

Mindfulness-based training attenuates insula response to an aversive interoceptive challenge

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Neuroimaging studies of mindfulness training (MT) modulate anterior cingulate cortex (ACC) and insula among other brain regions, which are important for attentional control, emotional regulation and interoception. Inspiratory breathing load (IBL) is an experimental approach to examine how an individual responds to an aversive stimulus. Military personnel are at increased risk for cognitive, emotional and physiological compromise as a consequence of prolonged exposure to stressful environments and, therefore, may benefit from MT. This study investigated whether MT modulates neural processing of interoceptive distress in infantry marines scheduled to undergo pre-deployment training and deployment to Afghanistan. Marines were divided into two groups: individuals who received training as usual (control) and individuals who received an additional 20-h mindfulness-based mind fitness training (MMFT). All subjects completed an IBL task during functional magnetic resonance imaging at baseline and post-MMFT training. Marines who underwent MMFT relative to controls demonstrated a significant attenuation of right anterior insula and ACC during the experience of loaded breathing. These results support the hypothesis that MT changes brain activation such that individuals process more effectively an aversive interoceptive stimulus. Thus, MT may serve as a training technique to modulate the brain's response to negative interoceptive stimuli, which may help to improve resilience.

Keywords: mindfulness; fMRI; interoception; insula; military

INTRODUCTION

To improve the brain's ability to respond to stress is an important goal for both primary prevention of stress-related sequelae, but also for treatment of individuals with psychiatric disorders secondary to trauma exposure. An important component process to target is the brain's awareness of the body's internal physical state. Specifically, one approach is to improve interoception (Craig, 2002), i.e. the processing of the body's internal state and in particular the perturbation of this state as a result of external demands when an individual has to maintain goal-directed action and homeostatic balance (Paulus *et al.*, 2009). Anatomically, these processes take place in the posterior insula which provides topographic and modality-specific interoceptive signals to the anterior insular cortex for integration (Craig, 2003). The anterior insula has reciprocal connections with subcortical, limbic and executive control brain systems, which allows for the integration of interoceptive signals and hedonic evaluation, such as the anterior cingulate cortex (ACC), amygdala, nucleus accumbens and orbitofrontal cortex (Critchley *et al.*, 2004; Craig, 2009). Thus, modifying interoception can be considered an experimental marker for modifying an individual's ability to respond to stress.

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Resilience can be conceptualized as one's ability to positively adapt to severe stress, trauma and adversity (Luthar *et al.*, 2000), that may help to prevent the development of psychopathology (Campbell-Sills *et al.*, 2006), particularly in individuals with combat exposure (Pietrzak *et al.*, 2009; Green *et al.*, 2010). Recently, we have conducted a series of studies examining emotion and interoceptive processing in highly resilient individuals (e.g. elite athletes, special operations forces), and demonstrated differential activation of the insula and ACC in response to emotional processing and loaded inspiratory breathing (Paulus *et al.*, 2010; Paulus *et al.*, 2012; Simmons *et al.*, 2012; Thom *et al.*, 2012). Moreover, self-reported resilience during emotion processing task is associated with differential activation of insula, ACC and amygdala (Vaughn *et al.*, 2008b; Paulus *et al.*, 2010). These results suggest that the ability to perform well under stress, involves modulation of the neural systems are also important in processing interoceptive information.

Among interoceptive processes, modulation of breathing control and awareness has been a unique target for various treatment approaches. Breathing is an interoceptive process that is modulated in the periphery through several sensory airway receptors (Adriaensen and Timmermans, 2011) providing continuous sensory information, which provides discriminative (i.e. what is sensed) and affective information (i.e. how it feels; Davenport and Vovk, 2009). Affective reactions to breathing changes are experienced as equally or more aversive than negative visual stimuli (Pappens *et al.*, 2010), and can serve as a source of threat, leading to increased anxiety (von Leupoldt *et al.*, 2011). One effective method of inducing experimental breathing change is through loaded inspiratory breathing, which can be operationally defined as the degree to which an individual experiences resistance during inspiration (Lopata *et al.*, 1977; Gottfried *et al.*, 1978). In this investigation, resistance during breathing inspiration occurs when the airflow is re-directed through cindered disks that act as resistors during inspiration but not during expiration. Experientially, loaded inspiratory breathing has a sensory component of increased work to inhale but also an affective component that ranges

from mild discomfort to intense fear of breathing in. While inspiratory breathing loads (IBL) result in increased activation in the primary and secondary somatosensory cortices and the cerebellum, IBLs do not modulate task-specific brain activation (Hayen *et al.*, 2012). These characteristics, make breathing an ideal experimental probe for the interoceptive system, in particular the insular cortex, as well as a robust aversive interoceptive stimulus. Understanding the neural network involved in adaptive responses to aversive interoceptive stimuli is an important research question to answer when characterizing optimal performance under stress.

