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Stress reduction correlates with structural changes in the amygdala

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Stress has significant adverse effects on health and is a risk factor for many illnesses. Neurobiological studies have implicated the amygdala as a brain structure crucial in stress responses. Whereas hyperactive amygdala *function* is often observed during stress conditions, cross-sectional reports of differences in gray matter *structure* have been less consistent. We conducted a longitudinal MRI study to investigate the relationship between changes in perceived stress with changes in amygdala gray matter density following a stress-reduction intervention. Stressed but otherwise healthy individuals ($N = 26$) participated in an 8-week mindfulness-based stress reduction intervention. Perceived stress was rated on the perceived stress scale (PSS) and anatomical MR images were acquired pre- and post-intervention. PSS change was used as the predictive regressor for changes in gray matter density within the bilateral amygdalae. Following the intervention, participants reported significantly reduced perceived stress. Reductions in perceived stress correlated positively with decreases in right basolateral amygdala gray matter density. Whereas prior studies found gray matter modifications resulting from acquisition of abstract information, motor and language skills, this study demonstrates that neuroplastic changes are associated with improvements in a psychological state variable.

Keywords: stress; amygdala; gray matter; MRI; mindfulness

INTRODUCTION

Acute stress initiates hormonal and behavioral responses that enable an organism to make adaptations to environmental demands (Chrousos, 2000). The amygdala has been implicated in both human and animal studies as playing a crucial role during stress responses, including the detection of stressful and threatening stimuli and the initiation of adaptive coping responses (LeDoux, 2000; Hasler *et al.*, 2007). Amygdala-dependent cognition is facilitated during stressful conditions—a useful function for fear-related learning (Shors and Mathew, 1998; Sapolsky, 2003). However, prolonged exposure to stress increases the risk of being affected by a number of mental and physical illnesses (Johnson *et al.*, 1992; Chrousos, 2000; Sapolsky, Romero, & Munck, 2000).

Aberrant amygdala function has been consistently demonstrated across several stress-related psychopathologies. For example, exaggerated amygdala activation has been found in trait anxiety (Stein *et al.*, 2007), post-traumatic stress disorder (PTSD; Rauch *et al.*, 2000; Shin *et al.*, 2004, 2005), social phobia (Birbaumer *et al.*, 1998; Evans *et al.*, 2008; Phan *et al.*, 2006), depression (Drevets *et al.*, 1992; Abercrombie *et al.*, 1998; Sheline *et al.*, 2001; Siegle *et al.*, 2002; Dougherty *et al.*, 2004) and impulsive aggression (Coccaro *et al.*, 2007).

Reports of differences in gray matter structure of the amygdala in pathologic stress conditions have been less consistent (Drevets *et al.*, 2008). While some studies found enlarged amygdala volumes in subjects with affective disorders (Altshuler *et al.*, 1998; Strakowski *et al.*, 1999; Frodl *et al.*, 2002; Lange and Irle, 2004; Weniger *et al.*, 2006), others did not find altered volumes or reported volume reductions (Sheline *et al.*, 1998; Mervaala *et al.*, 2000; Frodl *et al.*, 2003; Frodl *et al.*, 2008). Amygdala findings for patients suffering from PTSD and other anxiety disorders have also been mixed (Gurvits *et al.*, 1996; De Bellis *et al.*, 2000; Gilbertson *et al.*, 2002; Massana *et al.*, 2003; Siegle *et al.*, 2003; Wignall *et al.*, 2004; Milham *et al.*, 2005; Karl *et al.*, 2006; Atmaca *et al.*, 2008; Woon and Hedges, 2008; Hayano *et al.*, 2009). One study with healthy individuals failed to find a correlation between chronic life stress and gray matter volume in the amygdala (Gianaros *et al.*, 2007). These inconsistencies in the literature might result from a number of factors that can impact gray matter measures, such as gender (Wilke *et al.*, 2007), genetics

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(Meyer-Lindenberg *et al*., 2006) and volumetry method (Doty *et al*., 2008).

