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ARTICLE

Meditation-induced neuroplastic changes in amygdala activity during negative affective processing

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ABSTRACT
Recent evidence suggests that the effects of meditation practice on affective processing and resilience have the potential to induce neuroplastic changes within the amygdala. Notably, literature speculates that meditation training may reduce amygdala activity during negative affective processing. Nonetheless, studies have thus far not verified this speculation. In this longitudinal study, participants (N = 21, 9 men) were trained in awareness-based compassion meditation (ABCM) or matched relaxation training. The effects of meditation training on amygdala activity were examined during passive viewing of affective and neutral stimuli in a non-meditative state. We found that the ABCM group exhibited significantly reduced anxiety and right amygdala activity during negative emotion processing than the relaxation group. Furthermore, ABCM participants who performed more compassion practice had stronger right amygdala activity reduction during negative emotion processing. The lower right amygdala activity after ABCM training may be associated with a general reduction in reactivity and distress. As all participants performed the emotion processing task in a non-meditative state, it appears likely that the changes in right amygdala activity are carried over from the meditation practice into the non-meditative state. These findings suggest that the distress-reducing effects of meditation practice on affective processing may transfer to ordinary states, which have important implications on stress management.

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Amygdala; meditation training; fMRI; negative emotion; anxiety

Introduction

The amygdala, a structure residing deep inside the anterior temporal lobe, has extensive connections with other cortico-limbic regions of affective processing. In normal condition, activation of the amygdala has been reported to be associated with the level of attentional processing, gustatory-olfactory, and visual stimuli and aversive learning in a large group of healthy adults in a meta-analysis (Costanfreda, Brammer, David, & Fu, 2008). In the same study, activation of the amygdala has also been shown to be associated better with negative emotions such as fear and disgust than positive emotions such as happiness, indicating the importance of the amygdala in modulating affective processing, particularly in negative affect. Structural and functional abnormalities of this brain region are associated with affective pathologies [e.g., depression (Henje Blom et al., 2015; Sacher et al., 2012); post-traumatic stress disorders (Felmingham et al., 2014); anxiety (Fonzo et al., 2015)]; and dysfunctional retrieval of emotional autobiographical memories in older people (Ge, Fu, Wang, Yao, & Long, 2014). Also, bilateral amygdala damage disrupts affective but not cognitive empathy (Hurlemann et al., 2010). Given the pivotal role of the amygdala in both normal and pathological emotional processing, mental training that helps regulate its activity could be promising intervention for promoting mental health by strengthening affective resilience.

Mental training in the form of meditation has been shown to have an effect on affective processing (Rubia, 2009). Meditation is a practice that usually involves the individual in turning attention or awareness to stay on a single object, sound, concept, or experience (West, 1979). The most common form of meditation, that is,

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attention-based or mindfulness-based meditation emphasizes acknowledging the "knowing" of moment-to-moment experiences, while focusing the attention on an object or a physical sensation (e.g., breathing), any distracting thoughts/sensation is to be experienced rather than suppressed or actively regulated (Bishop, 2002). Among the different forms of meditation, compassion meditation is the one that focuses more on voluntary affective regulation, which is supported by a neural basis (Lee et al., 2012). Compassion/loving-kindness meditation practice centers upon the cultivation of a peaceful and warm feeling to kindly wish for happiness, health, peace, and the alleviation of suffering in oneself and everyone else in the world. Throughout the practice, mindful understanding (cognitive empathy), but not emotional contagion (affective empathy) (Lee et al., 2012), and positive emotions to others are cultivated.

Previous studies have demonstrated that the amygdala structure and functioning in long-term meditation practitioners differ from that of meditation novices (e.g., Leung et al., 2015; Lutz, Brefczynski-Lewis, Johnstone, & Davidson, 2008a). Compared to novices (N = 15), compassion/loving-kindness meditation experts who have practiced meditation for more than 10,000 h (N = 15), showed increased activity in the amygdala in response to emotional sounds during meditation than during rest states (Lutz et al., 2008a). Our previous study also demonstrated increased amygdala connectivity with the dorsal anterior cingulate, premotor, and primary somatosensory cortices in meditation experts who have practiced attention and loving-kindness meditation for at least five years (N = 10) during positive emotion processing, compared to that of novices (N = 15) (Leung et al., 2015). Furthermore, recent longitudinal studies show that short-term mindfulness or compassion meditation training reduces behavioral and physiological responses of stress and anxiety (e.g., Hölzel et al., 2010; Pace et al., 2009, 2013; Serpa, Taylor, & Tillisch, 2014), and changes amygdala activity during emotion processing (Desbordes et al., 2012). Desbordes et al. (2012) observed reduced right amygdala activity during viewing positive pictures after 8 weeks of Mindful Attention Training (N = 12), but a trend increase in right amygdala activity during viewing negative pictures after 8 weeks of cognitively-based compassion training (CBCT) (N = 12). All of these suggest the potential of meditation as a form of mental training in regulating amygdala activity that may lay the path of quality mental health.