Although interoception has been identified as an important function in responding to, and recovering from, high-magnitude stressors, it remains unclear whether underlying substrates can be modified through training. There is evidence to suggest that mindfulness training (MT), that emphasizes interoceptive awareness and attentional control, can alter brain-behavior relationships involved in response to stress. Mindfulness is 'the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment' (Kabat-Zinn, 2003). Mindful awareness is cultivated by providing guided instruction in mindfulness meditation practices, such as, breath-focused attention and body-scanning of sensory experiences, which require non-judgmental, moment-to-moment awareness of the breath or body part. Mindfulness-based stress reduction (MBSR) developed by Kabat-Zinn (1982, 1990), has been shown to reduce stress-related sequelae (e.g. self-reported stress, medical symptoms, neuroendocrine changes) associated with chronic mental health disorders (e.g. Bowen *et al.*, 2006; Hofmann *et al.*, 2010), medical conditions (e.g. Kabat-Zinn *et al.*, 1985; Carlson *et al.*, 2007) and in nonclinical populations (e.g. Grossman *et al.*, 2004; Chiesa and Serretti, 2009; Wolever *et al.*, 2012). There is converging evidence to suggest anatomical (Kang *et al.*, 2013; Lazar *et al.*, 2005; Holzel *et al.*, 2008; Grant *et al.*, 2010; Kang *et al.*, 2013) and functional (Cahn and Polich, 2006; Brefczynski-Lewis *et al.*, 2007; Farb *et al.*, 2007; Ives-Deliperi *et al.*, 2011; Zeidan *et al.*, 2011; Tang *et al.*, 2012; Dickenson *et al.*, 2013) brain changes are associated with MT, particularly in the insula, ACC and prefrontal cortices. Specifically, several studies have documented posterior cingulate cortex (PCC) and medial prefrontal cortex deactivation in experienced meditators (Brewer *et al.*, 2011; Taylor *et al.*, 2011; Pagnoni, 2012; Brewer *et al.*, 2013), suggesting multiple brain regions are actively involved during meditation practices. Taken together mindfulness mediation has the potential to modulate the effects stress exposure across multiple domains including cognitive, behavioral, physiological, functional and neuroanatomical. Of note, while there are multiple effective interventions for the treatment of stress-related sequelae (e.g. PTSD), such as Cognitive Processing Therapy (Resick and Schnicke, 1992) and Prolonged Exposure (McLean and Foa, 2011), MBSR is an evidence based therapy that can be initiated prior to trauma exposure—and thus may have potential as a preventative method.

MT may have some beneficial effects in military populations who are routinely exposed to extreme environments and are challenged by highly stressful events. The MT intervention, referred to as mindfulness-based mental fitness training (MMFT), was created by a former U.S. Army officer with many years of training in MBSR and trauma resilience, and contains many features of the well-established MBSR protocol. MMFT was previously found to improve working memory capacity in active-duty military (Jha *et al.*, 2010). The primary aim of this study was to determine if MMFT affects how individuals process aversive interoceptive stimuli. In other words, is MMFT able to modulate the brains response to interoceptive distress in marines preparing for combat deployment.

METHODS

Participants

The study was conducted at the Marine Corps Base, Camp Pendleton, California, and at the University of California, San Diego (UCSD) Keck Center for Functional MRI. The Naval Health Research Center (NHRC) and UCSD Institutional Review Boards approved this study and all participants signed informed consents. Participants were recruited from a convenience sample of two Marine infantry battalions scheduled to undergo pre-deployment training. Within those battalions, eight platoons were randomly selected for study assignment; four platoons were assigned to the MMFT group ($n=153$) and four platoons to the control group ($n=134$). Throughout the experiment, participants remained within their organic platoon, which was organized for an upcoming deployment. Approximately five participants from each platoon ($n=42$) volunteered for functional MRI (fMRI); additional written consent was obtained from the volunteers prior to the baseline assessment. From the original sub-sample of marines that agreed to complete the fMRI component of the study ($n=42$), 19 MMFT and 16 control group marines completed both fMRI scans, and will be included in the analysis (see Study Design for details). The groups did not differ in age ($F(1,34)=2.943$, $P>0.05$) or years of education ($F(1,34)=3.733$, $P>0.05$; Table 1).

Study design

Participants underwent two fMRI scans: (i) baseline assessment, which occurred prior to the MMFT course and (ii) post-training, which occurred approximately two weeks following the MMFT course and one week following the Infantry Immersive Trainer. For a more detailed description of the study see Johnson *et al.*, submitted).

Intervention

MMFT is a 20-h course taught over 8 weeks, including eight 2-h sessions (four in the first 2 weeks), an individual practice interview in week 3 and a 4-h workshop with extended silent practice to refine skills in week 6. Designed for individuals with prior exposure to prolonged stress and trauma, MMFT blends MT with concepts and skills from sensorimotor psychotherapy and Somatic Experiencing. MMFT emphasizes interoceptive awareness by cultivating attentional control and tolerance for challenging experience, both external (e.g. harsh environments) and internal (e.g. physical pain, intense emotions). It focuses on enhancing stress resilience by teaching body-based skills for supporting self-regulation of the stress response, its effects and emotions. Didactics highlight how these skills are applicable to military stress inoculation training, complex decision making and operational missions. Outside of class sessions, Marines were encouraged to practice mindfulness and self-regulation skills, for at least 30 min, in several practice periods daily. Exercises are initially guided with audio CDs, but over time, audio support is not necessary. See Stanley (2014) for details.

