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Modifying Resilience Mechanisms in At-Risk Individuals: A Controlled Study of Mindfulness Training in Marines Preparing for Deployment

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Abstract

Objective—Military deployment can have profound effects on physical and mental health. Few studies have examined whether interventions prior to deployment can improve mechanisms underlying resilience. Mindfulness-based techniques have been shown to aid recovery from stress and may affect brain-behavior relationships prior to deployment. The authors examined the effect of mindfulness training on resilience mechanisms in active-duty Marines preparing for deployment.

Method—Eight Marine infantry platoons (N=281) were randomly selected. Four platoons were assigned to receive mindfulness training (N=147) and four were assigned to a training-as-usual control condition (N=134). Platoons were assessed at baseline, 8 weeks after baseline, and during and after a stressful combat training session approximately 9 weeks after baseline. The mindfulness training condition was delivered in the form of 8 weeks of Mindfulness-Based Mind Fitness Training (MMFT), a program comprising 20 hours of classroom instruction plus daily homework exercises. MMFT emphasizes interoceptive awareness, attentional control, and tolerance of present-moment experiences. The main outcome measures were heart rate, breathing rate, plasma neuropeptide Y concentration, score on the Response to Stressful Experiences Scale, and brain activation as measured by functional MRI.

Results—Marines who received MMFT showed greater reactivity (heart rate [d=0.43]) and enhanced recovery (heart rate [d=0.67], breathing rate [d=0.93]) after stressful training; lower

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plasma neuropeptide Y concentration after stressful training ($d=0.38$); and attenuated blood-oxygen-level-dependent signal in the right insula and anterior cingulate.

Conclusions—The results show that mechanisms related to stress recovery can be modified in healthy individuals prior to stress exposure, with important implications for evidence-based mental health research and treatment.

The ability to quickly anticipate, respond to, and recover from recurrent stressors is fundamental to a healthy homeostatic system and essential for long-term behavioral and psychological health. In particular, stress recovery is critical to the optimal functioning of military personnel during deployment and integral to their postdeployment reintegration. Population-based studies of military personnel serving in combat indicate prevalences of stress-related mental health disorders between 11.3% and 19.1% (1). Military operations in Iraq and Afghanistan now span a decade, marking America's longest sustained combat operations. Studies of trauma-related pathology and resilience highlight the fact that while intense stress chronically perturbs homeostatic mechanisms for some individuals, others are able to recover (2–4). Available neuroscientific evidence suggests that maladaptation to stress is associated with disruption of neural networks that communicate and integrate information about the response to stress (5). However, our understanding of these mechanisms is incomplete, and a translational knowledge gap remains regarding whether brain-behavior relationships can be reliably modified prior to stressful experiences in a way that confers an enhanced ability to recover.

Successful recovery from stress is multifaceted, with complex interactions between brain, behavior, and environment. The brain is the central organ of stress response and recovery, and essential to these processes is an individual's awareness of his or her internal physiological state, also known as interoception (6, 7). Interoception, which is functionally and neuroanatomically distinct from the traditional “five senses” (8), is a process through which the brain monitors and updates the body about its overall physical state, including its ability to recognize bodily sensations, be aware of emotional states, and maintain physiologic homeostasis. Inefficient interoceptive function has been shown to play a critical role in the development of mood and anxiety disorders (9–12). Conversely, interoceptive exposure, the intentional induction of symptoms of sympathetic arousal, has been shown to be effective in treating anxiety disorders (13), panic disorder (14, 15), posttraumatic stress disorder (16), chronic pain (17), and irritable bowel syndrome (18, 19).

Functional neuroimaging studies have identified the insular cortex as a critical brain structure for modulating interoceptive function (20, 21). A series of neuroimaging studies by our group has shown that altered insula activation differentiates individuals known to perform well under severe stress (e.g., “exceptional performers”) from healthy control subjects (22–25). In other words, more efficient functioning in the insular cortex and enhanced interoceptive processing distinguishes those who perform well under high-magnitude stress from those who do not.

Growing evidence suggests that deliberate modification of interoceptive function can be achieved through mindfulness training (MT). Mindfulness is a mental mode characterized by full attention to present-moment experience without elaboration, judgment, or emotional

reactivity. It includes the ability to pay attention to, describe, and act with full awareness of sensations, perceptions, thoughts, and emotions (26). MT programs that offer exercises and didactic instruction to help participants cultivate this mental mode.

Modification of insula activation has been reported in experienced practitioners of meditation compared with nonpractitioners (27), as well as in healthy participants in an 8-week MT course compared with control subjects (28, 29). Other studies have shown that MT practice corresponds to “more efficient” functional activity profiles within prefrontal regions during attention-demanding tasks (30). These results suggest that alteration of insula function may be associated with mindfulness-based improvements in the capacity to appraise emotion as “innocuous sensory information rather than as affect-laden threat to self requiring a regulatory response” (29, p. 31).

Our primary aim in this study was to examine the capacity of a mindfulness-based intervention called Mindfulness-Based Mind Fitness Training (MMFT) (31) to modulate mechanisms underlying recovery from stress in active-duty military personnel prior to deployment. We obtained evidence in multiple domains (physiological measures, biomarkers, fMRI, and self-report clinical measures), consistent with the multiple levels of investigation mandated by the Research Domain Criteria, to further elucidate the capacity for MT to modulate brain-behavior mechanisms involved in recovery from stress. We hypothesized that an MT program emphasizing interoceptive awareness, as MMFT does, could create desirable changes across several functional domains implicated in response to, and recovery from, stressful training.

Method

Study Participants

We conducted this study during the summer of 2011 at Marine Corps Base Camp Pendleton, Calif., and at the University of California, San Diego (UCSD) Center for Functional MRI. The institutional review boards of the Naval Health Research Center and UCSD approved the study protocol. Participants were recruited from a convenience sample of two Marine infantry battalions scheduled to undergo predeployment training. Within those battalions, eight platoons (N=287) were randomly selected for study assignment; four platoons were assigned to the MT group (N=153) and four to a training-as-usual control condition (N=134). Five Marines from each of the eight platoons (N=40) comprised the functional MRI (fMRI) subsample.

