec, QC, Canada G1J 2G3

HIGHLIGHTS

- Hippocampal damage is central in MCI/AD and could be prevented or delayed by MBI.
- MBI reduce MCI/AD adverse factors (stress, depression, metabolic syndrome).
- Multiple pathways could explain MBI's effects on modifiable adverse factors.
- Effects seem based on neuro- endocrine, immune, and transmission regulation.
- MBI show great potential to prevent the neurodegenerative cascade leading to AD.

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ABSTRACT

The present article is based on the premise that the risk of developing Alzheimer's disease (AD) from its prodromal phase (mild cognitive impairment; MCI) is higher when adverse factors (e.g., stress, depression, and metabolic syndrome) are present and accumulate. Such factors augment the likelihood of hippocampal damage central in MCI/AD aetiology, as well as compensatory mechanisms failure triggering a switch toward neurodegeneration. Because of the devastating consequences of AD, there is a need for early interventions that can delay, perhaps prevent, the transition from MCI to AD. We hypothesize that mindfulness-based interventions (MBI) show promise with regard to this goal. The present review discusses the associations between modifiable adverse factors and MCI/AD decline, MBI's impacts on adverse factors, and the mechanisms that could underlie the benefits of MBI. A schematic model is proposed to illustrate the course of neurodegeneration specific to MCI/AD, as well as the possible preventive mechanisms of MBI. Whereas regulation of glucocorticosteroids, inflammation, and serotonin could mediate MBI's effects on stress and depression, resolution of the metabolic syndrome might happen through a reduction of inflammation and white matter hyperintensities, and normalization of insulin and oxidation. The literature reviewed in this paper suggests that the main reach of MBI over MCI/AD development involves the management of stress, depressive symptoms, and inflammation. Future research must focus on achieving deeper understanding of MBI's mechanisms of action in the context of MCI and AD. This necessitates bridging the gap between neuroscientific subfields and a cross-domain integration between basic and clinical knowledge.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that affected about 35,560,000 people worldwide in 2010; this prevalence is expected to increase to 115,380,000 by 2050 given population aging in several countries [1]. AD is preceded by a prodromal phase that can be identified in individuals with mild cognitive impairment (MCI) [2]. MCI generally encompasses a wide range of cognitive deficits affecting episodic memory [3], semantic memory [4], executive functioning and attention [5], language [6], and visuospatial skills [7]. The loss of episodic memory characterizes a subset of people with MCI most at risk to develop AD [2]. In fact, memory impairment is the most significant cognitive predictor of dementia in people with MCI [8]. In those individuals, memory

* Corresponding author at: Université Laval, École de psychologie, CRIUSMQ, 2601 de la Canardière (F-2400), Québec, QC, Canada G1J 2G3.
Tel.: +1 418 663 5000x6805.
E-mail address: sonia.goulet@psy.ulaval.ca (S. Goulet).

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deficits can be explained by early AD-related brain pathology that starts in structures of the medial temporal lobe [9]. More precisely, transentorhinal and parahippocampal cortices are the earliest brain regions showing neurofibrillary tangles, followed by the hippocampus and then, in later stages of AD, neocortical areas [9]. The decaying hippocampus is a biomarker of MCI [10,11] and a good predictor of conversion from MCI to AD [11–18], as well as of AD onset [19]. Loss of entorhinal cortex volume can predict the development of AD as well [13,15,18,20] and its combination with hippocampal pathology is associated with memory decline [14,21,22]. There is growing evidence that timely interventions in MCI can restore cognition in affected individuals [23]. Benefits may extend to hippocampal volume as well, and this should constitute one of two forefront premises of future research, the second being that the diagnosis of AD may be postponed by early interventions through the interruption of the neuropathological cascade leading to AD [24].

A specific class of contemplative approaches may transform the way we envision MCI and AD prevention in the coming years. Mindfulness-based interventions (MBI), such as *mindfulness-based cognitive therapy* (MBCT; [25]), were derived from mindfulness-based stress reduction (MBSR) developed by Jon Kabat-Zinn at the University of Massachusetts [26]. These interventions require stable and non-judgmental attention to internal (e.g., the breath, a body sensation) or external (e.g., a sound, the feeling of the ground underneath the feet) experiences in the present moment [26]. Typically taught in the context of an 8-week program, MBI include a variety of formal meditative exercises: body scan, gentle yoga, sitting meditation, and walking meditation. These are introduced in a small group setting, and practiced at home several days a week with the help of CDs and written instructions. Also, mindful attitudes (e.g., acceptation, patience, beginner's mind) are discussed during the program. It is assumed that informal application of such attitudes in daily life can help counteract suffering induced by mindlessness, stress, depression, and so forth. Although MBI based on MBSR received significant attention from researchers in the recent years, many published studies chose to exploit specific mindfulness components, such as breathing-centered strategies (e.g., various types of meditation techniques and diaphragmatic breathing) or mindful movements (e.g., Tai Chi). Since the active ingredients of MBI have yet to be clearly identified, it appears justified to consider practices not typical of MBSR in a literature review on MBI. Readers are invited to consult Nash & Newberg [27] for detailed descriptions of meditative/contemplative practices outside MBSR.