Self-report measures

Several personality and symptom assessment questionnaires were administered at baseline and post-training including: five facets of mindfulness questionnaire (FFMQ; Baer *et al.*, 2006), designed to measure the five primary facets of mindfulness (observing, describing, acting with awareness, non-judging of inner experience and non-reactivity to inner experience); response to stressful experiences scale (RSES; Johnson *et al.*, 2011) designed to measure 6-processes that promote resilient responses to high-magnitude stressors (active-coping, spirituality, cognitive flexibility, meaning-making, self-efficacy, restoration); and the Pittsburgh Sleep Scale (Buysse *et al.*, 1989),

Table 1 Demographics and self-report measures of study participants

	MMFT (n = 19)	Control (n = 16)		
Variable	<i>Mean(Std)</i>			
Age	22.35(3.30)	20.81(1.10)		
Years of education	12.37(0.76)	12.00(0.00)		
	MMFT T1	Control T1	MMFT T2	Control T2
	(n = 14)	(n = 14)	(n = 14)	(n = 14)
Pittsburgh sleep quality index	9.93(4.62)	6.57(3.76)	8.79(4.48)	6.79(3.80)
	(n = 12)	(n = 10)	(n = 12)	(n = 10)
Response to stressful experiences scale	58.92(13.11)	66.10(13.44)	59.42(11.25)	64.20(14.13)
	(n = 11)	(n = 9)	(n = 11)	(n = 9)
Five facets of mindfulness questionnaire	129.55(14.50)	125.55(17.24)	120.64(7.75)	128.44(15.57)

MMFT, mindfulness-based mental fitness training; T1, baseline assessment; T2 post-training assessment.

designed to assess subjective sleep quality and disturbance over the preceding 1-month time interval.

Behavioral interoceptive assessment

Using an IBL task, we have demonstrated that this task reliably generates a stress response and robust brain activation of the interoceptive system (Paulus et al., 2012). Participants wore a nose clip and breathed through a mouthpiece with a non-breathing valve (2600 series, Hans Rudolph) that maintained an airtight seal. The resistance loads consisted of sintered bronze disk placed in a series in a Plexiglas tube (loading manifold), with stoppered ports inserted between the disks. Prior to entering the scanner, each participant completed three different levels of breathing restriction: baseline (no-load), 10, 20 and 40 cm H₂O/l/s, breathing loads were presented in ascending order, lasted 1-min each with a minute break in between each load. Of note, during the fMRI task only the 40 cm H₂O/l/s breathing restriction was employed. The following instructions were given: 'This task examines how people feel when breathing becomes difficult. You will breathe through a hose, which makes breathing-in more difficult. It is important for you to know that this test is not physically harmful, but you may feel uncomfortable when you breathe through the hose. You can stop at any time if breathing becomes too difficult. You will be asked to breathe through the hose several times. We would like you to complete a one-page rating scale after each trial'. Participants were asked to rate their experience on a 10 cm Visual Analog Scale, which ranged from 'not at all' to 'extremely' on the following dimensions: pleasant; unpleasant; and intense.

Functional MRI IBL task

The basic experimental approach is analogous to the task described above. Inside the scanner, the mouthpiece was positioned comfortably between the lips and was attached to the scanner head coil to eliminate the need to for the participant to contract mouth muscles. Participants performed a simple continuous performance task during the paradigm; they were instructed to press a button that corresponded to the direction pointed by an arrow on the screen (left arrow = left button, right arrow = right button). Participants' accuracy and response latency were recorded and analyzed to determine effects of anticipation and stimulus presentation. At the same time, the background color of the arrow served as a cue to the impending presentation of the breathing load (grey = no load, yellow = 25% chance of load). We utilized

randomly varied inter-trial intervals between each anticipation phase. There were three conditions: (i) anticipation: the background color of the stimulus signals an impending restricted period; and (ii) breathing load: during the change in background color there was a 25% probability that the participant experienced a 40 s period of restricted breathing; and (iii) post-breathing load: immediately following the 40 s period of restricted breathing. Subjects were requested to maintain a consistent breathing pace during the scan and exhaled CO₂ was measured. The 25% probability was introduced in order to maximize the opportunity to measure the effects of anticipating an aversive interoceptive stimulus. This event-related paradigm consisted of 2 scans with 256 repetitions, yielding a total scan duration of 17 min and 4 s. The duration of each condition was 'jittered' in time to maximize the resolution of the hemodynamic response function. The primary behavioral variable was performance accuracy and latency during the three conditions, and the primary neuroimaging dependent measure was the activation in functionally constrained regions of interest during the anticipation and stimulus condition relative to the baseline condition (for additional task-related details see Paulus et al., 2012).