Study Design

Written informed consent was obtained from all participants prior to the baseline assessment. Additional written consent for the subsample of participants undergoing fMRI was obtained prior to the baseline scan. Participants were assigned a unique study participant identification number for use throughout the study. A second assessment was conducted 8 weeks after baseline, and a third assessment was conducted 5–10 days after that (at approximately 9 weeks), at the Infantry Immersion Trainer (IIT) facility, during and after stressful combat training. Participants in the fMRI subsample underwent a second scan

within 2 weeks of completing training exercises at the IIT facility (at approximately 10 weeks).

IIT facility—The primary platform for evaluating recovery from stress was the IIT facility. Marine units preparing for deployment spend 1 day training at this facility as part of the standard predeployment training cycle. The IIT facility is a 32,000 square-foot compound located at Camp Pendleton. It comprises several one- and two-story huts, a religious center, a marketplace, and numerous walls, gates, and alleyways modeled on those typically found in a rural Middle East village. The IIT facility exposes Marines to close-quarters combat scenarios with the aid of foreign-national role players and realistic sensory (e.g., smells, sounds) and environmental (e.g., interpreters, pyrotechnics) stimuli. Real-time scenarios include a variety of operational challenges that vary in intensity and duration. For the present study, participants were exposed to three specified scenarios, each increasing in complexity. The first scenario involved a passive village patrol; the second focused on meeting village leadership (“a key leader engagement”); and the third required responding to a complex ambush.

MT Intervention

MMFT is a 20-hour course taught over 8 weeks, including eight 2-hour sessions of classroom instruction, an individual practice interview in week 3, and a 4-hour workshop with a longer session of silent practice to refine mindfulness skills in week 6. Outside of class sessions, participants are asked to complete at least 30 minutes of daily mindfulness and self-regulation exercises, divided into several practice periods each day. MMFT provides a novel approach to MT designed for individuals with prior exposure to prolonged significant stress. The program emphasizes interoceptive awareness by cultivating attentional control and tolerance for challenging experience, both external (i.e., harsh environmental conditions) and internal (e.g., physical pain, intense emotions, distressing thoughts). It also focuses on enhancing stress resilience, with didactic content and concrete skills for supporting self-regulation of the stress response and its effects. These skills and information incorporate and extend concepts from sensorimotor psychotherapy and somatic experiencing, and they inform the model of resilience taught in MMFT. The program was designed for the high-stress organizational context, with ways to integrate practices into the work setting and with didactic content focused on the relationship between mindfulness, military stress inoculation, and complex decision making.

Measures

The primary physiological measures were heart rate and breathing rate. These were measured at the IIT facility and included continuous monitoring through the following sequence of periods: rest (45 minutes), anticipatory (10 minutes), stress (30 minutes), recovery (10 minutes), and rest (45 minutes). The primary biomarkers of interest were plasma concentrations of neuropeptide Y and norepinephrine. Neuropeptide Y is co-released with norepinephrine and at low concentrations is a secondary indicator of sympathetic activation. It is also released at high concentrations during intense or prolonged sympathetic activation and is a well-known stress modulator (32).

For the fMRI component of the study, an emotion face processing task (33) was used to assess quantitatively the functional status of the neural circuitry that has been implicated in emotion processing and interoception. This task examines brain activation when individuals process emotional faces when compared with simple geometric shapes and reliably produces insula activation. Previous studies of exceptional performers have shown altered activation patterns in this circuitry consistent with more efficient interoceptive processing (22, 25). Behavioral characteristics of resilience were assessed with the Response to Stressful Experiences Scale, a self-report measure that was developed and validated in a large active-duty military and veteran sample (34).

Procedures

Physiological monitoring (heart rate and breathing rate), blood draw, and self-report measures (including the Response to Stressful Experiences Scale) were completed at baseline, at 8 weeks, and during and after the stressful IIT session at approximately 9 weeks. A mobile lab was established at the study site, and samples were spun in a refrigerated centrifuge within 20 minutes of being drawn. Plasma was aliquotted and immediately placed on dry ice until transfer to a -80 freezer at the end of the training day. A subset of participants ($N=40$) underwent fMRI scanning at baseline and again within 2 weeks after the stressful IIT session, at approximately 10 weeks.

Analysis

Groups were contrasted on demographic variables. The interaction of group and time was analyzed for physiological, neuroendocrine, fMRI, and self-report data. The threshold for statistical significance was set at 0.05, with adjustments made for multiple comparisons. Main effects and interactions were analyzed using a general linear model for repeated measures and mixed-factorial designs. Brain imaging was analyzed using the AFNI software package (<http://afni.nimh.nih.gov/afni/>). fMRI is predicated on cerebral blood flow and hemodynamic properties of deoxygenated hemoglobin, known as the blood-oxygen-level-dependent signal (35). Based on our own and other studies with elite performers and anxious individuals and on pharmacological studies, we used a priori brain regions of interest (i.e., entire regions of the insula, the dorsal anterior cingulate cortex, and the medial prefrontal cortex) and restricted our analyses to those regions. Robust (Huber) regression analyses were performed between fMRI data and key variables to establish relationships between changes in brain activation patterns and neuroendocrine and physiological variables.

Results

Participant Flow

U.S. Marine Corps predeployment training requirements are intensive, and Marines' training schedules are generally full and complex, and as a result, not all participants were able to attend each of the assessments. The scheduling conflicts cited below were related to training schedules, medical appointments, and temporary assigned duty to other locations. In addition, a few Marines declined the blood draw or the questionnaire containing the Pittsburgh Sleep Quality Index and the Response to Stressful Experiences Scale. The

participant flow through the study is summarized below, as well in Figure S1 in the data supplement that accompanies the online edition of this article.

MT group—From the four platoons assigned to the MT group (N=153), 151 Marines were present at the baseline assessment (two had scheduling conflicts). Of these, four declined questionnaires and nine declined blood draw. Because of time constraints, 22 Marines in the MT group were unable to participate in the heart and breathing rate assessments. A total of 147 Marines consented to participate in the MT intervention, and all of them completed the intervention.

At the 8-week assessment, 134 Marines in the MT intervention group were present (13 had scheduling conflicts). Of these, 10 declined blood draw and eight were unable to participate in the heart and breathing rate assessments because of time constraints. For eight Marines, questionnaire data were lost by unintentional overwriting.