In contrast to studies of humans, the stress literature with animals is more consistent. Several studies have shown that prolonged stress exposure leads to increases in measures of amygdala structure in rodents (Vyas *et al*., 2002, 2003; Mitra *et al*., 2005). Increased dendritic length and increased arborization were reported within the basolateral complex of the amygdala and in the extended amygdala as a result of exposure to chronic immobilization stress (Vyas *et al*., 2002, 2003). Differences between the results from the human and animal studies might be due to methodological differences. First, the human studies have often investigated amygdaloid volume using MRI, while animal studies have used invasive techniques to look at specific cellular changes within this structure. Second, while most human studies have been cross-sectional investigations of pathologic conditions, the animal studies have been longitudinal, with presumably healthy animals undergoing a controlled chronic stress manipulation. While individual differences are difficult to control and can confound findings in cross-sectional studies, in longitudinal studies these variables remain constant, allowing researchers to selectively vary the factor of interest. However, to our knowledge, no longitudinal neuroimaging studies have examined the influence of stress on amygdala morphology in healthy human beings.

Here, we report a longitudinal MRI study in humans that investigated the correlation between changes in perceived stress and changes in amygdaloid gray matter density following a stress-reduction intervention. Mindfulness-based stress reduction (MBSR; Kabat-Zinn, 1990) is a popular 8-week program developed to help individuals reduce their stress levels and increase psychological well-being. Mindfulness is defined as the non-judgmental awareness of present moment experiences (Kabat-Zinn, 1990). Participants practise meditation techniques designed to increase awareness of present moment experiences such as thoughts, emotions and physical sensations. They also learn to use this awareness in responding more skillfully to stress in their everyday lives. Numerous studies have demonstrated the efficacy of this program in reducing subjective reports of stress and increasing well-being (e.g. Chang *et al*., 2004; Carmody and Baer, 2008). However, the underlying neural mechanisms of these changes are largely unknown. Since the amygdala has been repeatedly shown to be involved in, and responsive to, an individual's experience of stress, we hypothesized that changes in perceived stress would be associated with changes in amygdala gray matter density. Correlations within the whole brain were also explored on an exploratory basis.

METHODS AND MATERIALS

Twenty-seven participants (41% males; mean age 35.2 years; SD 6.7 years) who reported high levels of stress during the previous month were enrolled in the study. Individuals were eligible if their score on the perceived stress scale (PSS; Cohen and Williamson, 1988) was $\geq$1 SD above the population mean. The PSS is a validated self-report questionnaire widely used for assessing an individual's self-perception of stress. The PSS has 14-, 10- and 4-item versions and has been shown to yield adequate reliability and validity (Cohen *et al*., 1983; Cohen and Williamson, 1988). In this study, the 4-item version was used to screen potential subjects while the 10-item version was used to assess change in perceived stress before and after the training. Participants gave their responses on a 5-point Likert scale, ranging from never (0) to very often (4). Inclusion criteria was based on the population means according to Cohen *et al*. (1983; Cohen and Williamson, 1988), namely 4.2 (SD 2.8) for females and 4.7 (SD 3.1) for males.

Further exclusion criteria were: current psychiatric illness or medical illness, ineligibility for MRI scanning (claustrophobia, metallic implants, pregnancy, etc.), or significant previous meditation or yoga experience. The protocol was approved by the Massachusetts General Hospital Institutional Review Board. Written informed consent was obtained from all study participants and they were compensated for completion of assessment procedures.

All participants completed the 8-week MBSR program, consisting of weekly group meetings and daily home mindfulness practises, including sitting meditation and yoga. The sample described here includes participants from two similar studies that both assess the effect of MBSR on brain structure. Sixteen participants received the standard MBSR class held at the Center for Mindfulness at the University of Massachusetts Medical School. Eleven subjects received a shorter version of the MBSR course held at Massachusetts General Hospital that consisted of only 12 contact hours (versus the standard 23 h) and 20 min daily homework practise (versus the standard 40 min). The intervention has been comprehensively described elsewhere (Kabat-Zinn, 1990). Classes took place between April 2005 and June 2008 and were led by several instructors. One enrolled participant was excluded from the data analyses due to non-adherence to home practise requirements (<4 h total of home practise). Data from 26 healthy, right-handed individuals (44% males; mean age 35.7 years, SD 6.3 years) were included in the analyses. Home practise logs demonstrated that participants reported an average of 19.77 h (SD 6.53 h) of prescribed out-of-class mindfulness practise over the 8-week study period. To test whether the amount of practise had an influence on the improvement in stress, a Pearson correlation between the number of hours of mindfulness home practise and the change in PSS scores was performed in SPSS ('Statistical Package for Social Sciences, Release 12.0.2.', 2004).