Scanning parameters

Imaging data was acquired at the UCSD Center for Functional MRI on a 3T GE shortbore scanner (GE MR750), equipped with an eight-channel high bandwidth receiver. A high-resolution anatomical image was obtained, which consisted of a sagittally acquired spoiled gradient recalled (SPGR) sequence (172 sagittal slices; FOV 25 cm; matrix: 192 x 256 (interpolated to 256 x 256); slices thickness: 1 mm; TR: 8 ms; TE: 3 ms; flip angle: 12°). A standard gradient echo-planar images (EPI) pulse sequence was used to acquire T2*-weighted functional images (40 axial slices, FOV: 230 mm, matrix: 64 x 64; slice thickness: 3 mm; TR: 2000 ms; TE 32 ms; flip angle: 90°). Rapid image T2* acquisition was obtained via GE's ASSET scanning, a form of sensitivity encoding (SENSE), which uses parallel imaging reconstruction to allow for sub k-space sampling.

Image analysis pathway

Participant-level data were processed with Analysis of Functional Neuroimages (AFNI) software package (Cox, 1996), including temporal and spatial alignment, motion and outlier detection, concatenation, deconvolution and Talairach transformation. Orthogonal regressors were computed for four conditions: (i) anticipation, (ii) breathing load and (iii) post-breathing interval. A task-based reference function corresponding to time interval of the regressor of interest was convolved with a gamma variate function (Boynton et al., 1996) that modeled the prototypical 6- to 8-s delay hemodynamic response function (Friston, 1995) and the temporal dynamics of the hemodynamic response (typically 12–16 sec; Cohen, 1997). In addition, three motion parameters were obtained for each participant and were used to adjust for EPI intensity changes due to motion artifacts. In addition, if the average of any one of these parameters exceeded 2 standard deviations from the mean or if movement exceeded the size of the voxel (4 mm) participants were excluded; however, no participant was excluded based on this criterion. Using the AFNI program, 3dDeconvolve, multivariate regressor analysis was used to relate changes in EPI intensity to differences in task characteristics. The main dependent measure was present signal change, which was spatially smoothed with a 6 mm full-width half-maximum Gaussian filter.

Regions of interest

Analyses were constrained to a priori regions of interest (ROI), which included the ACC and anterior insula. These, a priori, anatomically

defined ROIs were constructed using a data-driven approach that combined Talairach stereotactic definition and grey matter probabilities based on high resolution T1 images from a group of 43 healthy adults (Fonzo *et al.*, 2013). Using SPM5 (Statistical Parametric Mapping software; <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab 7.5.0 (MathWorks, Natick, Massachusetts), grey matter probabilities were determined by applying grey matter segmentation for each subject, which yielded voxel-wise probabilities of assignment to grey matter, across all subjects. The grey matter probability maps were spatially normalized to Talairach stereotactic space, with the boundaries of each region determined based on maximizing sensitivity and specificity for each ROI. The masks were then applied to functional MRI datasets to extract signals from voxels located in selected regions.

Group level analysis

The main dependent measure was percent signal change during the anticipation, stimulation and post-stimulation period, which were entered into a mixed effects model (Littell *et al.*, 2000). Data were analyzed with linear mixed effects models in R (<http://cran.r-project.org/>), which estimates parameters using Maximum Likelihood Estimation and estimates effects using specific contrast matrices. The fixed factors were defined as the group (MMFT *vs* control), experimental condition (anticipation, stimulation and post-stimulus intervals), and time (baseline *vs* post-training), and subject was entered as a random factor. To guard against Type I error, voxel-wise statistics were calculated using the AFNI program *Alphasim*, which estimates statistical significance based on Monte Carlo simulations. Based on the *Alphasim* program, it was determined that, given the spatial smoothing of 6 mm FWHM and a voxel-wise $P < 0.01$, the volume threshold for clusterwise probability of 0.05 for the anterior insula was 256 μ l, for the ACC was 448 μ l. Only clusters meeting these criteria were considered for further analysis.

Behavioral data analysis

All behavioral data analyses were carried out with SPSS 20.0 (IBM, Chicago, IL). Repeated measures ANOVA (RM-ANOVA) were run to examine group differences (MMFT *vs* control) across time (baseline *vs* post-training), separately, for the FFMQ, RSES and PSQI. In addition, RM-ANOVA were run to examine group differences (MMFT *vs* control) across time (baseline *vs* post-training), separately for accuracy and response latency performance during the IBL task (baseline, anticipation, breathing load and post-breathing load), and for VAS ratings of pleasantness, unpleasantness and intensity during behavioral IBL task (breathing load: baseline, 10, 20 and 40 cm H₂O/l/s).

RESULTS

Self-report results

The scores of FFMQ, RSES and PSQI did not differ between groups and did not change differentially across time (group-by-time; Table 1). However, it should be noted that due to scheduling conflicts (e.g. attending mandatory training during data collection times), there are several missing data points at baseline and post-training for the self-report measures. Specifically, of the marines from the control group that participated in both fMRI sessions ($n = 16$), only nine had self-report data at both time points. As such, correlational analyses between self-report measures and brain activation were not conducted

Subjective breathing load

There was an overall effect for breathing load (baseline, 10, 20 and 40 cm H₂O/l/s) for VAS pleasantness ratings [$F(3,99) = 151.225$,