At the IIT assessment, 118 of the 147 Marines in the MT intervention group were present (29 had scheduling conflicts). Of these, three declined questionnaires and 10 declined blood draw. During the IIT session, heart and breathing rate data could be collected for only 54 Marines in the MT group because of the time constraints of the training and the time required to download data from sensors and transfer the monitoring harnesses to Marines in the next training group.

Control group—From the four platoons assigned to the control group (N=134), 113 Marines were present at the baseline assessment (21 had scheduling conflicts). Of these, four declined questionnaires, six declined blood draw, and 22 were unable to participate in heart and breathing rate assessments because of time constraints.

At the 8-week assessment, 121 Marines from the control group were present (13 had scheduling conflicts). Of these, two declined blood draw, and 12 were unable to participate in the heart and breathing rate assessments because of time constraints.

At the IIT assessment, 95 of the 134 Marines in the control group were present (39 had scheduling conflicts). Of these, three declined blood draw. During the IIT session, heart and breathing rate data could be collected for only 53 Marines in the control group because of competing demands of training and time required to download data and transfer harnesses.

fMRI subgroup—A total of 40 Marines—20 from the MT group and 20 from the control group (five from each of the eight platoons)—were randomly selected for fMRI assessments. All 40 Marines in the fMRI subgroup underwent scanning at baseline. At the follow-up fMRI assessment at approximately 10 weeks, one Marine from the control group was absent because of a scheduling conflict.

Sample Characteristics

The baseline characteristics of study participants are summarized in Table 1. The MT and control groups did not differ significantly in age, duration of military service, race, education, height, or weight. The MT group had a smaller proportion of Marines who were

married. Physical fitness did not differ significantly between the groups, except that the MT group had a slightly faster 3-mile run time. There were no differences between the groups regarding military operational specialty, number of combat deployments, combat exposure, or proportion taking prescribed medication. Self-report of resilience characteristics (based on the Response to Stressful Experiences Scale) did not differ between the groups at baseline. In both the overall study sample and the fMRI subsample, Marines in the MT group reported significantly worse quality of sleep at baseline compared with those in the control group. The fMRI subsample did not differ from the larger sample in age, duration of military service, combat exposure, height, weight, or physical fitness.

MT Intervention

Attendance was recorded for each platoon at each of the eight MT classroom sessions and the 4-hour workshop. The mean attendance rate for all sessions was 92.6% (SD=8.1, range=68-100). The mean practice time in excess of the 20 hours of classroom instruction was 205.1 minutes (SD=243.5, range=0-1750). Attendance rate and practice time did not differ significantly between platoons.

Stress Exposure

IIT scenario duration did not differ significantly between groups; the mean duration was 30.9 minutes (SD=10.3) for the MT group and 29.2 minutes (SD=11.1) for the control group.

Autonomic Physiology

Heart rate—Using data collected at the IIT facility, we tested for group differences during the anticipation ($t=2.13$, $df=99$, $p=0.036$), response (n.s.), and recovery phases (n.s.), with results suggesting that the groups were significantly different only during anticipation (Figure 1A). However, we also separately tested the rate of recovery (recovery heart rate minus response heart rate) within each group. The rate of recovery differed significantly between the groups, with the MT group showing a sharper reduction in heart rate (mean= -7.1 , $SD=14.5$; $t=3.52$, $df=51$, $p<0.001$) than the control group (mean= -0.3 , $SD=10.6$; n.s.).

Breathing rate—We tested for group differences during the anticipation (n.s.), response (n.s.), and recovery phases ($t=-2.59$, $df=99$, $p=0.011$), with results suggesting that the groups were different only during recovery (Figure 1B). We also separately tested the rate of recovery (recovery breathing rate minus response breathing rate) within each group. As with heart rate, the rate of recovery for breathing rate differed significantly between the groups, with the MT group showing a sharper reduction (mean= -3.3 , $SD=0.6$; $t=5.18$, $df=51$, $p<0.001$) than the control group (mean= -0.5 , $SD=0.6$; n.s.).

Biomarkers

Group-by-time interaction analysis revealed that plasma concentrations of neuropeptide Y did not differ significantly between the MT and control groups at baseline or at 8 weeks; however, after the stressful IIT session, the MT group had lower concentrations of neuropeptide Y than the control group (Figure 2). The mean elapsed time from cessation of

IIT scenario to plasma extraction did not differ significantly between the MT group (mean=48.2 minutes, SD=20.9) and the control group (mean=45.8 minutes, SD=11.6).

Relationships Between Physiology and Biomarkers

Heart rate was positively correlated with plasma neuropeptide Y concentration during the response ($r=0.49$, $p<0.001$) and recovery periods ($r=0.50$, $p<0.001$). Breathing rate was negatively correlated with epinephrine concentration during the anticipatory period ($r=-0.23$, $p<0.01$).

fMRI

Group differences—Participants in the MT group showed significant attenuation of brain activation, whereas those in the control group did not (Figure 3). The MT group showed less activation to emotional faces in the right insula ($F=7.88$, $df=1, 150$, $p=0.015$; $d=0.92$) and the dorsal anterior cingulate ($F=6.83$, $df=1, 150$, $p=0.02$; $d=0.86$), which are regions that have been implicated in cognitive control, emotion regulation, reward monitoring, and interoception. Region-specific differences in the group-by-time interaction during the emotion recognition task are summarized in Table 2.

Individual differences—Interestingly, those individuals who reported greater resilience improvements after MT (as measured by the Response to Stressful Experiences Scale) also showed the greatest reduction of brain activation in the right anterior insula ($r=-0.42$, $p<0.05$) (Figure 4).

Discussion

To our knowledge, this is the first study of the effect of MT utilizing multiple domains of measurement to examine mechanisms underlying recovery from stress in active-duty military personnel prior to deployment. We used a multidimensional approach assessing brain-behavior relationships in a stressful military training environment (Infantry Immersion Training) with high ecological validity (see Table 3 for a summary of results). Our investigation yielded three main results. First, MT altered heart rate and breathing rate recovery following stressful training. Second, MT modulated a strongly correlated set of peripheral biomarkers before, during, and after exposure to a stressful training session. Third, the neuroimaging results support the hypothesis that MT affects brain structures that are important in integrating information about the internal physiological state and the body's response to stress. Thus, MT demonstrated beneficial effects across multiple domains indicating enhanced recovery from stress. Moreover, these effects were observed in a nonclinical sample and suggest that responses to stress may be improved through training prior to stress exposure, even in individuals without a mental health condition. Given these results, it is reasonable to speculate that even stronger treatment effects may be observed in treatment-seeking clinical populations. Taken together, these findings constitute evidence for the prevention and treatment of stress-related pathology. In addition, using measures in multiple domains, this study is an important step toward the application of Research Domain Criteria and neuroscience-based diagnoses. The results also have important implications for

stress-related mental health research and evidence-based foundations for nonpharmacological prevention and treatment options.