According to Davidson (2004), low basal levels of amygdala activity are one of the key components of a resilient affective style that is crucial to well-being. It has been proposed that an initial decrease in activity within the amygdala during effortful regulation of emotional responses to aversive stimuli is followed by an increase immediately afterward (Walter et al., 2009). Research suggests that this so-called rebound effect is prevented by the non-regulatory nature of meditation practice, while mindfulness and/or compassion meditation simultaneously contributes to lower amygdala activity during negative affective processing (e.g., Klimecki, Leiberg, Lamm, & Singer, 2013; Mascaro, Rilling, Negi, & Raison, 2013b; Weng et al., 2013). Taken together, current literature suggests that meditation practice, in particular compassion meditation, as a form of mental training has the potential to be effective in down-regulating amygdala responses during negative affective processing.

Phillips, Ladouceur, and Drevets (2008) proposed a neural model of affective processing that depicts a *ventral system* consisting of brain regions such as the amygdala, insula, and orbitofrontal cortex for automatic emotion perception via the identification of emotional significance and the generation of an affective state in response to the stimuli. The ventral system then feeds affective information to the *dorsal system*, including the dorsal parts of the prefrontal and cingulate cortices for higher-order and regulatory processes. Hence, examining how passive viewing of affective stimuli is impacted by meditation training in a non-meditative state, which will facilitate our understanding of its influence on other higher-order processing and beyond. The majority of the studies have focused on the neural effects of mindfulness/compassionate mediation training on affective inhibition (Allen et al., 2012), empathy under active affective regulation strategies (e.g., Klimecki et al., 2013; Klimecki, Leiberg, Ricard, & Singer, 2014; Weng et al., 2013), or theory of mind (e.g., Mascaro, Rilling, Negi, & Raison, 2013a). However, observable changes in amygdala activity during passive viewing that are specific to mindfulness/compassionate meditation training were not reported. Neuroimaging studies on meditation that ask the participants to passively view affective stimuli are scarce. Thus far, only one study showed that the right amygdala activity was reduced when viewing positive pictures in a non-meditative state after 8 weeks mindful attention training, but it was increased when viewing negative pictures in a non-meditative state after CBCT (Desbordes et al., 2012). However, such an increase was only at the trend level in a region-of-interest (ROI) analysis and did not correlate with the amount of practice performed in the CBCT group, which contradicts the general prediction of lower amygdala activity during negative emotion processing after meditation training.

Therefore, it remains to be elucidated whether and how the amygdala activity in response to affective stimuli in an ordinary state may be modulated by short-term meditation training.

This study examined the neuroplastic effect of meditation training on the passive viewing of affective stimuli in a non-meditative state after a 6-week training program of awareness-based compassion meditation (ABCM) that combines the practice of cultivating awareness and compassion. To delineate the specific effect of ABCM training from the general placebo/expectation effect of any other training, relaxation training that taught three common relaxation techniques was employed as the active control condition. To confirm the effect of meditation training, we administered an anxiety questionnaire to assess the changes in anxiety symptoms after training. We hypothesized that ABCM would be more effective than common relaxation techniques in reducing subjective anxiety and reducing amygdala activity during affective processing.

Material and methods

Participants

Participants were recruited from the local community and the alumni network of HKU via online flyers and email announcements. A total of 27 right-handed Chinese participants were recruited, of which 21 successfully completed the training (missed no more than three out of seven sessions) and all assessments. The resting-state data of these participants were reported in another study (Lau, Leung, Chan, Wong, & Lee, 2015). The drop-out rate was similar across the two groups. However, one of the control participants in the relaxation group had excessive movement (>3 mm) during performing the emotion processing task in the scanner, thus leaving a final sample of 20 participants in this study (10 in each group). Inclusion criteria were 25–55 years old, with an interest in practicing both meditation and relaxation, and commitment to attending all lessons and assessments. Exclusion criteria were magnetic resonance imaging (MRI) incompatibility, prior experience of meditation/relaxation training, history of brain injuries, neurological or psychiatric disease, and current engagement in any psychotherapy or pharmacotherapy that may affect the functioning of autonomic and/or central nervous systems. (Figure 1).

Due to time and resource constraints (i.e., limited MRI scanning slots within three weeks before the start of ABCM or relaxation training), participants were recruited and tested sequentially and the allocation of participants to training groups depended on when their pre-training assessments were completed. However, this underlying mechanism was unknown to the participants, who were informed that they would be randomly assigned to either group. To ensure that they were equally motivated for both trainings, their group membership was announced after completing a pre-training assessment and none dropped out because of the group assignment.

