# Impact of short- and long-term mindfulness meditation training on amygdala reactivity to emotional stimuli

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## ARTICLE INFO

## ABSTRACT

Meditation training can improve mood and emotion regulation, yet the neural mechanisms of these affective changes have yet to be fully elucidated. We evaluated the impact of long- and short-term mindfulness meditation training on the amygdala response to emotional pictures in a healthy, non-clinical population of adults using blood-oxygen level dependent functional magnetic resonance imaging. Long-term meditators (N = 30, 16 female) had 9081 h of lifetime practice on average, primarily in mindfulness meditation. Short-term training consisted of an 8-week Mindfulness- Based Stress Reduction course (N = 32, 22 female), which was compared to an active control condition (N = 35, 19 female) in a randomized controlled trial. Meditation training was associated with less amygdala reactivity to positive pictures relative to controls, but there were no group differences in response to negative pictures. Reductions in reactivity to negative stimuli may require more practice experience or concentrated practice, as hours of retreat practice in long-term meditators was associated with lower amygdala reactivity to negative pictures – yet we did not see this relationship for practice time with MBSR. Short-term training, compared to the control intervention, also led to increased functional connectivity between the amygdala and a region implicated in emotion regulation – ventromedial prefrontal cortex (VMPFC) – during affective pictures. Thus, meditation training may improve affective responding through reduced amygdala reactivity, and heightened amygdala–VMPFC connectivity during affective stimuli may reflect a potential mechanism by which MBSR exerts salutary effects on emotion regulation ability.

## 1. Introduction

Mindfulness meditation practices, which aim to cultivate an accepting awareness of the present moment (Bishop et al., 2004; Brown and Ryan, 2003; Kabat-Zinn, 1990) can improve emotion regulation, ameliorate symptoms underlying anxiety and depression and boost positive mood (Goyal et al., 2014; Hofmann et al., 2010; Jain et al., 2007). Mindfulness-Based Stress Reduction (MBSR) is a widely used form of meditation practice taught by a trained professional that involves didactics, individual and group practices including: breath awareness meditation, body scans, walking meditation and yoga. Each of the practices involves focusing attention on present-moment experience (Kabat-Zinn, 1990). MBSR has been shown to lead to reduced negative

experience (Goldin and Gross, 2010; Kaviani et al., 2011) and quicker recovery from a negative challenge (Britton et al., 2012; Raes et al., 2009). Improvements in affective responses following mindfulness meditation training have also been shown in non-clinical populations, including reductions in emotional interference (Ortner et al., 2007) and decreased negative mood (Jha et al., 2010). Research on the neural mechanisms underlying these affective changes that utilizes active control conditions is sparse, and systematic examination of the impact of mindfulness meditation training on functional connectivity in emotion regulation networks has not been investigated.

Allen et al. provide initial evidence that mindfulness meditation alters neural processing to affective stimuli following a short-term intervention – participants who practiced longer had more insula activation during

negative pictures in a whole-brain analysis (Allen et al., 2012). The current study investigated a greater range of practice by including long- and short-term practitioners and expands upon prior work by probing the neural response to positive pictures – in addition to negative pictures – in an important emotion regulation circuit using *a-priori* amygdala and ventromedial prefrontal cortex (VMPFC) regions of interest (ROIs). Research using a similar approach demonstrated decreased amygdala activation during positive affective pictures following short-term mindfulness meditation training, however it was limited to 12 participants per group (Desbordes et al., 2012). Precisely how mindfulness-based meditation impacts the neural circuitry of emotion regulation remains unclear.

The amygdala is central to emotion generation (Phelps and LeDoux, 2005) and regulation (Buhle et al., 2014), and VMPFC is implicated in automatic emotion regulation (Phelps et al., 2004; Urry et al., 2006), possibly through functional coupling with the amygdala (Banks et al., 2007; Lee et al., 2012). Automatic, or implicit emotion regulation consists of processes that alter the course of affective experience outside explicit, conscious attempts to do so. Affect labeling is a process which may engage automatic emotion regulation even absent an intention to volitionally regulate emotion, as affect labeling has been shown to dampen the amygdala response (Lieberman et al., 2007). Extinction learning is another example of an automatic emotion regulation process and involves both amygdala and VMPFC (Phelps et al., 2004). Non-human primate research reveals a specific mechanism for these effects whereby monosynaptic input to basolateral amygdala from MPFC inhibits activity from the central nucleus of the amygdala (Kim et al., 2011). Moreover, research in non-human primates indicates functional specificity of VMPFC for value updating (Rudebeck et al., 2013), providing evidence that VMPFC automatically processes information regarding the changing salience of stimuli. Recent studies in humans have also found converging support for the role of VMPFC in value updating (Levy and Glimcher, 2012).

We systematically examined the impact of mindfulness meditation training on affective processing by assessing amygdala activation and amygdala-VMPFC functional connectivity during an automatic emotion regulation task in a non-clinical, healthy population of adults who were in a normal state, not explicitly practicing any form of meditation. Brain activation was assessed using blood-oxygen level dependent functional magnetic resonance imaging (BOLD fMRI). We employed a rigorous design combining cross-sectional analysis of long-term meditators (LTM) compared to meditation-naïve participants (MNP), and a randomized controlled trial (RCT) in which a subset of MNP completed either an 8-week intervention with MBSR or a validated, active control condition (the health enhancement program; HEP) that was matched for intervention effects non-specific to mindfulness meditation (MacCoon et al., 2012). The LTM had a daily sitting meditation practice of at least 30 min for at least three years, and the primary type of meditation practice was most similar to that taught in MBSR — Vipassana (i.e. open monitoring; OM). In this form of meditation, practitioners cultivate sustained awareness to experience without attempting to control the focus of attention, but rather maintaining openness to any feelings that arise in awareness (Lutz et al., 2015).

We hypothesized that mindfulness meditation training would decrease reactivity to affective stimuli, as assessed by amygdala activation to positive and negative pictures (relative to neutral). We further hypothesized that mindfulness meditation training would enhance automatic emotion regulation, as reflected by greater amygdala- VMPFC functional connectivity during affective pictures (negative, positive) relative to neutral. First, we tested for differences in LTM compared to MNP, and then we tested for a similar pattern of effects following training with MBSR compared to HEP, while controlling for pre-treatment baseline (i.e. data collected prior to randomization). Using RCT data to follow up on cross-sectional analyses allowed us to rigorously control for influential factors that may have systematically differed between LTM and MNP. Finally, we assessed the length and type of meditation practice to test how variations in practice predicted differences in the brain and behavior.

## 2. Methods

### 2.1. Participants

We recruited 158 healthy human subjects from a non-clinical population, comprised of 127 meditation-naïve participants (MNP) and 31 long-term meditators (LTM). The MNP (average age 48.1 ± 10.7 years, 81 female) comprised a much larger group as they participated in both the RCT and cross-sectional arms of the study, and were recruited within Madison, WI and the surrounding community using flyers, online advertisements, and advertisements in local media. Recruitment materials requested participation in a study of "health and well-being" or the "benefits of health wellness classes." Following baseline data collection, a sub-set of MNPs who participated in the cross-sectional arm of the study were randomly assigned to mindfulness meditation training or an active control intervention for the RCT: Mindfulness Based Stress Reduction (MBSR; N = 43, average age 48.2 ± 10.0 years, 27 female) or the Health Enhancement Program (HEP; N = 43, average age 48.0 ± 12.2 years, 27 female), which has been validated in a separate study (MacCoon et al., 2012). The intervention and randomization procedures were identical to that detailed by MacCoon et al. (2012) Four participants did not complete the fMRI task following the intervention, and an additional 15 participants left the study prior to post-intervention data collection due to logistical reasons, resulting in 32 participants who completed MBSR (average age 50.8 ± 8.8 years, 22 female) and 35 participants who completed HEP (average age 48.1 ± 12.6 years, 19 female).

The LTM (average age 50.7 ± 10.1 years, 17 female) were recruited at meditation centers and through related mailing lists throughout the United States, in addition to flyers and advertisements in newspapers similar to the recruitment strategy for MNP. The LTM did not differ from the MNP in terms of age, gender, motion during the fMRI task, level of education, or socio-economic status measured with the Hollingshead index (Hollingshead, 1975), nor were there statistically significant effects of any of these demographic factors on any of the outcome variables, except in 2 cases as described in the Results section. Meditation recruitment criteria included at least three years of daily practice (at least 30 min per day of sitting meditation), experience with Vipassana, concentration and compassion/loving-kindness meditations, and at least 3 intensive retreats lasting 5 or more days. LTM had an average of 9081 lifetime hours of meditation practice, ranging from 1439 to 32,612 total hours, and which primarily consisted of mindfulness-based practices (focused attention and OM; 86% of daily practice hours), in addition to some practice with compassion/loving kindness meditations (14% of daily practice hours). Lifetime hours of practice were calculated based on subjects reports of their average hours of formal meditation practice per week and their total years of practice. Participants in either group were excluded if they had used medication for anxiety, depression, or other psychological issues, or had a psychiatric diagnosis in the past year. Participants were also excluded if they had any history of bipolar or schizophrenic disorders, brain damage or seizures.

