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Beneficial effects of mindfulness-based intervention on hippocampal volumes and episodic memory for childhood adversity survivors

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Abstract

Background: Adverse Childhood Experience (ACE) has detrimental impacts on neural development, especially hippocampal morphometry. Mindfulness-Based Interventions (MBI) has been shown to induce adaptive hippocampal changes especially at the subiculum. The present study aims to investigate the effects of MBI on subiculum volumes among ACE survivors, as well as the effects on episodic memory as a probe into hippocampal functionality.

Methods: We analyzed anatomical MRI data and performance indices from an episodic memory task called the Mnemonic Similarity Task (MST) collected from a randomized controlled longitudinal study that compared an 8-week MBI ($N = 20$) to an active control condition of Stress Management Education (SME) ($N = 19$). FreeSurfer 6.0 was used for automated hippocampal subfield segmentation and volumetric estimation.

Results: Significant group differences were observed with the volumetric changes of the right whole hippocampus and right subiculum. Only the MBI group showed improved pattern separation capability from MST, which was associated with stress reduction and right subiculum volumetric changes.

Limitations: Modest sample size. MST task was performed outside of MRI.

Conclusions: These findings suggest beneficial effects of MBI for hippocampal volumes and episodic memory, while highlighting the importance of the subiculum for MBI-induced neural

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CRediT authorship contribution statement
Diane Joss: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Martin H. Teicher:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Data curation, Funding acquisition, Conceptualization, Methodology, Visualization. **Sara W. Lazar:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization, Data curation, Formal analysis, Visualization.

Declaration of competing interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. DJ and SWL are practitioners of mindfulness meditation.

and cognitive changes. The subiculum's known role in inhibitory control was interpreted as a potential mechanism for it to exhibit MBI-induced volumetric changes, which sheds light on the potential neural underpinnings of mindfulness meditation for reducing stress reactivity among ACE survivors.

Keywords

Meditation; Episodic memory; Subiculum; Cognition; Trauma; Early life stress

1. Introduction

1.1. Childhood adversity is associated with reduced hippocampal volumes

Accumulating research has demonstrated the detrimental impact of Adverse Childhood Experiences (ACEs) on neural development (Teicher et al., 2003), with structural and functional abnormalities persisting into adulthood (Teicher et al., 2016), especially in the hippocampus (Dannlowski et al., 2012; McEwen, 1999; Stein et al., 1997; Teicher et al., 2016; Woon and Hedges, 2008). In particular, left hippocampal subfields CA2-3 and CA4-dentate gyrus, as well as presubicular and subicular components of the hippocampal formation, exhibited reduced gray matter volumes among young adults with ACEs compared to age matched controls (Teicher et al., 2012). Hippocampal subfields CA2-3 and CA4-dentate gyrus are known to be the most stress-sensitive subfields from preclinical and translational studies (McEwen, 2000, 2002). Preclinical studies suggest that early life stress stimulates excessive release of glucocorticoids, which compromises hippocampal integrity by inducing dendritic atrophy of CA3 pyramidal neurons and inhibiting neurogenesis of the granule cells in the dentate gyrus (McEwen, 1999; Mirescu et al., 2004), which are also subfields that showed the robust ACE-related volumetric reduction in human neuroimaging research (Teicher et al., 2012). Similarly, the subiculum also has a high density of glucocorticoid binding sites (Sarrieau et al., 1986) rendering it vulnerable to stress and alterations in corticosterone levels (Zach et al., 2010). Teicher et al (2012) proposed that reduced subiculum volumes in individuals with ACEs may underlie their enhanced stress reactivity given the role of ventral subiculum in inhibiting hypothalamic-pituitary-adrenal (HPA) axis activity to psychological stressors (Herman et al., 1998; Nettles et al., 2000).

Preclinical studies suggest that the detrimental impact of early life stress on hippocampus structures may be reversible. For example, social enrichment was found to increase neuronal proliferation and neurogenesis in the same hippocampal subregions that were reduced by post-weaning social isolation in laboratory rats (Biggio et al., 2019). Environmental enrichment during adolescence has been observed to induce increased spine density in dentate gyrus, while physical enrichment induced increased spine density in CA1 in adult rats (Gabriel et al., 2020). Social enrichment in adult rats was observed to induce increased neurogenesis in the dentate gyrus of the hippocampus accompanied by improved social recognition memory (Monteiro et al., 2014). Such findings on hippocampal plasticity in adulthood suggest that ACE-induced hippocampal abnormality in adult humans may also be reversed through appropriate interventions.

1.2. Impact of ACE on cognitive functioning

ACEs have also been found to be associated with deficits in various cognitive functions (Bremner and Narayan, 1998; Pechtel and Pizzagalli, 2011). Preclinical studies have demonstrated early life stress impairs hippocampus-dependent learning and memory (Karten et al., 2005). Human research has also demonstrated deficiency in memory functioning among ACE survivors (Pechtel and Pizzagalli, 2011). Previous studies have revealed deficits in general intelligence and academic performance in children with a history of institutional care (Pechtel and Pizzagalli, 2011), with particular deficits in visual memory and executive functioning (Bos et al., 2009). College women with a history of sexual abuse were also found to have reduction in short-term, verbal, visual and global memory scores (Navalta et al., 2006). Compromised hippocampal structure and functioning (e.g., pattern separation capability) can account for various information processing distortions among ACE survivors, e.g., compromised ability to accurately recognize one's emotions (e.g., alexithymia) and ineffective update of internal belief systems based on new information (Herzog et al., 2022).

In the domain of cognitive functioning, compromised pattern separation capability has been speculated to amplify risks for the development of affective, anxiety and psychotic symptoms (Lecei and van Winkel, 2020). Pattern separation is the brain's ability to distinguish minor differences in similar experiences, which is thought to involve reducing overlap in neuronal activity patterns that represent these experiences (Madar et al., 2019). It is specifically associated with certain cells in the hippocampus, such as the dentate gyrus granule cells and CA3 pyramidal cells (Madar et al., 2019; Yassa and Stark, 2011), and recent research indicates the subiculum also contributes to this process (Nash et al., 2021). Impaired pattern separation capability has been proposed as a candidate mechanistic link to explain the association between compromised hippocampal function and elevated risk for mood and anxiety disorders (Anacker and Hen, 2017; Liberzon and Abelson, 2016). These disorders are characterized by *negativity biases* (Williams et al., 2009) that favors pattern *completion* over pattern *separation*. For example, instead of discerning whether a stimulus is an actual or merely a *perceived* threat, individuals with severe negativity biases, due to impaired pattern separation capabilities, are more likely to conclude that it is an actual threat and respond as such. Compromised pattern separation capability is particularly evident among ACE survivors (Lecei and van Winkel, 2020), resulting in over-generalization of fear (Lange et al., 2017) and hyper-vigilant threat detection (Lecei and van Winkel, 2020).