There was no statistical difference in gender composition between the two groups [five males in ABCM, four males in relaxation; $X^2(1) = .202$, $p = .653$]. The average age and years of education of the ABCM group were 37.8 ± 11.2 and 15.6 ± 5.4 years, respectively. The average age and years of education of the relaxation group were 42.2 ± 8.5 and 19.8 ± 3.6 years, respectively. The two groups of participants did not differ significantly in age [$t(18) = -.976$, $p = .342$], but the ABCM group had relatively fewer years of education [$t(18) = -2.060$, $p = .054$]. According to the literature, education attainment was found to be significantly associated with amygdala activity during emotion perception, in particular the activity of the right amygdala (Demenescu et al., 2014). In line with such literature, we also found that the years of education negatively correlated with pre-training right amygdala activity during both positive ($r = -.661$; $p = .002$) and negative emotion processing ($r = -.538$; $p = .015$) across groups. To ensure that the results were not affected by education attainment, the number of years of education was included as a nuisance variable in all subsequent between-group analyses.

Experimental procedures

The pre-training assessments were performed within 3 weeks before training. Likewise, the post-training assessments were performed within 3 weeks after training. After being fully informed about the study, participants gave their written informed consent before pre-training assessment. This study was approved by the non-clinical ethics committee at the University of Hong Kong. Both assessments included the same set of self-report questionnaire and brain scans. Participants who successfully completed the whole training and pre- and post-training assessments were compensated for their time and travel expenses. The content of the two trainings was briefly listed in Figure 1. The ABCM training consists of attention and compassion training, as well as didactic teaching. Attention training involves basic techniques that enhance attention by methods such as listening closely to the sounds in the environment or the own breathing, as well as focusing on the own

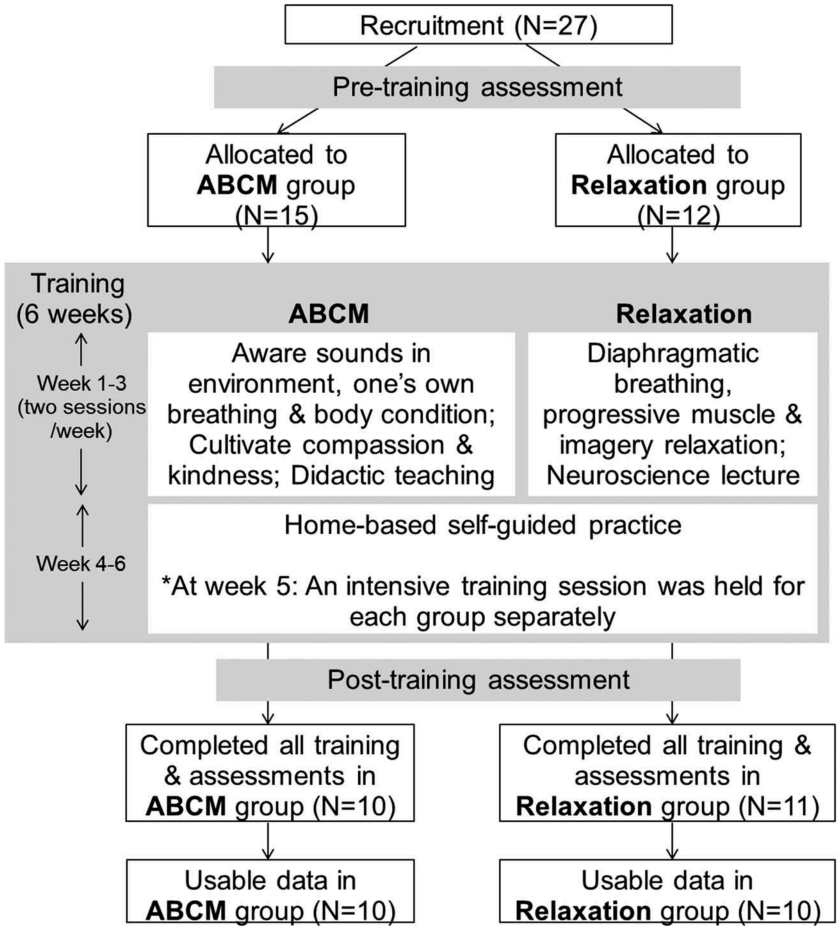

Figure 1. The flow of study and brief content of the two forms of training. Both pre- and post-training assessments include the same set of self-reported questionnaire and MRI scanning. One control subject had excessive movement (>3 mm) during the emotion processing task and thus, was excluded from analysis.

body condition. On the other hand, compassion training requires subjects to cultivate compassion and kindness toward the self and spread it to people close to oneself, such as family members or friends, and finally to all living beings. These trainings aim to instill mindfulness, peace, calm, and liberation. It is believed that effects of enhanced attention and compassion are complimentary to each other: a focused state enables people to sustain universal, non-referential love and compassion; conversely, the feeling of love and kindness helps people achieve a peace of mind useful for entering into a focused state (Salzberg, 1995). It is noteworthy that there was not any religious element involved in the ABCM training. Relaxation training consists of diaphragmatic breathing, progressive muscle relaxation, imagery relaxation, and a neuroscience lecture that matched with the didactic teaching in ABCM training. Attention training in ABCM emphasizes on maintaining the awareness from moment to moment (e.g., aware of the surrounding sounds, one's own breathing or one's own body condition), whereas relaxation training focuses on pursuing a relaxed state for both body and mind, without the requirement of maintaining the same level of awareness as for ABCM.