The automatic emotion regulation task was one of a number of tasks administered during a 24-h lab visit as part of a larger, multi-session study. Meditation-naïve participants completed one lab visit prior to randomization, and then following the 8-week MBSR or HEP intervention participants returned for a post-training visit during which the same measures were collected. Experimenters were blind to the group assignment of meditation-naïve participants during data collection for the RCT. Subjects also completed a series of questionnaires, including the Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2006), which includes a sub-scale that was used as a self-report measure of non-reactivity. Example items from the non-reactivity scale include: "When I have distressing thoughts or images, I just notice them and let them go", and "I watch my feelings without getting lost in them". A panel

of other domain-specific questionnaires was included to address hypotheses from aspects of the larger study that were focused on relationships between meditation and sleep, health, response to social stress and pain processing, and which were irrelevant to the current analysis. UW-Madison's Health Sciences Institutional Review Board approved the protocol, and all participants provided consent and were given monetary compensation for their participation. Two MNPs were excluded due to brain abnormalities, one dropped out of the study before the task was completed, and three were unable to complete the task due to technical difficulties. This left a total of 121 MNP's (78 female, 119 right-handed) with average age of $48.3 \pm 10.8$ years, and an age range of 26–66 years. One LTM was excluded due to a dental implant which distorted the functional fMRI data, leaving a total of 30 LTM's (16 female, 29 right-handed) with an average age of $50.5 \pm 10.2$ years and an age range of 28–62 years. We recruited a larger sample of MNP than LTM, due to the unique study design that incorporated an RCT for which we needed at least 30 MNP participants per group following randomization. The MNP in the RCT were a subset of the participants whose pre-randomization baseline data were included in the cross-sectional arm of this study.

### 2.2. Automatic emotion regulation task

Seventy-two pictures selected from the International Affective Picture Set (Lang et al., 2008 "The XM2VTS Database," n.d.) were presented during fMRI scanning, and evenly split between negative, neutral and positive pictures. This resulted in 24 pictures in each of the three valence categories, and each picture was presented for 4 s. The average normative valence (V) and arousal (A) ratings of the pictures in the three categories were negative $(V = 2.87 \pm 0.87, \quad A = 5.51 \pm 0.47)$, neutral $(V = 5.08 \pm 0.60, \quad A = 3.86 \pm 0.63)$ and positive $(V = 7.10 \pm 0.47, A = 5.36 \pm 0.37)$, where both valence and arousal are measured on 9-point scales (1 = *most unpleasant or least arousing* and 9 = *most pleasant* or *most arousing*, respectively). Valence order was pseudo-randomized and picture order was completely randomized within the task. The positive pictures did not include erotic images from the IAPS set, and all the pictures in this task were evenly split between social and non-social categories. The task also included the presentation of neutral (male and female) faces from the Extended Multimodal Face Database ("The XM2VTS Database," n.d.), which were presented for 500 ms after the offset of the picture in two-thirds of the trials, and appeared either 1 s ($8\times$ per valence) or 3 s ($8\times$ per valence) post-picture offset. There were also eight trials in which a face did not follow the image. The faces were included as a way to probe emotional spillover from the preceding IAPS stimuli, however there were no differences in BOLD activation to faces following negative and positive pictures compared to faces following neutral pictures. Thus, we focused solely on the picture presentation period.

Automatic emotion regulation is assumed to be a process that occurs in the absence of volitional attention and without explicit instructions. Thus, the task used in the current study entailed examining automatic emotion regulation processes in response to emotional pictures in the absence of an explicit request to voluntarily regulate emotion. Participants were instructed to press a button indicating the valence category of the picture (either negative, neutral, or positive) to ensure they were paying attention. Button order was counterbalanced across subjects. Participants were instructed to passively view the faces following the images. All stimuli were presented using E-Prime software (E-Prime, 2012) and participants viewed these images with a fiber-optic goggle system (Avotec, Inc., Stuart, FL) while inside the MRI scanner. Due to a technical error the button box response was not recorded for 85 participants (19 LTM), in which case they were sent a link to complete the picture categorizations online at home following the scan. Sixty-one participants (11 LTM) completed the online task at home to categorize the pictures. The task consisted of 4 runs of approximately 5 min each. In order to familiarize participants with the task and the scanning environment, they completed 6 practice trials (with a separate set of pictures

not included in the scanner task) in a mock scanner prior to beginning the experiment.

### 2.3. Image acquisition

Images were acquired on a GE X750–3.0 Tesla MRI scanner device with an 8- channel head coil. Anatomical scans consisted of a high-resolution 3D T1-weighted inversion recovery fast gradient echo image (inversion time = 450 msec, $256 \times 256$ in-plane resolution, 256 mm FOV, $124 \times 1.0$ mm axial slices). Four functional scan runs were acquired for the Automatic Emotion Regulation Paradigm using a gradient echo EPI sequence ($64 \times 64$ in-plane resolution, 240 mm FOV, TR/TE/ Flip = 2000 ms/25 ms/60°, $40 \times 4$ mm interleaved sagittal slices, and 159 3D volumes per run).

### 2.4. Image processing

Functional images were processed using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library) including a high pass temporal filter of 100 s, motion correction with MCFLIRT (Jenkinson et al., 2002), BET (Smith, 2002) brain extraction, spatial smoothing at 5 mm FWHM, and FILM prewhitening (Woolrich et al., 2001). Transformation matrices for registration were computed at the first level (within scan run) and applied at the second level using FSL in a two stage process where the Boundary Based Registration (BBR) approach (Greve and Fischl, 2009) was used to register the subject's time series data to their anatomical template, and a 12 DOF affine transformation was used to register the subject's anatomical scans to Montreal Neurological Institute (MNI) space using FLIRT (Jenkinson et al., 2002).

### 2.5. Experimental design and statistical analysis

The functional data from individual subjects were analyzed using a General Linear Model (GLM) in 3 levels, where the first level (within-scan) modeled stimulus presentation with a double-gamma hemodynamic response function as defined in FSL. Each trial type was modeled with up to two regressors for each of two events; the 4 s presentation period of the IAPS image, and the 0.5 s presentation of the neutral face on the 2/3 of trials in which a face was presented (1/3 of trials did not have a face) for a total of 9 regressors (trials with faces were modeled separately but were collapsed together in the higher level analysis). Additional regressors of no interest were included to model the 24 total motion-related parameters (the standard plus extended parameters, which include the squares, derivatives, and squares of derivatives). To further address motion, high motion time points with a framewise displacement larger than 0.9 mm (Siegel et al., 2014) were modeled out of the data with an individual regressor. There were no scans with greater than 25% of the data censored for motion, and thus no participants or scans were excluded for excessive motion. The second level combined data within subject and across scans using a fixed effects modeling approach. Group analysis to check for whole-brain, voxelwise effects was done at the third level in which we modeled data across subjects using the Flame1 mixed effects model estimation. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 3.1$ and a (family-wise error corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001) for the voxelwise, whole-brain analyses.

Functional amygdala ROIs were identified from the contrast of Negative > Neutral IAPS pictures during a 4 s picture presentation period (analogous to the task used in the current study except participants did not make a button press response) and using data from an independent sample of 90 participants enrolled in a separate study (mean age(SD) = 45.1(10.0) years, 52 female) (Grupe et al., 2017). The right and left functional amygdala ROIs were then masked with anatomical amygdala ROIs from the Harvard- Oxford Atlas (Desikan et al., 2006) with a threshold at 50% probability to remove any non-amygdala voxels, resulting in a left and right amygdala ROIs of 104 and 164 voxels,

respectively. Mean percent signal change across each amygdala ROI was extracted for all participants from the output of the second level model.

The functional ROI for the right amygdala was used to extract the timeseries, which was deconvolved (Gitelman et al., 2003) prior to computing the psychophysiological interaction (PPI) for the connectivity analysis. We then ran a second model to examine right amygdala-VMPFC connectivity, which included (in this order) all the regressors as the basic task model described above (9 task regressors and 24 motion regressors), a PPI regressor for each of the 3 task conditions (negative, neutral and positive IAPS), as well as the right amygdala seed timeseries, otherwise known as the gPPI approach (McLaren et al., 2012). The regressors were not orthogonalized. We computed contrasts for negative versus neutral and positive versus neutral PPIs, which were then used for a group level connectivity analysis from which we extracted values from a MPFC ROI based on the Harvard-Oxford Atlas containing 976 voxels (depicted in purple in Fig. 2a). We used an anatomical mask for MPFC as we did not have an independent, functional localizer for this region. We also did not want to restrict the ROI based on a different task or analysis, which may not include regions of VMPFC that are differentially connected to amygdala due to training in mindfulness meditation. Statistical analysis for regions of interest was done using the lm function from the stats package in the statistical analysis software R (R Core Team, 2015; version 3.2.2), and $p$-value computation used the model Summary function of the lmSupport package (Curtin, 2015).

