Psychological Medicine

cambridge.org/psm

Original Article

Cite this article: Leibovitz SE *et al* (2024). Mindfulness training and exercise differentially impact fear extinction neurocircuitry. *Psychological Medicine* **54**, 835–846. https://doi.org/10.1017/S0033291723002593

Received: 5 December 2022
Revised: 26 June 2023
Accepted: 8 August 2023
First published online: 1 September 2023

Keywords:
fear-extinction; hippocampus; mindfulness; salience network; thalamus

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Mindfulness training and exercise differentially impact fear extinction neurocircuitry

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Abstract

Background. The ability to extinguish a maladaptive conditioned fear response is crucial for healthy emotional processing and resiliency to aversive experiences. Therefore, enhancing fear extinction learning has immense potential emotional and health benefits. Mindfulness training enhances both fear conditioning and recall of extinguished fear; however, its effects on fear extinction learning are unknown. Here we investigated the impact of mindfulness training on brain mechanisms associated with fear-extinction learning, compared to an exercise-based program.

Methods. We investigated BOLD activations in response to a previously learned fear-inducing cue during an extinction paradigm, before and after an 8-week mindfulness-based stress reduction program (MBSR, $n = 49$) or exercise-based stress management education program ($n = 27$).

Results. The groups exhibited similar reductions in stress, but the MBSR group was uniquely associated with enhanced activation of salience network nodes and increased hippocampal engagement.

Conclusions. Our results suggest that mindfulness training increases attention to anticipatory aversive stimuli, which in turn facilitates decreased aversive subjective responses and enhanced reappraisal of the memory.

Introduction

Distinguishing between signals of threat and safety, and adaptively responding to changes in the environment, are crucial for healthy emotional functioning (LeDoux & Pine, 2016). Failure to identify that a cue no longer predicts a threat leads to persistent fear responses, which are a core component of anxiety, trauma, and other psychiatric conditions (Alexandra Kredlow, Fenster, Laurent, Ressler, & Phelps, 2022). Therefore, enhancing the ability to identify the saliency of a cue presented in a specific context serves as a basis for exposure-based therapies that are used to treat various psychological disorders and promote recovery from trauma (Maren, Phan, & Liberzon, 2013; Milad, Orr, Pitman, & Rauch, 2005). Mindfulness meditation training is thought to create an optimal state for exposure therapy by increasing present-moment interoceptive and sensory awareness while strengthening attentional control and emotional regulation (Brown & Ryan, 2003; Hölzel et al., 2011b; Treanor, 2011). Studies have revealed unique and unexpected neural mechanisms by which mindfulness training affects pain processing (Grant & Zeidan, 2019), fear conditioning (Hölzel et al., 2016; Taylor et al., 2018), and enhances recall of extinguished fear (Sevinc et al., 2020, 2019), yet its effects on fear extinction learning are unknown.

When presented with an aversive pain-inducing stimulus, non-meditators and novices exert top-down regulation of pain by blocking or diminishing the sensory signal from entering the conscious experience, a strategy characterized by increased activation of frontal executive areas and decreased activity in sensory regions (Gard et al., 2012; Grant & Zeidan, 2019). Conversely, highly experienced mindfulness meditation practitioners demonstrate enhanced conscious awareness of the sensory stimulus that is characterized by increased activation of sensory regions, including the salience network (SN), and decreased activation of frontal cognitive-control regions (Gard et al., 2012; Grant & Zeidan, 2019), a pattern associated with enhanced pain attenuation, reduced anxiety (Gard et al., 2012), and higher pain tolerance (Zeidan & Vago, 2016). Similarly, we and others have reported that 8 weeks of mindfulness meditation training is associated with a unique fear-processing mechanism during a fear-conditioning paradigm (Hölzel et al., 2016; Taylor et al., 2018). Compared to a waitlist control group, mindfulness training was associated with retention of the startle response to the conditioned stimulus (CS+) and retention of the lower response to the not-conditioned stimulus (CS−). This differential retention was correlated with diminished stress and increased fractional anisotropy within the right uncinate fasciculus, a major white matter tract associated with the amygdala (Hölzel et al., 2016). These findings suggest that the mindfulness group refrained from avoiding behaviors and maintained a high level of conscious awareness of both the conditioned and unconditioned stimuli (Hölzel et al., 2016). These findings are all consistent with the definition of mindfulness as present-moment awareness of experience without judgment (Kabat-Zinn, 2013).

Recognizing that a cue is no longer associated with a threat requires interoceptive attention and conscious awareness of the saliency of the stimuli presented during the extinction learning phase. These processes are mediated by the SN, which guides attention to the stimulus and modulates behavior in response to it (Seeley et al., 2007; Uddin, Yeo, & Spreng, 2019). Several cortical nodes of the SN are thought to be part of a system responsible for generating the conscious subjective experience and psychological response to threats, in contrast to a subcortical system responsible for generating the primal physiological and behavioral automatic responses to threats (LeDoux & Pine, 2016; Wen, Chen, & Milad, 2021). Those cortical nodes are the insula which directs interoceptive awareness and the conscious experience of the sensory information (Craig, 2009; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004), and the anterior cingulate cortex (ACC) which is responsible for error detection (Ham, Leff, de Boissezon, Joffe, & Sharp, 2013; Maren et al., 2013; Seeley et al., 2007). The nodes are connected by the thalamus which facilitates the flow of information (Uddin et al., 2019).

Successful fear extinction requires reappraisal of the memory and encoding of the cue and its new context as safe. Reappraisal of an emotionally salient stimulus is heavily dependent on dorsolateral prefrontal cortex (dlPFC) activation (Golkar et al., 2012), which is responsible for working memory, cognitive control, and emotional regulation (Uddin et al., 2019). The dlPFC is a key node of the frontoparietal control network (FPCN) and is part of the cortical system responsible for the conscious subjective experience of threat (LeDoux & Pine, 2016). Importantly, the dlPFC often coactivates with SN nodes (Seeley et al., 2007) and thus is responsible for regulating emotional and behavioral responses according to the detected salient information (Peters, Dunlop, & Downar, 2016; Seeley et al., 2007).