Studies have reported positive impacts of MBI on hippocampus' structural and functional integrity, warranting more attention to such interventions in the fight against MCI and AD neurodegeneration. In healthy young adults, bilateral hippocampal volumes were larger after an 8-week MBSR program [28], a gain reported as well in a group of meditators compared to non-meditators [29,30]. In elders suffering from Parkinson's disease, a neurodegenerative condition with motor, cognitive, and psychological symptoms, MBSR resulted in greater volumes in the hippocampus [31]. Even though the contribution of neurogenesis to hippocampal growth was not demonstrated in these contexts, such interpretation is likely. There is hope also for the AD population. A recent pilot study showed a trend toward reduced hippocampal atrophy in MCI patients who completed an 8-week MBSR program compared to MCI patients assigned to usual care; unfortunately, the sample size was too small to reach significance [32]. Nevertheless, the same study showed improved functional connectivity post-MBSR between the hippocampus and the posterior cingulate cortex [33], an interesting outcome since hypometabolism in the posterior cingulate cortex has been associated with memory impairments and a greater risk of evolution toward AD [34]. Functional connectivity between the hippocampus and the medial prefrontal cortex, which is implicated in episodic memory [33], was also strengthened after MBSR. MBI effects on functional connectivity may underlie in part changes in default mode network connectivity. Activated in the absence of a task requiring focused attention [35], the default mode network is a set of cerebral regions implicated in normal auto-referential processes such as autobiographical memory, future planning, and social cognition [36,37]. In depression [38], anxiety and, more pertinently, MCI [39], hyperactivation of the default mode network occurs along with a decreased proficiency to disengage from auto-referential thoughts and excessive anxious or mood-related ruminations.

Current understanding of the mechanisms underlying improved brain morphology and functions after MBI points to greater integration at the intra- and inter- hemispheric levels (also referred to as vertical versus horizontal integration). Increased connectivity and control associated with the default mode network can reflect a greater integration of cortical cognitive functions over sub-cortical emotional processes [40,41]. With regards to inter-hemispheric integration, a recent meta-analysis of neuroimaging studies revealed that experienced meditators display increased volume and lower diffusion in the anterior corpus callosum [42]. Increased myelinization of neurons in the same region was also shown in long-term meditators [43]. The anterior portion of corpus callosum supports integration of complex executive functions and attention processes. Healthy aging results in diminished volume and increased diffusion in the corpus callosum [44]. Significant atrophy of this brain region was found in elders with cognitive complaints, MCI, or AD, with atrophy being more important in patients with AD [45]. Moreover, smaller corpus callosum volumes were associated with lower general cognitive performance [46,47]. In sum, increased inter-hemispherical callosal integration post-MBI appears to be a suitable mechanism favoring strong frontal executive functions necessary for effective disengagement of the default mode network and for regulating emotions arising from limbic areas. Thus, both intra- and inter-hemispherical integration mechanisms would contribute to improvement of brain functions, cognition, and mood following MBI.

There is some support for MBI efficacy to improve memory and general cognition, including attention, executive functions, and processing speed [48]. Wells, Yeh et al. [33] reported preliminary findings where patients with MCI who received MBSR instead of usual care showed a trend toward better cognitive functioning post-intervention. Encouraging results were also reported with contemplative activities not typically included in MBI, or with one of the MBI practices administered in isolation. In another study that included elders with subjective memory impairment, MCI, or mild AD all groups showed memory enhancement following MBI [49,50]. One such study conducted with AD patients and their caregivers reported gains in retrospective memory, for both groups pooled together, after an 8-week meditation program [51]. In healthy adult men, memory performance was higher after 6 months of yoga training contrasted with physical exercise, and there were also significant improvements in depressive and anxious symptoms [52]. In healthy elders, a combination of meditation and physical exercise led to greater memory performance than the practice of either activity [53]. In addition, healthy elders from Tai Chi groups had better attention and memory performances compared to those enrolled in physical exercise or no particular activity [54–56]. Such results argue in favor of the complementary benefits of meditation and movement, a union that is often present in MBI.

Data available to date motivate further investigations to test the efficacy of MBI for primary and secondary prevention of cerebral and cognitive decline in older adults. To support this endeavour, one must pursue research: (1) to understand the associations between MCI/AD adverse factors, neurodegeneration, and symptomatology; (2) to elucidate the effects of MBI on variables