Participants were scanned at the Martinos Center for Biomedical Imaging in Charlestown, MA. Pre-intervention scans were acquired approximately 1 week before the intervention began and post-intervention scans were acquired within the 2 weeks following the intervention. High-resolution MRI data were acquired with a Siemens

Magnetom Avanto 1.5 T scanner, using a T1-weighted, magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence, consisting of 128 sagittal slices (voxel size: $1.0 \times 1.0 \times 1.3$ mm, TI = 1000 ms; TE = 3.39 ms; TR = 2730 ms; flip angle 7° and matrix 256×256 mm).

Anatomical MR images were compared for differences in gray matter density using voxel-based morphometry (VBM; Gaser, 2008), within the SPM5 neuroimaging statistical software (www.fil.ion.ucl.ac.uk/spm/software/spm5/) based in MATLAB 7.1, release 14 (Mathworks Inc., Natick, MA, USA). VBM permits an automated voxel-wise whole-brain statistical comparison of MRI scans. Images were first manually aligned to the anterior commissure after which gray matter, white matter and cerebral spinal fluid components were segmented within native space. We analyzed unmodulated images, which contain the probability within each voxel for being gray matter, i.e. the proportion of gray matter to other tissue types within a region (Good *et al.*, 2001). For each individual, the gray matter segmentations of the post-intervention time-point were co-registered to the image of the pre-intervention time-point. The normalization parameters were calculated for the pre-intervention image only and then applied to the post-intervention image to make sure that regional differences between the images were not removed because of scan-specific normalization. Images were smoothed at 8-mm full width at half maximum with an Isotropic Gaussian Kernel.

Improvement in PSS (post-intervention score minus pre-intervention score; where negative values indicate decreases in PSS scores and positive values indicate increases) was used as the predictive regressor for changes in gray matter density (post-intervention image minus pre-intervention image; where negative values represent a decrease in gray matter density and positive values indicate increases) in a regression analysis. The significance threshold was defined as $P < 0.05$, corrected for multiple comparisons (false discovery rate) within the search region (height threshold = 0.01, uncorrected). The region of interest was defined as the bilateral amygdalae, according to Tzourio-Mazoyer *et al.* (2002). Exploratory correlation with gray matter density in the whole brain was performed at a significance threshold of $P < 0.01$ (uncorrected, 10 voxels).

RESULTS

PSS scores decreased pre- (mean 20.7; SD 5.6) to post-intervention (mean 15.2; SD 4.7; T = 3.7; df = 25; $P < 0.001$), indicating that the participants benefited from the course. The internal consistency of the PSS was high at both the pre- and post-intervention evaluation (Cronbach's-α values 0.85 and 0.81, respectively), confirming an adequate reliability of the scale.

To assess whether the amount of individual meditation home practise predicted the improvement in stress, the number of minutes of meditation practise that participants reported on daily logs was correlated with the magnitude of their reduction in stress. With a Pearson correlation coefficient of $r = 0.35$, the amount of training was mildly correlated with the improvement in stress, though this correlation did not reach statistical significance ($P = 0.079$; df = 25).

Pre- to post-intervention analyses of the MRI data in SPM confirmed a correlation between change in PSS scores and change in gray matter density within the right amygdala (cluster size: 10 voxels, MNI coordinates of peak voxel $x = 32$, $y = 0$, $z = -26$; voxel-level $T = 3.18$; $P = 0.042$, multiple comparisons correction within the amygdala search territory; Figure 1). Larger decreases in perceived stress were associated with larger decreases in amygdaloid gray matter density. The identified region appears to be located in basolateral/lateral regions of the amygdala, based on the atlas by Mai *et al.* (1997). The correlation of the change in perceived stress and amygdala gray matter density within the left amygdala was not significant.