The didactic teaching in ABCM consists of explanations of concepts, types, and importance of meditation practice, as well as experiential sharing of meditation practice and question-and-answer sessions. It is comparable to the neuroscience lecture in terms of duration, mode of knowledge delivery (lecture-based teaching), and interactive discussions between the teacher and participants. For example, both have experiential sharing of meditation/relaxation practice and question-and-answer sessions. Likewise, both trainings aim at promoting mental health. The time that was used to explain concepts and types of meditation was matched by delivering knowledge relating to neurological and mental disorders in the relaxation training.

A quasi-experimental design was adopted in this study because of time and resource constraints (i.e., limited MRI scanning slots). The allocation of participants to training groups depended on the date of completion of their pre-training assessments. As the ABCM training was launched first, those who could complete the assessment before the start of ABCM training were assigned to the ABCM group. Some procedures were undertaken to minimize the potential self-selection bias. First, the selection mechanism was unbeknown to participants, who were informed that they would be randomly assigned to either group. Second, their group membership was announced after completing pre-training assessment in order to ensure that they were equally motivated for both trainings. None of the participant dropped out because of the group assignment.

Prior to scanning, participants received verbal instructions on the emotion processing task (EPT) and performed a practice trial. The participants gave ratings to the affective stimuli outside the scanner after scanning.

Home-based practice assessment

The amount of home-based practice was assessed by self-report. Participants were given logbooks at the beginning of the training to record their daily practice in minutes. They were asked to reflect on the percentage of time they spent on specific types of practice at the post-training assessment. For example, the amount of a specific practice (i.e., cultivation of attention and cultivation of compassion for ABCM training; diaphragmatic breathing, progressive muscle relaxation, and imagery relaxation for relaxation training) performed by each participant was calculated by multiplying the percentage of time (%) that he/she spent on the specific practice with the total amount of practice (minutes) summarized across all logbooks.

Emotion processing task (EPT)

The EPT included 20 happy, 20 sad, and 20 neutral pictures from the IAPS with the highest valence and arousal ratings in published norms (Bradley & Lang, 2007). The IAPS image numbers for positive condition were 1440, 1610, 1710, 1750, 1920, 2040, 2050, 2057, 2058, 2070, 2080, 2150, 2260, 2340, 2530, 2550, 5760, 5910, 8190, and 8470; for negative condition were 2141, 2205, 2800, 2900, 3220, 3230, 3301, 3350, 9050, 9140, 9181, 9220, 9410, 9421, 9520, 9560, 9571, 9910, 9911, and 9921; and for neutral condition were 1616, 2381, 2487, 2495, 2514, 2702, 2850, 2870, 5395, 5520, 5532, 5533, 5740, 6910, 7080, 7090, 7100, 7500, 7550, and 7830. Each emotion valence had equal proportions of pictures with human and nonhuman images. The participants were instructed to simply view the pictures carefully. There were no other instructions given to the participants in order to avoid any active regulation during viewing that may affect the activity in the amygdala (Taylor, Phan, Decker, & Liberzon, 2003). All images were randomized and appeared once for 3000 ms on a dark background in two 30-trial runs. Each trial was separated by a white central fixation cross with varying inter-stimuli intervals (500 ms, 1000 ms, 1500 ms, 2000 ms, and 2500 ms). The mean and standard deviation of inter-stimuli intervals were 1500 ± 713 ms. The experimental conditions were the trials viewing happy and sad pictures, whereas the trials viewing neutral pictures represented the control condition. All stimuli were generated by E-Prime on a control computer and displayed using a back projection screen. The EPT run lasted for about 5 min (while the whole scanning duration was about 40 min, including other structural and functional scans that were not relevant in this study).

Picture ratings

When rating the affective pictures display in the EPT, the participants rated the valence from 1 (*very negative*) to 9 (*very positive*) and arousal from 1 (*not arousing*) to 9 (*very arousing*) for each happy and sad picture. The valence scores were above 5 when rating happy pictures, while valence scores were below 5 when rating sad pictures before and after training in both groups. This indicated that participants evaluated the pictures according to its valence (Table 1).

Anxiety measure

The Taylor Manifest Anxiety Scale (Bendig, 1956) was used to assess the change in trait anxiety symptoms. It is a true-false questionnaire that consists of 20 statements describing symptoms of anxiety or distress.

Table 1. Descriptive statistics of behavioral data.