The memory encoding of the new meaning of the cue is dependent on the hippocampus (Lissek, Glaubitz, Uengoer, & Tegenthoff, 2013), and the retrosplenial cortex (Kwapis, Jarome, Lee, & Helmstetter, 2015). In the current study population, we have previously shown that mindfulness training enhanced hippocampal activity, hippocampal–dlPFC connectivity, and hippocampal–retrosplenial connectivity during the recall of extinguished fear memory (Sevinc et al., 2019). Synchronous activation between the dlPFC and the hippocampus mediates the intentional forgetting (retrieval suppression) that is crucial for the reappraisal of memory from threatening to safe (Paz-Alonso, Bunge, Anderson, & Ghetti, 2013), and activation of the retrosplenial cortex is important for contextual memory formation (Kwapis et al., 2015).

Based on the above, we hypothesized that mindfulness training would enhance the activation of SN nodes in response to the fear-provoking cue during fear extinction learning. Our model suggests that enhanced SN activation will promote correct saliency identification according to the newly learned visual context and sensory information, which can help counter unconscious automatic defensive responses (LeDoux & Pine, 2016) such as the maladaptive responses present in psychological disorders. In addition, we hypothesized that mindfulness training would promote engagement of the hippocampus, dlPFC, and the retrosplenial cortex, consistent with the reappraisal of the stimulus from associating with a threat to associating with safety.

Lastly, mindfulness interventions have been shown to promote increases in hippocampal gray matter (Hölzel et al., 2011a; Pickut et al., 2013; Wells et al., 2013), which are associated with clinical or behavioral outcomes (Greenberg et al., 2019; Pickut et al., 2013), including beneficial emotional responses during the recall of extinguished fear memories (Sevinc et al., 2020, 2019). Previously, our group (Sevinc et al., 2020) reported morphometric changes in the subiculum and presubiculum following mindfulness training in the current study population and revealed a correlation between subiculum morphometric changes and functional changes in the hippocampus during recall of extinguished fear. The subiculum is consistently activated during contextual memory retrieval (Ledergerber & Moser, 2017), while the presubiculum is crucial for visual and spatial processing and scene-based cognitive processing (Dalton & Maguire, 2017), and is thought to contribute to visuospatial contextual memory updating (Robinson & Bucci, 2012; Zeidman & Maguire, 2016) that is essential for fear extinction learning. Based on these distinctions, we focused on presubiculum morphometric changes in this analysis and examined their correlation with hippocampal function during extinction learning.

Materials and methods

Participants

Subjects 18–50 years of age were recruited via public transportation advertisements for stress-reduction programs. In addition to the standard MRI safety exclusion criteria, participants were required to be right-handed, have no current psychiatric or neurological disorders, and not be engaged in psychotherapy or have taken psychotropic medications within 12 months prior to the study. They were required to have had minimal prior experience with meditation or yoga practice, as defined by having taken no more than four meditation classes of any kind in the past 12 months, or more than 10 classes in their lifetime. Participants were remunerated up to $100 for participation. Participants were randomized to 1–2 stress reduction programs, mindfulness-based stress reduction (MBSR) or stress management education (SME) on a 2:1 ratio, stratified by gender. This ratio was chosen to maximize power for correlational analyses in the MBSR group. In total, 94 participants completed initial testing and were randomized; 89 attended at least one class (58 MBSR, 31 SME), and 49 MBSR and 27 SME participants completed MRI scanning at the post-time point. The Partners Health Care Institutional Review Board approved the study protocol; all participants provided written informed consent. There were no significant differences between groups in terms of gender [MBSR: 28 women, 14 men; SME: 15 women, 10 men ($\chi^2 = 0.30$, $p = 0.58$)], age [MBSR 31.14 ± 7.71 years; SME 33.08 ± 18.02 years ($t_{65} = 20.94$, $p = 0.35$)], or years of education [MBSR 17.40 ± 3.08 years, SME 18.02 ± 2.51 years ($t_{65} = 20.84$, $p = 0.40$)]. Total hours of home practice did differ between the groups (23.50 ± 10.87 h for MBSR and 34.82 ± 19.74 h for SME; $t = 2.65$, $p = 0.013$). This difference is likely due to differences in demand characteristics in terms of emotional and physical effort and readily perceived benefits.

Stress reduction programs

The 8-week MBSR program (Kabat-Zinn, 2013) consisted of weekly 2 h classes that included didactic teaching about mindfulness, experiential practice of mindfulness, and group discussions on impediments to effective practice as well as practical day-to-day applications of mindfulness. Formal meditation practices included body scan meditation, breath awareness meditation, and mindful yoga. The SME program, adapted from Hoge et al. (2013), consisted of 2 h weekly group sessions over 8 weeks. Didactic content included the effects of stress on health and optimizing one's personal health care, understanding positive coping behavior, optimizing nutrition to decrease stress, the role of exercise in reducing stress, sleep hygiene, and humor. Participants learned light strength training and aerobic exercises which they also practiced at home. Both classes included an additional 4 h class at the end of the 6th week. Both groups were instructed to practice at home for 40 min daily and were given audio recordings to facilitate practice. The MBSR course was led by a certified MBSR instructor (Zayda Vallejo); the SME program was led by a licensed physical therapist (Jen Kelly).

Fear-conditioning and extinction paradigm

The scanning protocol comprised a 2-day classical fear-conditioning and extinction procedure validated in several healthy (Linnman et al., 2012; Milad et al., 2007) and patient (Milad et al., 2009) populations. Briefly, the fear-conditioning procedure consisted of acquisition (conditioning) and extinction phases on day 1, and an extinction recall phase on day 2. Total time in the scanner was approximately 30–45 min each day, which included the acquisition of localizer, anatomical, and resting-state scans, in addition to the fear-conditioning protocol. Before scanning, participants were presented with different levels of electric stimulation to the fingers and asked to choose a 'highly annoying but not painful' level, which would serve as the unconditioned stimulus (US) during the fear-conditioning task. A brief electric stimulus was applied to the fingers on the left hand to create the US during conditioning. Images of two different rooms provided contextual information. Each room contained a blue, red, or yellow lamp light, which constituted the conditioned stimuli (CS). There were two CS+ colors and one CS− color (see online Supplementary Fig. S2) that were randomly determined and counterbalanced across participants and time points. During the conditioning phase, two CS (CS+) were paired with the 500 ms US to the left hand at a partial reinforcement rate of 60%. During the conditioning phase, the US was delivered immediately following the CS+ (two colors of lamp light) offset, and the third CS (CS−) was also presented but never paired with the US. One CS+ was extinguished during the subsequent extinction phase on day 1, on which we focus our analysis, whereas the other CS+ was not. For each trial (32 trials total in 13 min of conditioning or extinction protocol) during the experiment, the virtual context was presented for 18 s: 6 s alone followed by 12 s in combination with a CS+ or CS−. The mean inter-trial interval was 16 s (range: 12–21 s). On day 2, during the extinction recall phase, all three CS+ and CS− images were presented, with the same context as during the extinction phase, and no electrical shock (US) was delivered. See online Supplementary figures for a schematic of the scanning protocol.