1.3. Mindfulness meditation is associated with hippocampal volumetric changes and cognitive improvements

Decades of large-scale population research have demonstrated that ACEs exert a pervasive impact on physical and mental health (Felitti et al., 1998; Finkelhor, 2020; Kalmakis and Chandler, 2015). In particular, ACEs are leading risk factors for a host of psychiatric disorders, which typically have an earlier onset, more severe course and poorer response to traditional treatments such as psychopharmacology or cognitive behavioral therapy in individuals with versus without ACEs (Nanni et al., 2012; Nemeroff et al., 2003). Therefore it has been a pressing matter to identify or develop effective interventions for ACE survivors (Lorenc et al., 2020).

Mindfulness-Based Interventions (MBIs) have been shown to be beneficial for a wide range of psychopathologies, including depression (Hofmann and Gómez, 2017; Teasdale et al., 2000), anxiety (Evans et al., 2008; Hofmann et al., 2010) and PTSD (Boyd et al., 2018), which are some of the most common adverse consequences of ACEs (Nelson et al., 2020). A randomized clinical trial (N = 274) found that Mindfulness Based Cognitive Therapy (MBCT), a MBI designed for recurrent depression, was only more effective than control conditions in preventing relapse of recurrent depression for patients with childhood trauma (Williams et al., 2014). Such findings highlight the clinical benefits of MBIs for ACE survivors, which were further confirmed in later studies (Joss et al., 2019; Kuyken et al., 2015).

Furthermore, an expanding body of neuroimaging research suggests that the clinical benefits of MBIs are substantiated by neural changes (Afonso et al., 2020; Kwak et al., 2019; Yang et al., 2019). Long term meditators have been shown to have larger bilateral hippocampal (Fox et al., 2014; Hölzel et al., 2008; Luders and Kurth, 2019; Luders et al., 2009) and bilateral subiculum (Luders et al., 2013) volumes. Longitudinal studies showed that MBIs led to increase in hippocampal gray matter density among highly stressed adults (Hölzel et al., 2011) and patients with Parkinson's disease (Pickut et al., 2013), as well as attenuated hippocampal atrophy in elderly individuals with mild cognitive impairments (Wells et al., 2013). Post-MBI increase of subiculum volume was also found to be associated with improved cognitive performance among healthy individuals (Sevinc et al., 2020). Our recent research findings also suggest that MBI can increase hippocampal volumes in adult ACE survivors (Joss et al., 2020), but the prior study did not investigate any particular hippocampal subfields. Based on prior finding on subiculum volumes among long term meditators (Luders et al., 2013) or after an 8-week MBI (Sevinc et al., 2020), the current study is particularly interested in whether MBI can induce subiculum volumetric increases among ACE survivors.

The subiculum is a pivotal part of the hippocampal formation with widespread connections to other cortical and subcortical areas (O'Mara et al., 2001). As a result, the subiculum plays a critical role in the process of inhibitory control, in which the subiculum processes incompatible goal-related information and prevents responses towards conflicting goals (McNaughton, 2006). Inhibitory control is a fundamental process in meditation, because a primary goal of meditation is to replace *mindless reactivity* with *mindful responsivity*. For example, instead of mindlessly reacting to stressors out of habitual behavioral patterns, meditation practices eventually enable individuals to mindfully recognize and evaluate behavioral options in order to choose *wise* responses to situations in life (Lacaille et al., 2018). Therefore, the prior findings of enlarged subiculum among meditators were interpreted as major neural substrates for improved inhibitory control as a result of meditation practices (Luders et al., 2013).

Given that ACEs are associated with reduced subiculum volume (Teicher et al., 2012) and that MBI can promote subicular enlargement (Luders et al., 2013; Sevinc et al., 2020), we conducted a randomized control trial to assess whether MBI is more effective than an active control in increasing subiculum volumes among individuals with ACEs. We are specifically focusing on the subiculum as opposed to other stress-susceptible components of the hippocampal formation because MBI has not been reported to increase the volume of other subfields. This study builds on our prior work (Joss et al., 2021, 2020) but represents a significant advancement through the use of an active versus waiting list control, and the use of hippocampal segmentation software rather than voxel-based morphometry to more precisely gauge the effects of MBI on the subiculum (Joss et al., 2020).

Furthermore, research suggests that MBIs are associated with improvement in multiple cognitive domains including attention, memory, executive functioning and higher order processes (Gill et al., 2020; Whitfield et al., 2022). In particular, mindfulness training has been shown to improve the accuracy of discerning positive and negative stimuli (Kiken and Shook, 2011) and for reducing negative interpretations (Gibb et al., 2022). Our recent study using the Mnemonic Similarity Task (MST) also demonstrated that improved performance accuracy was associated with increased hippocampal volumes among ACE survivors (Joss et al., 2020). In the present study we used the pattern separation index from MST (Stark et al., 2013, 2019; Yassa et al., 2010) as a behavioral measurement for pattern separation capability, in order to assess whether MBI is more effective than an active control in enhancing this ability, and whether improvement in pattern separation is associated with hippocampal and subfield volumetric changes.

1.4. Summary of research plans and hypotheses

In summary, the present study aims to investigate the effects of MBI for ACE survivors on hippocampal volumes through a randomized controlled mechanistic clinical trial comparing MBI with an active control condition. In particular, based on prior studies that demonstrated MBI-related subiculum volumetric changes (Luders et al., 2013; Sevinc et al., 2020), we are particularly interested in the volumetric changes of the subiculum. Exploratory analyses will also be conducted to investigate the effect of MBI on other hippocampal subfields. The MST task is utilized to reflect pattern separation capability, and the contribution of subiculum, CA3, and dentate gyrus volumetric changes will be investigated.

