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A pilot study on amygdala volumetric changes among young adults with childhood maltreatment histories after a mindfulness intervention

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Abstract

The amygdala morphometry is highly sensitive to stress and is implicated in various psychopathologies that are common among individuals with childhood maltreatment histories. This pilot study investigated bilateral amygdala volumetric changes among 15 young adults with childhood maltreatment histories undergoing an eight-week mindfulness intervention compared to 19 matched participants in a waitlist control group. Results indicated significant cross-individual variability in amygdala volumetric changes after the intervention, which resulted in no significant group by time interaction effect. Degree and direction of changes in right amygdala volume correlated with baseline volumes, with larger than average right amygdala showing an increase in volume and smaller amygdala a decrease. Increasing right amygdala volume was also associated with higher intervention compliance, and a greater increase in self-compassion. Increasing left amygdala volume was associated with more reduction in perceived stress, rejection sensitivity and interpersonal distress. Findings from the present study highlight the importance of investigating individual variability and its contributing factors in future studies on neural responses of mindfulness interventions, as well as the distinct responses of the left and right amygdala.

Keywords

stress reduction; childhood maltreatment; neural plasticity; anxiety; MBSR; MRI

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[5]Conflict of 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.

1 Introduction

Over 60% of Americans have experienced at least one category of adverse childhood experience and 20% experienced three or more [1]. Studies indicate that childhood maltreatment is a significant risk factor for various mental health issues [2]; 37% adults who were abused during childhood had a lifetime diagnosis of major depressive disorder, 39.6% had an anxiety disorder and 19% had PTSD [2]. Furthermore, these individuals also tend to have earlier symptom onset, more recurrent episodes, more comorbid disorders [3], as well as poorer response to traditional treatments [4].

The amygdala is an important brain structure for fear and stress response [5]. Developmental studies have found that the amygdala is particularly sensitive to early life stress [6] and that early life stress induces long lasting structural and functional changes in the amygdala [7] [8]. As a behavioral result, the victim's threshold of emotional reaction is often lowered, resulting in heightened excitability of the neural system for emotional response, which puts the individual at risk of various psychiatric disorders [7].

An increasing number of studies suggest that mindfulness-based intervention are helpful for various psychological symptoms including depression, anxiety and PTSD [9,10]. It was suggested that mindfulness practices enhance awareness of present moment experiences which facilitates emotion regulation [11], and provides a healthy alternative for past-focused ruminations and future-oriented worries which are common symptoms of depressive and anxiety disorders [12]. Our recent studies also showed reduced stress, depression, anxiety and PTSD symptoms among young adults with childhood maltreatment history after a mindfulness-based intervention [13,14].

Studies also suggest associations between mindfulness and amygdala morphometry. For example, one study found that dispositional mindfulness was associated with smaller amygdala volumes in community adults [15], while another study showed that reduction in perceived stress after a Mindfulness Based Stress Reduction (MBSR) program was associated with decrease in the right amygdala gray matter density [16]. These prior studies suggest that amygdala morphometry may be influenced by mindfulness practices.

Given the intricacies of the interplay between childhood maltreatment and amygdala development, this pilot study aimed to investigate whether a mindfulness-based intervention induces similar amygdala morphometric changes among young adults with histories of childhood maltreatment as previously reported in non-trauma exposed populations [11,17]. We further explored the relationship between these changes and changes in psychological symptoms.

2 Methods

2.1 Subject enrollment

This study was approved by the Partners Human Research Committee (PHRC), the Institutional Review Board (IRB) of Partners HealthCare (IRB#: 2014P000295), which serves the Massachusetts General Hospital, McLean Hospital and several other hospitals in the area. Clinical trial information of this study is publicly available at https://clinicaltrials.gov/ct2/show/NCT02447744.

Comprehensive clinical assessment on childhood experience and psychiatric history were performed through structured clinical interview as well as quantitative self-report questionnaires, as detailed in our recent publication [14]. Childhood maltreatment was measured with the Adverse Childhood Experience (ACE) questionnaire [1], and the Maltreatment and Abuse Chronology of Exposure (MACE) questionnaire [18]. Participants were enrolled into the study if they (1) had at least a score of 1 on ACE or at least one types of maltreatment based on their response on the MACE questionnaire, (2) were between 21–35 years old, (3) had no suicide attempts during the past six months, (4) had no history of neurological disorders or psychiatric disorders with psychotic features, (5) currently not on medications that alter cerebral metabolism, (6) were eligible for MRI, and (7) had no prior experience with the MBSR program [19] or other systematic meditation programs.

A total of forty-three participants were enrolled into the present study (Figure 1.A), with 21 allocated to the mindfulness-based intervention while the other 22 were placed on the waitlist. A total of 7 participants did not yield complete research data due to drop out (N=1 in the waitlist and N=3 in the mindfulness group) or logistic reasons (N=3 in the mindfulness group). Among the originally allocated participants, the mindfulness group had a total of 15 participants who completed both *pre*- and *post*-intervention MRIs and questionnaires; the control group had 21 participants who completed both pre- and post-intervention MRIs, however, one control participant did not complete baseline questionnaires but completed post-waiting questionnaires, while another two control participants completed questionnaires at baseline (*pre*-waiting period) but did not complete them at *post*-waiting period, thus the final subject number in the waitlist control group was 21 for MRI analyses and 18 for questionnaire analyses who provided data from both pre- and post-waiting periods. In addition, six control participants completed the intervention after their waiting period. All of the six completed post-intervention MRI, which is their 3rd MRI. However due to statistical concerns, the 3rd MRI was not included in the data analyses.

2.2 Research Procedures

Overall procedure—Participants first went through a clinical interview to determine their eligibility, then eligible participants were instructed to fill out a battery of online questionnaires and to complete an MRI visit which were typically within a month before the start of the mindfulness intervention program, or the corresponding time for participants in the waitlist. At the MRI visit, all participants underwent a urine drug test and female participants also completed a urine pregnancy test. Participants also completed an episodic memory task on the computer outside the MRI scanner, which was reported in a previous publication [20]. Then participants attended the mindfulness-based intervention program for 8 continuous weeks, which consisted of eight 2.5 hour long weekly sessions that took place on a weekday evening plus one 6-hour session on a weekend day. Within a month after the intervention program was finished, participants came back for a second MRI visit during which they repeated the same MRI and computer test procedures and completed the same online questionnaires. Participants on the waitlist were administered the same research procedures around the same time as participants of the intervention program.

MRI parameters—MRIs were acquired on a 3T Siemens magnetom Skyra system at the Martinos Center for Biomedical Imaging of the Massachusetts General Hospital. A 32-channel head coil was used to acquire all MRI images. The MRI procedures included a 6-minute anatomical scan, and a 7-minute resting state fMRI scan that is not included in this manuscript. High resolution anatomical image was acquired using a T1-weighted multi-echo MPRAGE (MEMPRAGE) sequence [21], which acquires 4 separate structural scans with different TE values ranging from 1.5 to 7 ms, but in the same amount of 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 256mm, base resolution is 256, and there are 176 slices per slab. Phase encoding direction is A>>P. TR=2530ms, TI=1100ms, TE 1=1.69ms. Flip angle =7.0 degrees.