Skin conductance responses were collected and scored (Sevinc et al., 2019); however, due to low data quality, much of the data did not comply with our criteria for inclusion in the analysis. Only 16 participants (8 per group) had both complete functional neuroimaging and useable skin conductance data. Thus, we did not attempt to analyze the data given the low statistical power.

Image acquisition

Imaging data were acquired on a Siemen's Prisma 3.0 T equipped for echo-planar imaging (Siemens Medical Systems, Iselin, NJ, USA) with a 32-channel gradient head coil. An automated scout image was obtained to facilitate the alignment of pre- and post-intervention scans. High-resolution three-dimensional magnetization-prepared rapid acquisition gradient-echo sequences were acquired (repetition time/echo time/flip angle = 2.53 ms/1.74 ms/7 degrees; 1 mm isotropic voxels; field of view = 256 cm; 176 axial slices). Functional images were acquired with gradient-echo T2*-weighted sequences (repetition time/echo time/flip angle = 3 s/30 ms/90 degrees; field of view = 1400 x 1400; slice thickness = 2.5 mm isotropic voxels).

Functional MRI data and analysis

All participants ($n = 76$) were scanned within 2 weeks before and after the MBSR and SME courses. Data from seven participants were unusable owing to technical problems during scanning ($n = 2$) or clerical errors ($n = 5$). Usable data were available for 42 MBSR and 27 SME participants. Both whole-brain and *a priori* region-of-interest (ROI) analyses were conducted. Functional MRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration of the functional data to the high-resolution structural image was carried out using the boundary-based registration algorithm (Greve & Fischl, 2009). The high-resolution structural to standard space registration was carried out using FLIRT (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002) and was then further refined using FNIRT nonlinear registration (Andersson, Jenkinson, & Andersson, 2007a; Andersson, Jenkinson, & Smith, 2007b). The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson et al., 2002); non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight-line fitting, with sigma = 50.0 s). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). The time-series general linear model included CS+ (the conditioned stimulus that was paired with an electric stimulus during the conditioning phase; 6 s each) and CS− (the conditioned stimulus that was never paired with an electric stimulus; 6 s each) as regressors and the contrast CS+ > CS−, and CS+ alone were the only two contrasts used. During fear extinction, both CS+ and CS− signify safety after learning has occurred, thus the difference between the two conditions, CS+ minus CS−, is expected to be minimal by the end of the scan, which can result in the two responses canceling each other (Wen et al., 2021, 2022a). Double-gamma HRF, temporal derivative, and temporal filtering were applied. Nuisance motion regressors were used for each high motion TR, which were identified using an indicator function to model out single TRs which have excessive motion according to framewise displacement >0.9. Third-level analysis was performed to identify baseline activation using all subjects in the study and was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). The Z (Gaussianised T/F) statistic images of the third-level analysis were thresholded using clusters determined by $Z > 3.1$ and FWE corrected for multiple comparisons using a corrected cluster significance threshold of $p \leqslant 0.05$ (Worsley, n.d.).

We defined *a priori* functional ROIs based on activations in response to a fear-provoking cue (CS+) from the third-level analysis with all subjects combined at baseline. Our ROI comprised: the SN (insula, dorsal ACC, and thalamus) (Peters et al., 2016; Seeley et al., 2007; Uddin et al., 2019), the dlPFC, the hippocampus, and retrosplenial cortex. The third-level baseline activation analysis revealed seven significant clusters which survived cluster FWE correction (Woo, Krishnan, & Wager, 2014) with z score > 0 in response to CS+ (Table 1A), and 11 clusters that survived FWE cluster correction (Woo et al., 2014) with z score < 0 in response to CS+ (Table 1B). To identify the brain structures spanned by the clusters, FSL Harvard-Oxford Atlas was used. We selected five of the 18 clusters identified at baseline that survived FWE correction and that fell within our ROIs for the longitudinal analysis, including the right thalamus (Table 1A: clusters 2 and 4 combined), left thalamus (Table 1A: cluster 3), right dlPFC (Table 1B: cluster 6), the right hippocampus extending to the amygdala (Table 1B: cluster 7), and left hippocampus extending to the amygdala (Table 1B: cluster 4).

ROI analysis was conducted by extracting z scores from the first-level analysis using fslmaths and fslmeans and performing repeated-measures multivariate analyses of variance (MANOVA), repeated-measures ANOVA, and repeated measures t test using the statistical software R. We applied Bonferroni correction to correct for multiple tests.

We then performed an exploratory second-level analysis (within-group analysis) and compared pre- to post-intervention (post > pre-contrast) for each subject which was carried out using FLAME stage 1 (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004) to then produce post > pre-whole-brain statistical map for each group separately. The Z (Gaussianised T/F) statistic images of the second-level analysis were thresholded using clusters determined by $Z > 3.1$ and FWE corrected for multiple comparisons using a corrected cluster significance threshold of $p \leqslant 0.05$ (Worsley, n.d.).We did not perform a whole-brain exploratory group-by-time analysis as it is less recommended in FSL due to the complexity of the contrast matrix and our unbalanced group design.

Gray matter volume change in the left presubiculum subfield of the hippocampus, which was reported in the analysis of the recall phase (Sevinc et al., 2020), was used for Pearson correlation with activation of the cluster spanning the left hippocampus extending to the amygdala. Two extreme outliers were identified using the Mahalanobis distance multivariate approach and were excluded from the correlation calculation.