2. Methods

2.1. Subject enrollment

This study was approved by the Institutional Review Board (IRB) of Mass General Brigham. Childhood adversity was assessed with the ACE questionnaire (Felitti et al., 1998) and the ‘Maltreatment and Abuse Chronology of Exposure’ (MACE) Scale (Teicher and Parigger, 2015). Clinical profiles were determined through structured clinical interviews based on DSM-IV-TR. Inclusion criteria included: (1) Current age between 21 and 35 years old. (2) Right-handed. (3) ACE exposure with ACE score above 1 or MACE score above 3; (4) Meeting MRI eligibility criteria. Exclusion criteria included psychosis, neurological disorders, use of psychotropic medications and supplements, routine use of illicit drugs during the past month, ongoing psychotherapy, prior participation of systematic meditation or mindfulness programs within the past 2 years or routine meditation practice during the past 6 months . ACE questionnaire (Felitti et al., 1998) is a 10-item questionnaire to inquire existence of 10 scenarios of childhood experiences such as abuse, neglect or household dysfunction (e.g., domestic violence, substance misuse, incarceration). The total number of questions to which a subject answer “Yes” adds up to a score between 0 abd 10. ACE questionnaire is widely utilized but does not capture all forms of childhood maltreatment. MACE is a 75-item questionnaire that includes additional assessments for various types of childhood maltreatment (e.g., non-verbal emotional abuse, peer verbal abuse, peer physical abuse, witnessing siblings abused by parents), but it’s relatively new and not yet as widely utilized. Scoring of MACE is based on the published scoring code (Teicher and Parigger, 2015). The cutoff score of 3 was experimented to be a minimum score to be considered to endorse childhood maltreatment. The reason for using both ACE and MACE for screening purposes was to overcome the possible limitation of a particular instrument and to include sufficient variability in the sample to investigate the potential contribution of childhood maltreatment severity on post-MBI neural changes that was found in our previous research (Joss et al., 2021, 2024). A total of sixty-four subjects were enrolled into the study, with 35 randomly allocated to MBI while the other 29 allocated to an active control condition called Stress Management Education (SME) (Hoge et al., 2013; Holzel et al., 2013; Sevinc et al., 2019) at a ratio of 1.2:1 stratified with gender. Randomization procedure was carried out with the randomization module in RedCap, which implements an allocation table generated in MATLAB with the above specified stratifications. Twenty-one subjects in the MBI group and 19 subjects in the SME control group completed the study. The rest of the subjects dropped out of the study and did not yield any post-intervention data, thus were not included in the analyses. There was no significant difference in the dropout rates between the two groups (40 % vs 38 %, X^2= 0.002, p = 0.96).

2.2. Research procedures

2.2.1. Overall procedure—After being determined as eligible, subjects were instructed to fill out online questionnaires and complete an MRI visit within a month before the intervention programs started. The MRI procedures included a 6 min anatomical scan and a 7 min resting state fMRI scan (the resting state fMRI will be reported in a future manuscript). Subjects completed the MST task on a Windows laptop outside the MRI scanner. Then subjects were randomized to attend either MBI or SME. Both intervention programs lasted 8 continuous weeks, which consisted of eight two-hour long *in-person* weekly meetings plus one 6 h whole day session on a weekend. Within a month after the intervention programs ended, subjects were administered the same research procedures.

2.2.2. MRI parameters—MRIs were acquired on a Siemens 3T Prisma system at the Imaging center of McLean hospital. A 64-channel head coil was used to acquire all MRI images. High resolution anatomical image was acquired using a T1-weighted multi-echo MPRAGE (MEMPRAGE) sequence (van der Kouwe et al., 2008), which acquires 4 separate structural scans with different TE values ranging from 1.69 to 7.27 ms, but in the same time as a conventional scan, and then the 4 separate images were averaged to increase the signal to noise ratio. Voxel size is 1.0 × 1.0 × 1.0 mm, Field of View (FOV) read is 256 mm, base resolution is 256, and there are 176 slices per slab. Phase encoding direction is A>>P. TR=2530 ms, TI=1100 ms, TE-1=1.6 9ms, TE-2=3.55 ms, TE-3=5.41, TE4=7.27 ms. Flip angle =7.0°. MRI anatomical data was visually inspected during data acquisition, any data that showed signs of motion artifact was re-acquired after reiterating to the subjects on the importance of staying still for the duration of MRI data acquisition.

2.3. Interventions

2.3.1. Mindfulness based intervention (MBI)—The MBI program was modeled after the Mindfulness Based Stress Reduction (MBSR) program (Kabat-Zinn, 1982, 1990; Kabat-Zinn et al., 1992), which covered a wide range of topics such as mindfulness and awareness, perception and perspectives, being present, responding vs. reacting to stress, stress coping strategies, dealing with difficult emotions, handling difficult communications, and using mindfulness in everyday life (Santorelli et al., 2017). Based on prior research on specific difficulties faced by trauma survivors (Vallejo and Amaro, 2009), the MBSR program was adapted into a trauma-sensitive MBI with emphasis on empowering the participants by using suggestive instead of directive language, incorporating more mindful movements, implementing more flexibility with homework, and providing options and choices whenever possible (Joss et al., 2019).

2.3.2. Stress Management Education (SME)—The SME program was adapted from our previous studies that used this intervention as the active control condition for MBSR (Hoge et al., 2013; Holzel et al., 2013; Sevinc et al., 2019), it was designed to closely match with the psycho-education component of the MBSR program except for the mindfulness component. The SME protocol closely matched the MBI protocol in the amount of time of weekly meetings and requirements for home practice of skills learned in class. Both MBI and SME groups were taught by licensed independent social workers with prior clinical experience, with the MBI instructor specialized in mindfulness meditation whereas the SME instructor specialized in cognitive behavioral therapy. The SME program includes psychoeducation about stress and stress physiology, sleep hygiene, time management, nutrition and healthy diet, as well as resilience and altruism.

2.4. Questionnaires

All subjects filled out a battery of psychological questionnaires through the REDCap secure online platform (Harris et al., 2009) before and after the intervention programs. Two questionnaires were analyzed in the present study: (1) Perceived Stress Scale (PSS): A brief, validated and widely used psychological instrument for assessing a subject's perception of stress (Cole, 1999). It consists of 10 questions that measure the degree to which situations in the subject's life are perceived as stressful, including questions related to how unpredictable or uncontrollable those events are perceived to be. (2) Mindful Attention Awareness Scale (MAAS): A 15 item questionnaire assessing the frequency of mindful states over time with a focus on the presence or absence of attention to and awareness of what is occurring in the present (Brown and Ryan, 2003). Additional questionnaires for comprehensive assessment of psychological symptoms were also administered and have been reported in other manuscripts.