## 3. Results

All results are reported after removing outliers based on Cook's D using a cutoff threshold of 4/(N-P) for data points disconnected from the

distribution, where N and P correspond to the sample size and number of model parameters, respectively. When outliers were removed from the analysis they were also removed from the corresponding figure(s). Across all tests, 4 model outliers had extreme motion and 2 model outliers had extreme values in change in FFMQ non-reactivity, where points greater than 3 standard deviations (SD) from the mean are considered extreme. Thirty-seven percent of model outliers were outliers in multiple statistical tests. All findings remain consistent when outliers are included in the model, except in 3 cases as noted in the text. When comparing model outliers from all tests (N = 38) we found that the outlier participants had significantly more motion ($p = 0.02$) and lower non-reactivity ($p = 0.003$) compared to participants who never appear as outliers (N = 117). Descriptive statistics for all variables are available in Table 1.

### 3.1. Mindfulness meditation practice and amygdala reactivity: analytic strategy

We tested for group differences in amygdala reactivity to affective pictures, as assessed via BOLD fMRI signal for the contrast of negative (NEG) and positive (POS) picture trials minus neutral (NEU) picture trials (hereafter referred to as NEGPOS > NEU). As our hypotheses were specific to the amygdala (and its connectivity with VMPFC), we focused on the ROI analysis. However, a whole-brain, voxelwise analysis did not reveal any regions in which there were differences between groups (neither for LTM versus MNP, nor MBSR versus HEP post-intervention controlling for baseline).

Significant clusters for LTM and MNP for each contrast of interest are presented in Table 3, and for MBSR and HEP participants at T2 (controlling for T1) in Table 4. Un-thresholded statistical maps for each group

**Table 1**
Descriptive statistics by group including mean (M), standard deviation (SD), minimum (Min), and maximum (Max) for all variables reported in the Results section. Pre- and post-intervention statistics are presented for the right amygdala. LTM = long-term meditators; MNP = meditation-naïve participants; MBSR = randomized to Mindfulness-Based Stress Reduction; HEP = randomized to health enhancement program control intervention; T1=pre-intervention; T2=post-intervention; NEG = negative IAPS; POS = positive IAPS; NEU = neutral IAPS.

| | Right amygdala activation | | | | | | | | | | | |
| | NEGPOS > NEU | | | | NEG > NEU | | | | POS > NEU | | | |
| Group | M | SD | Min | Max | M | SD | Min | Max | M | SD | Min | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LTM | 0.02 | 0.13 | −0.34 | 0.28 | 0.06 | 0.14 | −0.37 | 0.33 | −0.02 | 0.16 | −0.38 | 0.22 |
| MNP | 0.12 | 0.22 | −0.93 | 1.11 | 0.15 | 0.24 | −0.51 | 1.13 | 0.11 | 0.25 | −1.35 | 1.03 |
| T1 MBSR | 0.13 | 0.17 | −0.32 | 0.60 | 0.16 | 0.21 | −0.49 | 0.55 | 0.09 | 0.17 | −0.16 | 0.60 |
| T1 HEP | 0.11 | 0.19 | −0.23 | 0.80 | 0.11 | 0.25 | −0.37 | 1.09 | 0.11 | 0.18 | −0.16 | 0.53 |
| T2 MBSR | 0.05 | 0.20 | −0.49 | 0.52 | 0.13 | 0.20 | −0.20 | 0.71 | −0.02 | 0.26 | −0.80 | 0.75 |
| T2 HEP | 0.11 | 0.16 | −0.35 | 0.41 | 0.15 | 0.19 | −0.36 | 0.71 | 0.06 | 0.20 | −0.45 | 0.59 |

| | Left amygdala activation | | | | | | | | | | | |
| | NEGPOS > NEU | | | | NEG > NEU | | | | POS > NEU | | | |
| Group | M | SD | Min | Max | M | SD | Min | Max | M | SD | Min | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LTM | 0.08 | 0.17 | −0.45 | 0.42 | 0.10 | 0.22 | −0.40 | 0.64 | 0.06 | 0.21 | −0.61 | 0.43 |
| MNP | 0.11 | 0.25 | −0.41 | 1.07 | 0.15 | 0.26 | −0.58 | 1.01 | 0.08 | 0.28 | −0.57 | 1.09 |

| | Right amygdala-VMPFC PPI | | | | | | | | Self-reported non-reactivity (FFMQ) | | | |
| | NEG > NEU | | | | POS > NEU | | | | | | | |
| Group | M | SD | Min | Max | M | SD | Min | Max | M | SD | Min | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LTM | 0.20 | 0.40 | −0.42 | 1.34 | 0.00 | 0.27 | −0.55 | 0.69 | 28.77 | 4.32 | 15 | 35 |
| MNP | 0.03 | 0.42 | −2.18 | 1.77 | −0.04 | 0.33 | −1.12 | 1.64 | 23.42 | 3.91 | 14 | 33 |
| T1 MBSR | 0.02 | 0.61 | −2.21 | 1.81 | −0.10 | 0.46 | −1.15 | 1.69 | 23.44 | 3.93 | 15 | 33 |
| T1 HEP | 0.08 | 0.38 | −0.85 | 0.75 | −0.01 | 0.24 | −0.47 | 0.53 | 23.49 | 4.25 | 14 | 31 |
| T2 MBSR | 0.21 | 0.40 | −0.88 | 0.93 | 0.08 | 0.34 | −0.63 | 0.86 | 25.16 | 4.37 | 17 | 35 |
| T2 HEP | −0.07 | 0.25 | −0.58 | 0.52 | −0.06 | 0.27 | −0.64 | 0.72 | 24.63 | 4.14 | 9 | 32 |

| | Percent pictures categorized as neutral | | | | | | | | | | | |
| | Negative | | | | Positive | | | | Neutral | | | |
| Group | M | SD | Min | Max | M | SD | Min | Max | M | SD | Min | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LTM | 0.20 | 0.26 | 0.00 | 1.00 | 0.37 | 0.24 | 0.04 | 1.00 | 0.58 | 0.22 | 0.21 | 1.00 |
| MNP | 0.08 | 0.10 | 0.00 | 0.50 | 0.18 | 0.16 | 0.00 | 0.75 | 0.52 | 0.19 | 0.12 | 1.00 |

**Table 2**

Summary of statistical results for all tests reported in the Results section, including degrees of freedom (df), *t-value, p-value,* parameter estimates (*b*), and confidence intervals (*CI*). LTM = long-term meditators; MNP = meditation-naïve participants; MBSR = randomized to Mindfulness-Based Stress Reduction; HEP = randomized to health enhancement program control intervention; NEG = negative IAPS; POS = positive IAPS; NEU = neutral IAPS.

| Right amygdala activation (NEGPOS > NEU) | | | | | | Left amygdala activation (NEGPOS > NEU) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | df | t | b | p | CI | | df | t | b | p | CI |
| LTM vs MNP | 145 | 2.66 | 0.09 | 0.01 | [0.02, 0.15] | LTM vs MNP | 146 | −0.12 | −0.01 | 0.90 | [−0.09, 0.08] |
| MBSR vs HEP | 64 | −1.45 | −0.06 | 0.15 | [−0.01, 0.47] | MBSR vs HEP | 64 | −1.15 | −0.07 | 0.25 | [−0.19, 0.05] |

| Right amygdala activation (NEG > NEU) | | | | | | Left amygdala activation (NEG > NEU) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | df | t | b | p | CI | | df | t | b | p | CI |
| LTM vs MNP | 145 | 1.65 | 0.06 | 0.10 | [−0.01, 0.14] | LTM vs MNP | 145 | 0.53 | 0.03 | 0.60 | [−0.07, 0.13] |
| MBSR vs HEP | 57 | −1.84 | −0.06 | 0.07 | [−0.13, 0.01] | MBSR vs HEP | 63 | −0.76 | −0.05 | 0.45 | [−0.18, 0.08] |

| Right amygdala activation (POS > NEU) | | | | | | Left amygdala activation (POS > NEU) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | df | t | b | p | CI | | df | t | b | p | CI |
| LTM vs MNP | 147 | 3.86 | 0.13 | 0.001 | [0.06, 0.21] | LTM vs MNP | 146 | −0.33 | −0.02 | 0.75 | [−0.11, 0.08] |
| MBSR vs HEP | 58 | −2.65 | −0.10 | 0.01 | [−0.18, −0.02] | MBSR vs HEP | 59 | −1.54 | −0.08 | 0.13 | [−0.19, 0.02] |

| Right amygdala-VMPFC PPI (NEG > NEU) | | | | | | Right amygdala-VMPFC PPI (POS > NEU) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | df | t | b | p | CI | | df | t | b | p | CI |
| LTM vs MNP | 145 | −1.29 | −0.09 | 0.20 | [−0.23, 0.05] | LTM vs MNP | 149 | −0.71 | −0.05 | 0.48 | [−0.17, 0.02] |
| LTM Retreat Practice | 27 | 0.18 | 0.01 | 0.86 | [−0.12, 0.14] | LTM Retreat Practice | 28 | 0.08 | 0.003 | 0.93 | [−0.08, 0.09] |
| LTM OM Retreat | 25 | 0.37 | 0.02 | 0.72 | [−0.10, 0.15] | LTM OM Retreat | 26 | 0.17 | 0.01 | 0.87 | [−0.07, 0.09] |
| LTM Daily Practice | 26 | 0.35 | 0.05 | 0.73 | [−0.23, 0.32] | LTM Daily Practice | 28 | −0.05 | −0.003 | 0.96 | [−0.16, 0.16] |
| MBSR vs HEP | 62 | 3.99 | 0.29 | <0.01 | [0.15, 0.44] | MBSR vs HEP | 58 | 2.57 | 0.16 | 0.01 | [0.04, 0.29] |
| MBSR Practice | 28 | 1.65 | <0.01 | 0.11 | [0.00, 0.00] | MBSR Practice | 29 | −1.20 | <0.01 | 0.24 | [0.00, 0.00] |