Table 1. All subjects baseline activation to CS+

Cluster index	Voxels	*p* Value	Z-MAX	Z-MAX [X, Y, Z] (mm)	Structure
A. Contrast CS + > 0					
1	11 729	0	9.14	[18, −88, −6]	Occipital pole
2	**275**	**5.25×10^{-5}**	**8.53**	**[22, −28, −2]**	**Right thalamus**
3	**263**	**7.74×10^{-5}**	**7.97**	**[−20, −30, −2]**	**Left thalamus**
4	**209**	**0.000484**	**4.87**	**[8, −12, 2]**	**Right thalamus**
5	123	0.013	4.47	[−2, −28, 26]	Posterior cingulate gyrus
6	101	0.0335	5.49	[0, −52, −38]	Vermis IX
7	101	0.0335	4.02	[−26, −64, 34]	Lateral occipital cortex
B. Contrast CS + < 0					
1	31 924	0	9.31	[−12, −68, −2]	Lingual gyrus
2	418	7.15×10^{-7}	4.82	[−24, −42, 54]	Superior parietal lobule
3	373	2.62×10^{-6}	4.16	[−46, 32, 2]	Inferior frontal gyrus, pars triangularis
4	**352**	**4.89×10^{-6}**	**5.24**	**[−24, −18, −12]**	**Left hippocampus + left amygdala**
5	350	5.19×10^{-6}	4.62	[30, −72, −36]	Cerebellum, right crus II
6	**286**	**3.69×10^{-5}**	**4.8**	**[−30, 36, 20]**	**Left middle frontal gyrus (dlPFC)**
7	**238**	**0.000178**	**4.43**	**[24, −6, −18]**	**Right hippocampus + amygdala**
8	236	0.00019	4.55	[−22, −54, −52]	Cerebellum, left VIIIb
9	223	0.000297	4.59	[−28, 4, 12]	Left putamen
10	134	0.00825	4.06	[−54, 12, −20]	Left temporal pole
11	105	0.0281	4.6	[44, 26, −26]	Right temporal pole

Whole-brain cluster analysis. Bold rows are ROIs. All clusters thresholded ($p < 0.05$; FWE-corrected).

Results

Significant group-by-time interaction within the right thalamus

We proposed in our model that mindfulness training would enhance saliency detection and interoceptive attention by promoting increased activation of SN nodes and promote hippocampal, and dlPFC engagement which is crucial for memory encoding and reappraisal. To account for multiple comparisons between our five ROIs defined from baseline (see methods) including the bilateral thalamus, the left dlPFC, and the bilateral hippocampus extending to the amygdala, we performed a repeated-measures MANOVA on BOLD activations in response to the fear-provoking cue (CS+). The results revealed a significant time effect [Wald-type statistic (WTS), $F_{(5)} = 19.165$, $p = 0.002$], indicating a significant difference in brain activation between pre- and post-8-week stress reduction programs. The group effect [WTS, $F_{(5)} = 2.543$, $p = 0.77$] and the interaction between group and time [WTS, $F_{(5)} = 7.751$, $p = 0.17$] were not significant.

We additionally performed repeated-measures ANOVAs on each region separately. The right thalamus revealed an uncorrected significant group-by-time interaction, supporting our hypothesis [$F_{(1,67)} = 4.405$, uncorrected p value = 0.04]. These findings suggest that the significant MANOVA time effect on the right thalamus may depend on the group. The MBSR group demonstrated increased right thalamic activation while the SME group revealed decreased right thalamic activation (Fig. 1a). Although baseline activation in the right thalamus was different between the groups, the difference was not significant [$t = 1.1842$, p value = 0.2423, confidence interval (CI) (−0.1063443 to 0.4105738)], hence the pre-intervention difference is probably due to randomness. A similar pattern was present in the left thalamus but did not yield a significant group-by-time effect (uncorrected p value = 0.229). The left dlPFC did not yield a significant group-by-time interaction but yielded a significant time effect that survived multiple comparisons correction [$F_{(1,67)} = 10.003$, Bonferroni-corrected p value = 0.01, uncorrected p value = 0.002]. Similarly, the left hippocampus extending to the amygdala cluster revealed a marginally uncorrected significant time effect [$F_{(1,67)} = 3.937$, uncorrected p value = 0.051] but not a significant group-by-time interaction. No significant results were found in the right hippocampus extending to the amygdala cluster.

No significant results were found in ROIs using the CS+ > CS− contrast. This, however, was expected as we chose to use the entire extinction learning scan in our analysis and expected less difference in brain response between CS+ and CS− toward the end of the scan during late extinction learning (Wen et al., 2021, 2022a). Therefore, we focused on the CS+ contrast in our longitudinal analyses.

Increased activation in ROIs in the MBSR group

We performed a within-group paired t test on activation of the right thalamic cluster to examine the basis of the group-by-time interaction. The MBSR group demonstrated an uncorrected significant increase in right thalamus activation [uncorrected p value = 0.01417, Bonferroni-corrected p value = 0.1417, 95% CI (−0.51496300 to −0.06100805)], while SME showed a non-significant decrease [uncorrected p value = 0.5514, 95% CI (−0.1877199 to 0.3437687)], therefore the significant uncorrected group-by-time effect was driven by increased thalamic activation following MBSR (Fig. 1a). In addition, we further explored within-group changes in the other *a priori* ROIs following the two interventions. We observed a similar pattern in the left thalamus, which did not yield significant results (MBSR-uncorrected p value = 0.1612, SME-uncorrected p value = 0.6847). A within-group paired t test of the left dlPFC revealed a significant increase in activation, that survived multiple comparisons correction, only in the MBSR group [MBSR Bonferroni-corrected p value = 0.02981, 95% CI (−0.5073154 to −0.1115320); SME-uncorrected p value = 0.1376, 95% CI (−0.3577526 to 0.0522241)] (Fig. 1b). Similarly, we identified a significant increase in left hippocampus extending to amygdala activation, that survived multiple comparisons correction, only in the MBSR group [MBSR Bonferroni-corrected p value= 0.048, 95% CI (−0.38965519 to −0.07469629); SME-uncorrected p value: 0.81, 95% CI (−0.2455978 to 0.1950826)] (Fig. 2a, b). No significant results were found in the right hippocampus extending to the amygdala cluster. The significant increase in the activation of the left dlPFC and left hippocampus extending to the amygdala in the MBSR group implies that the significant time effect of the MANOVA was mainly driven by increased activations in those regions following MBSR.