Research Questionnaires—The following research questionnaires were used in the present study to investigate their association with amygdala volumetric changes: Perceived Stress Scale (PSS) [22], Mindful Attention Awareness Scale (MAAS) [23], Self-Compassion Scale (SCS) [24], Adult Rejection Sensitivity Questionnaire (ARSQ) [25] and Interpersonal Reactivity Index-Personal Distress (IRI-PD) [26]. The intervention effects on these questionnaire scores have been reported and discussed in our recent publications [13,14].

2.3 Mindfulness Based Intervention Program

The mindfulness-based intervention program consisted of group meetings of about 2.5 hours with the instructor once a week for eight continuous weeks and an additional six-hour whole-day mindfulness “retreat” led by the instructor in week 6 (Figure 1.B). The intervention program was based on the MBSR program [19], which covered 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 [27]. Several modifications were adapted for our study population to promote the sense of safety and empowerment [13], such as providing meditation practice instruction audios of various length for participants to choose from and incorporating more mindful movement components, all of which are essential to trauma-sensitive mindfulness teaching [28].

2.4 Data Analysis

2.4.1 Amygdala volumetric estimation and analyses—Amygdala volumetric estimation was conducted with the high resolution T1-weighted MPRAGE MRI of each subject using the longitudinal module of Freesurfer 6.0 [29]. The following output was extracted from each subject for further statistical analyses: left and right amygdala volumes, and total subcortical gray matter volumes. Data from two participants in the control group was excluded from analyses because of minor MRI artifact.

Further statistical analyses were conducted using the statistical software R and MATLAB. First, we used independent two-sample *t*-tests to assess whether there was significant group difference of baseline bilateral amygdala volumes. Then, we performed Pearson correlation analyses between adjusted baseline bilateral amygdala volumes and childhood maltreatment severity measures. Furthermore, to investigate the effect of the mindfulness intervention, we used linear mixed effects models [30] to evaluate the group by time interaction effects, as well as the effects of time within each group, for left and right amygdala volumes, using the "lme" function of the "nlme" package in R. Age, sex, race, cohort, time-interval between the two assessments, as well as total subcortical gray matter volumes at each time point were used as covariates. Amygdala volumes of each research participant from each time point was adjusted with their total subcortical gray matter volumes. Percent change in amygdala volume was calculated as the difference between pre and post-intervention (or wait period) adjusted volumes divided by the pre-intervention adjusted volume times 100.

To assess the contributing factors to amygdala volumetric changes in the mindfulness group, baseline amygdala volumes, questionnaire score changes, number of intervention sessions attended, and total minutes of home practice were correlated with the percent change in left and right amygdala adjusted volumes, respectively using Pearson correlation analyses. Post-hoc power analysis was conducted with G*Power 3.1 [31] to determine the achieved power (1- β error probability) of each correlation coefficient with $p < 0.1$, based on an α error probability of 0.05. For purpose of comparison, similar analyses were also conducted with data from the control group.

2.4.2 Correlation of baseline amygdala volumes and post-intervention amygdala volumetric change—

We used Pearson correlation to investigate the association between baseline volumes and the percent change in left and right amygdala volumes. A statistical concern that arises in this type of analysis is "regression to the mean", which is frequently observed in test-retest analyses. Because a single measure of a parameter is an estimate, initial measures that overestimate the parameter will usually be followed by smaller subsequent measures whereas initial measures that underestimate the parameter will typically be followed by larger measures, producing a "regression to the mean" artifact. The degree to which this regression occurs depends on the test-retest reliability of the measure [32]. Highly reliable tests show little "regression to the mean" artifact, whereas tests with low reliability will demonstrate a large "regression to the mean" artifact. The magnitude of the "regression to the mean" artifact varies from $r = -.707$ to $r = 0$, following the formula

$$-\sqrt{\frac{(1-\rho)}{2}},$$

where ρ is the test-retest reliability of the measure. A treatment is considered to be 'rate dependent' if the correlation between percent change is significantly different than the null effect line derived from the test-retest reliability of the measure. The test-retest reliability of FreeSurfer volumetric estimate was reported to be 0.88 [33], thus for the null hypothesis, i.e., the intervention is ineffective and the sample is random, the correlation coefficient between baseline measurement and the amounts of change should be −0.24 according to the above formula. Fisher's test was used to evaluate whether the observed correlation in the mindfulness group was significantly different from −0.24.

2.4.3 Analyses on behavioral implications of amygdala volumetric changes

—To explore the behavioral implications of amygdala volumetric changes, in addition to Pearson correlation analyses between amygdala volumetric changes and questionnaire score changes in each group, multiple regression analysis was used to ascertain the degree to which change in adjusted right and left amygdala volumes in each group were associated with changes in MAAS, SCS, PSS, IRI-PD and A-RSQ scores. To assess the relative contribution of each psychological measure, the Lindeman, Merenda, and Gold [34](“lmg”) variance decomposition technique embedded in the “calc.relimp” function in the “relaimpo” package of R statistical software [35] was used to apportion variance in models with cross-correlated predictor variables.

3 Results

3.1 Subject demographic information and self-report questionnaire data

As expected, there was no significant group difference (p > 0.22) on demographic information between the two groups (Table 1). Detailed information on self-report questionnaire data were reported in our prior publications [13,14]. There were significant group by time interaction effects with all five research questionnaires in this study: PSS, MAAS, SCS, A-RSQ and IRI-PD (Table 1), with the mindfulness group showing significant improvement in perceived stress, mindfulness, self-compassion, rejection sensitivity and interpersonal distress ($p < 0.05$).

3.2 Association between childhood trauma and amygdala baseline volumes and volumetric changes

At baseline, the two groups did not have significant group difference with bilateral amygdala volumes ($p > 0.42$). Among all participants from both groups, there were no significant correlations between baseline adjusted amygdala volumes and ACE scores or total number of types of childhood trauma from MACE ($p > 0.34$).

Within the mindfulness group, MACE early exposure severity scores were associated with the percent change of the adjusted volumes of the left amygdala ($r = 0.57$, $p < 0.05$, Figure 2.A), whereas MACE late exposure severity scores were associated with the percent change of the right amygdala ($r = 0.45$, $p = 0.09$, Figure 2.B).

3.3 Group statistics and individual variability of amygdala volumetric changes

There was no significant main effect of group, time, or group by time interaction for either left or right amygdala (all $p > 0.32$) volumes. Within group analyses also revealed no significant effect of time point (post vs. pre-intervention/waiting) with either amygdala ($p > 0.39$). Considerable individual variability was observed with regard to the amount of post-intervention volumetric changes, which contributed to the non-significant group statistics. The percent change of each individual subject from each group are plotted in Figure 3.