| Meditation time vs right amygdala activation (NEG > NEU) | | | | | | Meditation time vs right amygdala activation (POS > NEU) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | df | t | b | p | CI | | df | t | b | p | CI |
| LTM Retreat | 25 | −2.10 | −0.03 | 0.05 | [−0.07, 0.00] | LTM Retreat | 25 | −0.72 | −0.02 | 0.50 | [−0.07, 0.03] |
| LTM OM Retreat | 23 | −2.62 | −0.04 | 0.02 | [−0.06, −0.01] | LTM OM Retreat | 23 | −0.95 | −0.02 | 0.35 | [−0.07, 0.03] |
| LTM Daily | 25 | −0.48 | −0.02 | 0.64 | [−0.09, 0.05] | LTM Daily | 25 | −0.51 | −0.02 | 0.62 | [−0.12, 0.07] |
| MBSR Minutes | 26 | −1.19 | <0.01 | 0.24 | [0.00, 0.00] | MBSR Minutes | 28 | 0.17 | <0.01 | 0.87 | [0.00, 0.00] |

| Self-reported non-reactivity (FFMQ) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | df | t | b | p | CI | | df | t | b | p | CI |
| LTM vs MNP | 151 | −6.61 | −4.92 | <0.01 | [−6.39, −0.36] | MBSR vs HEP | 57 | −0.48 | −0.28 | 0.64 | [−1.48, 0.91] |

| Non-reactivity vs right amygdala activation (NEG > NEU) | | | | | | Non-reactivity vs right amygdala activation (POS > NEU) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | df | t | b | p | CI | | df | t | b | p | CI |
| LTM+MNP | 148 | −1.33 | −2.19 | 0.19 | [−5.43. 1.06] | LTM+MNP | 148 | −3.20 | −5.38 | <0.01 | [−8.70, −2.06 |
| MBSR+HEP | 60 | 1.51 | 3.10 | 0.14 | [−0.99, 7.00] | MBSR+HEP | 53 | 1.67 | 2.81 | 0.10 | [−0.57, 6.20] |

| Percent pictures categorized as neutral | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LTM vs MNP | df | t | b | p | CI | LTM vs MNP | df | t | b | p | CI |
| NEG IAPS | 119 | −2.18 | −0.04 | 0.03 | [−0.08, −0.01] | All IAPS | 122 | −2.52 | −0.07 | 0.01 | [−0.12, −0.01] |
| POS IAPS | 122 | −3.77 | −0.14 | <0.01 | [−0.22, −0.07] | | | | | | |
| NEU IAPS | 120 | −0.45 | −0.02 | 0.65 | [−0.11, 0.07] | | | | | | |

for these contrasts are also available at NeuroVault: https://neurovault.org/collections/3755/.

### 3.2. Long-term mindfulness meditation practice and amygdala reactivity

Long-term meditators had significantly lower right amygdala activation than meditation-naïve participants for the contrast NEGPOS > NEU (*t*(145) = 2.66, *b* = 0.09, *p* = 0.01, CI = [0.02,0.15], 1 LTM and 3 MNP outliers removed, partial *r* = 0.20). In order to decompose this effect, we conducted separate analyses on the negative and positive picture trials. Long-term meditators had significantly lower right amygdala activation for POS > NEU than meditation-naïve participants (*t*(147) = 3.86, *b* = 0.13, *p* = 0.001, CI = [0.06,0.21], 2 MNP outliers removed, partial *r* = 0.26; Fig. 1b), however there was only a marginal, non-significant

difference for the contrast NEG > NEU (*t*(145) = 1.65, *b* = 0.06, *p* = 0.10, CI = [-0.01,0.14], 1 LTM and 3 MNP outliers removed, partial *r* = 0.11; Fig. 1a). When outliers were included in the model the group difference for NEG > NEU was significant (*p* = 0.05). Results of all statistical tests, including non-significant results for the left amygdala, are reported in Table 2.

While participants' valence categorization of the pictures was intended to keep their attention on-task, rather than as a behavioral assay of emotion regulation or reactivity, we examined these behavioral responses in an exploratory fashion. Due to a technical error, button presses for 84 participants were not recorded during the scan: 23 participants (5 LTM) were completely missing the categorization data, and 61 participants (11 LTM) categorized the pictures online after the scan. We included a covariate to control for whether participants' behavioral data

**Table 3**

Significant clusters for long-term meditators (LTM) and meditation-naïve participants (MNP) at baseline (T1) (cluster-forming threshold Z > 3.1 and family-wise error corrected cluster significance threshold of $p = 0.05$). NEG = negative IAPS; POS = positive IAPS; NEU = neutral IAPS.

| Region (Peak) | | | Peak | | | | |
|---|---|---|---|---|---|---|---|
| | | | Max (Z) | X | Y | Z | Volume (mm) |
| NEGPOS > NEU | LTM | Precuneus | 5.8 | −4 | −60 | 22 | 1138 |
| | | Occipital Pole | 4.5 | 4 | −90 | 4 | 845 |
| | | Left Inferior Lateral Occipital Cortex | 4.4 | −50 | −74 | 10 | 487 |
| | | Right Temporal Pole | 4.2 | 48 | 22 | −20 | 219 |
| | | Right Inferior Lateral Occipital Cortex | 4.1 | 46 | −62 | 8 | 177 |
| | MNP | Right Amygdala | 8.9 | 24 | −10 | −12 | 7561 |
| | | Right Superior Temporal Gyrus | 9.1 | 48 | −64 | 10 | 6628 |
| | | Precuneus | 9.9 | 2 | −60 | 28 | 3208 |
| | | Left Inferior Lateral Occipital Cortex | 8.4 | −48 | −74 | 10 | 3123 |
| | | Superior Frontal Gyrus | 6.5 | 6 | 56 | 24 | 2740 |
| | | Right Superior Parietal Lobule | 4.2 | 22 | −46 | 72 | 353 |
| NEG > NEU | LTM | Right Superior Temporal Gyrus | 4.8 | 58 | −4 | −14 | 455 |
| | | Precuneus | 4.4 | −6 | −48 | 42 | 449 |
| | | Middle Temporal Gyrus | 4.0 | −56 | −60 | 8 | 315 |
| | | Occipital Pole | 3.9 | 4 | −92 | 2 | 163 |
| | MNP | Right Amygdala | 9.3 | 24 | −8 | −10 | 3782 |
| | | Left Lateral Occipital Cortex | 8.3 | −54 | −64 | 12 | 2767 |
| | | Middle Temporal Gyrus | 7.8 | 46 | −58 | 14 | 2330 |
| | | Precuneus | 6.9 | −4 | −52 | 48 | 2050 |
| | | Left Amygdala | 8.6 | −28 | −12 | −14 | 1987 |
| | | Right Occipital Pole | 6.3 | 24 | −98 | 4 | 770 |
| | | Left Occipital Pole | 5.9 | −14 | −100 | 0 | 546 |
| | | Superior Frontal Gyrus | 5.6 | 6 | 50 | 32 | 511 |
| | | Right Anterior Supramarginal Gyrus | 5.3 | 68 | −24 | 34 | 429 |
| | | Left Anterior Supramarginal Gyrus | 4.0 | −58 | −28 | 28 | 313 |
| | | Left Subcallosal Cortex | 5.6 | −2 | 0 | −12 | 258 |
| POS > NEU | LTM | Precuneus | 5.7 | −4 | −60 | 24 | 1071 |
| | | Occipital Pole | 5.0 | 2 | −90 | 14 | 729 |
| | | Left Lateral Occipital Cortex | 4.8 | −40 | −70 | 40 | 331 |
| | | Frontal Pole | 4.8 | −10 | 66 | 8 | 252 |
| | MNP | Precuneus | 11.2 | 0 | −62 | 30 | 32,003 |
| | | Left Hippocampus | 6.6 | −24 | −18 | −12 | 933 |
| | | Right Fusiform Cortex | 6.0 | 44 | −54 | −20 | 323 |
| | | Left Temporal Pole | 4.5 | −48 | 2 | −24 | 271 |
| | | Left Middle Temporal Gyrus | 5.1 | −66 | −10 | −16 | 260 |

was collected concurrently in the scanner, or online afterward, and the results are consistent whether or not this covariate is included. Including all the available data, LTM categorized a significantly higher proportion of the pictures as neutral compared to MNP ($t(122) = -2.52$, $b = −0.07$, $p = 0.01$, CI = [-0.12, −0.02]). Upon further inspection of this group difference broken down by the standardized IAPS valence categories, we found that the LTM categorized significantly more pictures as neutral than MNP for the negative IAPS pictures ($t(119) = - 2.18$, $b = −0.04$, $p = 0.03$, CI = [-0.08, −0.004], 2 MNP and 1 LTM outliers removed), and positive IAPS pictures ($t(122) = -3.77$, $b = −0.14$, $p < 0.001$, CI = [-0.22, −0.07]). There was no difference between groups in the percentage of neutral IAPS pictures categorized as neutral ($t(120) = -0.45$, $b = −0.02$, $p = 0.65$, CI = [-0.11, 0.07], 2 LTM outliers removed). The percent of negative and positive pictures that LTM categorized as neutral did not relate to the intensity of amygdala activation for NEGPOS > NEU ($t(20) = 0.87$, $b = 0.15$, $p = 0.39$, CI = [-0.21, 0.52]).