$P < 0.001$], VAS unpleasantness ratings [$F(3,99) = 81.938$, $P < 0.001$] and VAS intensity ratings [$F(3,99) = 4.625$, $P < 0.005$; Figure 1]. Post hoc analysis revealed that VAS pleasantness ratings significantly decreased as load increased ($P < 0.001$). For VAS unpleasantness ratings, although there were no significant differences in unpleasantness ratings between baseline and 10 cm H₂O/l/s, all other conditions were significantly more unpleasant than baseline. For VAS intensity ratings, 40 cm H₂O/l/s was rated as significantly more intense than all of the conditions. There was a main effect of time for VAS unpleasantness ratings [$F(1,33) = 7.399$, $P < 0.01$] and VAS intensity ratings [$F(1,33) = 10.378$, $P < 0.003$], such that, for both ratings, unpleasantness and intensity significantly decreased from baseline to post-training (Figure 1). Finally, there was a main effect of group for VAS pleasantness [$F(1,33) = 5.408$, $P = 0.027$]; overall, across time and breathing condition, the control group rated the breathing restriction task as more pleasant than the MMFT group (Figure 2). Although breathing load resulted in a more aversive experience (decreased pleasantness, increased unpleasantness and intensity), there were no differences in VAS ratings between the MMFT and control groups across time; in other words, there was no effect on the MMFT course in the self-report ratings during the breathing restriction task.

Behavioral performance during fMRI breathing load

For response latency, there was no group-by-time-condition interaction. However, there was a time-by-condition interaction for response latency [$F(4,99) = 4.223$, $P = 0.007$]; for both time points, individuals (MMFT and control) took longer to respond to the anticipation of the breathing load and the post-breathing load, there were no significant differences between baseline and load (Figure 3). There was also a group-by-condition interaction for response latency [$F(3,99) = 3.95$, $P = 0.036$]. The control group has significantly longer response latencies than the MMFT group in the post-load condition (Data not shown). There was a main effect of task for response latency [$F(3,99) = 185.696$, $P < 0.0001$]; relative to baseline and load, individuals took longer to respond to the anticipation of the breathing load and the post-breathing load; all latencies were significantly different from one another (Data not shown). There were no significant differences in response latency between baseline and breathing load. Overall, the response latency results show longer response latencies for the anticipation and post-breathing load conditions for all individuals at baseline and post-training.

There were no significant main effects or interactions for accuracy during the breathing restriction task, indicating no effect of the MMFT course on behavioral performance during the fMRI breathing restriction task.

Neuroimaging results

Group-by-time interaction

There was a significant group-by-time interaction for breathing restriction in the right anterior insula and ACC (Table 2 and Figures 4 and 5, respectively). Specifically, for the right anterior insula, the MMFT group demonstrated significant attenuated activation following the MMFT course, whereas the control group showed no significant change in activation. Additionally, for the averaged breathing task, the MMFT group demonstrated significant attenuation in ACC, whereas the control group demonstrated a trend for increased brain activation in the post-training period.

DISCUSSION

This investigation aimed to investigate whether individuals who undergo mindfulness-based training will show attenuated behavioral and brain response to aversive interoceptive stimulation. Although we