2.5. MST Episodic memory task

The MST episodic memory task (Stark et al., 2019) is an explicit 3-alternative forced choice task, in which participants view novel (new), repeated (old) and lure (similar) stimuli. Stimuli are color photographs of common everyday objects. Each run consists of 16 similar pairs, 16 identical pairs and 44 unrelated novel items (foils), fully randomized throughout the run. Each stimulus is presented for 2000 ms with a 500 ms inter-stimulus-interval. Participants are instructed to make a judgment as to whether the object seen was new (i.e., novel items), old (i.e., repeated items) or similar but not identical (i.e., lure items). The whole task included 768 trials that were equally divided into 8 blocks, with 576 foil trials for which "new" was the correct answer, 96 target trials for which "old" was the correct answer, and 96 lure trials for which "similar" was the correct answer. Of critical interest are the participants' responses on the lure items. A response of "old" to a lure (i.e., similar) item would suggest that the participant was more biased towards *pattern completion*, whereas an accurate response of "similar" to a lure would suggest a bias towards *pattern separation* instead. The Lure Discrimination Index (LDI) (Stark et al., 2019) was calculated as:

$$LDI = \frac{\#\,of\ answering\ similar}{\#\,of\ lures\ tests} - \frac{\#\,of\ answering\ similar}{\#\,of\ target\ tests},$$

and the Corrected Recognition Memory (REC) score (Stark et al., 2019) was calculated as:

$$REC = \frac{\#\,of\ answering\ ``old"}{\#\,of\ target\ tests} - \frac{\#\,of\ answering\ ``old"}{\#\,of\ lures\ tests}.$$

2.6. Data analysis

2.6.1. Statistical analysis of questionnaire scores—We used Linear Mixed Effects Models (LME) (Lindstrom and Bates, 1988) to evaluate the treatment effects on PSS and MAAS scores. LME analyses were conducted with the "*nlme*" and "*MuMIn*" packages in statistical software R. The scores of each questionnaire were used as the dependent variable for each model, with "group" (i.e., MBI or SME) and "time point" (i.e., before or after the intervention) and group by time interaction as independent variables, with age, sex, race, and time-interval between the two measurements as covariates. Separate variance for each group and time point was used, and "REML" method was chosen to maximize the restricted log-likelihood.

2.6.2. Analyses of hippocampal subfields volumes—All anatomical MRI data was visually inspected for motion artifacts; for subjects that needed re-acquisition due to motion artifact, only the data without motion artifact was used for further analyses. Anatomical MRI data of each subject was analyzed with the longitudinal module of the FreeSurfer 6.0 software, which performs automated hippocampal subfield segmentation using a probabilistic atlas built with ultra-high-resolution *ex vivo* MRI data (Iglesias et al., 2015, 2016). A total of 12 hippocampal subfields (CA1, CA3, CA4, molecular layer, hippocampus tail, hippocampal fissure, para-subiculum, hippocampus-amygdala-transitional-area, pre-subiculum, fimbria, subiculum, dentate gyrus) were automatically segmented for each hippocampus with estimated volumes, but only the subiculum was included in hypothesis-driven group statistics.

Volumetric changes were further calculated as Symmetrized Percent Change (SPC) (Reuter et al., 2012), which is the rate of change with respect to the average of Baseline Volume (BV) and Post-Intervention Volume (PV), as outlined in Eq. (1). SPC is a more robust measure than the traditional calculation of Percent Change (PC) in Eq. (2), because the denominator is the average of BV and PV instead of BV alone, thereby SPC reduces the influence of BV on the quantification of post-intervention change. SPC also takes into the consideration of the individual variability with time interval between the two MRI measurements in number of days.

$$SPC = \frac{\frac{PV - - BV}{Time\ interval}}{0.5 * (BV + PV)} \tag{1}$$

$$PC = \frac{PV - BV}{BV} \tag{2}$$

LME analyses were conducted for group statistics, with SPC of the right whole hippocampus and subiculum as dependent variables, and "group" (MBI or SME) as independent variable, with Total Intracranial Volume (TIV), age, sex and race as demographic covariates.

Exploratory two-sample *t*-tests were conducted with the SPC values of other hippocampal subfields. To investigate whether maltreatment severity affects the effects of MBI on hippocampal volumes, exploratory Pearson correlation analyses were conducted, with pooled data from both groups, and separately with data from MBI group alone, between maltreatment measures including scores of ACE, MACE-number of types of maltreatment and MACE-total severity scores, and SPC of bilateral hippocampus and subiculum. Correction for multiple comparison was conducted with the "*p.adjust*" function in R using the Benjamini & Hochberg method (Benjamini and Hochberg, 1995).

In order to identify major factors contributing to hippocampal and subiculum volumetric changes, *post hoc* Variance Decomposition Analyses (VDA) were conducted with data from the MBI group using the R package "*relaimpo*". VDA is a widely utilized statistical technique to partition the total variance in an outcome variable into components of interest in order to quantify the amount of contribution of each regressor and to identify regressors that explain the most amount of variance in the regression model (Callen and Segal, 2004; Isakin and Ngo, 2020; Zaefarian et al., 2022). VDA analysis in this study started with a linear regression then utilized the "*calc.relimp*" R function to generate an estimated percentage of the amount of variance explained by each independent variable. The algorithm implemented in this R function (Lindeman, 1980) particularly takes into consideration of the correlations among regressors to more accurately gauge the relative importance of each regressor. The same algorithm was used in our previous cross-sectional study to quantify the amount of variance in hippocampal subfield volumes explained by ACE scores (Teicher et al., 2012). For VDA analyses in the present study, dependent variables in the linear regression models were SPCs of the right hippocampus and right subiculum volumes, with regressors included scores of the ACE questionnaire, total hours of intervention session attendance, and score changes of MAAS and score changes of PSS.

2.6.3. Analyses of performance from the MST episodic memory task—
LME models were used to analyze group statistics of MST task performance. LDI or REC were used as dependent variables, with scores of the ACE questionnaire, pre-intervention and post-intervention scores of MAAS and pre-intervention and post-intervention scores of PSS, as well as group, time point (i.e., pre- or post-intervention) and group by time interaction as independent variables, with age, sex, race, and time-interval between the two measurements as covariates.

In order to quantify the amount of contributions of neural changes to changes of LDI and REC, *post hoc* VDA were conducted with data from the MBI group with the same procedure as the VDA analyses described in Section 2.6.2. Dependent variables were score changes of LDI or REC, with predictors include SPC values of bilateral CA3, dentate gyrus and subiculum based on exiting MST literature (Bakker et al., 2012; Nash et al., 2021; Stark et al., 2013).