3.4 Right amygdala volumetric changes were correlated with baseline volumes and intervention compliance

Among participants in the mindfulness group, there was a positive correlation between adjusted baseline volumes and percent change of right amygdala volumes ($r = 0.65$, $p < 0.01$; Figure 4.A). Participants with lower baseline right amygdala volumes tended to have decreased volume after the intervention, while participants with higher baseline volume tended to have increased volumes after the intervention. The relationship appeared similar with the left amygdala although not significant ($r = 0.22$, $p = 0.43$). Fisher's test of correlations against a fixed value [36] indicated that both of the above correlation coefficients are significantly different from that of the null hypothesis (i.e., $r = -0.24$), with Z = 1.65, $p < 0.05$ for the left amygdala and Z = 3.56, $p < 0.0001$ for the right amygdala. Moreover, the direction of change was opposite to that which could be attributed to a regression to the mean artifact as larger baseline measures were associated with larger rather than smaller post-treatment measures of amygdala volume. The correlation patterns are very different for the control group, with $r = -0.23$, $p = 0.35$ for the left amygdala and $r = 0.10$, $p = 0.67$ for the right amygdala.

Within the mindfulness group, percent changes of the right amygdala volumes had positive correlations with the number of intervention sessions attended ($r = 0.51$, $p = 0.05$, Figure 4.B), and total minutes of home practice ($r = 0.47$, $p = 0.08$, Figure 4.C). SCS score change was positively correlated with baseline adjusted volume of the right amygdala ($r = 0.52$, $p < 0.05$, Figure 4. D), as well as right amygdala volume percent changes ($r = 0.55$, $p < 0.05$, Figure 4.E, Table 2).

In contrast, in the waiting list control group, right amygdala volumetric changes had no significant correlation with baseline right amygdala volume ($r = 0.10$, $p = 0.67$) or changes in self-compassion ($r = 0.20$, $p = 0.41$).

3.5 Left amygdala volumetric changes were correlated with stress reduction

Within the mindfulness group, there was a significant negative correlation between PSS score changes and percent change of total adjusted left amygdala volumes ($r = -0.73$, $p < 0.01$, Figure 5.A). Pearson correlation between bilateral amygdala volumetric changes and score changes of IRI-PD and A-RSQ within the mindfulness group showed score changes of IRI-PD ($r = -0.59$, $p < 0.05$, Figure 5.B) and A-RSQ ($r = -0.63$, $p = 0.01$, Figure 5.C) only had significant correlations with volumetric changes of the left but not the right amygdala (Table 2).

In contrast, in the waiting list control group, left amygdala volumetric changes were not significantly correlated with any of the above symptom changes (PSS: $r = 0.32$, $p = 0.25$, ARSQ: $r = -0.33$, $p = 0.25$, IRI-PD: $r = 0.31$, $p = 0.27$).

3.6 Percent variance of amygdala volumetric changes explained by questionnaire scores

Further analyses were conducted to investigate the percent variance of amygdala volumetric changes explained by questionnaire scores in the mindfulness group. Questionnaire score changes in total explained 77.24% inter-subject variance of the percent change of adjusted volumes of the left amygdala, among which PSS score change explained 26.05% ($p < 0.01$), and A-RSQ score change explained 32.36% ($p < 0.05$) (Figure 6). Questionnaire score changes in total explained 56.47% variance of the right amygdala, among which SCS score change explained 34.79% ($p < 0.05$).

In contrast, within the waiting list control group, these questionnaires only explained 22.27% of the variance with volumetric changes of the left amygdala, and none of them was a significant regressor ($p > 0.38$). The questionnaire that explained the most variance was A-RSQ, which explained 8.34%. With regard to volumetric changes of the right amygdala, these questionnaires in total explained 42.24% variance, none of them was a significant regressor ($p > 0.11$), and SCS explained the most variance (12.46%) among all questionnaires.

4 Discussion

This pilot study investigated amygdala volumetric changes after a mindfulness-based intervention among young adults with childhood maltreatment histories. Primary findings from this study include:

1. There were different associations of early vs. late childhood maltreatment with amygdala volumetric changes, with the left amygdala showing more influence from early childhood maltreatment whereas the right amygdala showing more influence from maltreatment during adolescence.
2. There was no significant main effect of group, time, or group by time interaction for either left or right amygdala volumes.
3. The mindfulness intervention had different effects on left and right amygdala volumetric changes, with the right amygdala volumetric change associated with intervention compliance and improvement in self-compassion, whereas the left amygdala volumetric change associated with reduction in perceived stress and interpersonal distress.
4. Baseline volumes of the right amygdala were significantly correlated with post-intervention volumetric changes.

These findings provide directions for further investigation on factors concerning childhood maltreatment and individual variability in neural responses to mindfulness intervention, as well as future research on potential clinical applications. The following sections will discuss these findings in more detail.

4.1 Impact of childhood maltreatment on amygdala baseline volumes and post-intervention volumetric changes

Human neuroimaging studies on the effects of childhood maltreatment on amygdala morphometry have conflicted findings [6,7]. For example, some studies found institutionalized children had larger amygdala volumes than controls [7,37], while other studies found adults with childhood trauma history had smaller amygdala volumes [38,39]. The complexity arises from multiple factors such as the timing of the stress during the course of neural development (e.g., neonatal vs. early life vs. adulthood) [7], types of maltreatment (e.g., abuse vs. neglect), and timing of measurement in research (e.g., effect of childhood maltreatment measured in adult research participants vs. measured in children). A myriad of factors can cumulatively affect the amygdala morphometry, giving rising to the variability across different samples and individuals. This study did not find a significant correlation between overall childhood maltreatment severity and baseline bilateral amygdala volumes, which is similar to the insignificant finding in several prior studies [6]. Due to the complex contributing factors, this study did not have sufficient statistical power to detect the nuances in the association between childhood maltreatment severity and baseline amygdala volumes.

Previous studies suggest the left and right amygdala could be impacted differently by childhood trauma. For example, studies showed that the right amygdala was sensitive to childhood maltreatment exposure during preadolescence [40], whereas the left amygdala was more sensitive to disorganized maternal attachment during infancy [41]. Their interpretation was that the left and right amygdala responds differently to the two critical developmental threats, with the left amygdala responds strongly to rejection or neglect, which is a critical developmental threat during infancy, whereas the right amygdala responds strongly to abuse, which is a more likely developmental threat during preadolescence [41].

The present study also observed different impacts of childhood maltreatment on the left and right amygdala volumetric changes. We found that individuals with more severe late exposure (between ages 13–18) to childhood trauma had more volumetric increase of the right amygdala after the intervention. In contrast, early exposure (between ages 1–6) severity to childhood trauma were associated with left amygdala volumetric increase after the intervention. Further analyses showed that right amygdala volumetric increase was associated with better intervention compliance and improvement in self-compassion, whereas left amygdala volumetric increase was associated with stress reduction related therapeutic effects. These preliminary findings suggest that the left amygdala was sensitized by early childhood trauma, and mostly responds to the stress reduction component of the intervention, whereas the right amygdala was more impacted by childhood trauma during adolescence and responds more to the mindfulness/self-compassion elements of the intervention.