The profile of heart and breathing rate reactivity with MT indicates a more potent response to stress followed by quicker recovery, an effect that remained after controlling for baseline differences in self-reported aerobic fitness as indicated by 3-mile run time. This result is consistent with evidence indicating that cardiorespiratory fitness is associated with greater reactivity to stress followed by enhanced recovery (36). Furthermore, physiological results from this study directly support the idea that flexibility within a system facilitates adaptive response to stress.

Heart rate and breathing rate are controlled by via regions of the brainstem under the influence of higher-order brain regions like the insula. That we found changes in insula function suggests that MT alters function in higher-order brain regions that in turn modulates autonomic outflow to heart rate and breathing rate control centers. This, too, is consistent with evidence suggesting that individuals who adapt well to stress have more efficient deployment of neural processing resources and autonomic responses to stress (37). Relative to Marines in the control group, those who received MT showed lower sympathetic activation during recovery from stressful immersive training.

Brain activity changes on fMRI in the MT group are consistent with studies identifying a key role for interoceptive networks in responding to affective perturbation. Evidence indicates that higher self-report of mindfulness is associated with reduced activation in the right anterior insula while viewing negative affect images (38). Similarly, Brefczynski-Lewis et al. (30) found that relative to nonmeditators, experienced meditators showed attenuated posterior insula activation during a task of attentional control. There is also evidence for an inverse dose-response relationship between insula activation and benzodiazepine administration, suggesting that decreased insula function is associated with reduced perturbation of the interoceptive system (39). Our findings were similar, with the MT group showing decreased activation in the right insula while responding to emotional faces. Taken together, these findings suggest that a mindful approach to affective perturbation requires fewer cognitive resources. However, such an interpretation regarding the directionality of insula function is incomplete. For example, Farb et al. (28) found increased functional connectivity between the insula and the medial prefrontal cortex during tasks that demanded self-referencing. Differences in the directionality of activation may speak to functional differences between anterior and posterior insula. Evidence suggests that functional differences between anterior and posterior may correspond to distinctions in awareness of the internal self versus awareness and regulation of affective states (40). It remains unclear whether self-referential states perturb homeostasis or are different from regulatory modes of interoception.

Relative to the control group, the MT group showed a pattern of altered activation in the right anterior insula and dorsal anterior cingulate cortex after the stressful training session similar to that observed in previous studies by our group in “elite performers” (in both military and civilian samples) relative to healthy subjects (22–25). These results suggest that

MT may directly modulate interoceptive function toward more efficient processing of cues signaling perturbation of homeostasis and further facilitates improved response to stress.

A limitation of this study was the lack of an active control group. Predeployment training preparation was identical for the MT and control groups with the exception of the MT intervention. Thus, it is possible that some group differences had more to do with the extra time and attention spent on a focused task, not just with the MT content. However, the moderate interaction effect sizes for fMRI, neuropeptide Y, physiology, and sleep quality measures make this explanation less plausible and underscore the value of multidimensional outcome measures in mindfulness research. Moreover, these findings are consistent with independent fMRI studies showing mindfulness-based meditation effects on the anterior insula and anterior cingulate cortex. The extent to which these brain-behavior relationships remain modified as a result of MT and affect behavioral health remains unknown and is worthy of study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hoge CW, Auchterlonie JL, Milliken CS. Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. *JAMA*. 2006; 295:1023–1032. [PubMed: 16507803]
2. Haglund MEM, Nestadt PS, Cooper NS, Southwick SM, Charney DS. Psychobiological mechanisms of resilience: relevance to prevention and treatment of stress-related psychopathology. *Dev Psychopathol*. 2007; 19:889–920. [PubMed: 17705907]
3. Southwick SM, Vythilingam M, Charney DS. The psychobiology of depression and resilience to stress: implications for prevention and treatment. *Annu Rev Clin Psychol*. 2005; 1:255–291. [PubMed: 17716089]
4. Southwick SM, Charney DS. The science of resilience: implications for the prevention and treatment of depression. *Science*. 2012; 338:79–82. [PubMed: 23042887]
5. Sousa N, Almeida OF. Disconnection and reconnection: the morphological basis of (mal)adaptation to stress. *Trends Neurosci*. 2012; 35:742–751. [PubMed: 23000140]
6. Khalsa SS, Rudrauf D, Feinstein JS, Tranel D. The pathways of interoceptive awareness. *Nat Neurosci*. 2009; 12:1494–1496. [PubMed: 19881506]
7. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci*. 2002; 3:655–666. [PubMed: 12154366]
8. Craig AD. How do you feel—now? The anterior insula and human awareness. *Nat Rev Neurosci*. 2009; 10:59–70. [PubMed: 19096369]