3. Results

3.1. Demographics and intervention compliance

The two groups did not differ significantly in the distribution of age, sex, race, childhood adversity, lifetime DSM diagnoses, or amount of intervention attendance (Table 1). The percentages of subjects with ACE scores of 0, 1, 2, 3, 4, and ≥5 are: 25 %, 20 %, 15 %, 10 %, 12.5 % and 17.5 %. As measured by MACE, the percentages of subjects having 0, 1, 2, 3, 4, and ≥5 types of childhood maltreatment are: 37.5 %, 12.5 %, 10 %, 10 %, 5 % and 25 %. One subject in the MBI group was excluded from further analyses due to incidental finding of neurological abnormality in MRI. A total of 20 subjects in MBI and 19 subjects in SME group were included in the rest of analyses.

3.2. Self-report questionnaires

LME analyses of PSS and MAAS scores demonstrated a significant effect of time ($p <$ 0.0001) with no significant group by time interaction. *Post hoc t*-tests showed that both groups had reduced PSS scores ($p < 0.01$) and increased MAAS scores ($p < 0.05$). Score changes were calculated as post-intervention scores minus pre-intervention scores, and there was no significant group difference with MAAS or PSS score changes.

3.3. Hippocampal volumetric changes

LME analyses of SPC values revealed significant group effects with the right whole hippocampus ($F = 5.43$, $p = 0.027$, effect size Cohen's $d = 0.55$) and the right subiculum ($F = 4.56$, $p = 0.041$, $d = 0.70$) (Fig. 1A). TIV was not a significant predictor for SPC of whole right hippocampus ($F = 1.01$, $p = 0.32$) or the right subiculum ($F = 0.68$, $p = 0.42$).

Exploratory two-sample *t*-test analyses were conducted with the SPC values of other hippocampal subfields, and no significant group difference was found. No significant correlations were found from exploratory analyses between measures of maltreatment severity and SPC values of bilateral hippocampus or subiculum.

Post hoc VDA analysis demonstrated that score changes (Δ) of MAAS (6 %) and score changes of PSS (5 %) were major contributors to SPC of the whole right hippocampus, whereas amount of intervention session attendance (4 %) was a major contributor to right subiculum SPC (Fig.1B).

3.4. Episodic memory performance changes and contributing factors

LME analysis demonstrated a significant group by time interaction effect for LDI ($p < 0.05$) with PSS score as a significant predictor ($p < 0.01$). *Post hoc* analysis with paired *t*-test showed that the MBI group had increased LDI ($p < 0.01$) while the SME group had no significant change (Fig. 2A). There was no significant group by time interaction effect for REC and neither group had significant change. *Post hoc* analysis with Pearson correlation revealed a significant correlation between LDI changes (ΔLDI) and PSS score changes (ΔPSS) in the MBI group ($r = -0.58$, $p < 0.01$, $N = 20$, Fig. 2B).

VDA shows that right subiculum SPC explained 10.05 % of the individual variability in ΔLDI in the MBI group, whereas the individual variability in ΔREC was mostly explained by SPC of the right subiculum (10.66 %), left CA3 (10.37 %), and left dentate gyrus (5.26 %) (Fig. 2C).

4. Discussion

Major findings from the present study include significant group differences with volumetric changes of the right whole hippocampus and right subiculum, as well as significant post-MBI improvement in pattern separation capability as reflected from LDI of the MST task.

4.1. Beneficial effects of MBI for hippocampal volumes

Our findings add to the growing body of literature demonstrating morphometric changes in the hippocampus following mindfulness training (Fotuhi et al., 2016; Hölzel et al., 2011; Joss et al., 2020; Pickut et al., 2013), in addition to cross-sectional findings of larger hippocampal volumes among long term meditators (Fox et al., 2014; Hölzel et al., 2008; Luders and Kurth, 2019; Luders et al., 2009). The longitudinal studies in particular have provided insights on the possible causality between MBI and hippocampus morphometric changes. For example, one VMB study identified a *left* hippocampus cluster that showed increased gray matter concentration after MBSR while the waiting list control had no significant change (Hölzel et al., 2011). Another study with a 12-week “brain fitness program” that included meditation training reported volumetric growth of the hippocampus in elderly with mild cognitive impairment (Fotuhi et al., 2016). A randomized controlled trial on MBI for patients with Parkinson’s disease (Pickut et al., 2013) showed increased gray matter density in bilateral hippocampus. Our prior study with ACE survivors also identified a right hippocampal cluster with post-MBI volumetric increase that was associated with amounts of stress reduction (Joss et al., 2020). Consistently, the present study also found group differences of volumetric changes of the right whole hippocampus and right subiculum. A recent study with healthy adults did not find significant post-MBI hippocampal volumetric changes (Kral et al., 2022), however there were multiple methodological issues such as overly extended data collection periods before and after MBI that might have compromised the sensitivity of neuroimaging discovery. Post-MBI hippocampal volumetric changes were also found to be associated with memory improvement (Greenberg et al., 2019). Our finding also revealed that improvement in mindfulness (ΔMAAS) and perceived stress (ΔPSS) contributed to the overall volumetric change of the whole right hippocampus, demonstrating a brain-behavior association with regard to the psychological and neural effects of MBI.

Very few prior studies investigated meditation related volumetric changes of specific hippocampal subfields, among which the subiculum in particular was identified to have morphological changes among long-term meditators (Luders et al., 2013) or in response to an 8-week MBI (Sevinc et al., 2020). The current study not only revealed a significant group difference with subiculum volumetric changes, but also found that the amount of intervention attendance specifically contributed to the volumetric changes of the right subiculum in the MBI group. Detailed discussions in the following paragraphs will comprehensively review the function of the subiculum and potential mechanisms for its involvement in MBIs.