While it's far-fetched to imagine that childhood experiences from many years ago can still influence neural responses to an eight-week mindfulness program, it's reasonable to suggest that childhood maltreatment experience affects the susceptibility of the neural system to certain stimuli, which eventually affects the therapeutic effects of a particular intervention for an individual with such susceptibility.

4.2 Mindfulness intervention had different effects on left and right amygdala volumes

4.2.1 No significant group by time interaction effect with bilateral amygdala volumes—Firstly, it's important to note that due to considerable individual variability, there was no significant main effect of group, time, or group by time interaction for either left or right amygdala volumes in this study. However, this does not necessarily lead to the conclusion that the intervention had the same effect as the waiting list control. Further analyses showed that only in the mindfulness intervention group, but not in the waiting list control group, amygdala volumetric changes had significant correlations with symptom reduction, e.g., left amygdala volumetric increase was significantly correlated with reductions of perceived stress, rejection sensitivity and interpersonal distress. Similarly, also only in the mindfulness group but not in the control group, baseline right amygdala volume was significantly correlated with post-intervention volumetric changes. These findings suggest that compared to the waiting list control group, the mindfulness group still had distinct amygdala volumetric changes that are associated with symptom changes.

Similarly, a previous MBSR study [16] also found no significant post- vs. pre- intervention change of amygdala volumes with group mean, but found significant associations between individual variance in amygdala volumetric changes and amounts of reduction in perceived stress. Similar findings of non-significance of group mean in the present study and the previous study highlight the importance of investigating individual variability and its contributing factors in future studies on neural responses to mindfulness interventions.

Analyses on percent variance explained by questionnaire score changes showed that score change of A-RSQ, an indicator of changes in rejection sensitivity, explained the most variance in *left* amygdala volumetric changes, both in the mindfulness (32.36%) and the control group (8.34%), although to drastically different extent; similarly, score change of SCS, an indicator of changes in self-compassion, explained the most variance in *right* amygdala volumetric changes, both in the mindfulness (34.79%) and the control group (12.46%). Such similarity points out the possibility that there are fundamental behavioral correlates of amygdala volumetric changes, e.g., association of attachment/rejection with the left amygdala, and self-compassion with the right amygdala, regardless whether changes in these psychological factors occurred naturally (as in the waiting list control group) or induced by the mindfulness intervention. Nevertheless, the fact that the behavioral correlates were only significant in the mindfulness group but not in the control group suggest that the mindfulness intervention augmented those specific fundamental brain-behavior connections and facilitated these brain-behavior changes more reliably compared to naturally occurring processes without the intervention.

The different effects of the mindfulness intervention on the left and right amygdala volumetric changes will be discussed in further detail in following sections.

4.2.2 Baseline volumes of right amygdala were associated with post-intervention volumetric change and changes in self-compassion—The present study found both baseline right amygdala volumes and right amygdala volumetric change were significantly correlated with score change of self-compassion. Our recent study on the clinical effects of a mindfulness intervention for young adults with childhood maltreatment histories [14] showed that increase in self-compassion was an mediating factor between changes in mindfulness levels and reduction of perceived stress and anxiety [14]. Childhood maltreatment often leads to low self-esteem [42] and self-criticism [43], which underlies various psychopathology [42,43]. Therefore, cultivating self-compassion is a necessary component for healing from childhood maltreatment. Because baseline volumes of the right amygdala were found to be associated with post-intervention score changes of self-compassion and right amygdala volumetric changes, it can be a potential biomarker to predict therapeutic values of mindfulness interventions for adults with childhood maltreatment histories, which is worth further investigation on potential clinical applications.

4.2.3 Left amygdala volumetric change were associated with changes in perceived stress and rejection sensitivity—

The present study also found a positive correlation between severity of early (age 1–6) childhood maltreatment exposure and the amount of left amygdala volumetric changes after the mindfulness intervention, suggesting the long-lasting impact of early childhood maltreatment on the malleability of the left amygdala to behavioral changes later in life. This is consistent with the previous finding that the left but not right amygdala was sensitive to quality of attachment at 18 months [41]. We also found negative correlations between left amygdala volumetric change and the score change of interpersonal distress and rejection sensitivity, two behavioral indicators of fear and threat detection in interpersonal relations, which also support the specific role of the left amygdala on processing rejection related developmental threat.

The childhood maltreatment measured in the present study are focused on adverse interpersonal experiences (e.g., abuse and neglect from caregivers), which often has long lasting impact on individuals' interpersonal relationships [44], especially on their fundamental perception of social inclusion/isolation, leading to heighted sensitivity to cues of rejection and distress during interpersonal interactions [45]. Therefore, reduction of interpersonal stress is an important aspect of healing for childhood maltreatment survivors. Our recent study found significantly reduced rejection sensitivity after the same groups of research participants went through the mindfulness intervention [13], and findings in the present study further relates these psychological changes with the underlying neural changes, which enriches our understanding on the therapeutic mechanisms of the mindfulness intervention for individuals with childhood maltreatment histories.

4.2.4 Theoretical background of the different behavioral implications of left and right amygdala volumetric changes—

The volumetric changes of the left and right amygdala appear to have different behavioral implications in the present study. Volumetric changes of the right amygdala were correlated with intervention compliance and changes in self-compassion, whereas volumetric changes of the left amygdala were correlated with changes in overall perceived stress and particularly interpersonal stress.

Several studies have sought to differentiate the response of the left versus right amygdala to emotional stimuli. In general, the right amygdala shows a greater response to fearful faces versus neutral faces than the left amygdala, which is particularly true among individuals with histories of childhood maltreatment [46]. In contrast, the left amygdala appears to be more selective and shows a differential response to fearful stimuli versus non-fearful stimuli that produce comparable increases in eye white area [47]. A proposed possibility is that the right amygdala is involved in the rapid and automatic detection of possible danger sources while the left amygdala provides a more nuanced determination of whether a potential threat is real [47].

During the mindfulness intervention program, a lot of the teaching and practices emphasized alteration of the “auto-pilot” behavioral pattern, and the intervention aimed to teach “responding instead of reacting” to stressful situations. In other words, the mindfulness intervention aimed to cultivate meta-awareness of individuals’ ongoing mental status, and to enable choices of behavioral responses instead of falling prey for habitual “automatic” reactivity. The dose-dependent volumetric increase of the right amygdala could be a result of such practice of “de-automaticity”, which is similar to prior findings of skill learning related gray matter increase in brain areas associated with the learned skill, such as increased gray matter in the motor and auditory cortices after music training [48]. The positive correlation between baseline right amygdala volumes and right amygdala volumetric changes after the intervention indicates that larger baseline right amygdala volumes could have facilitated corresponding individuals’ mindfulness learning, which in turn further promoted the volumetric increase of the right amygdala as a result of the mindfulness learning and practices.