9. Paulus MP, Stein MB. An insular view of anxiety. *Biol Psychiatry*. 2006; 60:383–387. [PubMed: 16780813]
10. Stein MB, Simmons AN, Feinstein JS, Paulus MP. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *Am J Psychiatry*. 2007; 164:318–327. [PubMed: 17267796]
11. Domschke K, Stevens S, Pfleiderer B, Gerlach AL. Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. *Clin Psychol Rev*. 2010; 30:1–11. [PubMed: 19751958]
12. Paulus MP, Stein MB. Interoception in anxiety and depression. *Brain Struct Funct*. 2010; 214:451–463. [PubMed: 20490545]
13. Norton PJ, Price EC. A meta-analytic review of adult cognitive-behavioral treatment outcome across the anxiety disorders. *J Nerv Ment Dis*. 2007; 195:521–531. [PubMed: 17568301]
14. Lee K, Noda Y, Nakano Y, Ogawa S, Kinoshita Y, Funayama T, Furukawa TA. Interoceptive hypersensitivity and interoceptive exposure in patients with panic disorder: specificity and effectiveness. *BMC Psychiatry*. 2006; 6:32. [PubMed: 16911803]
15. Craske MG, Rowe M, Lewin M, Noriega-Dimitri R. Interoceptive exposure versus breathing retraining within cognitive-behavioural therapy for panic disorder with agoraphobia. *Br J Clin Psychol*. 1997; 36(Pt 1):85–99. [PubMed: 9051281]
16. Wald J, Taylor S. Responses to interoceptive exposure in people with posttraumatic stress disorder (PTSD): a preliminary analysis of induced anxiety reactions and trauma memories and their relationship to anxiety sensitivity and PTSD symptom severity. *Cogn Behav Ther*. 2008; 37:90–100. [PubMed: 18470740]
17. Wald J, Taylor S, Chiri LR, Sica C. Posttraumatic stress disorder and chronic pain arising from motor vehicle accidents: efficacy of interoceptive exposure plus trauma-related exposure therapy. *Cogn Behav Ther*. 2010; 39:104–113. [PubMed: 19941177]
18. Craske MG, Wolitzky-Taylor KB, Labus J, Wu S, Frese M, Mayer EA, Naliboff BD. A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. *Behav Res Ther*. 2011; 49:413–421. [PubMed: 21565328]
19. Labus JS, Naliboff BD, Berman SM, Suyenobu B, Vianna EP, Tillisch K, Mayer EA. Brain networks underlying perceptual habituation to repeated aversive visceral stimuli in patients with irritable bowel syndrome. *Neuroimage*. 2009; 47:952–960. [PubMed: 19501173]
20. Critchley HD, Melmed RN, Featherstone E, Mathias CJ, Dolan RJ. Volitional control of autonomic arousal: a functional magnetic resonance study. *Neuroimage*. 2002; 16:909–919. [PubMed: 12202079]
21. Cameron OG, Minoshima S. Regional brain activation due to pharmacologically induced adrenergic interoceptive stimulation in humans. *Psychosom Med*. 2002; 64:851–861. [PubMed: 12461189]
22. Paulus MP, Simmons AN, Fitzpatrick SN, Poterat EG, Van Orden KF, Bauman J, Swain JL. Differential brain activation to angry faces by elite warfighters: neural processing evidence for enhanced threat detection. *PLoS One*. 2010; 5:e10096. [PubMed: 20418943]
23. Paulus MP, Flagan T, Simmons AN, Gillis K, Kotturi S, Thom N, Johnson DC, Van Orden KF, Davenport PW, Swain JL. Subjecting elite athletes to inspiratory breathing load reveals behavioral and neural signatures of optimal performers in extreme environments. *PLoS ONE*. 2012; 7:e29394. [PubMed: 22276111]
24. Simmons AN, Fitzpatrick S, Strigo IA, Poterat EG, Johnson DC, Matthews SC, Orden KF, Swain JL, Paulus MP. Altered insula activation in anticipation of changing emotional states: neural mechanisms underlying cognitive flexibility in Special Operations Forces personnel. *Neuroreport*. 2012; 23:234–239. [PubMed: 22222502]
25. Thom N, Johnson DC, Flagan T, Simmons AN, Kotturi SA, Van Orden KF, Poterat EG, Swain JL, Paulus MP. Detecting emotion in others: increased insula and decreased medial prefrontal cortex activation during emotion processing in elite adventure racers. *Soc Cogn Affect Neurosci*. 2014; 9:225–231. [PubMed: 23171614]
26. Kabat-Zinn, J. *Full Catastrophe Living: The Program of the Stress Reduction Clinic at the University of Massachusetts Medical Center*. New York, Delta: 1990.

27. Lutz A, Brefczynski-Lewis J, Johnstone T, Davidson RJ. Regulation of the neural circuitry of emotion by compassion meditation: effects of meditative expertise. *PLoS One*. 2008; 3:e1897. [PubMed: 18365029]
28. Farb NAS, Segal ZV, Mayberg H, Bean J, McKeon D, Fatima Z, Anderson AK. Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. *Soc Cogn Affect Neurosci*. 2007; 2:313–322. [PubMed: 18985137]
29. Farb NAS, Anderson AK, Mayberg H, Bean J, McKeon D, Segal ZV. Minding one's emotions: mindfulness training alters the neural expression of sadness. *Emotion*. 2010; 10:25–33. [PubMed: 20141299]
30. Brefczynski-Lewis JA, Lutz A, Schaefer HS, Levinson DB, Davidson RJ. Neural correlates of attentional expertise in long-term meditation practitioners. *Proc Natl Acad Sci USA*. 2007; 104:11483–11488. [PubMed: 17596341]
31. Stanley EA, Schaldach JM, Kiyonaga A, Jha AP. Mindfulness-Based Mind Fitness Training: a case study of a high-stress predeployment military cohort. *Cogn Behav Pract*. 2011; 18:566–576.
32. Russo SJ, Murrough JW, Han M-H, Charney DS, Nestler EJ. Neurobiology of resilience. *Nat Neurosci*. 2012; 15:1475–1484. [PubMed: 23064380]
33. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002; 297:400–403. [PubMed: 12130784]
34. Johnson DC, Polusny MA, Erbes CR, King D, King L, Litz BT, Schnurr PP, Friedman M, Pietrzak RH, Southwick SM. Development and initial validation of the Response to Stressful Experiences Scale. *Mil Med*. 2011; 176:161–169. [PubMed: 21366078]
35. Logothetis NK. The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos Trans R Soc Lond B Biol Sci*. 2002; 357:1003–1037. [PubMed: 12217171]
36. Jackson EM, Dishman RK. Cardiorespiratory fitness and laboratory stress: a meta-regression analysis. *Psychophysiology*. 2006; 43:57–72. [PubMed: 16629686]
37. Paulus MP, Potterat EG, Taylor MK, Van Orden KF, Bauman J, Momen N, Padilla GA, Swain JL. A neuroscience approach to optimizing brain resources for human performance in extreme environments. *Neurosci Biobehav Rev*. 2009; 33:1080–1088. [PubMed: 19447132]
38. Lutz J, Herwig U, Opialla S, Hittmeyer A, Jäncke L, Rufer M, Grosse Holtforth M, Brühl AB. Mindfulness and emotion regulation: an fMRI study. *Soc Cogn Affect Neurosci*. Epub ahead of print, May 29, 2013.
39. Paulus MP, Feinstein JS, Castillo G, Simmons AN, Stein MB. Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. *Arch Gen Psychiatry*. 2005; 62:282–288. [PubMed: 15753241]
40. Chang LJ, Yarkoni T, Khaw MW, Sanfey AG. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cereb Cortex*. 2013; 23:739–749. [PubMed: 22437053]