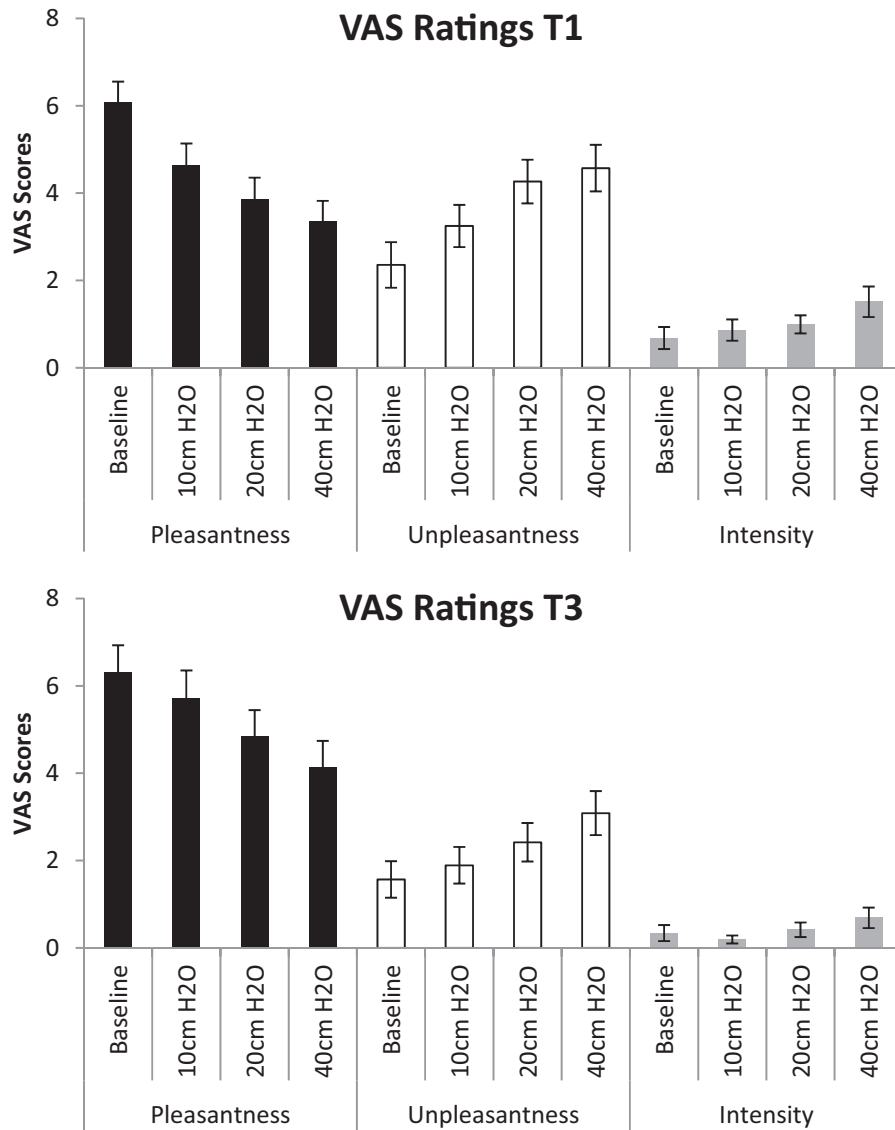


Fig. 1 There was a main effect load, averaged over time (baseline and post-training) and group (MMFT and control); for pleasantness, both groups' ratings decreased with increasing load. For unpleasantness, both groups' ratings increased for 20 and 40 cm H₂O. For intensity, both groups' ratings for 40 cm H₂O were significantly greater than the other loads. Additionally, there was a main effect of time averaged over load (10, 20, and 40 cm H₂O/l/s) and group (MMFT and control); VAS unpleasantness and intensity ratings decreased from baseline to post-training.

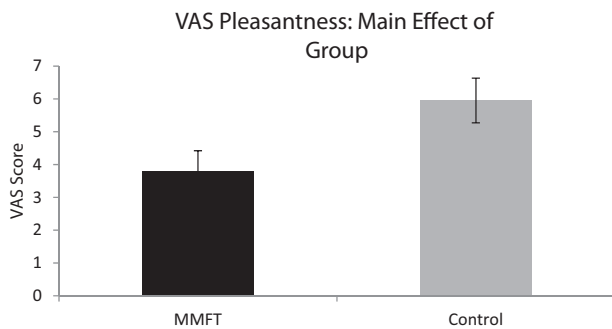


Fig. 2 There was a main effect group, averaged over time (baseline and post-training) and load (10, 20, and 40 H₂O/l/s) for pleasantness, such that the control group rated the breathing restriction task as more pleasant than the MMFT group.

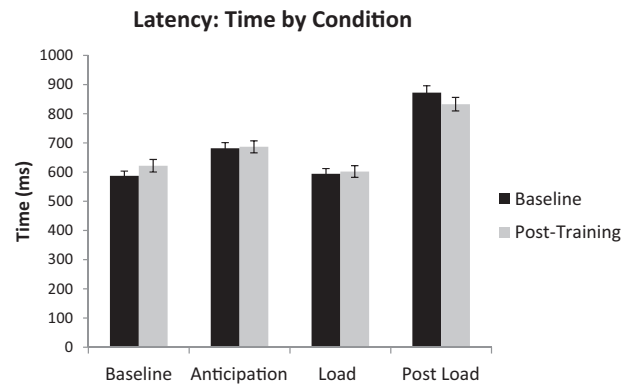


Fig. 3 Interaction effect of task by condition for reaction time (latency) during the continuous performance task averaged group (MMFT and control).

Table 2 Group-by-time interaction of breathing restriction on brain activation

Volume	x	y	z	Brain area	BA
576	4	44	−3	Anterior cingulate	32
256	45	4	−4	Right anterior insula	

BA, Brodmann area; Volume (μl), center of mass coordinate, and brain area based on the voxel-wise mixed model group-by-time interaction of breathing restriction.

did not find a significant effect of MMFT training on subjective ratings and behavioral measures during aversive interoception, we did find a significant attenuation in neural systems that are important for interoceptive processing. Specifically, marines after MT showed significant attenuation of right anterior insula and ACC, in contrast to those in the training as usual condition who showed a trend for increased brain activation during loaded breathing. These results are consistent with the hypothesis that MT modulates the brain's response to an aversive interoceptive stimulus such that individuals who have undergone MMFT demonstrate more effective neural modulation when exposed to an aversive interoceptive stimulus.

Exposure to extreme environments can result in declines in emotional, cognitive and physiological functioning. Combat deployment has been associated with neurocognitive changes (Vasterling *et al.*, 2006), and there is evidence to suggest that pre-deployment training compromises cognitive function including learning, memory, and visual vigilance (Lieberman *et al.*, 2002). Moreover, a recent meta-analysis indicates that 13.2% of operational infantry units following deployment to Iraqi and Afghanistan meet criteria for post-traumatic stress disorder (Kok *et al.*, 2012). Finding ways to improve resilience, that is—an individual's ability to successfully cope with (and bounce back from) stress, may help to reduce the short- and long-term sequelae associated with exposure to extreme environments. In this study, MT resulted in significant attenuation of right insular activation during an aversive breathing load task. These findings are consistent with (i) the proposed role of the insula as part of the neural network subserving interoception (Craig, 2002; Critchley *et al.*, 2004), (ii) attenuated right insular activation in elite athletes during aversive interoceptive breathing load (Paulus *et al.*, 2012), (iii) literature documenting the effectiveness of MT in the treatment of stress-related sequelae for a number of clinical disorder and medical disorders (e.g. Carlson *et al.*, 2007; Hofmann *et al.*, 2010) and (iv) modulation of insula activation during interoceptive attention following MT (Farb *et al.*, 2013).