One reason for the subiculum to be particularly responsive to MBI may be related to its critical role in *inhibitory control* (McNaughton, 2006) and *latent inhibition* (Weiner and Feldon, 1997) (Mingote et al., 2019), which is the essence of meditation practices (Cásedas et al.,2020). *Inhibitory control* refers to the conscious effort for inhibiting impulses, e.g., as measured by “go-no-go” cognitive tasks (Durston et al., 2002; Schall et al., 2017; Williams et al., 1999), whereas “*latent inhibition”* refers to the ability to ignore irrelevant stimuli, a concept originated from schizophrenia research to describe the inability to ignore non-salient stimuli (Lubow, 1973; Lubow and Gewirtz, 1995; Weiner and Feldon, 1997). Despite the subtle differences of these two concepts from respective literature background, both inhibitory processes are practiced during meditation, e.g., inhibiting the impulses to stop meditating (e.g., the urge to get up from the cushion) and practicing the ability to ignore any stimuli that’s not the prespecified focus of awareness (e.g., ignoring the sound of traffic from outside and focus the awareness on breathing). Another example is the cognitive processes during the MST task in this study, e.g., because 75 % trials in MST was foil (for which “new” was the correct answer), subjects had to inhibit the impulse to answer “new” to the less frequent target and lure trials, which is an example of *inhibitory control*. Because it was a lengthy task (~40 min), in order to stay focused, subjects had to ignore internal and external distractors, such as fatigue, boredom, ruminative thoughts or background noise from the external environment, which is an example of latent inhibition.

Meditation is essentially an *inhibitory* process. Meditation training includes the instruction to remain still for the duration of the meditation period, thus requiring repeated inhibition of urges to adjust posture, stretch, or get up and do something else (Kabat-Zinn, 2003). Furthermore, meditation is not a *thought-free* state, but rather a dynamic process during which “*mind wandering*” spontaneously occur (Hasenkamp et al., 2012) while the meditator repeatedly makes a conscious effort to bring awareness back to pre-specified focal point of attention such as breathing or body sensations (Feruglio et al., 2021; Hasenkamp et al., 2012). In other words, the meditator consciously inhibits the impulse to engage with the content of mind wandering (e.g., ruminating about the past or actively planning for the future). Prior meditation research have demonstrated enhanced response inhibition among experienced meditators (Andreu et al., 2019) or after intensive meditation training (Sahdra et al., 2011), or after several weeks of MBI (Greenberg et al., 2019). Such practice of inhibitory control may be particularly beneficial for trauma survivors, who are not only vulnerable to spontaneous mind wandering (Brosowsky et al., 2022; Nayda and Takarangi, 2021; Takarangi et al., 2014) but also susceptible to negative emotional reactivity in response to mind wandering (Green et al., 2016; Marcusson-Clavertz et al., 2017).

Anatomical research has demonstrated that the subiculum has widespread cortical and subcortical connectivity, enabling it to influence neural activity in disparate brain regions (O'Mara et al., 2001; Quintero et al., 2011), thereby substantiating its role in inhibitory control. For example, the subiculum has been found to have functional connectivity with the precuneus and posterior cingulate cortex of the Default Mode Network (DMN) (de Flores et al., 2017; Vos de Wael et al., 2018), in particular, a recent study found the subiculum has stronger functional connectivity with DMN than other hippocampal subfields (Katsumi et al., 2023). DMN is heavily involved in mind wandering (Mittner et al., 2016; Poerio et al., 2017), while numerous studies have shown mindfulness meditation modulates the DMN (Brewer and Garrison, 2014; Garrison et al., 2015) as well as its connectivity with other neural circuitries (Bremer et al., 2022; Rahrig et al., 2022). These findings further indicate that during meditation practices, the inhibitory control against mind wandering may extensively utilize the subiculum due to its connectivity with the DMN.

The subiculum's role in *latent inhibition* is another possible mechanism for its involvement in MBI. When impulses are *effortfully* inhibited during meditation (e.g., noticing being lost in mind wandering and bring attention back to focal point), it mostly engages the behavioral inhibition system in which the subiculum plays a pivotal role in resolving conflicts between incompatible goals hence achieving inhibitory control (McNaughton, 2006). Another mechanism is for meditators to ignore distraction by allowing the spontaneous thoughts from mind wandering to pass without engaging with them, which involves the process of *latent inhibition* (Weiner and Feldon, 1997), which refers to inhibited neural reactivity to non-salient stimuli and reflects the ability to ignore irrelevant stimuli (Weiner and Feldon, 1997). Preclinical and lesion studies have demonstrated that latent inhibition relies on input from the ventral subiculum to the nucleus accumbens (Quintero et al., 2011; Weiner and Feldon, 1997). As a major neural substrate for latent inhibition, the ventral subiculum acts as an interface between the hippocampus circuitry for contextual information processing and the ventral striatum of the motivation system, and modulates the dopamine levels in the mesolimbic system thereby affecting the expression of latent inhibition (Quintero et al., 2011).

Therefore, due to its pivotal role in the *inhibitory control* and *latent inhibition* processes that are heavily utilized in meditation practices, the observed post-MBI subiculum volumetric changes could be resulted from the increased utilization of this structure (Luders et al., 2013; Sevinc et al., 2020). Gray matter increases have been observed in other brain areas following repeated concentrated utilization of these brain regions during skill acquisition and expertise development. For example, motor skill learning (Sampaio-Baptista et al., 2014) and music training (Hyde et al., 2009) have been shown to lead to increased gray matter in motor

(Sampaio-Baptista et al., 2014) and auditory cortices (Hyde et al., 2009). Hippocampal morphological changes can be induced by various physiological mechanisms. Preclinical studies have demonstrated that social (Biggio et al., 2019), physical (Gabriel et al., 2020) or environmental enrichment (Monteiro et al., 2014) can stimulate neurogenesis of rodent hippocampus through restoring BDNF, NGF and Arc gene expression, increasing the density and morphology of dendritic spines, neuronal tree arborisation in granule cells (Biggio et al., 2019), or decreasing dopamine D2 receptor expression (Gabriel et al., 2020). The beneficial effect of MBI for hippocampal volumes likely works through similar processes, the exact cellular and molecular mechanisms of which are worth further investigation.

From a computational neuroscience perspective, the inhibitory control practiced during meditation interrupts existing habitual thought-feeling-behavior associations and rebuild new associations for new behavioral response patterns, which is a learning process that the hippocampus plays a pivotal role in Aitken and Kok (2022). A recent fMRI study showed the hippocampus engages in retrieval of existing associations at the beginning of the learning process and preferentially encodes unexpected stimuli according to the old framework, and as the learning of new association progresses and completes, the hippocampus switches to encode stimuli as predicted by the newly learned associations; in particular, in this process, the subiculum relays predictions from the hippocampal circuitry to the sensory cortex for processing the visual and auditory stimuli (Aitken and Kok, 2022). Such “belief updating” computational models (Nassar et al., 2010) are also endorsed in the meditation research field where the inhibition process in meditation practices facilitates the update of prior internal prediction model in response to unexpected sensory input to reduce prediction error, leading to adaptive behaviors well-adjusted to new contexts (Barrett, 2017; Barrett and Simmons, 2015; Farb et al., 2015; Kirk et al., 2019; Laukkonen and Slagter, 2021).