	Baseline		Post-training	
Behavioral data, mean (SD)	ABCM	Relaxation	ABCM	Relaxation
Affective picture rating				
Happy picture (arousal)	6.18 (1.17)	5.72 (1.03)	6.15 (1.49)	5.64 (0.67)
Happy picture (valence)	7.16 (0.99)	6.85 (0.58)	6.88 (1.34)	6.63 (0.43)
Sad picture (arousal)	5.78 (1.32)	6.37 (1.23)	5.67 (1.81)	6.44 (1.08)
Sad picture (valence)	3.43 (0.76)	3.02 (0.58)	3.22 (1.24)	2.98 (0.55)
Anxiety	7.90 (3.73)	7.10 (3.90)	6.00 (3.02)	7.40 (3.57)

ABCM = Awareness-based compassion meditation, SD = Standard deviation

Image acquisition

High-resolution MRI brain images were acquired via a 3.0 T Philips Medical Systems Achieva scanner with an 8-channel SENSE head coil (SENSE = 2). A three-dimensional, T1-weighted, magnetization-prepared rapid-acquisition gradient-echo (MP-RAGE) sequence was used with 164 contiguous sagittal slices 1 mm in thickness; time to repetition (TR) = 7 ms, time to echo (TE) = 3.2 ms, flip angle = 8°, field of view (FOV) = 164 mm, matrix = 256 x 240 mm, voxel size = 1 mm^3. Thirty-two functional slices were acquired using a T2*-weighted gradient echo planar imaging sequence [slice thickness = 4 mm, TR = 1800 ms, TE = 30 ms, flip angle = 90°, matrix = 64 × 64, FOV = 230 × 230 × 128 mm, voxel size = 3.59 × 3.59 × 4 mm^3]. The axial slices were adjusted to be parallel to the AC-PC plane. The first six volumes were discarded to allow for T1 equilibration effects.

Data analysis

Behavioral data

Between-group differences were examined using independent-samples *t*-test or chi-square test. The group-by-time interactions in anxiety, valence, and arousal ratings for happy and sad pictures were examined using ANOVA and ANCOVA (adjusted for years of education). For any significant group-by-time interactions, post hoc, two-tailed paired *t*-tests were conducted.

fMRI data

The fMRI data were preprocessed using DPARSFA v2.1 (http://rfmri.org/dparsf/) in the MATLAB environment (R2012a, Mathworks Inc., Natick, MA, USA). Default setting was used unless otherwise specified. The functional images were corrected for slice-timing (reference slice was the slice in the middle) and then motion (realigned to the first image of the scan session using rigid-body transformation). The T1 image was coregistered to the mean functional image after motion correction. The functional images were normalized by using unified segmentation (affine regularization using the East Asian template). The normalized images were spatially smoothed with an isotropic 6 mm full width at half maximum (FWHM) Gaussian filter. Smoothed fMRI data of each participant (pre- and post-training) were entered into a first-level (single-subject) design matrix for fixed-effects modeling in Statistical Parametric Mapping (SPM8, version r4290, Wellcome Department of Cognitive Neurology, London, UK). Each set of fMRI data was modeled using three event-related regressors for the happy, sad, and neutral conditions. Temporal and dispersion derivatives were also incorporated into the basis functions. The six movement-related parameters were modeled as nuisance variables to correct for motion artifacts. Two sets of contrast images were built using linear *t* contrasts at the first-level by subtracting the neutral condition from the happy and sad conditions for the data of each participant at each time-point. Given that the arousal and valence levels of neutral pictures are approximately in the middle of positive and negative pictures ratings (Dolcos, LaBar, & Cabeza, 2004; Spalek et al., 2015), viewing neutral pictures is often regarded as a baseline condition to account for visual components of viewing objects/scenes that do not have affective elements. By contrasting the experimental and control conditions (i.e., happy > neutral or sad > neutral), emotion-related activation could be obtained, and the baseline difference across different subjects at different time-points could be eliminated.

Second-level random-effects analyses were performed using the flexible factorial design with a between-subjects factor “group” and a within-subject factor “time,” in addition to the other between-subjects factor “subject.” The pre- and post-training contrast images (happy > neutral or sad > neutral) for BOLD signals of each participant were entered into the model accordingly. The number of years of education was included as a nuisance covariate. After model estimation, the group-by-time interaction was first tested with a *F*-test using small-volume correction only (no whole-brain analysis was performed in this study). For significant interaction findings, follow-up *t*-tests were conducted to differentiate the direction of changes between the two groups. Small-volume correction was performed using an anatomical mask that contains both the left amygdala and right amygdala. The left amygdala and right amygdala masks were defined using the MarsBar toolbox (v0.42, http://marsbar.sourceforge.net/) (Brett, Johnsrude, & Owen, 2002) as the seed ROI, based on the anatomical masks provided by the anatomical automatic labeling package (Tzourio-Mazoyer et al., 2002) defined in Montreal Neurological Institute (MNI) space. Significance was defined by peak-level FWE corrected $p < .05$.

For any significant result, the mean value of BOLD signals was extracted for each time-point of each subject. The changes after training were calculated by subtracting the pre-training data from the post-training data. Correlational analyses were then performed on changes in BOLD signals and self-reported measures to test for an association between changes in brain function and behavior induced by the training.