4.2.5 Increased amygdala volumes were associated with positive behavioral changes—Regardless of the laterality difference, findings in the present study suggest amygdala volumetric increases were associated with positive behavioral changes, e.g., more mindfulness practices and increased self-compassion (right amygdala) or more stress reduction (left amygdala). This beneficial volumetric increase is similar to a previous finding of increased gray matter density after a mindfulness-based intervention among patients with Parkinson’s disorder [49]. Previous cross-sectional studies had similar findings on the beneficial effects of larger amygdala volumes, for example, one study found that individuals with larger amygdala volume tended to have less stress-evoked amygdala activation and blood pressure reactivity [50], another study found that individuals with larger amygdala volumes had more people in their social networks [51]. The findings from this study further highlighted the potential therapeutic value of amygdala volumetric increase in certain populations.

4.3 Comparison with previous findings

The present study found a negative correlation between PSS score change and left amygdala volumetric change, which is contradictory with findings from a prior study of reduced stress being associated with decreased right amygdala gray matter density after the MBSR program [16]. There were technical differences between the studies, as the previous study used VBM protocol for gray matter concentrations to identify a significant cluster of 10 voxels within the amygdala mask, whereas the present study used Freesurfer volume estimation of the whole amygdala. Our additional analyses using the same VBM protocol for gray matter concentration found that decreased stress was associated with increased left amygdala gray matter concentration (see supplementary material, Figure S1, Table S1), which is still contradictory with the previous finding [16] in terms of the direction of the association between post-mindfulness amygdala morphometric changes and stress reduction.

The present study has several important differences with the previous study that could account for the contradictory findings. First, participants in the present study all experienced some extent of childhood maltreatment and demonstrated multiple psychological symptoms at the time of study, while participants in the previous study were "stressed but otherwise healthy" [16]. The impact of childhood maltreatment on amygdala development could have affected how the amygdala responded to the mindfulness intervention. Second, the present study made several adaptations to the standard MBSR program to accommodate the trauma exposed population. In particular, length of meditation practice was adapted with flexibility [13] as opposed to the standard requirements of 45 minutes daily home practice. As a result, participants in the previous study had much more total home practice (average ~20 hours) than those in the present study (average ~12 hours [14]). Different patterns of neural changes with different amounts of skill practices have been previously observed in other domains [52,53]. For example, a prior study found different patterns of neural changes after six weeks of juggling practice following either a low or high intensity regime. Although the two groups achieved similar performance level in the end despite the different practice intensity [52,53], the group with the low intensity practice regime had a negative association between skill performance scores and percent change of gray matter volume change in the left motor and dorsal medial prefrontal cortex, whereas the group that had high intensity practice had the opposite association patterns [52].

Existing knowledge suggests that the time course of gray matter structural change is not necessarily linear [52,54], thus different cellular mechanisms might be involved at different phases of learning, which could be reflected as different morphometric change patterns observed with the limited capacity of current MRI technologies [52]. Findings from animal studies demonstrated different stages of neural changes in the early as opposed to late learning phases [54]. For example, synaptogenesis was only observed in the late but not early learning phase of a rat reaching task [54], and in-vivo photon imaging during rat motor learning observed both formation and stabilization of new dendritic spines and destabilization and elimination of older dendritic spines [55], with both spine formation and elimination associated with behavioral performance [55]. Therefore, both neural growth and circuit pruning are essential aspects of neural plasticity [52].

4.4 Significance, limitations and future directions

There has not been much prior research on whether the adverse neural impact of childhood maltreatment on amygdala development could be ameliorated in adulthood. Animal studies showed that stress-affected cellular growth in the adult amygdala, unlike in the hippocampus, failed to reverse during recovery [56]. Some human studies also seem to suggest that the amygdala is "resistant to ameliorative environmental influences" [7], which was speculated to be "one way the organism ensures that it is prepared for future adversity" [7]. Nevertheless, the present study showed that a mindfulness intervention was able to elicit dose-dependent amygdala morphometric changes among young adults with childhood maltreatment histories that were associated with corresponding behavioral changes, suggesting that amygdala plasticity in adult humans is possible under proper conditions. Furthermore, our study showed that individuals' baseline amygdala volumes affected post-intervention volumetric changes. Hence, studies that look for a unidirectional change in amygdala volume with treatment may fail to detect any significant change, as the magnitude and direction of the change may depend on baseline volume. There were also nuanced bilateral difference between the two amygdalae in terms of how they responded to the mindfulness intervention, with the left mostly responded to the stress reduction component whereas the right responded to the mindfulness component.

Several limitations with the present study need to be acknowledged. Most critically the sample size was relatively small, the study lacked an active comparator group and the mindfulness intervention was only 8-weeks long. Hence, the findings should be considered preliminary and in great need of replication. A more comprehensive study should also evaluate measures of amygdala function and connectivity in addition to morphometry. Generalizability of the findings are also limited as the participants were mostly female, were all between 22–29 years of age and had a heterogeneous history of self-reported childhood maltreatment in terms of types and severity.

Therefore, we suggest the following directions for future studies:

1. Future studies should include multiple longitudinal MRI collections over the course of a longer-term mindfulness intervention (e.g., monthly MRI over a year) to observe the neural changes over a longer period of time. Due to the influence of childhood maltreatment on neural development on the pre-intervention neural characteristics, the short-term neural changes might primarily reflect a compensatory change for their abnormal baseline neural characteristics, while longer-term follow-up might be able to observe the mindfulness-related neural change eventually converging to the pattern reported among non-trauma population.

2. This study only investigated amygdala volumetric changes with morphometric MRI. Future studies can utilize other neuroimaging techniques to further investigate other aspects of amygdala changes in response to the mindfulness intervention, such as using resting state fMRI to study alterations in amygdala functional connectivity with the rest of the brain, using diffusion tensor imaging (DTI) to study structural connectivity, or using task-based fMRI to observe amygdala activity and functionality.

In particular, our recent publication [20] reported volumetric changes of the hippocampus which was associated with reduction of perceived stress and depression severity. The amygdala and hippocampus are both impacted by childhood trauma [6]. Prior studies with animal models [57] and human subjects [58] showed that the two structures respond differently to antidepressants, while another study showed increase of both amygdala and hippocampal volumes after electroconvulsive therapy among patients with refractory depression [59]. Our preliminary study, consistent with other studies [16,60] in the mindfulness literature, suggests that their responses to the mindfulness intervention have similarities as well as differences. For example, while there was a significant group difference on hippocampus volumetric changes [20], there was much more individual variability with amygdala volumetric changes that yielded no significant group difference in both studies [16]. In addition, both left and right hippocampus volumetric increases were associated with reduction of perceived stress [20], but only the left, not the right, amygdala volumetric increase showed significant association with perceived stress reduction. Further exploratory analyses found a positive correlation between the volumetric changes of the right amygdala and right hippocampus (see Supplementary Material, Figure S2). Future studies shall closely investigate the effect of mindfulness interventions on the functionality of and the connectivity between the hippocampus and the amygdala.