Although multiple subfields of the *left* hippocampus (the left CA2-3, CA4-dentate gyrus, pre-subiculum and subiculum) were found with smaller volumes among young adults with ACE compared to controls in the previous study (Teicher et al., 2012), our exploratory analyses of these subfields did not identify significant group differences with their SPC values. This could be attributed to multiple reasons: (1) the developmental impairment of these subfields might have compromised their ability for neural changes in response to MBI, or perhaps longer training periods are required to achieve observable effects. Therefore the current findings of post-MBI volumetric change of the *right* hippocampus could reflect a neural compensatory mechanism (Martins et al., 2015), e.g., working through areas with less developmental impairment to achieve behavioral improvements. (2) It is also possible that MBI does not influence all hippocampal subfields equally, and may particularly have selective effects on the subiculum (Luders et al., 2013; Sevinc et al., 2020) due to its pivotal role in inhibitory control and latent inhibition as extensively discussed above. Nevertheless the fact that the present study only observed significant group difference with the *right*, but not the *left* subiculum is still intriguing since prior meditation study has found effects with either bilateral (Luders et al., 2013) or left (Sevinc et al., 2020) subiculum. This could be due to the detrimental impact of ACE on the *left* subiculum (Teicher et al., 2012).

4.2. MBI improved pattern separation capability

The present study found that the MBI group, but not the SME group, had improved “pattern separation” capability of episodic memory as reflected from the LDI score from MST (Stark et al., 2019). Traumatic experience often results in compromised ability to discern perceived threats from actual threats (Miller, 2015), leading to the “hypervigilance” (Kimble et al., 2014) typically seen among trauma survivors (Dalgleish et al., 2001). The present study found that post-MBI reduction of perceived stress was significantly associated with LDI improvement (Fig. 2B), which is consistent with a recent finding that LDI was predicted by individual variability in PSS scores (Grupe et al., 2022). Such association is consistent with prior knowledge about the detrimental effects of stress on cognitive function, especially memory formation (McEwen and Sapolsky, 1995; Sandi, 2013). The finding from this longitudinal MBI study highlights the malleability of LDI in response to changes in stress levels, thus has potential clinical implications for treatments of stress-related disorders.

MST is known to reflect hippocampal functionality, particularly that of the CA3 and dentate gyrus (Bakker et al., 2012; Stark et al., 2013), as well as the subiculum (Nash et al., 2021). In the present study, the individual variability with volumetric changes of the right subiculum was a major contributor to the individual variability of post-MBI LDI changes (Fig. 2C), which elucidated the possibility of subiculum volumetric increase as potential neural substrates for post-MBI improvement in pattern separation capabilities. Post-MBI improvement in pattern separation capability is consistent with prior findings on the effect of mindfulness training for improving sensory acuity such as visual acuity (García-Martin et al., 2016; Langer et al., 2010) or tactile acuity (Kerr et al., 2008), which collectively reflect mindfulness-induced improvements in multiple domains such as attention control (Moore et al., 2012) and somatosensory awareness (Kerr et al., 2013). From the perspective of fundamental hippocampal function, the subiculum plays a key role in coordinating hippocampal-cortical interactions (O’Mara et al., 2001). A recent fMRI study identified right subiculum activation as well as right subiculum functional connectivity with DMN structures and temporal cortices during the pattern separation process of the MST experiment (Nash et al., 2021). Another fMRI study found post-MBI subiculum volumetric increase was associated with hippocampal-cortical functional connectivity during a fear conditioning task (Sevinc et al., 2020). Therefore, the observed contribution of subiculum volumetric change to the individual variability in post-MBI LDI change sheds light on potential neural mechanisms of MBI-induced pattern separation cognitive ability improvements in which the subiculum might play a critical role.

The REC index from MST reflects recognition memory for repeated items in the task, thus reflecting the tendency for *pattern completion*. Studies from the aging literature suggest that LDI declines with age whereas REC remains fairly stable (Dillon et al., 2017; Stark et al., 2019). Although the present study did not find significant longitudinal changes with REC at the group level, VDA analysis revealed that the individual variability in post-intervention REC changes were mostly driven by hippocampal subfield volumetric changes including that of CA3, dentate gyrus and subiculum. Such neural correlates are consistent with existing knowledge about the critical role of CA3 for identical object recognition (Dillon et al., 2017) and its activation during the pattern completion process of the MST task (Kirwan and Stark, 2007; Lee et al., 2004). Although the dentate gyrus (Bakker et al., 2012; Stark et al., 2013) and subiculum (Nash et al., 2021) were previously reported to primarily involve in the pattern separation process, their contribution to the individual variability in REC in the present study may reflect their potential role in substantiating MBI-related changes in episodic memory functioning.

4.3. Limitations and future directions

There are several major limitations with the present study that shall be addressed in future research: (1) The sample size is modest due to budget limitations, although it is comparable to several prior MBI neuroscience studies, e.g., $N = 26$ of the previous report on MBI-induced amygdala volumetric changes (Hölzel et al., 2010), $N = 27$ of an MRI study on the neural effects of MBI for Parkinson's disease (Pickut et al., 2013) as well as $N = 34$ of our previous study on a similar topic (Joss et al., 2020). Nevertheless, a larger sample is still desirable for yielding more robust findings. (2) This study included subjects with a wide range of severity and types of childhood maltreatment for the purpose of enabling investigation of the possible influence of childhood maltreatment severity on post-MBI neural changes. Such variability enabled our recent discovery of maltreatment severity modulating post-MBI amygdala volumetric changes (Joss et al., 2024). Nevertheless, this study did not find maltreatment severity significantly affecting post-MBI hippocampal volumetric changes. In future studies, an alternative approach would be purposeful selection of a relatively homogenous patient population, which can be more advantageous for illuminating MBI's effects for healing specific neural impacts of specific childhood adversity experiences with specific current psychopathology (e.g., target patient population of childhood sexual abuse survivors with current diagnosis of PTSD). (3) Despite our speculation on the involvement of the subiculum during the inhibitory control process in meditation, the current study did not have an fMRI experiment to directly observe such effects. Future studies with well-designed fMRI paradigms may shed light on real-time subiculum engagement during meditation. (4) The MST task was originally planned to be implemented as an fMRI task, but due to budget limitation, the task was administered outside the MRI scanner. It would have been more informative to directly investigate the hippocampal subfield activations during the MST task. (5) The interpretation for the role of subiculum in meditation practices is highly speculative due to lack of operationalized measures for inhibitory control or latent inhibition. To obtain further understanding on this topic, future research shall develop quantitative measures to probe the engagement of subiculum during these inhibitory processes in the context of meditation practices during fMRI experiments. (6) Human neuroimaging studies on the impact of ACE on hippocampal morphometry is fundamentally limited by the methodological limitations of MRI. Despite the tremendous progress with MRI technology and analyses algorithms during the past decades, there are still limited accuracy and precision for making definitive conclusions, and the investigation is constrained by the resolution of MRI signal and data analyses algorithms. Prior research also demonstrated different neural impacts of childhood maltreatment depending on the gender as well as the types and timing of the maltreatment (Teicher et al., 2018), therefore, depending on the sample composition of a particular study, the effects on a particular hippocampal subfield may not be significant. Similarly, investigation of neural effects of MBI is also constrained by the methodological limitations of MRI technology.