Sensitivity analysis

To test for the reproducibility of the main fMRI findings, a systematic jack-knife sensitivity analysis was conducted on any significant interaction effect. The main statistical analysis was repeated 20 times but discarding one different subjects each time, generating a 10 versus 9 subjects (ABCM versus Relaxation) or 9 versus 10 subjects (ABCM versus Relaxation) analysis for each time. This method assumes that if a previously significant brain region remains significant in all or most of the combinations of the kept samples, the finding can be regarded as highly reproducible (Radua & Mataix-Cols, 2009).

Results

Behavioral data

There was no significant group difference in all behavioral measures at baseline, including the anxiety level [$t(18) = .469$, $p = .645$], and all kinds of picture ratings (all were $p > .5$).

The group-by-time interaction on changes in anxiety was significant [$F(1,18) = 10.13$, $p = .005$], even after controlling for the effect of years of education [$F(1,17) = 6.028$, $p = .025$]. Significantly less anxiety was found after the ABCM training [$t(9) = -3.943$, $p = .003$], but not the relaxation training [$t(9) = .605$, $p = .560$].

No significant group-by-time interactions were detected for the change in valence and arousal ratings for happy and sad pictures (all were $p > .5$) neither before nor after controlling for the effects of years of education.

Amount of practice

The average amount of total home-based practice completed by the ABCM and relaxation groups was 509.1 ± 156.7 and 543.4 ± 256.5 min, respectively. There was no significant difference on the home-based practice performed by the two groups [$t(18) = -.361$, $p = .722$]. Based on the proportion of practice reported in the post-training assessment, the average duration of practice on cultivation of attention and compassion carried out by the ABCM group was 416.8 and 92.3 min. The average duration of practice on diaphragmatic breathing, progressive muscle relaxation, and imagery relaxation carried out by the relaxation group was 375.2, 81.1, and 87.2 min.

Changes in neural activity during positive emotion processing

There was no significant group difference in the baseline activity during positive emotion processing (peak-level FWE corrected $p > .05$).

No significant group-by-time interaction effect was detected on the changes in the bilateral amygdalae during positive emotion processing, neither before nor after controlling for the effects of years of education.

Changes in neural activity during negative emotion processing

There was a significant baseline group difference in the right amygdala activity (MNI coordinates: 27, 0, −21; peak-level FWE corrected $p = .014$; t-value = 4.21). The ABCM group had a higher right amygdala activity at baseline during negative emotion processing compared to the relaxation group.

Significant group-by-time interaction effect was only detected on the right amygdala during negative emotion processing, after controlling for the effect of years of education (MNI coordinates: 27, 0, −18; peak-level FWE corrected $p = .012$; F-value = 17.65) (Figure 2(a)). Although this interaction effect was not significant when the covariate of education was removed (MNI coordinates: 27, 0, −18; peak-level FWE corrected $p = .141$; F-value = 9.70), we consider that it is needed to control for the effect of years of education because of the potential influences of education attainment on amygdala activity during emotion processing (Demenescu et al., 2014). Post hoc t-tests found that the decrease in right amygdala activity after the ABCM training was stronger than that after the relaxation training (Figure 2(b)). Using the Group factor to predict changes in right amygdala activity in a regression model, 47.4% of variance in changes in right amygdala activity was explained [R = .709, adjusted R2 = .474, $F(1, 18) = 18.147$, $p < .001$]. Years of education did not explain any significant additional variance [R = .709, adjusted R2 = .444, *F Change* (1, 17) = .021, $p = .886$]. When baseline right amygdala activity was added as an additional predictor in the above regression model, it did not explain any significant additional variance in changes in right amygdala activity [R = .717, adjusted $R^2 = .423$, *F Change* (1, 16) = .390, $p = .541$]. Therefore, the group differences in education and baseline right amygdala activity did not affect changes in right amygdala activity.

It is noteworthy that a significant group-by-time interaction effect was detected on the right amygdala activity during the neutral condition. Post hoc t-tests revealed a significant training effect in the ABCM group only (for more details, please refer to Supplemental Data).