### 3.3. Short-term mindfulness meditation practice and amygdala reactivity

In order to determine whether short-term meditation training would lead to similar reductions in amygdala reactivity to affective pictures as seen with long-term training, we compared post-training right amygdala activation in participants randomized to MBSR with the active control condition (HEP), while controlling for pre-treatment baseline activation (i.e. an analysis of covariance approach – ANCOVA). Since participants were randomized to either MBSR or HEP subsequent to pre-treatment (i.e. baseline) data collection we were able to leverage this more

powerful, and more statistically appropriate, ANCOVA analytical approach as opposed to a repeated measures analysis of variance (ANOVA) (Van Breukelen, 2006). We computed the contrast NEG-POS > NEU to examine the impact of MBSR on emotional reactivity, and there was no post-intervention group difference in right amygdala activation between MBSR and HEP ($t(64) = -1.45$, $b = −0.06$, $p = 0.15$, CI = [-0.01,0.47], partial $r = 0.23$; controlling for pre-treatment baseline). In light of the differences between long-term meditators and meditation-naïve participants specific to positive pictures, we also conducted analyses separately for each valence contrast. Participants who trained in MBSR had significantly lower right amygdala activation for the contrast POS > NEU compared to participants who trained in HEP ($t(58) = -2.65$, $b = −0.10$, $p = 0.01$, CI = [-0.18,- 0.02], 3 MBSR and 3 HEP outliers removed], partial $r = 0.31$; Fig. 2b), while controlling for pre-treatment baseline. There were no baseline differences in right amygdala activation for POS > NEU in the same set of participants ($t(59) = -0.38$, $b = − 0.01$, $p = 0.71$, CI = [-0.09,0.06]). Similar to the results for long-term practice, participants who trained in MBSR had only marginally, and non-significantly lower right amygdala activation to the contrast NEG > NEU compared to HEP training ($t(57) = -1.84$, $p = 0.07$, CI = [-0.13,0.01], 4 MBSR and 3 HEP outliers removed], partial $r = 0.37$), while controlling for pre-treatment baseline. When outliers were included in the model the group difference for NEG > NEU was non-significant ($p = 0.46$). There were no significant differences in activation for the left amygdala (Table 2). We were unable to compare post-training differences in behavioral categorizations while controlling for baseline, due to a technical error by which many of the button presses

**Table 4**

Significant clusters for participants following training (T2) in Mindfulness-Based Stress Reduction (MBSR) or the health enhancement program (HEP) control intervention, controlling for baseline (T1) with a voxel-wise regressor (cluster-forming threshold Z > 3.1 and family-wise error corrected cluster significance threshold of p = 0.05). NEG = negative IAPS; POS = positive IAPS; NEU = neutral IAPS.

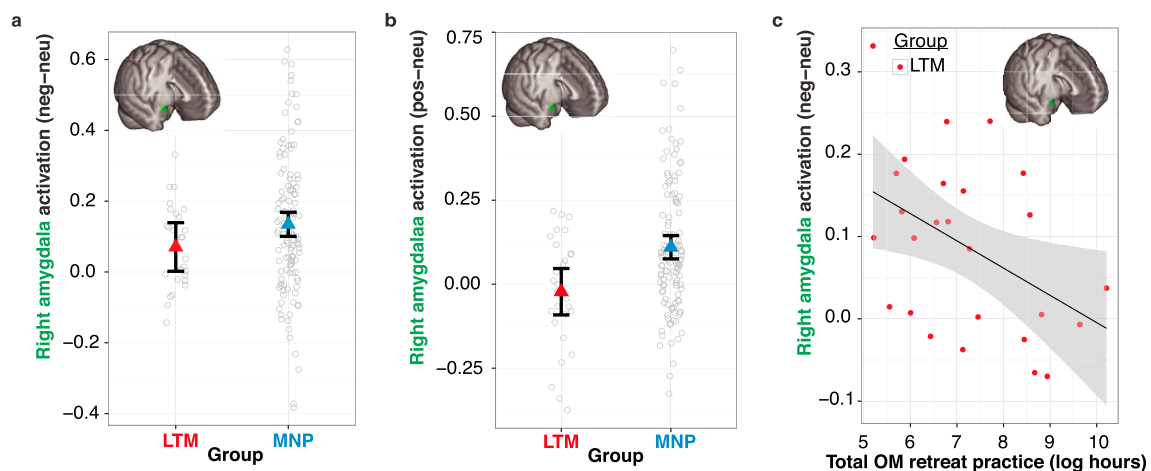| Region (Peak) | | | Peak | | | | |
|---|---|---|---|---|---|---|---|
| | | | Max (Z) | X | Y | Z | Volume (mm) |
| NEGPOS > NEU | MBSR | Left Inferior Lateral Occipital Cortex | 6.7 | −58 | −68 | 10 | 1864 |
| | | Right Middle Temporal Gyrus | 5.6 | 50 | −52 | 10 | 1741 |
| | | Right Superior Lateral Occipital Cortex | 4.7 | 24 | −82 | 42 | 260 |
| | | Left Superior Lateral Occipital Cortex | 4.7 | −18 | −84 | 42 | 200 |
| | HEP | Left Middle Temporal Gyrus | 6.8 | −48 | −62 | 6 | 3439 |
| | | Right Inferior Lateral Occipital Cortex | 5.7 | 50 | −62 | 4 | 1859 |
| | | Right Superior Parietal Lobule | 5.6 | 16 | −56 | 60 | 1286 |
| | | Left Supramarginal Gyrus | 4.6 | −58 | −30 | 36 | 573 |
| | | Right Supramarginal Gyrus | 4.6 | 56 | −30 | 38 | 448 |
| | | Right Superior Lateral Occipital Cortex | 5.3 | 24 | −82 | 40 | 439 |
| | | Left Occipital Pole | 4.7 | −20 | −92 | 26 | 433 |
| | | Right Intracalcarine Sulcus | 4.5 | 14 | −82 | 12 | 266 |
| | | Left Amygdala | 4.8 | −26 | −8 | −12 | 258 |
| | | Right Amygdala | 4.5 | 18 | −2 | −10 | 220 |
| | | Right Precentral Gyrus | 4.4 | 50 | 6 | 28 | 175 |
| NEG > NEU | MBSR | Left Inferior Lateral Occipital Cortex | 6.3 | −48 | −64 | 12 | 5334 |
| | | Right Lingual Gyrus | 6.6 | 16 | −64 | −6 | 4083 |
| | | Right Precentral Gyrus | 4.8 | 48 | 8 | 28 | 898 |
| | | Midbrain | 5.8 | −2 | −32 | −6 | 285 |
| | | Right Putamen | 4.3 | 30 | −16 | −8 | 167 |
| | | Precuneus | 4.3 | 0 | −54 | 60 | 154 |
| | HEP | Left Intracalcarine Cortex | 6.6 | −8 | −84 | 4 | 15,429 |
| | | Midbrain | 6.2 | −2 | −30 | −8 | 2627 |
| | | Precuneus | 4.7 | −8 | −52 | 52 | 1343 |
| | | Right Precentral Gyrus | 5.2 | 50 | 4 | 30 | 1254 |
| | | Left Supramarginal Gyrus | 5.5 | −60 | −36 | 44 | 1066 |
| | | Left Precentral Gyrus | 5.1 | −46 | 0 | 36 | 1065 |
| | | Right Supramarginal Gyrus | 4.3 | 64 | −28 | 30 | 440 |
| | | Right Amygdala | 5.8 | 18 | −2 | −10 | 414 |
| | | Occipital Pole | 4.7 | 32 | 26 | 6 | 257 |
| POS > NEU | MBSR | Right Inferior Lateral Occipital Cortex | 5.5 | 52 | −68 | 10 | 828 |
| | | Left Inferior Lateral Occipital Cortex | 6.2 | −58 | −66 | 10 | 705 |
| | HEP | Left Middle Temporal Gyrus | 6.4 | −46 | −62 | 8 | 1109 |
| | | Right Inferior Lateral Occipital Cortex | 6.2 | 48 | −64 | 2 | 1108 |
| | | Right Superior Parietal Lobule | 5.1 | 26 | −44 | 46 | 1062 |
| | | Right Superior Lateral Occipital Cortex | 4.7 | 24 | −82 | 40 | 172 |