Increased left hippocampus/amygdala activation positively correlates gray matter volume of the left presubiculum

The presubiculum has a crucial role in visual information processing (Dalton & Maguire, 2017; Zeidman & Maguire, 2016) and might support visual context identification and coding during extinction learning. Sevinc et al. (2020) reported on structural changes in the left presubiculum, following MBSR and SME, and strengthened hippocampal circuits associated with MBSR during recall of extinguished fear in this dataset. Given the plausible association between brain function and structure, we used gray matter volume change of the left presubiculum [reported by Sevinc et al. (2020)] to examine its correlation with activation change (post minus pre-activation) of the left hippocampus extending to the amygdala cluster during extinction learning. We found a significant positive correlation between left hippocampal activation change following MBSR intervention and left presubiculum volume change (Pearson $R = 0.37$, p value = 0.034), while the SME group showed a non-significant correlation (Pearson $R = -0.16$, p value = 0.45) (Fig. 2b). These results demonstrate that in addition to the association of functional and structural hippocampal changes during extinction recall (day 2 of the protocol) we observe an association of structural and functional hippocampal changes as early as extinction learning (day 1 of the protocol).

Exploratory analysis: within-group whole-brain longitudinal changes in nodes of the salience and dorsal attention networks

To further explore activation changes in response to the fear-provoking cue (CS+) following each intervention, we performed an exploratory within-group whole-brain analysis for MBSR and SME separately by applying the contrast post > pre. We identified five significant clusters that survived cluster correction ($p < 0.05$, FWE corrected) only in the MBSR group (Table 2). No significant clusters were identified using the contrast pre > post or post > pre (CS+ > CS−) in either group. The right dlPFC, left caudate, and right insular cortex extending to the putamen, which are all nodes of the SN (Peters et al., 2016), showed increased activation following MBSR in response to CS+, which indicates enhanced

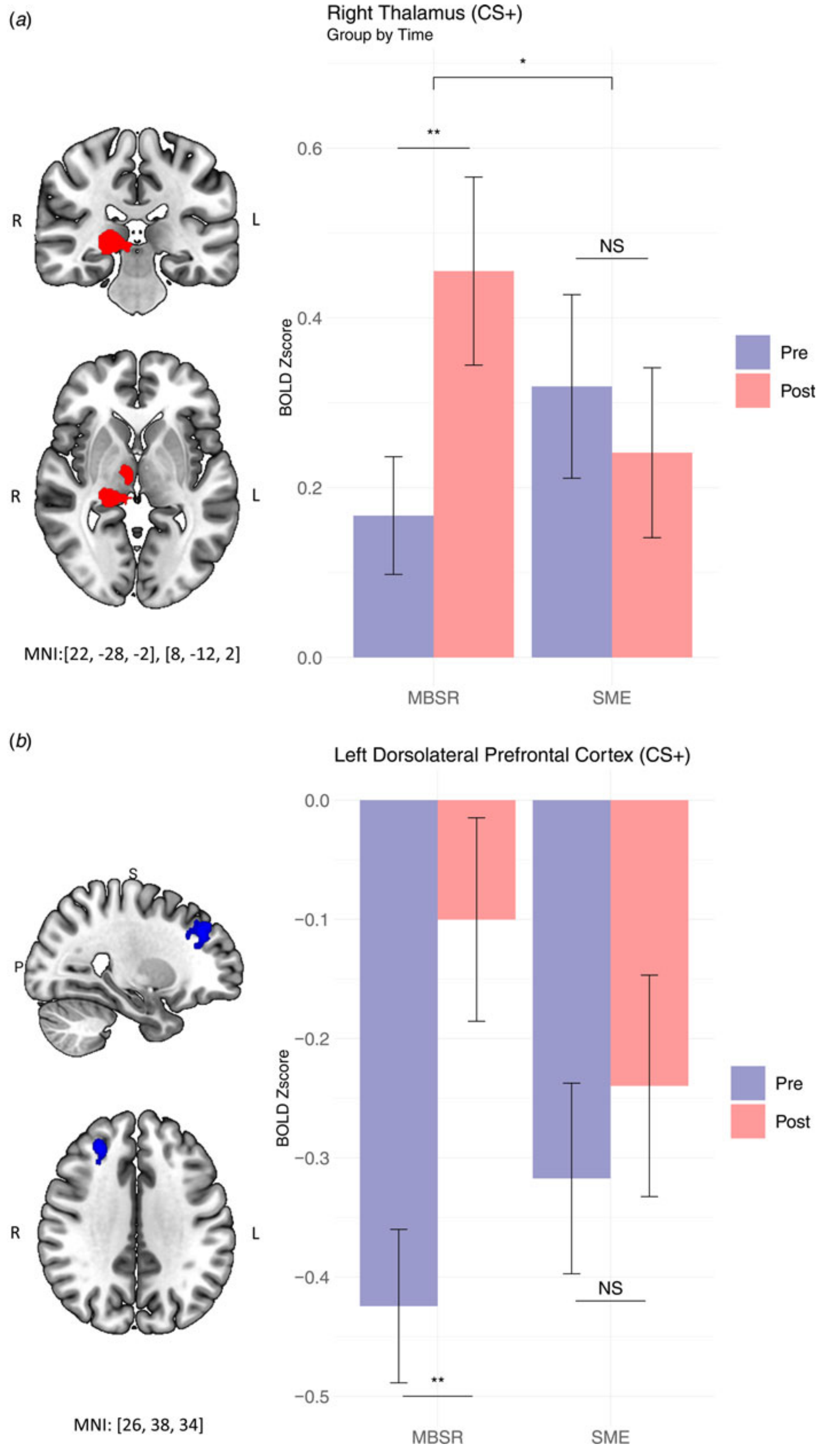

Figure 1. ROI analysis – extinction phase. (a) Brain slices depict right thalamus cluster corrected activation from baseline (CS+); bar plot shows group × time z score BOLD activation, ANOVA group-by-time revealed p value = 0.04; within-group activation change found significant only in MBSR (paired t test $p = 0.01417$). (b) Brain slices depict left dlPFC cluster-corrected activation from baseline (CS+); bar plot shows group × time z score BOLD activation, within-group analysis found significant only in the MBSR group (paired t test $p = 0.0048$). Error bars depict standard error from the mean. Stars correspond to significance level ($^{*}p \leqslant 0.5$; $^{**}p \leqslant 0.01$; $^{***}p \leqslant 0.001$; NS, not significant).

attention to the stimulus (Fig. 3). In addition, the lingual gyrus and right intraparietal sulcus (IPS), which is a node of the dorsal attention network (DAN) that extends to the lateral occipital cortex, demonstrated increased activation post-intervention in the MBSR group.