3. The finding that baseline right amygdala volumes were associated with post-intervention increase in self-compassion has potential clinical applications. This finding suggest that baseline right amygdala volume can potentially serve as a biomarker to predict an individual's therapeutic responses to mindfulness interventions, which may become feasible with the advancement of precision medicine [61], especially if the individual already has a pre-existing MRI from preventative care or other purposes. Future studies shall explore this possibility with a much larger sample to establish a population norm of amygdala volumes for making predictions for an individual patient.

4. Another limitation of the present study is that all subjects had experienced some level of childhood maltreatment. Future studies including a control group of subjects without childhood maltreatment history can help elucidate whether there are different neural responses to the mindfulness intervention among subjects with and without childhood maltreatment histories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Baseline right amygdala volumes were associated with post-intervention volumetric changes and changes in self-compassion among young adults with childhood maltreatment histories after a mindfulness-based intervention.
- Post-intervention changes in left and right amygdala volumes were associated with different psychological factors. The left amygdala volumetric change was associated with stress reduction, whereas the right amygdala volumetric change was associated with intervention compliance and improvement in self-compassion.

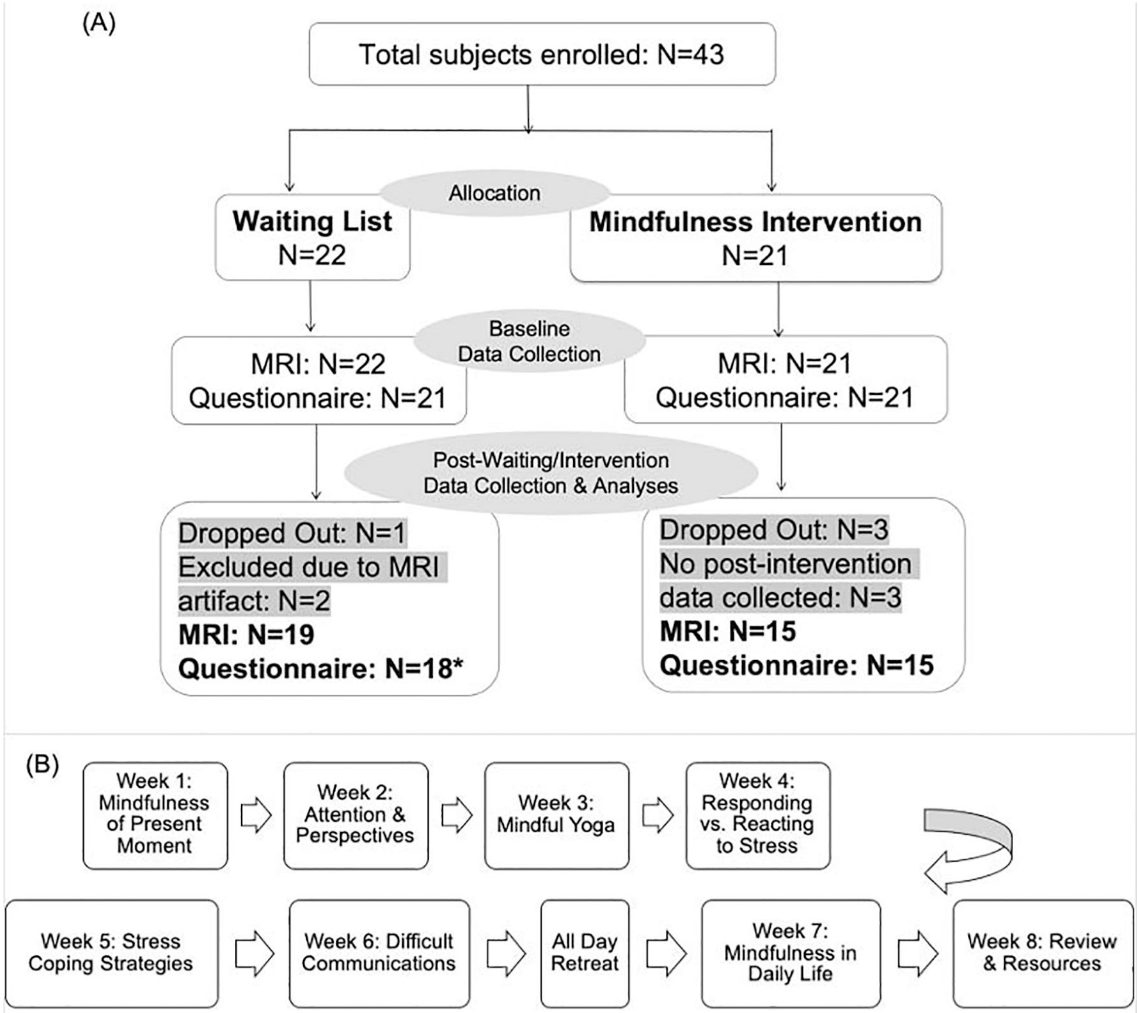

Figure 1:

(A) Flow chart of subject enrollment and retention. (B) Procedure of the mindfulness-based intervention and major topics for each week. Note: *: One subject in the control group did not complete baseline questionnaires but completed post-waiting questionnaires. Two participants in the control group completed baseline questionnaires but did not complete post-waiting questionnaires.

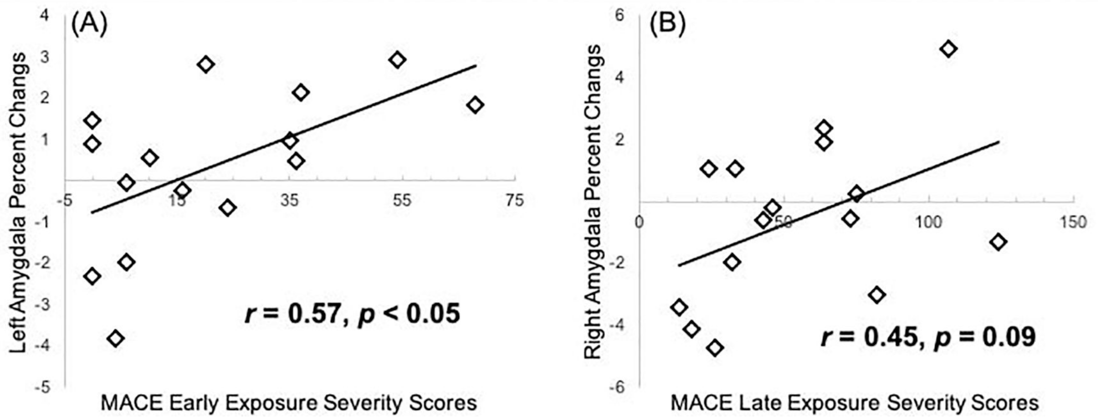

Figure 2:

Relationship between childhood maltreatment severity scores and amygdala volumetric changes in the mindfulness group. (A) Positive correlation between early exposure severity scores and percent change of left amygdala adjusted volumes. (B) Positive correlation between late exposure severity scores and percent change of right amygdala adjusted volumes.