**Fig. 1.** Long-term meditation training is associated with lower right amygdala reactivity to emotional pictures. Long-term meditators (LTM) had lower right amygdala activation for the negative versus neutral pictures at a trend level (a), and significantly lower activation for positive versus neutral pictures than mediation-naïve participants (MNP; b). Greater lifetime hours of open monitoring (OM) retreat practice predicted lower right amygdala activation for negative versus neutral pictures, controlling for age (c). The independently defined right amygdala region of interest from which mean percent signal change data were extracted is inset in each panel. Circles represent raw data points in a and b, and the raw data are adjusted for age in c. Error bars and envelopes are 95% confidence intervals around the point estimates.
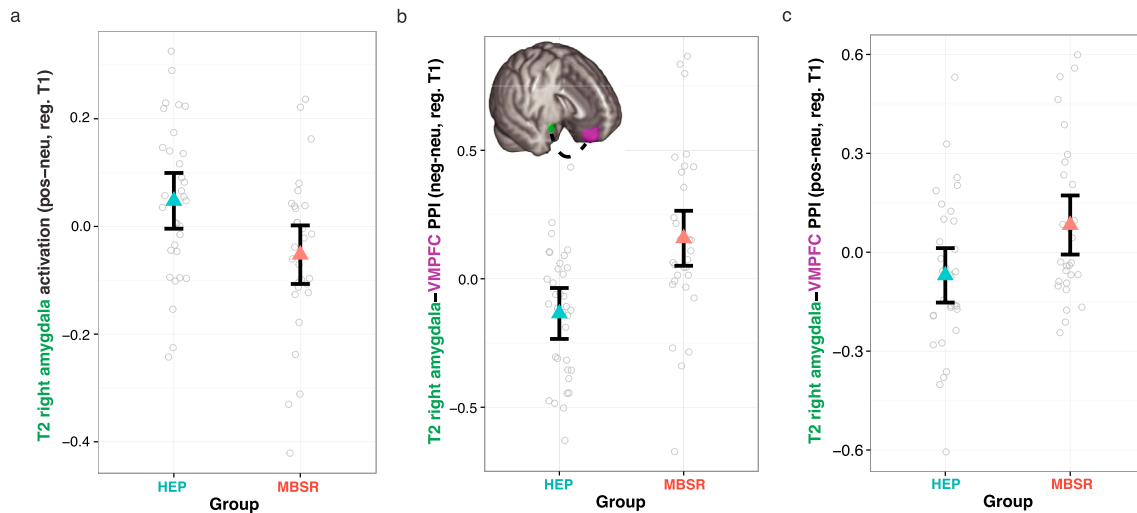
**Fig. 2.** Short-term meditation training causes less right amygdala reactivity and greater connectivity with VMPFC in response to emotional pictures. The ventral medial prefrontal cortex (VMPFC) region of interest (purple) from which we extracted mean psychophysiological interaction (PPI) weights (represented by the dashed line) with the right amygdala ROI (green) is inset in panel b. Participants had lower right amygdala activation following Mindfulness-Based Stress Reduction (MBSR) compared to the Health Enhancement Program (HEP) for positive versus neutral pictures (a), and increased right amygdala-VMPFC PPI for negative versus neutral pictures (b), and for positive versus neutral pictures (c). Analyses and data points are adjusted for pre-treatment baseline activation, and error bars are 95% confidence intervals around the point estimates.

were not recorded, and most participants were lacking data at both time-points.

All subsequent analyses focused on the right amygdala, since the group differences in amygdala reactivity were limited to the right side, and the contrasts were kept separate by valence due to differential effects by valence.

### 3.4. Practice duration and amygdala reactivity

The long-term meditator group had considerable variability in self-reported total lifetime daily practice (mean = 4281(2817) hours, range = 954–13,605 h) and in total lifetime retreat practice (mean = 4658 h, range = 258–29,710 h), which allowed us to test whether the amount of self-reported practice accounted for significant variance in amygdala activation. The distribution of lifetime hours of practice was skewed, so all practice variables were log-transformed prior to analysis. We controlled for age in the following analyses, as it was correlated with log total practice time ($r = 0.30$ with daily practice, and $r = 0.15$ with retreat practice), and 2 outliers were removed from all of the analyses with practice hours. One of the two model outliers was also an extreme point (greater than 3 SD from the mean) with regard to amygdala activation for NEG > NEU.

Long-term meditators with greater total lifetime hours of retreat practice had the lowest amygdala activation for the contrast NEG > NEU ($t(25) = -2.10$, $b = -0.03$, $p = 0.05$, CI = [-0.07,-0.001]). Due to the heterogeneous nature of meditation practices employed on retreats, we also conducted post-hoc analysis to test whether this relationship was true specifically for the type of meditation practice that is most similar to that taught in MBSR — Vipassana (i.e. OM) retreat practice. Greater total lifetime hours of OM retreat practice was negatively associated with amygdala activation for the contrast NEG > NEU ($t(23) = -2.62$, $b = -0.04$, $p = 0.02$, partial $r = -0.47$, CI = [-0.06,-0.01]; Fig. 1c).[1] This relationship was not significant for total lifetime hours of daily practice ($t(25) = -0.48$, $b = -0.02$, $p = 0.64$, CI = [-0.09,0.05]). There were no significant relationships between amygdala activation for the contrast POS > NEU and any of the measures of lifetime practice (Table 2). All the

results remained the same when age was not included as a covariate.

The total minutes of MBSR training (during class and at home) was not associated with amygdala activation for NEG > NEU following training ($t(26) = -1.19$, $b < 0.01$, $p = 0.24$, CI = [0.00,0.00], 3 outliers removed), nor with amygdala activation for POS > NEU ($t(28) = 0.17$, $b < 0.01$, $p = 0.87$, CI = [0.00,0.00], 1 outlier removed), while controlling for pre-treatment baseline.

### 3.5. Relation between amygdala activation and self-reported reactivity

We tested whether amygdala activation was associated with a self-report measure of emotional reactivity – the non-reactivity sub-scale of the FFMQ (Baer et al., 2006). Example items from the non-reactivity scale include: "When I have distressing thoughts or images, I just notice them and let them go", and "I watch my feelings without getting lost in them".

Participants (across LTM and MNP groups) with higher self-reported emotional non-reactivity had lower amygdala activation for the contrast POS > NEU ($t(148) = -3.20$, $b = -5.38$, $p < 0.01$, CI = [-8.70,-2.06], partial $r = 0.24$), and this relationship remained significant when controlling for social desirability as measured with the Marlowe-Crowne Social Desirability questionnaire (MCSD; Fig. 3a; $t(147) = -3.05$, $b = -4.79$, $p < 0.01$, CI = [-7.88,-1.69]). This relationship was specific to the non-reactivity sub-scale, as total FFMQ scores, which served as a measure of "mindfulness", were not associated with amygdala activation for the contrast POS > NEU ($t(148) = -1.57$, $b = -9.70$, $p = 0.12$, CI = [-21.9,2.54]). There was no relationship between amygdala activation for NEG > NEU with FFMQ non-reactivity ($t(148) = -1.33$, $b = -2.19$, $p = 0.19$, CI = [-5.43,1.06]), nor with total FFMQ scores ($t(148) = -0.33$, $b = -1.92$, $p = 0.74$, CI = [-13.44, 9.60]). One MNP model outlier was removed from each of these analyses, and this participant was also an extreme point with regard to self-reported non-reactivity. In line with the group differences in emotional reactivity as measured by amygdala activation, LTM reported greater non-reactivity on the FFMQ than MNP while controlling for social desirability from MCSD (Fig. 3b; $t(151) = -7.25$, $b = -5.36$, $p < 0.001$, CI = [-6.83,-3.90], 1 LTM outlier removed, partial $r = 0.53$).

The post-training amygdala activation for the contrast POS > NEU in MBSR and HEP participants did not predict post-training self-reported non-reactivity (FFMQ; $t(53) = 1.67$, $b = 2.81$, $p = 0.10$, CI = [-0.57,6.20], 4 MBSR and 5 HEP outliers removed), nor for NEG > NEU ($t(60) = 1.51$,
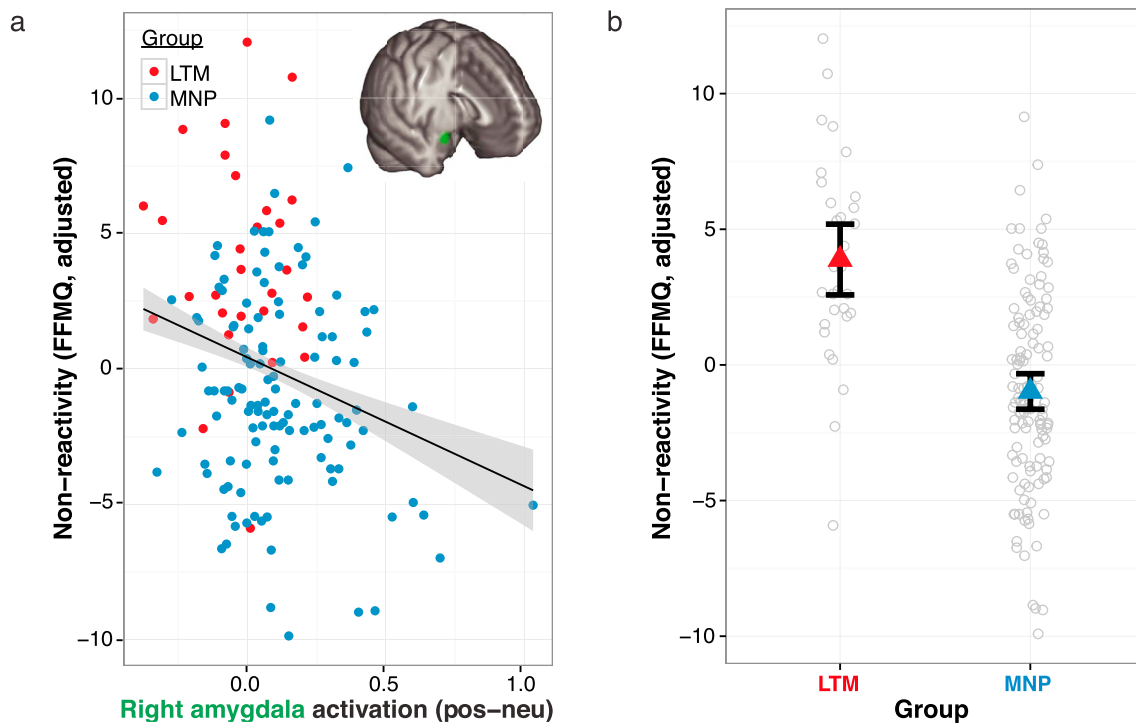
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[1] Two participants did not report retreat hours specific to OM practice, and so the degrees of freedom are different for models that include this variable.