Discussion

Flexibly adapting to changes in threat signals and updating behavioral and emotional responses are critical for mental health and well-being (LeDoux & Pine, 2016; Mobbs, Hagan, Dalgleish,

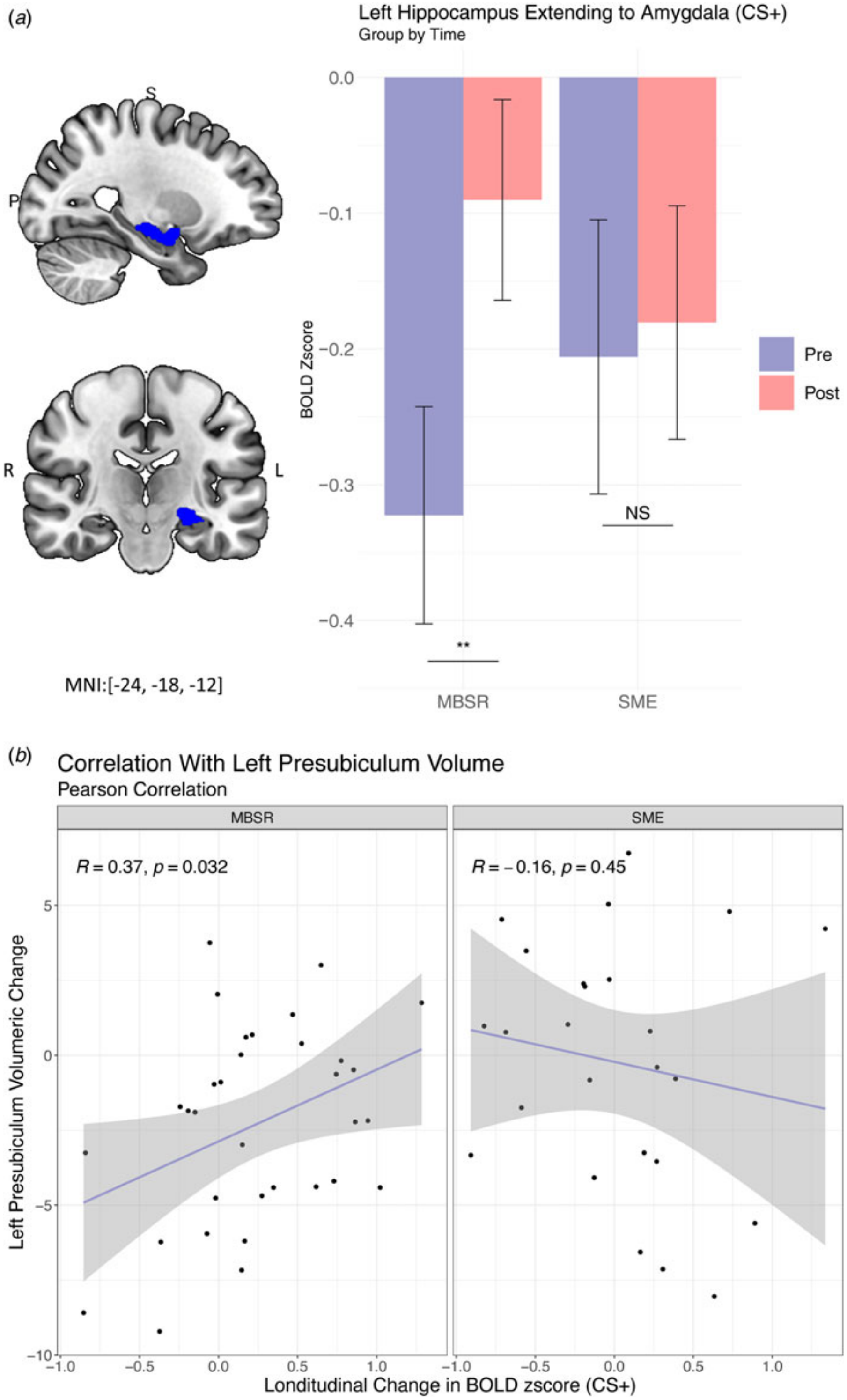

Figure 2. Left hippocampus extending to left amygdala – extinction phase. (a) Group × time graph of BOLD *z* score activation of the cluster presented in panel in the brain slices, depicting cluster-corrected activation from baseline (CS+); within-group activation change found significant only in the MBSR group (paired *t* test $p = 0.004862$). Error bars depict standard error from the mean. (b) Pearson correlation between left presubiculum volume change and left hippocampus extending to amygdala activation change. Shaded area is the standard deviation. Stars correspond to significance level ($*p \leqslant 0.5$; $**p \leqslant 0.01$; $***p \leqslant 0.001$; NS, not significant).

Silston, & Prévost, 2015). Failure to do so can lead to maladaptive fear responses such as that are implicated in trauma-related psychological disorders and anxiety (Graham & Milad, 2011). Enhancing the ability to learn that a cue is no longer associated with a threat could foster mental resiliency (Liberzon & Abelson, 2016). Conscious awareness of present moment sensory experience, as well as increased interoceptive attention and saliency detection, are required for learning to extinguish an unnecessary fearful response and are improved by mindfulness training (Hölzel et al., 2011b; Maren et al., 2013). Here we investigated mindfulness training's capacity to enhance brain mechanisms associated with fear-extinction learning, compared to an exercise-based program. Exercise is well known to improve higher-order cognitive skills and reduce stress. Our findings indicate that mindfulness training and exercise differentially impact brain regions associated with extinction. Our results suggest that mindfulness training increases mechanisms of attention to an anticipatory aversive stimulus, regardless of whether it provokes

Table 2. MBSR group post > pre in response to CS+

Cluster index	Voxels	*p* Value	Z-MAX	Z-MAX [X, Y, Z] (mm)	Structure
1	2033	2.65×10^{-22}	4.65	[2, −76, 2]	Lingual gyrus
2	291	1.48×10^{-5}	4.46	[28, −16, 6]	Right putamen and insula
3	138	0.00437	3.79	[44, −58, 50]	Lateral occipital cortex/intraparietal sulcus
4	119	0.00999	4.01	[40, 34, 34]	Right middle frontal gyrus (dlPFC)
5	117	0.0109	3.94	[−14, −6, 18]	Left caudate

Whole-brain cluster analysis. All clusters thresholded ($p < 0.05$; FWE-corrected).

pain (Grant & Zeidan, 2019) or fear, and increases activity in regions associated with memory reappraisal, which are needed for the regulation of aversive subjective responses. Thus, mindfulness training may potentially support the development of resiliency to aversive experiences and enhance extinction mechanisms in individuals with trauma or anxiety disorders, thereby ameliorating related symptoms.