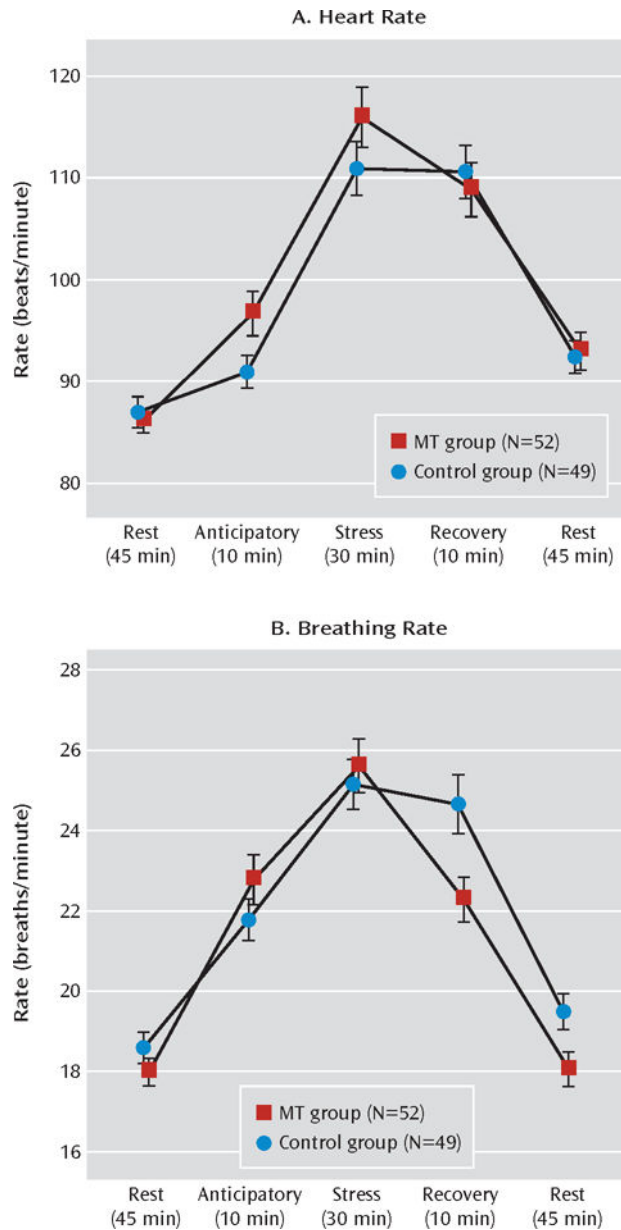


FIGURE 1. Heart and Breathing Rates Before, During, and After a Stressful Immersive Training Session in Marines Receiving Mindfulness Training (MT) or Training as Usual (Control)^a

^aThe stressful immersive training session took place at the Infantry Immersion Trainer facility approximately 9 weeks after baseline. In panel A, heart rate during the 10-minute anticipatory period prior to immersive training was higher for the MT group. Although peak heart rate did not differ between groups during the training, the MT group also showed quicker heart rate recovery during the 10-minute period immediately following stressful training. In panel B, there were no differences between groups in breathing rate during the anticipatory or stress periods. During the 10-minute recovery period, the mean breathing rate for the control group did not significantly differ from peak response; however, the mean breathing rate for the MT group decreased significantly from peak during the stress period

and was significantly lower than the rate for the control group during both the 10-minute recovery and the 45-minute rest period.

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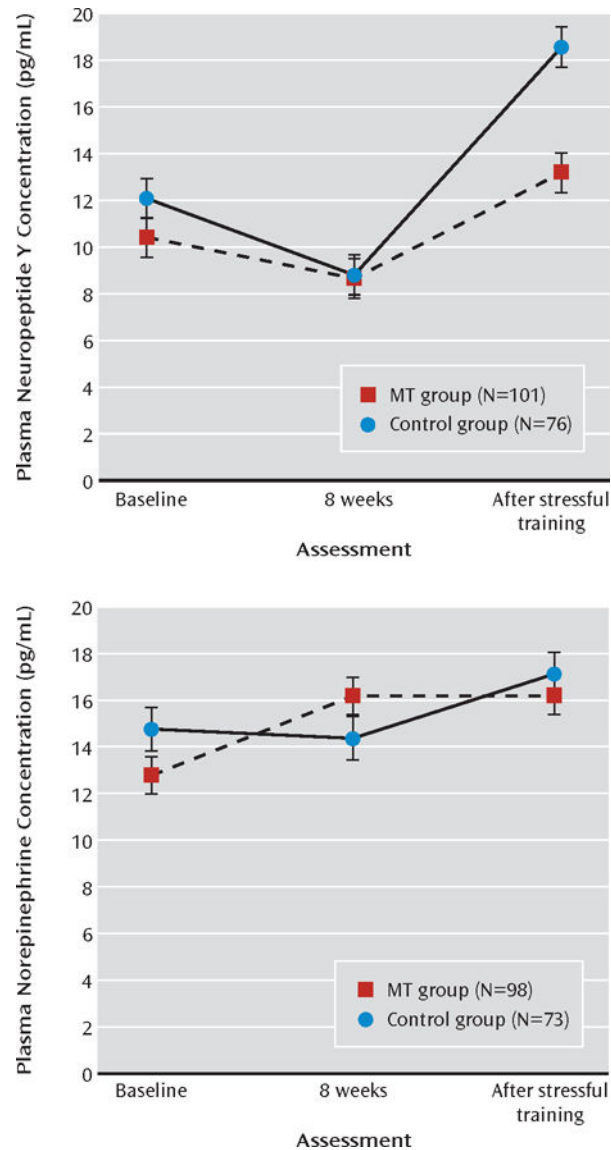


FIGURE 2.