**Fig. 3.** Reactivity in self-report and in right amygdala. Higher self-reported non-reactivity on the Five Facet Mindfulness Questionnaire (FFMQ) predicted lower right amygdala activation for negative versus neutral pictures (a). The independently defined right amygdala region of interest from which mean percent signal change data were extracted is inset in panel a. Long-term meditators (LTM) had overall higher self-reported non-reactivity than meditation-naive participants (MNP) (b). Example items from the non-reactivity scale include: "When I have distressing thoughts or images, I just notice them and let them go", and "I watch my feelings without getting lost in them". Error bars and envelopes are 95% confidence intervals around the point estimates.

$b = 3.10$, $p = 0.14$, CI = [-0.99,7.00], 1 MBSR and 1 HEP outlier removed), while controlling for baseline activation and baseline self-reported non-reactivity. Nor was there a group difference between MBSR and HEP in self-reported non-reactivity following training while controlling for baseline ($t(57) = -0.28$, $b = −0.28$, $p = 0.64$, CI = [-1.48,0.91], 3 MBSR and 3 HEP outliers removed).

### 3.6. Amygdala–VMPFC functional connectivity during affective pictures: analytic strategy

We tested for group differences in amygdala functional connectivity with an anatomically defined VMPFC ROI in order to understand the potential impact of mindfulness meditation practice on amygdala reactivity in the context of functional networks associated with emotion regulation. We used the same functionally defined amygdala ROI as a seed for a psychophysiological interaction (PPI) analysis to compare the relationship of the seed activation during negative versus neutral images, and positive versus neutral images by extracting the mean $Z$-values from VMPFC ROI for each PPI. A positive PPI result implies the slope between the BOLD response in the amygdala and the target voxels in VMPFC was larger during negative than neutral pictures (or during positive versus neutral pictures).

### 3.7. Long-term practice and amygdala functional connectivity

Long-term meditators had a significantly positive right amygdala-VMPFC PPI during NEG > NEU ($t(27) = 2.17$, $b = 0.13$, $p = 0.04$, CI = [0.01,0.24], 2 outliers removed), while for MNPs the right amygdala-VMPFC PPI for this contrast was not significant ($t(118) = 1.17$, $b = 0.04$, $p = 0.25$, CI = [-0.03,0.10], 2 outliers removed), though the difference between the groups was not significant ($t(145) = -1.29$, $b = −0.09$, $p = 0.20$, CI = [- 0.23,0.05], 2 LTM and 2 MNP outliers removed). When outliers were included in the model the group

difference for PPI effect of NEG > NEU was significant ($p = 0.05$). One LTM and one MNP model outlier were also extreme points with regard to the NEG > NEU PPI effect. There was no group difference in amygdala-VMPFC PPI for the contrast of POS > NEU ($t(149) = -0.71$, $b = −0.05$, $p = 0.48$, CI = [-0.17,0.08]), nor was there significant amygdala-VMPFC PPI for this contrast for either LTM ($t(29) = 0.04$, $b = 0.002$, $p = 0.97$, CI = [-0.10,0.10]), nor MNP ($t(120) = -1.47$, $b = −0.04$, $p = 0.14$, CI = [-0.10,0.02]).

Since there was a significant difference in the POS > NEU PPI effect by gender we also tested for group differences controlling for gender, and there were no changes in the result. There was no relationship between long-term meditators' amygdala-VMPFC PPI and any of the measures of lifetime practice (Table 2). We examined the association between amygdala-VMPFC connectivity and the behavioral categorization of affective stimuli. There was no relationship between the percentage of positive IAPS categorized as neutral and the amygdala-VMPFC PPI effect for POS > NEU ($t(20) = -1.05$, $b = −0.13$, $p = 0.31$, CI = [-0.37,0.13]), and there was only a trend-level effect for percentage of negative IAPS categorized as neutral and the PPI effect for NEG > NEU ($t(19) = 1.73$, $b = 0.12$, $p = 0.099$, CI = [-0.02,0.27]; 1 outlier removed).

### 3.8. Short-term practice and amygdala functional connectivity

We also investigated amygdala-VMPFC functional connectivity to determine if MBSR training enhanced connectivity of this emotion regulation circuit. These analyses utilized the identical VMPFC ROI used in the analyses with LTM. Participants randomly assigned to MBSR had greater post-treatment amygdala-VMPFC PPI than HEP participants during NEG > NEU ($t(62) = 3.99$, $b = 0.29$, $p < 0.001$, CI = [0.15,0.44], 2 MBSR outliers removed, partial $r = 0.42$; Fig. 2b), as well as for POS > NEU ($t(58) = 2.57$, $b = 0.16$, $p = 0.01$, CI = [0.04,0.29], 4 MBSR and 2 HEP outliers removed, partial $r = 0.30$; Fig. 2c), while controlling for pre-treatment baseline. Since there was a significant difference in the

POS > NEU PPI effect by gender (at baseline), and a significant difference in change in the NEG > NEU PPI effect by age, we also tested for group differences controlling for these variables in each model (respectively), and there were no changes in the results. There was no relationship between amygdala-VMPFC PPI connectivity and total practice with MBSR (Table 2). There were no significant differences in baseline PPI measures between groups in the same sample of participants for NEG > NEU ($t(63) = -.53$, $b = -0.05$, $p = 0.60$, CI = [-0.23,0.13]), or for POS > NEU ($t(59) = -1.92$, $b = -0.14$, $p = 0.06$, CI = [-0.28,0.01]).

## 4. Discussion

We rigorously tested the relationship between mindfulness meditation training and affective processing by combining a cross-sectional design comparing long-term mediators to non-mediators with an RCT comparing MBSR and HEP. We were able to examine mechanisms underlying changes in affective processing by examining both amygdala reactivity and connectivity with VMPFC during automatic emotion regulation, and in a much larger sample size than has been previously reported in the literature on the effect of mindfulness meditation on automatic emotion regulation (Desbordes et al., 2012). The automatic emotion regulation task used in this study was designed to specifically probe participants' automatic response to emotional pictures, whereby the degree to which emotion regulation processes were automatically engaged would be reflected by individual differences in the amygdala response to affective stimuli. We have argued in other contexts that this form of emotion regulation is ubiquitous and is likely the most common form of emotion regulation in everyday life (Lapate et al., 2014). The current study was limited to inferring that regulation occurred, as there were no measures of participants' emotional experience or regulation strategies during the task. Inclusion of trial-by-trial questions about regulation strategy and/or affective experience may have altered subsequent responses or primed participants to use an emotion regulation strategy, which we wanted to avoid in order to measure participants' natural response.

Emotional reactivity, as assessed via right amygdala activation to affective pictures (combined across positive and negative), was lower in participants who engaged in long-term mindfulness meditation training compared to controls. We tested separately by valence to decompose this effect and found that LTM had lower amygdala activation than MNP specifically to positive pictures, but not negative pictures (for which there was only a marginal difference between groups). The LTM also reported less emotional reactivity than MNP on a questionnaire measure (FFMQ), however we did not find a difference in self-reported emotional reactivity following MBSR compared to HEP. It is possible that it requires more practice or practice over a longer period of time to see movement on self-report measures of emotional reactivity in healthy, non-clinical populations, particularly in comparison to a well-matched active control intervention.

In an exploratory analysis we also found that the LTM categorized more affective pictures as neutral compared to MNP. This pattern of behavioral results mirrors the pattern of results in the fMRI data and lends further support to the hypothesis that long-term mindfulness meditation training improves emotion regulation through a reduction in emotional reactivity. However, we did not find a relationship between the percent of negative and positive pictures that LTM categorized as neutral and the amygdala activation, and there was only a trend-level relationship with amygdala-VMPFC connectivity during negative versus neutral pictures. The exploratory nature of our behavioral analysis, and the technical difficulties with recording button responses in the scanner, greatly limited inference from these results, as well as our power to detect an effect. Future research should follow up to more carefully examine whether (and how) behavioral changes in valence categorization are associated with mindfulness training-related changes in self-report and neurobiological measures of emotion regulation.