The thalamus is a key node of the SN that acts as a ‘relay center’ connecting cortical regions such as the dlPFC and the dACC (Uddin et al., 2019). The thalamus receives multimodal sensory and nociceptive information directly from the brainstem and exhibits signaling plasticity to the amygdala and the cortex, thereby, mediating contextual memory formation (Barsy et al., 2020). Importantly, the thalamus also guides valence assignment to the amygdala to promote behavior selection (Li et al., 2022). The present findings revealed an uncorrected significant group-by-time interaction for the right thalamus demonstrating an increase in activation following mindfulness training. (Fig. 1a). Increased thalamic activation implies enhanced information gating to other brain regions, including the SN, which might improve the detection of a stimulus’ motivational relevance and valence and, thereby, improve cognitive control and directing behavioral responses (Borsook, Edwards, Elman, Becerra, & Levine, 2013; Seeley et al., 2007). These processes are aberrant in PTSD patients who demonstrate maladaptive responses to cues that are thought to be associated with failed thalamic activation (Suarez-Jimenez et al., 2020). As predicted, our finding is consistent with meditators’ enhanced awareness of a painful stimulus that was associated with increased thalamic activation, demonstrating that even in the absence of imminent threat the thalamus is more engaged (Zeidan & Vago, 2016).

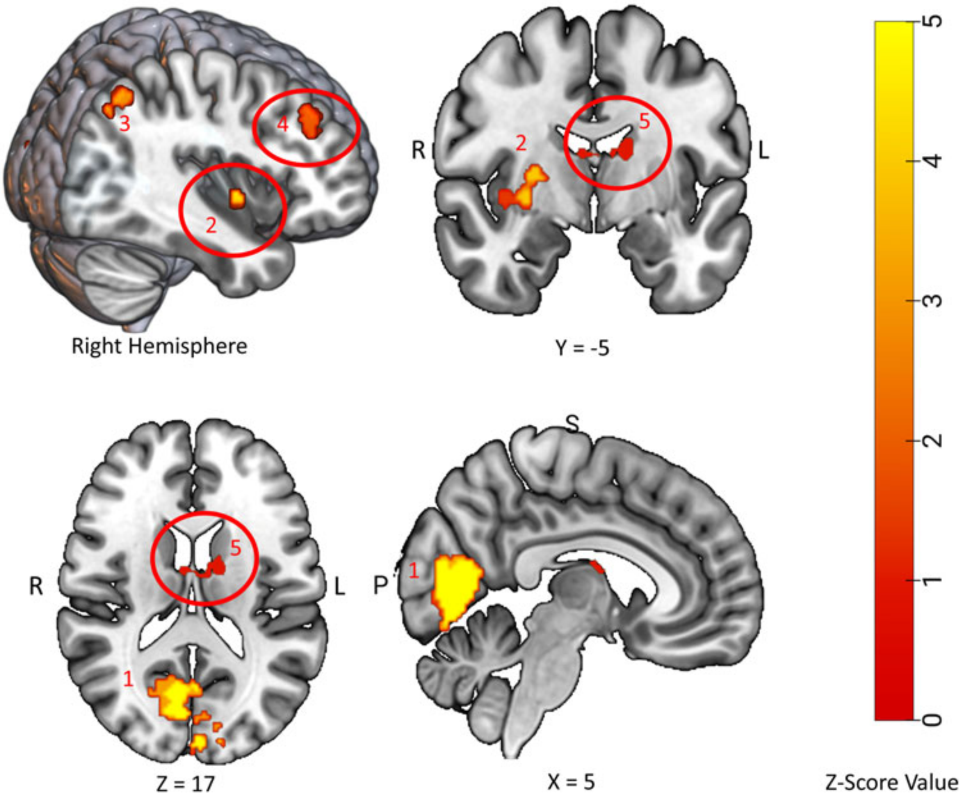

Figure 3. Whole-brain MBSR longitudinal activation change (CS+) – extinction phase. Results from post > pre contrast within the MBSR group in response to CS+. Clusters presented are FWE cluster-corrected $p < 0.05$. Cluster numbering corresponds to Table 2. Circled clusters are ROIs: right insula = 2; dorsolateral prefrontal cortex = 4; left caudate = 5.

The dlPFC is a node of the FPCN (Uddin et al., 2019) that often coactivates with the SN (Peters et al., 2016; Seeley et al., 2007). It has been identified by a meta-analysis to consistently activate during fear extinction learning and is crucial for the successful elimination of fear due to its role in emotional regulation (Fullana et al., 2018; Golkar et al., 2012). The MBSR and SME groups both demonstrated increased relative activation of the left dlPFC, compared to their baseline, but only the change in the MBSR group was statistically significant (Fig. 1b). Enhanced activation of the dlPFC implies enhanced engagement of the conscious-experience-of-threat network promoting awareness of the threat-associated cue (LeDoux & Pine, 2016). Information on saliency detected by the SN is used by the FPCN to direct attention, modulate behavior, and apply cognitive control (Doll, Hölzel, Boucard, Wohlschläger, & Sorg, 2015; Seeley et al., 2007) supporting the reappraisal process. Moreover, we previously reported increased functional connectivity between the dlPFC and the left hippocampus in the retrieval of extinguished fear following MBSR (Sevinc et al., 2019). The present finding further elucidates the influence of mindfulness meditation on dlPFC functioning starting at extinction learning and persisting through extinction recall.