Similar to other sensory modalities (i.e. vision, audition), interoceptive breathing loads are organized along the dimensions of valence and arousal, and represent a homeostatic balance between metabolic activity and affective arousal (Gomez *et al.*, 2008) are experienced as aversive (Pappens *et al.*, 2010), and can result in increased anxiety (von Leupoldt *et al.*, 2011). Self-reported anxiety, particularly concerns regarding the physical features of anxiety, is associated with increased anterior insula activation in response to negatively valenced stimuli (Killgore *et al.*, 2011). Activation in the anterior insula is associated with interoceptive awareness and level of anxiety, such that the level of attention to interoceptive body states was associated with increased levels of anxiety (Terasawa *et al.*, 2013). These findings are consistent with the proposed model suggesting the inability to adequately predict one's internal body state (i.e. the difference between the value of the anticipated/predicted and value of the current interoceptive state), is associated with insular dysfunction and increased risk for anxiety disorders (Paulus and Stein, 2006). Conversely, resilient individuals generate more efficient body prediction errors, as a way of adapting to

extreme environments (Paulus and Stein, 2006). In the support of this proposal, we have previously shown that highly resilient individuals, such as elite adventure racers (Paulus *et al.*, 2012) and U.S. NAVY Sea, Air and Land Forces (SEALS; Simmons *et al.*, 2012), demonstrate improved performance and attenuated insular activation during an aversive interoceptive breathing and emotion detection tasks. These findings suggest that relative to controls, highly resilient individuals are less affected by aversive interoceptive and emotionally demanding tasks. Behaviorally, higher levels of self-reported resilience are associated with a bias towards positive emotions when faced with uncertain or negative emotions (Tugade and Fredrickson, 2004; Arce *et al.*, 2009) and these individuals demonstrate faster recovery following the anticipation of an aversive stimulus (Vaughn *et al.*, 2008a), which may contribute to increased coping abilities. Taken together, these results suggest that insular cortex plays an important role in resilience, and MT may modulate the brains response to aversive interoceptive conditions in a manner similar to what has been observed in elite warfighters.

The anterior insula is part of the interoceptive neural network; it integrates information from multiple brain regions, ranging from physiologically driven motivational states to emotional awareness, which serves to maintain interoceptive homeostasis (Craig, 2002; Critchley *et al.*, 2004). This brain area has reciprocal connections with the ACC, which generates an error signal that determines allocation of attentional resources based on interoceptive information (Botvinick *et al.*, 1999; van Veen and Carter, 2002; Botvinick *et al.*, 2004). Anterior insula and the ACC facilitate cognitive control by switching between the central-executive control network and default-mode network (Sridharan *et al.*, 2008; Menon and Uddin, 2010). Mindful meditation is also associated with improved cognitive functioning (Jha *et al.*, 2010; Zeidan *et al.*, 2010). In particular, attentional control is thought to be one of the primary mechanisms of mediation (Baer, 2003; Shapiro *et al.*, 2006; Holzel *et al.*, 2011). As part of MT, individuals are trained to focus their attention and are instructed to return their attention to their focus point (e.g. breath, body sensations, emotions) when they become distracted. Research has shown that individuals who undergo meditation training show improved attention (Wenk-Sormaz, 2005; Jha *et al.*, 2007; Tang *et al.*, 2007; Jensen *et al.*, 2012). In the present study the CPT was designed to be easy so it would not draw attentional resources away from the interoceptive task, as such, we were not anticipating group differences or changes in performance secondary to the MMFT intervention. As expected, the failure to find significant differences in accuracy and reaction time is likely due to the relative ease of the behavioral CPT task and not a reflection of failure to improve attention. Neuroimaging studies of experienced meditators have documented increased ACC activation during tasks of attention (Holzel *et al.*, 2007) and focused meditation (Lazar *et al.*, 2000; Newberg *et al.*, 2001; Brewer *et al.*, 2011), and increased cortical thickness (Lazar *et al.*, 2005; Grant *et al.*, 2010). Given that previous studies have shown that meditation training results in improved attention, in combination with the present results of attenuated ACC and insular activation in response to aversive interoceptive stimulation, we speculate that MT may potentially improve attentional control, such that there is more efficient allocation of attentional resources during stressful experiences.