Controlling for age and gender did not change the significance of the results in the right amygdala (cluster size: 9 voxels, MNI coordinates of peak voxel $x = 32$, $y = 0$, $z = -26$; $T = 3.13$; $P = 0.045$). There were no significant correlations between change in gray matter density and age, nor any group differences between males and females, either in the amygdala or within the whole brain.

No other brain loci were significantly correlated with PSS change scores when exploratory whole brain analyses were performed in SPM, even at a liberal significance threshold of $P < 0.01$ (uncorrected, 10 voxels). There was also no correlation between PSS values and gray matter density at the pre-intervention time-point. Finally, there was no significant pre- to post-intervention decrease in amygdala gray matter density, i.e. no main effect of the MBSR intervention in the amygdala; however, pre- to post-changes were identified in other brain regions and are reported elsewhere (Hölzel *et al.*, under review).

DISCUSSION

The present study investigates the potential relationship between changes in perceived stress and morphological changes in the amygdala. As predicted, there was a significant correlation between changes in PSS scores and changes in amygdaloid gray matter density. The more participants' stress levels decreased, the greater the decrease of gray matter density in the right amygdala.

The amygdala is widely regarded as one of the most important limbic structures in prevailing models of stress states and anxiety disorders. It receives information from sensory modalities and projects to other subcortical structures, thereby mediating stress-related behavioral and physiological effects such as stress-hormone release, blood pressure elevation and facial expression of fear (LeDoux, 2000). The cluster identified here appears to be located in the lateral/basolateral region of the amygdala (Mai *et al.*, 1997). The basolateral region has been proposed to serve