Reappraisal, or the reinterpretation of a negative cue, is supported by hippocampal activation and neurogenesis, which have been shown to promote resiliency to aversive experiences and emotional regulation (Feder, Nestler, & Charney, 2009). Inactivation of the hippocampus disrupts the contextual encoding of fear extinction (Corcoran, Desmond, Frey, & Maren, 2005); the opposite may facilitate enhanced extinction learning, resiliency, and well-being (Liberzon & Abelson, 2016). The hippocampus also gates amygdala-related fear responses to the prefrontal cortex, which is critical for reappraisal during fear extinction learning (Maren et al., 2013; Sotres-Bayon, Sierra-Mercado, Pardilla-Delgado, & Quirk, 2012). In addition, plastic events in the amygdala are crucial for adaptively responding to cues (Whittle et al., 2021). The activity of the neuronal subpopulation of the central amygdala is responsible for tracking the emotional significance of fear-associated cues and promoting emotional learning and extinction memory formation (Whittle et al., 2021). The present study observed significantly increased activation in a cluster covering the left hippocampus and extending to the left amygdala in response to the fear-provoking cue following MBSR (Fig. 2). Given that statistically significant results were only identified in the combined hippocampus–amygdala cluster and not in each region separately, we postulate that the increased activation of this cluster facilitates the reappraisal process by updating the emotional significance of the cue and its encoding in memory.

We previously reported an increase in gray matter density in the left hippocampus associated with strengthened hippocampal circuits (Sevinc et al., 2020). In line with the plausible association between brain function and structure, we examined the correlation between hippocampal activation change during extinction learning and morphometric change in the presubiculum. The presubiculum is responsible for visuospatial information processing (Dalton & Maguire, 2017; Zeidman & Maguire, 2016) and could contribute to visual context processing during extinction learning. The present work found a significant positive correlation between left hippocampal activation change and left presubiculum volume change only in the MBSR group (Fig. 2c). The association between increased activation in the left hippocampus and volume increase of the presubiculum following mindfulness training highlight the neural mechanisms by which mindfulness might improve the visual contextual memory reappraisal.

To complete the assessment of our model, we explored whole-brain longitudinal activation changes in each group. The statistically significant increase in BOLD signal in the right insula, the left caudate, and right dlPFC post-mindfulness training implies increased recruitment of the SN (Seeley et al., 2007; Uddin et al., 2019) and the conscious-experience-of-threat network (LeDoux & Pine, 2016), further affirming our hypothesis (Fig. 3). Long-term meditation practitioners demonstrate increased gray matter in the insula (Lazar et al., 2005), and mindfulness training enhances insular engagement and functional connectivity (Farb, Segal, & Anderson, 2013), as well as SN intrinsic functional connectivity (Kilpatrick et al., 2011). Thus, our findings further reinforce that the SN is altered by mindfulness training and suggest a role for increased SN processing in fear extinction learning. Within the SN, the insula detects the motivational relevance of a stimulus and communicates this information to the dACC and dlPFC which promote behavioral adjustments (Ham et al., 2013; Seeley et al., 2007). Similar to our finding, increased activation of the right insula has been observed during noxious stimulus processing in experienced meditators and correlated with decreased pain unpleasantness. This was thought to facilitate objective conscious awareness and reduce the subjective experience of distress (Gard et al., 2012). The insula might improve objective conscious awareness during threat processing as well. Recent research has shown that fear extinction learning requires more diffuse areas than previously thought (Wen et al., 2021; Wen, Seo, Pace-Schott, & Milad, 2022b). Our findings suggest that MBSR targets a subset of those brain regions that are critical for attention and memory.

Lastly, we found increased activation in a cluster covering the intraparietal sulcus (IPS) and extending to the lateral occipital cortex in response to the fear-provoking cue only in the MBSR group. The IPS is a node of the DAN (Zamani, Carhart-Harris, & Christoff, 2022) that is critical for visuospatial attention (Gillebert et al., 2011) and stimulus-guided visuospatial memory encoding (Rosen, Stern, Michalka, Devaney, & Somers, 2015). Increased activation of the IPS suggests enhanced attention to the visual context during extinction and the formation of a new memory trace.

Due to low statistical power and imbalanced sample size ratio between the meditation group and the active control group, it is possible that we may have failed to detect potentially meaningful changes in the SME group. Future studies with a balanced design and larger sample sizes may reveal significant changes associated with SME. The present findings support mindfulness meditation as a promising candidate for targeting brain regions such as the hippocampus and thalamus that are believed to have aberrant functioning in psychiatric disorders (Suarez-Jimenez et al., 2020). However, our study involved healthy individuals. To examine the efficacy of mindfulness meditation training for improving fear extinction learning among the patient population, future studies should recruit participants with pathologies that are known to demonstrate aberrant extinction learning, such as those with anxiety disorders and/or PTSD.

Conclusions

Our findings reveal unique neural mechanisms associated with mindfulness meditation training during fear-extinction learning. Greater engagement of the salience and conscious-awareness-of-threat networks may improve attention to the motivational relevance of a stimulus and subjective emotional experience. This would promote correct identification of threats and safety, and would support the suppression of automatic responses (LeDoux & Pine, 2016). Enhanced engagement of the hippocampus following mindfulness training, which was correlated with gray matter increase of the presubiculum, could promote visual contextual memory encoding and reappraisal. Finally, behavioral and emotional responses might improve with enhanced involvement of the dlPFC and the IPS, both nodes of the FPCN/CEN and DAN. Taken together, the described mindfulness-training-associated mechanism could enhance fear extinction learning, thereby, supporting recovery from aversive experiences and potentially improving mental health and well-being.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723002593

Data availability statement. All data are available in the main text. Study materials will be available upon reasonable request under a data use agreement with Massachusetts General Hospital. Further information and request for data should be directed to Sara Lazar- slazar@mgh.harvard.edu.

Acknowledgment. We would like to thank intervention providers Zayada Vallejo and Jen Kelly. We also would like to thank all participants for their contribution.

Author contributions. Conceptualization: S. W. L., B. H., M. R. M.; methodology: S. W. L., B. H., M. R. M., T. G., S. P. O., M. V., G. S.; data collection: T. G., T. C.; analysis: S. E. L., J. G.; visualization: S. E. L.; supervision: S. W. L., M. R. M., G. S.; writing – original draft: S. E. L., S. W. L.; writing – review and editing: all authors.

Funding statement. **NIH R01AT006344,** *R21 AT003425*, *R01 AG048351*, Shared Instrumentation Grants: 1S10RR023401, S10RR019307, 1S10RR023043

Competing interest. None.

Ethical standards. The study was reviewed and approved by the Institutional Review Board of Partners HealthCare, approval number [2011P000030]. Informed consent was obtained from all the participants after the nature and possible consequences of the studies were explained.

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