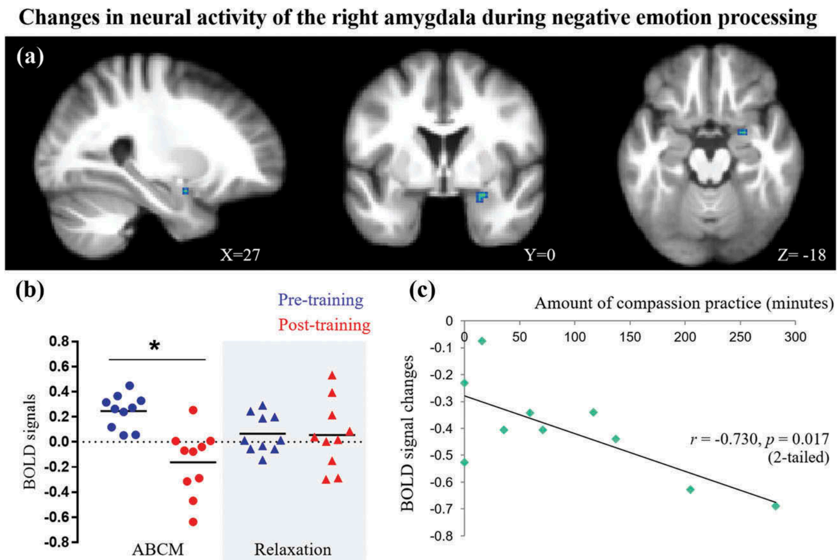

Figure 2. (a) Significant decreases in neural activity of the right amygdala during negative-emotion processing after the awareness-based compassion meditation (ABCM) training compared to relaxation training, controlled for years of education (Montreal Neurological Institute coordinates: X = 27, Y = 0, Z = −18). (b) Changes in the neural activity of the right amygdala during negative emotion processing before and after the training in each group. Horizontal lines represent the mean of the neural activity of the right amygdala. (c) A significant negative correlation between changes in the right amygdala activity and the amount of compassion practice in the ABCM group. * FWE-corrected $p < .05$.

Sensitivity analysis

All of the jack-knife sensitivity analyses demonstrated the significant group-by-time interaction effect on the right amygdala during negative emotion processing, and 19 out of 20 supported that such an effect could be observed on the same coordinates of the right amygdala as in the main result (MNI coordinates: 27, 0, −18). These findings suggest that our results are reproducible even with limited sample size, and our results were not biased by individual sample.

Association between changes of right amygdala activity and self-reported measures

Changes in the right amygdala activity during negative emotion processing negatively correlated with the amount of compassion practice in the ABCM group (r = -.730, p = .017, 2-tailed) (Figure 2(c)). No significant correlation between the right amygdala activity and any practice amount was observed in the relaxation group.

Discussion

ABCM, relative to relaxation training, was more effective in reducing anxiety. This observation is consistent with that reported in previous studies examining the effect of meditation on anxiety management (Davidson & McEwen, 2012; Feldman, Greeson, & Senville, 2010), therefore, confirming the effect of ABCM practice. The only neuroplastic effect of ABCM in the current study is that the right amygdala activity in the sad > neutral contrast condition declined significantly after ABCM, relative to that after the relaxation training. Furthermore, a reduction of the right amygdala activity was associated with the duration of compassion practice in the ABCM group. In other words, the participants who completed more compassion practice showed a more significant decline in their right amygdala activity in the sad > neutral contrast condition. Our result indicated that the ABCM training had an effect on the functioning of the ventral neural region for primary emotion processing, particularly for negative emotions. This finding fits well with the abundant literature on the unique role of the amygdala in negative emotion processing (Aldhafeeri, Mackenzie, Kay, Alghamdi, & Sluming, 2012; Davidson, 2002; LeDoux, 2000). It also highlights the specific effect of mindfulness/compassion meditation practice on the right amygdala, but not the left amygdala, in negative affective processing, using this contrast. Our finding is in line with the previous observation of a negative correlation between the right amygdala activation during processing of negative emotional sounds and hours of meditation training in 14 experienced meditators who had completed from 10,000 to 54,000 h of practice in attention-based meditation (Brefczynski-Lewis, Lutz, Schaefer, Levinson, &

Davidson, 2007). The nature of compassion practice that promotes the cultivation of mindful understanding (cognitive empathy) instead of emotional contagion (affective empathy), together with the specific role of the amygdala in affective empathy (Hurlemann et al., 2010), suggests that the observed decrease in the amygdala activity might be related to a general reduction in reactivity and distress associated with affective empathy, yet without losing sensitivity toward negative emotions of others. Indeed, participants who put in more hours of practice showed less emotional unrest toward negative stimuli. As all participants performed the EPT in an ordinary resting state, this neural change reflects a carry-over effect from the meditation practice. These findings, together with recent findings on meditation beginners (Allen et al., 2012; Desbordes et al., 2012; Mascaro et al., 2013a) and experts (Brewer et al., 2011; Taylor et al., 2013), support the notion that the effect of meditation practice may transfer to non-meditative states (Lutz, Dunne, & Davidson, 2007; Lutz, Slagter, Dunne, & Davidson, 2008b).

Changes of the amygdala activity in the happy > neutral contrast condition were not observed, which may suggest that the amygdala is more sensitive to negative emotional information (Aldhafeeri et al., 2012; Davidson, 2002; LeDoux, 2000). On the other hand, it is possible that the neuroplastic effect of meditation on the amygdala during positive emotion processing may be expressed via other types of neural functioning of the amygdala and/or other neural regions. For instance, we previously found that the amygdala has a stronger positive functional connectivity with the dorsal anterior cingulate cortex and other cortices during positive emotion processing in meditators who practice attention and loving-kindness meditation rather than novices, which may be important for the cultivation of positive emotion (Leung et al., 2015). Accordingly, further research is required to tease apart the effects of mindfulness and compassion meditation on positive emotion processing as mediated by the amygdala.