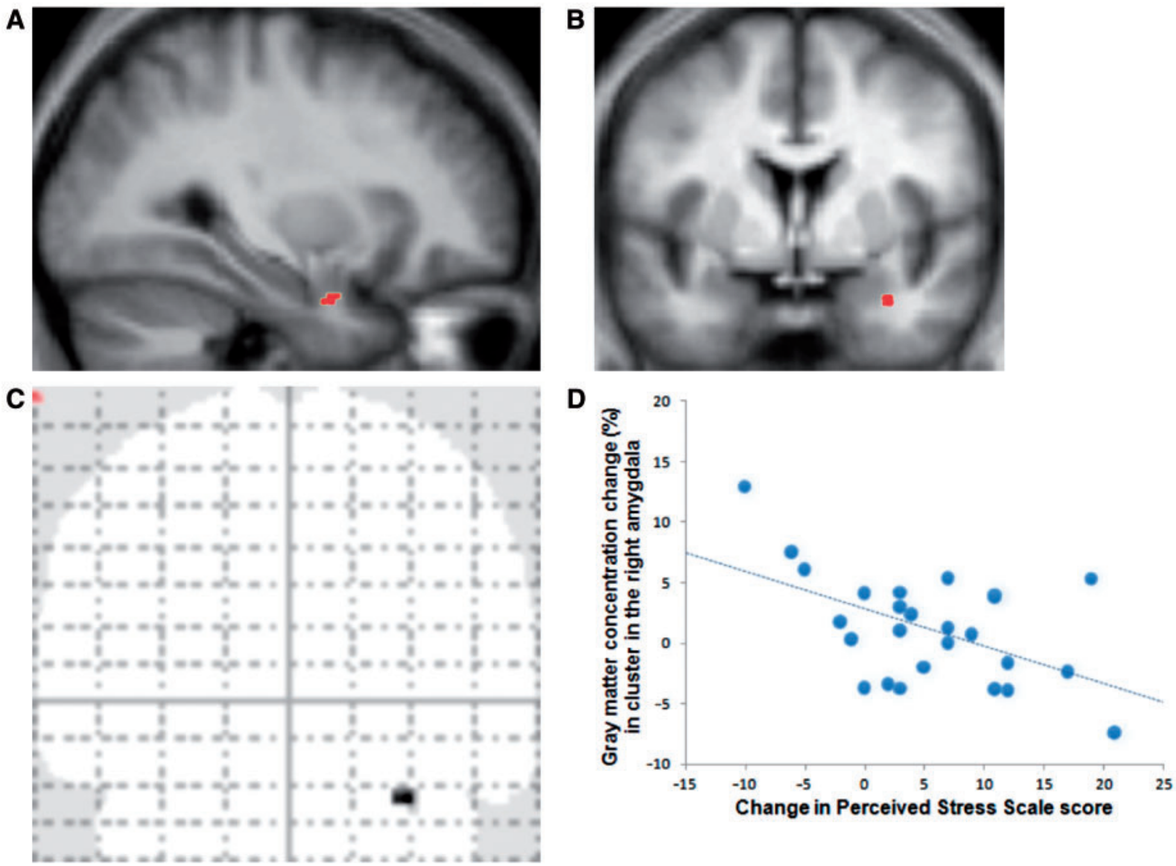

Fig. 1 (**A–C**) Location of positive correlation between gray matter density change in right amygdala and change in PSS score. Identified cluster overlaid on group-averaged sagittal (A) ($x = 32$) and coronal (B) ($y = 0$) structural image. (C) The coronal glass brain image illustrates that no other brain regions were correlated even at a liberal statistical threshold of uncorrected $P < 0.01$. **(D)** Average percent change (post-intervention minus pre-intervention) in gray matter density within the identified cluster extracted from each individual plotted against change in PSS scores. For illustrative purposes, voxel values within the identified cluster in the right amygdala were extracted and averaged using Marsbar (Brett *et al*., 2002), and values on the *x*-axis were reversed.

as the site for the relay of sensory information from subcortical and cortical sensory areas to the central nucleus of the amygdala during anxiety responses (Campeau and Davis, 1995). Evidence of stress-related plasticity in these regions has previously been found in animal studies, including increased dendritic length and arborization within the basolateral complex of the amygdala (Vyas *et al*., 2002; Mitra *et al*., 2005). Strikingly, the basolateral amygdaloid sub-region identified in these rodent studies corresponds to the region identified here. Cytoarchitectural modifications such as those observed in rodent studies could potentially contribute to the increased gray matter density observed in a subset of the individuals in the present study. However, studies designed to establish the cellular mechanisms underlying the observed differences in amygdaloid gray matter in humans would require postmortem investigations.

Our results indicated an association between changes in stress levels and morphometric changes in the right, but not the left amygdala. It has been suggested that the right amygdala mediates an initial, fast and perhaps automatic stimulus detection, followed by a more evaluative and discriminative response by the left amygdala (Morris *et al*., 1998; Wright *et al*., 2001; Glascher and Adolphs, 2003; Costafreda *et al*., 2008). Based on this model, our data suggest that this stress reduction intervention may strongly impact the participants' initial reaction to stimuli. This is consistent with a recent study demonstrating decreased autonomic arousal (skin conductance response) to affective stimuli following a stress reduction course similar to the one in this study (Ortner *et al*., 2007). However, further research will be required to directly test any relationship between gray matter changes and reactions to stimuli.

Previous longitudinal structural MRI studies in humans have shown that repeated activation of a neural region, either while learning new skills (Draganski *et al*., 2004; Ilg *et al*., 2008) or through transcranial magnetic stimulation (May *et al*., 2007), leads to an increase in the corresponding regional gray matter, whereas cessation of activation leads to a decrease. It seems plausible that this pattern could apply to the present findings—that changes in stress facilitate changes in amygdala activity, which in turn mediate changes in gray matter density. Interestingly, in rats, removal of experimental stressors after a period of chronic exposure did not lead to a reversal of the identified amygdaloid neuronal hypertrophy, or to the reversal of the associated enhanced anxiety-like behaviors within the observed time-frame of 21 days (Vyas *et al.*, 2004). Our results suggest that ameliorating the subjective experience of stress through a behavioral intervention may actually decrease amygdala gray matter density in humans. This finding is particularly interesting as it suggests that an active re-learning of emotional responses to stress (such as taught in MBSR) can lead to beneficial changes in neural structure and well-being even when there is presumably no change in the person's external environment. Future research will be required to address whether stress-induced alterations in the basolateral complex of the amygdala might influence a person's susceptibility to anxiety and other affective disorders (Sajdyk *et al.*, 1999; Shekhar *et al.*, 2003).