Mean Plasma Neuropeptide Y and Norepinephrine Concentrations in Marines Receiving Mindfulness Training (MT) or Training as Usual (Control)^a

^aNeuropeptide Y and norepinephrine levels are shown for baseline, after 8 weeks, and after a stressful immersive training session at the Infantry Immersion Trainer facility approximately 9 weeks after baseline. For neuropeptide Y, there were no group differences at baseline or at 8 weeks. There was a significant interaction in response to stressful training ($F=4.67$, $df=2$, 350 , $p<0.01$; $d=0.33$), with the control group showing significantly higher levels of neuropeptide Y 45 minutes after stressful training, whereas the MT group had recovered to near baseline levels.

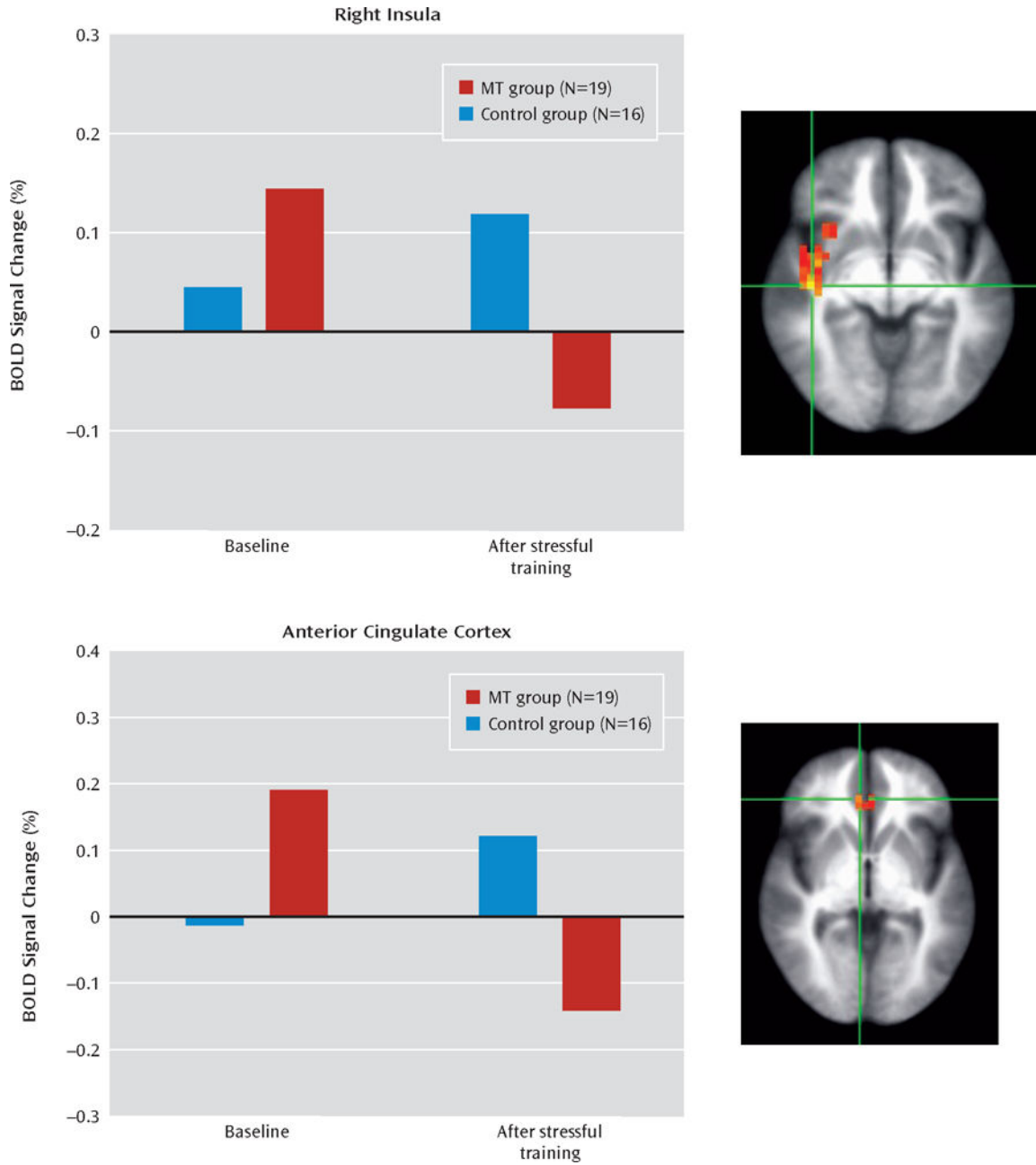


FIGURE 3. Activation of the Right Insula and Anterior Cingulate Cortex During Emotion Recognition in Marines Receiving Mindfulness Training (MT) or Training as Usual (Control)^a
^aFrom the original fMRI subsample of 20 Marines in each group, data from one Marine in the MT group and four in the control group were excluded from analyses because of excessive head-motion artifact at either the baseline or the follow-up assessment (at approximately 10 weeks). Analyses adjusted for baseline differences in sleep quality, combat exposure, and previous training at the Infantry Immersion Trainer facility. Compared with Marines in the control group, those in the MT group showed significantly decreased activation in the right insula and anterior cingulate cortex.