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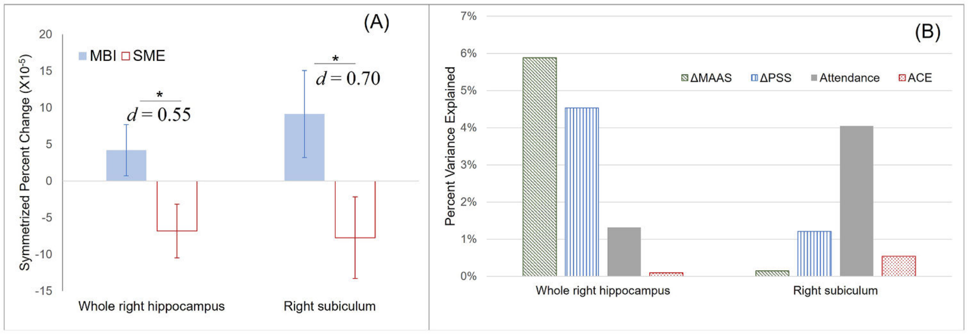

Fig. 1.

Findings on hippocampal volumetric changes. (A) Significant group differences ($p < 0.05$, medium effect sizes) with symmetrized percent change of the volumes of the whole right hippocampus and right subiculum. (B) Quantification of contributing factors to hippocampus and subiculum volumetric changes in the MBI group.

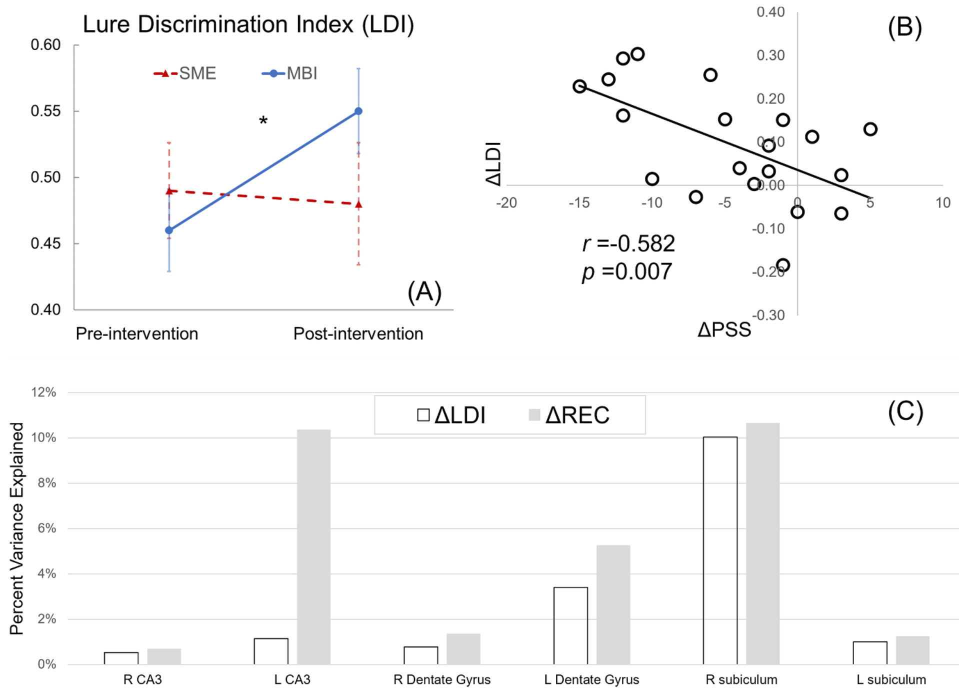

Fig. 2.

Findings from the MST episodic memory task. (A): Significant group by time interaction effect with LDI (reflecting pattern separation capability), with only the MBI group showing improvement. (B) Significant negative correlation between PSS score change and LDI change ($r = -0.33$, $p < 0.05$), suggesting stress reduction was associated with improvement of pattern separation capability.

Table 1

Subject demographic and clinical information.

	Mindfulness	**Control**	**Group Difference**
Sample Size (N)	21	19	
Sex: Female(F); Male(M)	F: 17; M: 4	F: 14; M: 5	Fisher's exact test: $p = 0.71$
Average Age (in years) (SE, range)	26.71 (0.88), 22-23	25.58 (0.74), 22-34	$t = 0.97$, $p = 0.34$
Race (Frequencies)			
White	10	8	Fisher's exact
Black/African American	0	3	test: $p = 0.21$
Asian	8	8	
Hispanic	2	0	
Unknown	1	0	
Childhood Maltreatment Assessments (Mean (SE), range)			One-Way ANOVA
ACE Scores	2.14 (0.48), 0-9	2.42 (0.46), 0-5	$F = 0.17$, $p = 0.68$
MACE-number of types of maltreatment	2.00 (0.58), 0-10	2.95 (0.66), 0-8	$F = 1.17$, $p = 0.29$
MACE-total severity scores	21.10 (3.69), 0-61	27.16 (4.06), 2-55	$F = 1.22$, $p = 0.28$
DSM-IV-TR lifetime diagnosis (Frequencies)			Fisher's exact test
Depressive Disorders	10	13	$p = 0.21$
Anxiety Disorders	15	15	$p = 0.72$
Average total hours of intervention class attendance (SE, range)	16.64 (1.01), 4-22	14.43 (0.84), 8-20	$t = 1.68$, $p = 0.10$