Gianaros *et al.* (2008) recently reported that lower gray matter volume in the bilateral amygdala predicted greater stressor-related amygdala activation, as well as greater blood pressure reactivity. However, the complexity and heterogeneity of amygdala subnuclei, in addition to the low spatial resolution of neuroimaging methods, make interpreting this seemingly contradictory finding difficult. As methods and technology improve, future studies could consider how effects of stress may vary across the several heterogeneous subregions of the amygdala. It should also be noted that Gianaros *et al.* (2008) investigated gray matter volume, which is distinct from gray matter density examined in the present study. The biological differences underlying these two neuroimaging techniques remain unclear.

Although a correlation was found between changes in amygdaloid structure and perceived stress, the present study did not show a significant overall main effect of the training on amygdaloid gray matter density. Thus, the results do not support the conclusion that MBSR training *per se* leads to decreases in gray matter in this region. As reported elsewhere (Hölzel *et al.*, under review), main effect analyses on a sub-cohort of the study participants did reveal significant changes in hippocampal, inferior temporal lobe, posterior cigulate, temporo-parietal and cerebellar gray matter density, though these regions were not correlated with changes in perceived stress.

The scatter plot (Figure 1D) illustrates that amygdaloid gray matter density increased for some participants, though it should be noted that a lot of those subjects also reported increases in perceived stress following the MBSR program. Some of the participants with improved perceived stress scores appear to have slight increases in gray matter density, but these small deviances may reflect noise. Alternatively, changes in amygdala gray matter may be temporally delayed relative to changes in perceived stress, perhaps requiring habitual activation in this region to subside prior to longer term structural changes. The results do support a bidirectional correlation; further work will be required to determine the precise relationship between the self-report measure and cellular changes. PSS values and gray matter density were not correlated at the pre-intervention time-point. This is in line with previous findings (Gianaros *et al.*, 2007) and is not unexpected, as numerous factors can influence brain gray matter variables (Meyer-Lindenberg *et al.*, 2006; Wilke *et al.*, 2007). Importantly, we assessed the relationship between the change in one variable, namely perceived stress and changes in gray matter density within the amygdala. By employing a longitudinal design most within-subject variables were kept relatively constant, while the factor of interest, perceived stress, varied. Some behavioral variables, such as smoking, diet or exercise, and psychological factors (e.g. neuroticism) can also co-vary with changes in perceived stress, however, and might mediate or drive the relationship between changes in perceived stress and structural changes (cf., Gianaros *et al.*, 2007). These variables were not assessed in the current study, and so it is unknown if the relationship between perceived stress and gray matter observed here is direct or indirect.

Several previous cross-sectional studies have investigated the impact of mindfulness meditation on brain morphology by comparing groups of experienced mindfulness meditators to nonmeditators (Lazar *et al.*, 2005; Pagnoni and Cekic, 2007; Hölzel *et al.*, 2008; Luders *et al.*, 2009). These studies identified several regions of altered brain morphology, but none within the amygdalae. However, none of these studies assessed the participants' perceived stress levels. Again, these data highlight the limitations of the cross-sectional study design. The unique hypothesis-driven, focused analysis employed in the present study revealed a novel link between changes in amygdaloid gray matter density and decreases in self-reported stress following stress-reduction training, marking a significant advance in our understanding of the association between both. Whereas previous studies have demonstrated that gray matter modifications can result from the acquisition of abstract information (Draganski *et al.*, 2006), motor skills (Draganski *et al.*, 2004) and language skills (Mechelli *et al.*, 2004), this is the first study to demonstrate neuroplastic changes associated with changes in a measure of a psychological state.

Conflict of interest

None declared.

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