The right amygdala, but not the left amygdala, showed neuroplastic effects on the sad > neutral contrast condition after ABCM training, suggesting that the two amygdalae participate differently during affective processing. This finding is consistent with the observed changes in the right amygdala in previous literature using visual stimuli (Desbordes et al., 2012). On the other hand, our findings contradict prior studies using auditory stimuli (Lutz et al., 2008a). Lutz et al. (2008a) observed enhanced activity in both the right and left amygdala in 15 meditators who had completed from 10,000 to 50,000 h of meditative training in a variety of practices, including compassion meditation, during the meditative state. These contrasting findings suggest that verbal versus visual stimuli may have a different effect on the amygdala activation. Indeed, the right amygdala or the right medial temporal lobe is more strongly linked with processing and recognition of visual cues such as facial expressions (Benuzzi et al., 2004; Meletti et al., 2003). Furthermore, the left and right temporal lobe epilepsy is associated with verbal and nonverbal impairments, respectively (Jambaque et al., 2007). Moreover, the left amygdala may play unique roles in the decoding of emotional cues, such as prosody via speech or speech-like material (Anderson & Phelps, 2001; Fruhholz, Ceravolo, & Grandjean, 2012; Fruhholz et al., 2015; Sander & Scheich, 2005).

It is noteworthy that the significant training effect on the right amygdala activation in the sad > neutral contrast condition was driven by a significant group-by-time interaction effect on the neutral condition induced by ABCM training. More specifically, increased amygdala activity during the neutral condition was found after ABCM training, but not after relaxation training. The arousal and valence levels of neutral pictures have been reported to be approximately in the middle of positive and negative pictures ratings (Dolcos et al., 2004; Spalek et al., 2015). Therefore, the neutral condition is considered to be relatively emotionally neutral compared to positive and negative conditions. Accordingly, neutral images should typically not be affected by changes in emotional processing and are thus, often regarded as baseline. In the current study, the activation for the neutral condition was subtracted from either the activation for the positive or negative conditions, in order to obtain activation for emotion-related stimuli only and eliminate the baseline difference across different subjects at different timepoints. Due to the unexpected nature of these findings, it remains unclear why the training effect was not observed directly in the negative condition, but indirectly via altering the activity for the neutral condition. One speculation is that, even though the neutral pictures are generally regarded as emotionally neutral, meditation training may induce changes in interpretation toward the neutral pictures. Since the current study applied a brief meditation training (6 weeks), the training effect might only be sufficient to induce a change in plasticity for the less emotionally charged condition (i.e., neutral condition). Our findings suggest that the neutral condition might not be the true baseline for ABCM training. This speculation requires future studies to confirm.

There are some limitations in the current study. First, the two groups had different right amygdala activity during negative emotion processing before training and an almost-significant group difference in years of education. Nonetheless, regression analyses showed that the changes in the right amygdala activity after training were unlikely to be affected by these group differences. Second, the small sample size of the current study limits the power of this study. Thus, it remains to be determined whether other significant differences will arise with the increased power. Third, only visual stimuli were used to depict the affective information, whether the left amygdala activity during affective processing via auditory cues could also be modified by ABCM awaits future examination. Fourth, the issue of the driving effect of changes in neutral images in the ABCM condition remains surprising and currently unexplained. It would be relevant to see if the changes in the right amygdala activity for the neutral condition correlated with the changes in ratings of neutral pictures. Unfortunately, such changes in the right amygdala activity for the neutral condition were unexpected, and as we originally expected the neutral condition to function as an unaffected baseline, we did not capture the rating for the neutral picture. Accordingly, a further study should follow exploring the speculation on the effects of training on the perception of neutral images. Fifth, the quasi-experimental design may generate potential self-selection bias. Participants who were less available might be busier or more employed and thus less likely to have completed the assessment earlier and was assigned to the relaxation group. Nonetheless, both groups had similar drop-out rates and duration of practice, suggesting that both groups had similar levels of motivation and effort. Furthermore, a passive control group was not included because of time and infrastructural constraints. Therefore, a maturation effect that might occur naturally with the passage of time cannot be excluded. Last, the current study adopted a relatively short training period (3-week sessions and 3-week home-based rehearsal). Future studies that adopt a multiple time-points design and with longer training period are essential to confirm the dosage effect of ABCM.

To summarize, our findings support the potential of short-term ABCM practice in alleviating anxiety and altering the right amygdala activity during a less emotionally charged condition. In particular, the neural change induced by ABCM may be a carried-over effect from meditation practice, which corroborates the notion that the effect of meditation practice may transfer to non-meditative states (Lutz et al., 2007, 2008b) and potentially have important implications on stress management. Pathologically elevated levels of both anxiety and the right amygdala activity are common in patients with affective disorders, suggesting that the revealed effects of ABCM may provide a platform from which its use in clinical populations can be further explored.

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