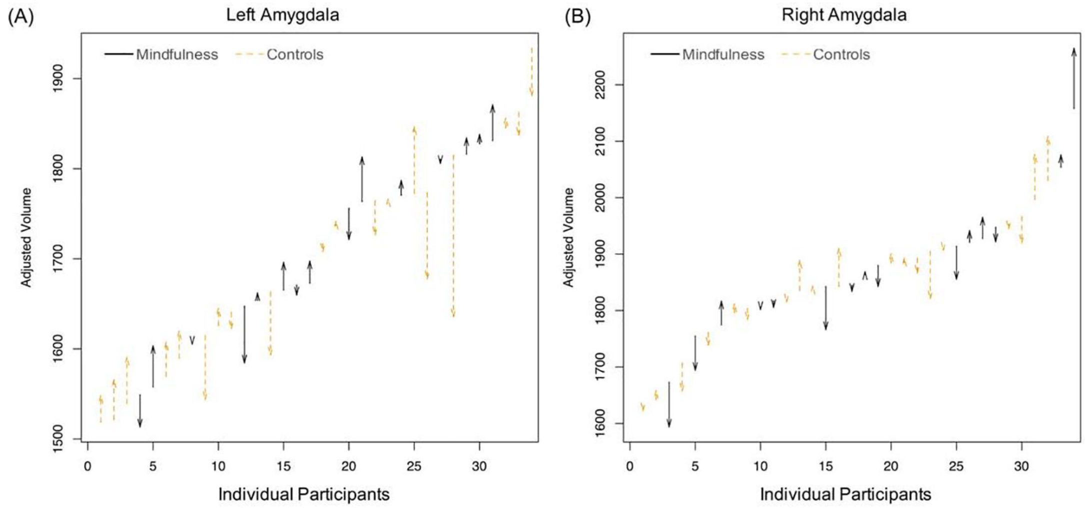

Figure 3:

Individual data of adjusted left (A) and right (B) amygdala volumes before and after the intervention or waiting period. The arrows point from the values at “before” to “after” the intervention or waiting period.

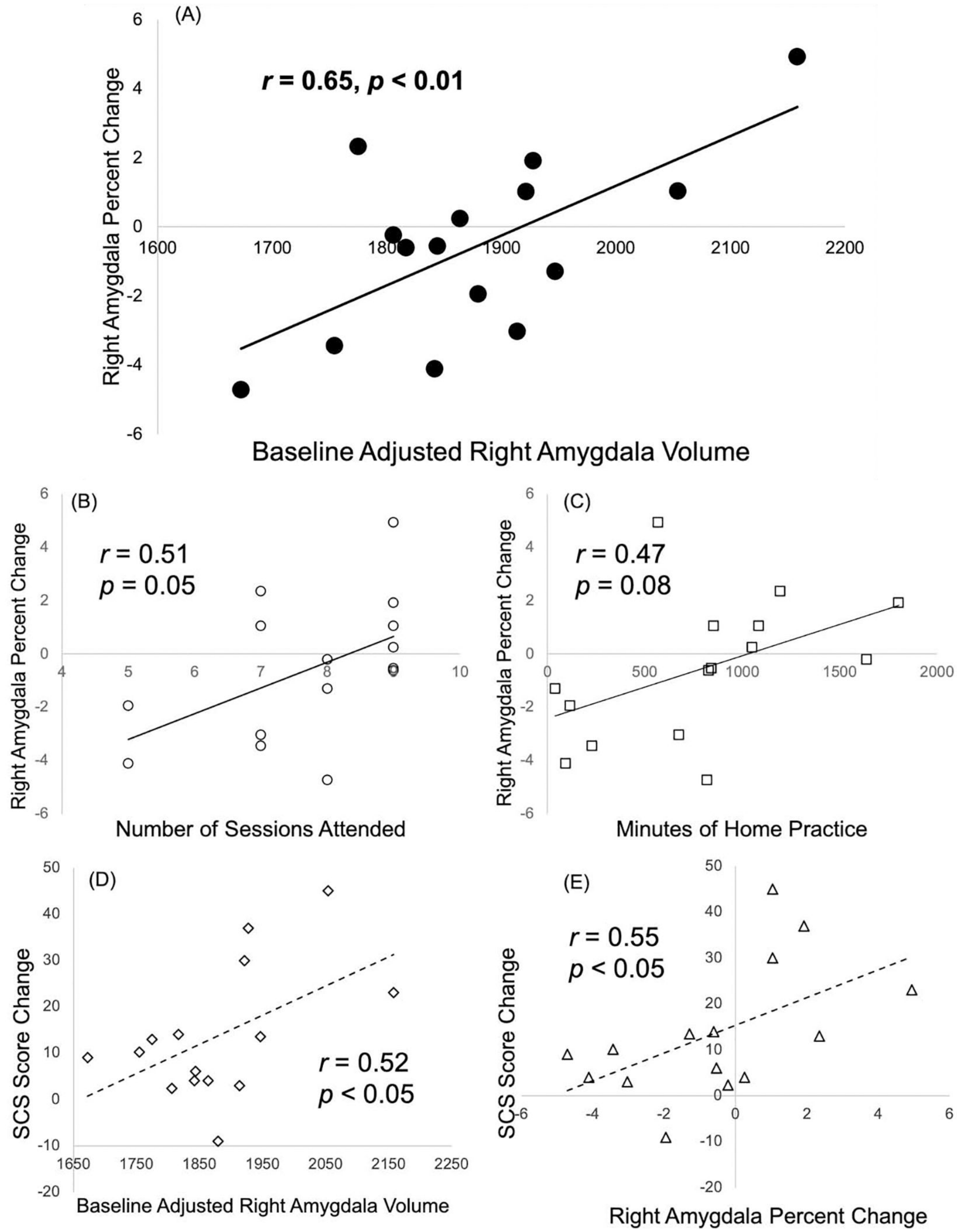

Figure 4:

Post-intervention percent change of adjusted right amygdala volumes are positively correlated with (A) baseline adjusted volumes, (B) number of intervention sessions attended, (C) total minutes of home practice and (E) score change of the Self-Compassion Scale (SCS), which was also correlated with baseline adjusted right amygdala volumes (D).