Participants naïve to meditation who were randomly assigned to

short-term mindfulness training showed a similar pattern: a reduction in amygdala reactivity specifically in response to positive images but not negative images when compared to HEP and controlling for the pre-treatment baseline activation. These results are consistent with prior work that meditation training decreased amygdala reactivity to positive pictures (Desbordes et al., 2012). Mindfulness meditation provides training in paying attention to thoughts and emotions as they unfold naturally and allowing them to pass without trying to avoid discomfort or to grasp onto pleasant experiences. One mechanism that could lead to decreased emotional reactivity with practice in mindfulness meditation is through increased exposure to the arising and passing of emotions accompanied by this new habit of attending to the experience non-reactively. Recent evidence that behavioral measures of mindfulness were associated with decreased attentional capture to rewarding stimuli provide additional evidence for this interpretation (Levinson et al., 2014). Importantly, decreased non-reactivity of the amygdala to positive stimuli does not preclude increased pleasure or liking of positive stimuli, similar to that found in prior work showing increased positive mood with mindfulness training (Jain et al., 2007). Prior research has dissociated the neural basis of pleasure from that of the "wanting" associated with approach behavior (Smith et al., 2011). It is likely that the amygdala, a key node in the salience network, marks wanting more than liking whereas the work of Berridge and colleagues suggests that local circuitry within the ventral pallidum is uniquely associated with liking (Smith et al., 2011). Therefore, our findings of decreased amygdala activation to positive stimuli are most consistent with a decreased desire to approach (or grasp at) a stimulus rather than a change in pleasure or appreciation.

Over time the practice of observing thoughts non-reactively may lead to greater automatic emotion regulation similar to extinction processes that recruit VMPFC (Phelps et al., 2004; Hölzel et al., 2011). The process strengthened by mindfulness meditation is not a specific decrease in reactivity to negative stimuli but rather may impact emotional responding more generally and is consistent with the view from contemplative traditions that this practice decreases "stickiness" – the power of emotions to linger and alter subsequent experience – by reducing the propensity to avoid unpleasant and grasp at pleasant experiences. This is summarized nicely by Hölzel: "nonreactivity leads to unlearning of previous connections (extinction and reconsolidation) and thereby to liberation from being bound to habitual emotional reactions" (2011). The fact that MBSR significantly increased the amygdala-VMPFC PPI effect relative to HEP training for both negative versus neutral pictures and positive versus neutral pictures lends further support to this explanation, and implies a similar emotion regulatory mechanism for reducing reactivity to affective stimuli independent of valence.

While prior research has provided evidence that amygdala-VMPFC functional connectivity correlates with improvements in emotion regulation, the current study had no direct, objective measures of emotion regulation behavior. Future research would benefit from including such behavioral measures. The paradigm used in the current study could also be improved in future research by including more naturalistic stimuli personally relevant to participants, as the small-to-medium effect sizes seen in the current study may in part reflect the generic nature of the stimuli and less likelihood to elicit strong, self-relevant affective experiences.

The fact that short-term MBSR training affected amygdala-VMPFC functional connectivity in ways that we did not detect in participants with long-term training is revealing and implies a curvilinear trajectory in the neural changes required for learning the skill of non-reactivity. On this view, with long-term training the reduction in reactivity to affective stimuli becomes more automatic such that VMPFC recruitment is less necessary. This explanation aligns with subjective reports from practitioners, and with the goals and expectations of mindfulness meditation practice: to practice being aware and accepting of (affective) experience so that over time this process becomes more automatic. The fact that we found a relationship between hours of retreat practice and reduced amygdala reactivity, but not with amygdala-VMPFC connectivity lends

further support to the idea that increased connectivity may only occur at earlier stages of practice, and fits with the nonlinear dosage-response curve of mindfulness meditation training (Brefczynski-Lewis et al., 2007). Moreover, the lack of relationships between individual differences in amygdala reactivity and the amount of MBSR practice (e.g. variation in the degree to which participants engaged in at-home practice, or 'homework' during MBSR) may also indicate an important distinction between short- and long-term practice: it may be that there is a more "all-or-nothing" effect of exposure to MBSR in terms of short-term effects while long-term changes may be more dependent upon practice dosage. Longitudinal research that follows practitioners as they progress from initial, to intermediate, and more advanced practice will be critical to provide insight into the trajectory of affective change with mindfulness meditation.

Of course, the fact that short-term MBSR training produced alterations in amygdala-VMPFC connectivity not seen among the LTM can also be due to other factors. All participants in the MBSR group received the same intervention and were recruited from the same geographic community (in Madison, WI), whereas the LTM had larger variation in practice type, duration and geographic location. The LTM likely also had greater variability in their motivations for engaging in practice. We attempted to minimize such variation by recruiting LTM who had similar practice that included primarily mindfulness-based meditation.

Interestingly, long term meditators' total lifetime practice while on retreat predicted reduced amygdala activation to negative pictures, while total hours of non-retreat practice (i.e. totally daily practice hours over the lifetime) was not associated with amygdala reactivity. This effect was stronger when looking specifically at retreat practice in OM meditation. All the long-term meditators had a daily practice that included OM meditation, and so engaging in this style of practice while on retreat appears to be particularly beneficial. The inverse relationship between OM retreat practice and reactivity to negative IAPS, combined with non-significant group differences in amygdala reactivity to negative IAPS implies that altering the response to negative affect may require more intense practice over time (specifically in OM meditation).

Retreats tend to differ from daily practice in many ways; the duration of practice is longer, the context promotes a continual focus on the goals of the training with fewer distractions than is typical for daily life, there is usually greater social support or accountability, and there is a release from daily work or family expectations. Any one or a combination of these and other factors that allow for a more intense focus on OM practice may facilitate change. Additionally, individual differences in factors relating to participants' choice and ability to go on retreat may be important to consider in relation to their emotional reactivity, though all the LTMs in this study by design were required to have participated in at least a few retreats. Future research could better assess the impact of retreat practice by assessing the different components of retreat practice, and by measuring responses before and after meditation retreats, as well as longitudinally across the development of participants' meditation practice from novice to expert.

We had also planned to test the impact of mindfulness meditation training on amygdala recovery to affective stimuli, as assessed by the intensity of amygdala activation during neutral faces following positive and negative pictures compared to neutral pictures. However, none of the groups had amygdala activation for the contrast NEGPOS > NEU during the face period with which we could examine group differences. There are a couple potential reasons why we failed to find a main effect of the preceding IAPS valence during the face period (i.e. emotional spillover from the affective stimuli onto the neutral faces that immediately followed). A subsequent study in our lab has shown that conscious awareness of affective stimuli dampens affective spillover onto subsequent neutral stimuli (Lapate et al., 2014). Since participants in this study were instructed to make a button press to indicate the valence of the IAPS, this brought awareness to the source of affective information very explicitly. Thus, the affective experience induced from the IAPS was less likely to be misattributed to the neutral face stimulus. Furthermore, research has

shown that affect labeling can serve as a form of implicit emotion regulation and result in dampening of the amygdala response, which was associated with increased ventrolateral PFC activation mediated by VMPFC (Lieberman et al., 2007). While the valence labeling aspect of the task likely contributed to the lack of a valence effect on the subsequent neutral face response, it also likely allowed us to more easily assess individual differences in the ability to engage with automatic (i.e. implicit) emotion regulation processes during the IAPS presentations.

Labeling experiences – including affective experiences – is also a component of mindfulness mediation training, and has been previously proposed as one possible mechanism by which such practices train emotion regulation (Lutz et al., 2008). Prior research has found associations between self-reported dispositional mindfulness and reduced amygdala activation during affect labeling tasks (Creswell et al., 2007). Therefore, participants with mindfulness meditation training may have more easily or robustly engaged this automatic form of emotion regulation due to the affect labeling component of the task, possibly leading to lower amygdala reactivity. The results of the current study extend this literature in novel ways by demonstrating similar effects with a much stronger, RCT design combined with cross-sectional data from LTM.

The present study provides evidence that long and short-term training in mindfulness meditation improves automatic emotion regulation and elucidates the neural correlates of this improvement. Long and short-term mindfulness meditation training were associated with lower amygdala activation while viewing affective pictures. Short-term mindfulness meditation training with MBSR was also associated with a stronger amygdala-VMPFC PPI effect during negative and positive pictures (versus neutral) compared to the active control condition (HEP), while controlling for pre-treatment baseline. These findings are consistent with other research suggesting that engagement of prefrontal regulatory resources may be more pronounced in the earlier stages of mindfulness training and dissipate with longer-term practice. Taken together, these findings provide novel evidence that training in mindfulness meditation alters the neural circuitry of automatic emotion regulation, which may be instantiated early on by modulating connectivity between the VMPFC and amygdala.

## Conflicts of interest

## Author contributions

T.R.A.K. and B.S.S. collected and processed the data. T.R.A.K. analyzed the data and wrote the manuscript. B.S.S. contributed to planning the analysis. M.A.R. and A.L. contributed to the design of the study. J.A.M. contributed to data processing and statistical analysis. R.J.D. designed and supervised the study. All authors contributed to writing the manuscript.

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