As part of the fMRI inspiratory breathing restriction task, Marines performed a simple continuous performance task, during which a change in the background color served as a cue for the possibility (25% chance) of an impending breathing load. This task served several purposes: (i) ensured that the Marines' maintained focus on the task, (ii) provided information regarding response accuracy and latency and (iii) provided the opportunity to measure the effects of anticipating an aversive interoceptive stimulus. There were no significant effects

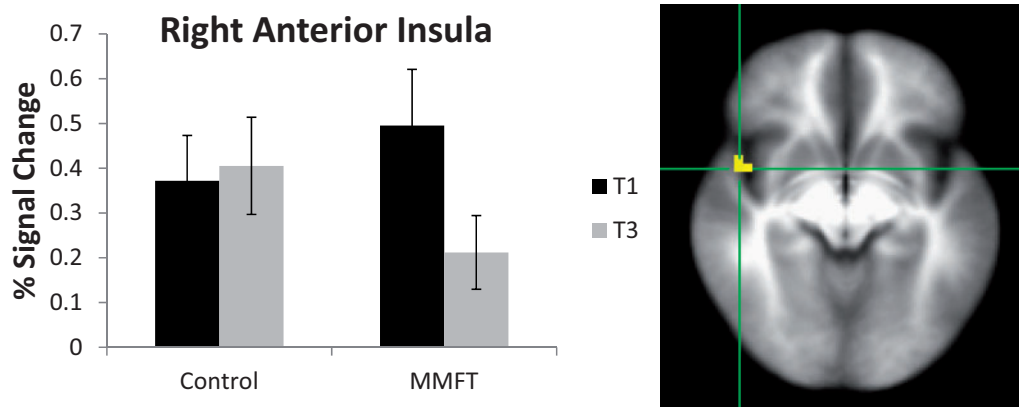


Fig. 4 Interaction of group-by-time. Right anterior insula showed attenuated activation in the MMFT group following the MMFT course, whereas the control group showed no change in activation.

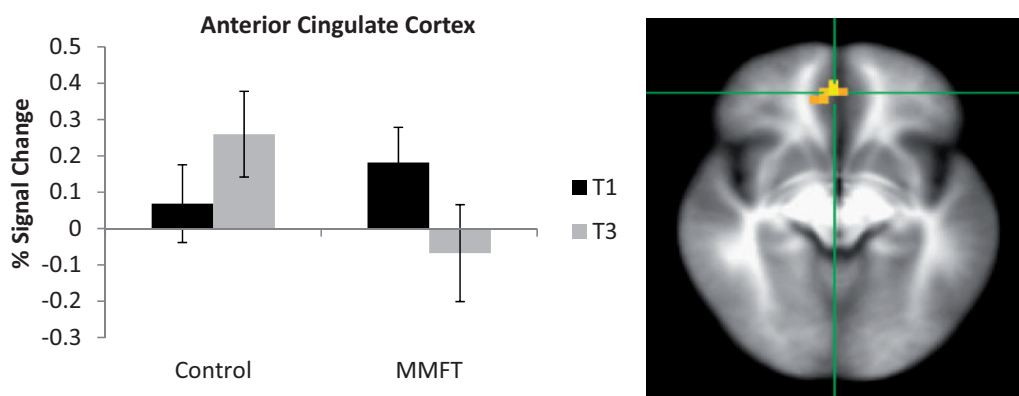


Fig. 5 Interaction of group-by-time. ACC showed attenuated activation in the MMFT group following the MMFT course, whereas the control group showed a trend for increased activation.

for response accuracy—average response accuracy performance for both groups was at or above the 96th percentile (data not shown), which suggests that the Marines maintained focus on the task. However, for response latency (i.e. reaction time), there was a main effect of task, such that reaction times were longer for the anticipation, post-anticipation and post-load conditions relative to the baseline and load condition. In other words, changes in reaction time indicated that individuals showed significant slowing whenever a change in the interoceptive condition occurred, i.e. when individuals had to prepare for or recover from changes in the interoceptive state. However, there was no group (control vs MMFT) by time (baseline vs post-training) interaction, suggesting that the MMFT training did not modulate behavioral performance during the fMRI loaded breathing task.

This study has several limitations. First, there was no active control group, i.e. marines who did not participate in MMFT training underwent the usual pre-deployment training. Therefore, it is possible that the mere time spent in MMFT training contributed to group differences. Second, we did not identify a clear brain behavior relationship, i.e. the brain activation results were not related to changes in measures of mindfulness or resiliency, which may be due to small sample size. Thus, future studies with larger sample sizes and active comparison groups are needed to elucidate the relationship between modulation of brain activation due to MT and self-report measures of mindfulness and resiliency is important for understanding the functional implications of MT. Nevertheless, this investigation contributes to the generalizability of potentially resilience-building effects of MT. Specifically, the subjects were not treatment seeking, did not suffer from a mental

health condition and had not been previously exposed to concepts of mindfulness and yet showed significant brain changes as a consequence of training.

CONCLUSIONS

In summary, this study found that an 8-week MT program in active duty infantry marines modulates the brain response to an aversive interoceptive stimulus. Relative to controls, marines who underwent MT showed attenuated right anterior insula and ACC activation during an aversive interoceptive condition. The present findings provide evidence that MT may serve as a training technique to modulate the brain's response to negative interoceptive stimuli, which may contribute to increased coping abilities.

Conflict of Interest

None declared.

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