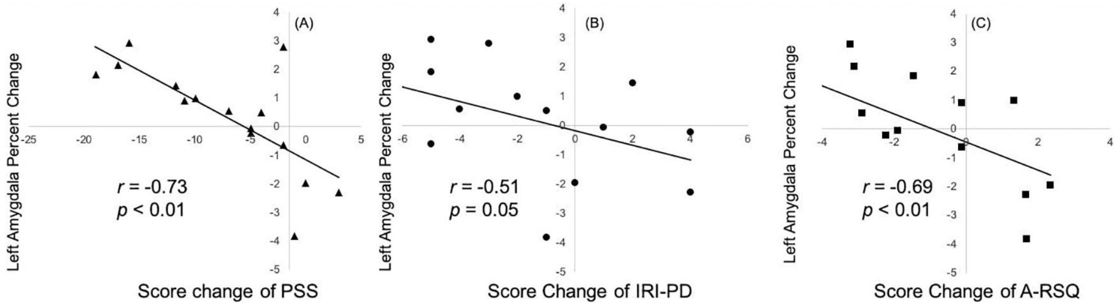

Figure 5:

Post-intervention percent change of adjusted left amygdala volumes are negatively correlated with score changes of (A) Perceived Stress Scale, (B)Interpersonal Reactivity Index-Personal Distress (IRI-PD) subscale, and (C) Adult Rejection Sensitivity Questionnaire (A-RSQ).

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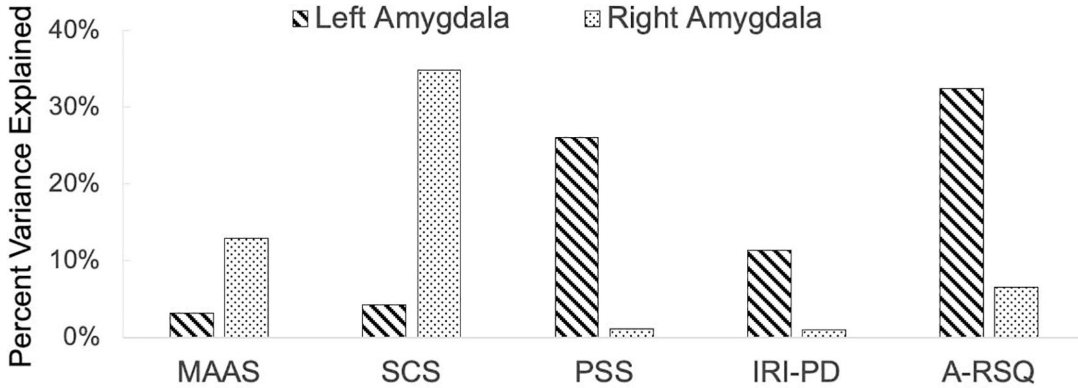

Figure 6:

Percent variance explained by score change of Mindful Attention Awareness Scale (MAAS), Self-Compassion Scale (SCS), Perceived Stress Scale (PSS), Interpersonal Reactivity Index-Personal Distress (IRI-PD) subscale, and Adult Rejection Sensitivity Questionnaire (A-RSQ) for the inter-subject variability in the percent change of the left and right amygdala adjusted volumes.

Table 1

Demographic, childhood maltreatment assessment and DSM diagnosis information of research participants.

		Mindfulness	Waitlist Control	Group Difference
Sample Size (N)		N=15	N=19	
Sex: Female(F); Male(M)		F:12, M:3	F:12, M:7	χ^2= 1.15, *p* = 0.25
Average Age (in years) (SE, range)		26.27 (SE=0.473, 22–29)	25.26 (SE=0.639, 22–29)	*t*= *1.26*, *p* = 0.22
Race (Frequencies)				
White		9	14	χ^2= 2.65, *p* = 0.72
Black/African American		3	1	
Asian		2	2	
Hispanic		1	1	
Unknown		0	1	
Childhood maltreatment screening (mean (SE), range)				
ACE		2.13 (0.48), 0–5	1.67 (0.58), 0–7	*t* =0.63, *p* = 0.54
MACE- number of maltreatment types		1.73 (0.55), 0–6	1.87 (0.61), 0–7	t =−0.16, p = 0.87
Self-report questionnaires (estimated marginal means (SE), 95%CI)				LME
PSS	pre	19.7(2.91), 13.67–25.8	15.5(2.49), 10.33–20.7	F = 9.41, *p* = 0.005
	post	12.5(2.91), 6.495–18.6	15.4(2.51), 10.16–20.6	
MAAS	pre	3.49 (0.32), 2.82–4.16	3.76(0.28), 3.17–4.34	F = 6.29, *p* = 0.02
	post	4.06 (0.32), 3.39–4.73	3.83(0.28), 3.25–4.42	
SCS	pre	81.3(8.90), 62.8–99.8	81.3(7.69), 65.3–97.3	F = 5.36, p = 0.03
	post	95.0(8.90), 76.5–113.5	83.4(7.73), 67.3–99.4	
IRI-PD	pre	5.23(2.21), 0.65–9.82	6.12(1.89), 2.19–10.06	F = 4.23, p = 0.05
	post	3.17(2.21), −1.42–7.75	6.71(1.90), 2.76–10.67	
A-RSQ	pre	6.10(1.69), 2.58–9.63	5.96(1.46), 2.92–9.00	F = 9.44 p = 0.005
	post	4.48(1.69), 0.95–8.00	7.23(1.49), 4.14–10.33	
Amygdala volumes (estimated marginal means (SE), 95% CI)				LME
Left Amygdala	Pre	1622(49.8), 1526–1730	1619(40.9), 1535–1703	F = 0.62, *p* = 0.44
	Post	1628(49.6), 1526–1730	1611 (40.3), 1529–1694	
Right Amygdala	Pre	1880(60.8), 1755--2006	1856(49.2), 1754–1957	F = 0.78, *p* = 0.38
	Post	1874(60.6), 1749–1998	1863(48.8), 1763–1964	
DSM-IV-TR diagnosis (Frequencies)				Fisher’s exact test
Depressive Disorders		7	4	*p* = 0.19
Anxiety Disorders		7	6	*p* = 0.14
Personality Disorders		1	3	*p* = 0.26

Abbreviations: SE: standard Error; CI: confidence interval; Pre: Pre-intervention/waiting period; Post: post-intervention/waiting period.

Table 2:

Correlation coefficients (*r*) between amygdala volumetric changes and questionnaire score changes.

	Left Amygdala Percent Change	Right Amygdala Percent Change	Achieved Power of Significant *r* Value
Left Amygdala Baseline Adjusted Volume	0.22	0.25	N/A
Right Amygdala Baseline Adjusted Volume	0.29	0.65 **	0.86
Number of Sessions Attended	0.11	0.51 *	0.57
Minutes of Home Practice	0.07	0.47#	0.48
Mindful Attention Awareness Scale	0.33	−0.18	N/A
Self-Compassion Scale	0.37	0.55 *	0.66
Perceived Stress Scale	−0.73 **	−0.12	0.97
Interpersonal Reactivity Index- Personal Distress	−0.51	−0.15	0.57
Adult Rejection Sensitivity Questionnaire	−0.69 **	−0.27	0.93

** p<=0.01

* p <=0.05

p = 0.08.

Achieved power of the significant ($p < 0.1$) correlation coefficient in each row is presented.