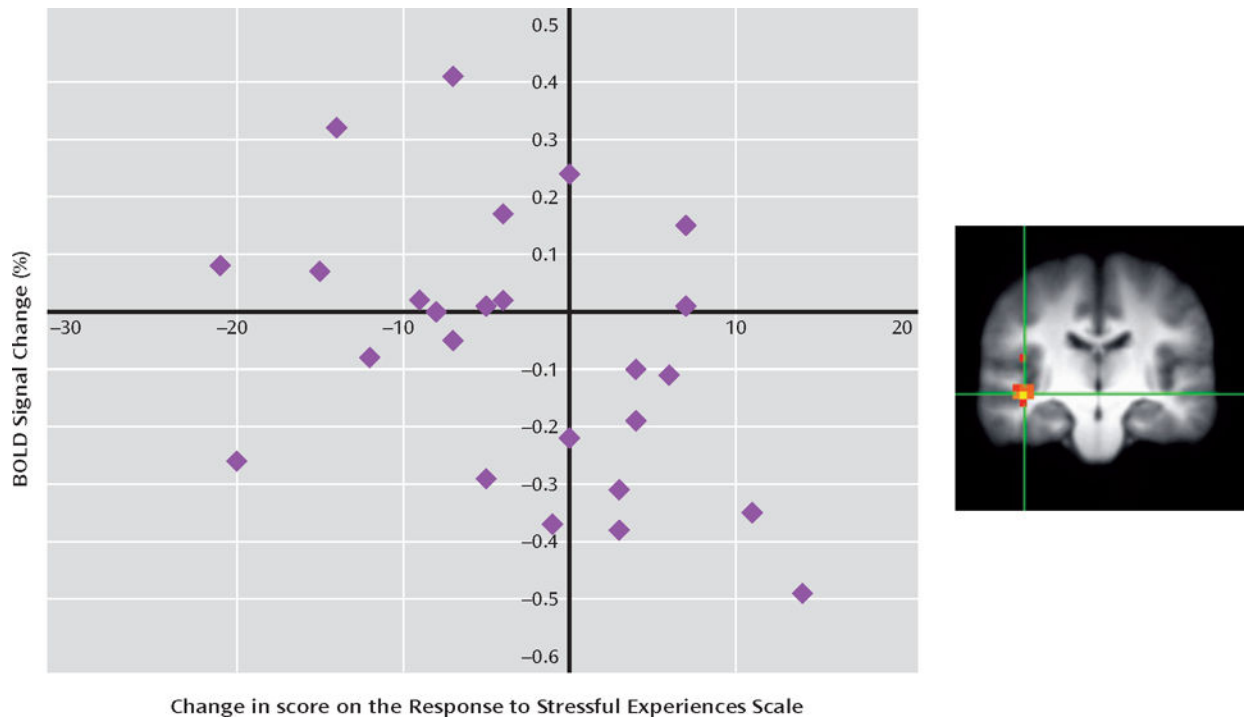


FIGURE 4. Relationship Between Change Score From Baseline to Follow-Up on the Response to Stressful Experiences Scale and Changes in Activation in the Right Anterior Insula (N=25)^a ^afMRI scanning took place at baseline and again approximately 10 weeks later, within 2 weeks after a stressful immersive training session at the Infantry Immersion Trainer. As insula activation decreased from baseline to follow-up, resilience characteristics increased ($r=-0.42$). BOLD=blood-oxygen-level-dependent.

TABLE 1
 Baseline Characteristics of Marines Receiving Mindfulness Training (MT Group) or Training as Usual (Control Group)

Variable	Main Sample				fMRI Subsample ^d			
	MT Group (N=147)	Control Group (N=134)	MT Group (N=19)	Control Group (N=16)	MT Group (N=19)	Control Group (N=16)	MT Group (N=19)	Control Group (N=16)
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	21.7	2.6	21.4	2.5	22.4	3.1	20.9	1.1
Military service (years)	2.7	2.0	2.9	2.2	3.8	3.0	2.5	1.1
Height (inches)	69.8	3.1	69.5	2.8	69.7	3.1	71.3	2.3
Weight (lb)	171.5	19.8	171.8	18.7	168.4	19.3	173.8	16.6
Physical fitness test								
Pull-ups (number completed)	16.3	4.9	16.0	3.9	17.2	4.6	15.1	2.8
Sit-ups (number completed)	101.3	15.7	99.7	8.0	99.3	2.9	100.0	0
3-mile run (minutes) ^b	20.5	1.9	21.2	1.8	20.3	2.0	21.0	1.8
Combat Experiences Scale score	2.7	4.7	2.6	3.7	3.4	5.4	3.9	4.4
Pittsburgh Sleep Quality Index score ^c	8.4	4.0	7.0	3.6	9.8	4.3	6.7	3.6
Response to Stressful Experiences Scale score	65.5	13.5	68.0	12.2	60.1	11.9	66.1	12.7
	N	%	N	%	N	%	N	%
White	103	70	77	61	12	63	11	69
Married ^d	20	14	37	29	1	5	7	44
Associate's degree or higher	13	9	5	4	1	5	0	0
Military occupational specialty: rifleman	139	95	126	96	16	94	16	100
Previous IIT exposure ^e	56	36	68	53	8	47	10	63
Combat experience	49	34	61	47	7	37	10	63
Taking medication	8	5	13	10	3	18	2	13

^a From the original fMRI subsample of 20 Marines in each group, data from one Marine in the MT group and four in the control group were excluded from analyses because of excessive head-motion artifact at either the baseline or the follow-up assessment (at approximately 10 weeks).

^b Significant difference between MT and control groups ($p=0.003$).

^c Significant difference between MT and control groups ($p=0.007$) and between fMRI subgroups ($p=0.03$).

^c Significant difference between MT and control groups ($p=0.002$) and between fMRI subgroups ($p=0.01$).
^d IIT=Infantry Immersion Trainer facility. Significant difference between MT and control groups ($p=0.02$).

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TABLE 2
 Group-by-Time Interaction of Emotion Recognition on Brain Activation in 35 Marines Receiving Mindfulness Training (N=19) or Training as Usual (N=16)^a

Brain Area	Volume (mm ³)	Coordinates			F (maximum)	p (maximum)
		x	y	z		
Right anterior insula	320	-34	-11	-4	6.34	0.03
Right posterior insula	2,178	-41	-10	-4	21.33	0.05
Ventral anterior cingulate	704	-6	-35	0	14.48	0.02
Dorsal anterior cingulate	832	-6	-27	20	13.29	0.04

^aMarines underwent functional MRI (fMRI) scanning at baseline and again approximately 10 weeks later. From the original fMRI subsample of 20 Marines in each group, data from one Marine in the MT group and four in the control group were excluded from analyses because of excessive head-motion artifact at either the baseline or the follow-up assessment. The table summarizes results of fMRI analysis of the linear mixed effects for group-by-time interaction of mindfulness training in Marines during an emotion recognition task. Coordinates are normalized to Talairach space. Analyses controlled for individual differences in baseline sleep quality (as assessed by the Pittsburgh Sleep Quality Index) and combat exposure.

TABLE 3

Summary of Results of Mindfulness Training Compared With Training as Usual in Marines

Domain	Unit of Analysis	Result	Effect Size
Stress physiology	Heart rate	Increased reactivity; greater recovery	d=0.43; d=0.67
	Breathing rate	Greater recovery	d=0.93
Sympathoadrenomedullary	Neuropeptide Y	Decreased	d=0.38
Interoception	fMRI percent signal change	Decreased activation in insula and anterior cingulate gyrus	d=0.92; d=0.86
Resilience	Response to Stressful Experiences Scale	As resilience increased, insula activation decreased	r=-0.42

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