Altered insula activation in anticipation of changing emotional states: neural mechanisms underlying cognitive flexibility in special operations forces personnel

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Introduction

The ability to anticipate and make mental adjustments to changing contexts is central to an adaptive stress response. Cognitive flexibility under stress requires the ability to predict, perceive, and process information not only from external cues but also from contextual cues for internal states such as pain, touch, or emotion [1]. Examination of individuals who function exceptionally well in high-stress situations provides an opportunity to identify neural mechanisms of cognitive flexibility that facilitate optimal performance. Set-shifting, or efficiently moving between opposing task demands, is an indicator of cognitive flexibility. Impaired cognitive flexibility can result from exposure to acute stress and creates vulnerability for the development of stress conditions [2]. In contrast, cognitive flexibility has been associated with the resilience and hardiness seen in military veterans [3,4].

The Committee on Opportunities in Neuroscience for Future Army Applications [5] identified the selection and identification of individuals who can excel in high-stress environments as a topic of great interest to the military and to a broad range of individuals in high-stress situations. Elite warfighters are superior athletes who are trained in, and often exposed to, situations that require extreme physical, mental, and emotional focus. Basic Underwater Demolition/SEAL training for Navy Sea, Air, and Land Forces (SEALs) has gained some notoriety for the extreme demands it places on those who successfully complete the training. Recent work in our group has highlighted the insula as an important situation-specific region in elite Navy SEALs [6]. In this work, Navy SEALs showed selectively greater bilateral insula activation to angry target faces relative to fearful or happy target faces in a face-matching task. This insula hyperactivation was coupled with slower response latencies to fearful and happy target faces but not to angry target faces, suggesting a neurobehavioral correlation of adaptive responding to stimuli that pose a potential threat. The relationship between insula activation and selective attention to threat may relate to the role of the insula in individuals’ experience of emotions [1,7]. The insula has projections through the thalamus from the vagal nerve, making it well placed for interpretation of changes in the internal body state [8]. In related research that considered the vagal tone in healthy participants exposed to high stress, Morgan et al. [9] found that decreased high-frequency variability in heart rate was related to superior performance and emotional regulation, specifically in elite military personnel. These same pathways appear less active in individuals with anxiety and mood disorders as they attempt to modulate their physiology in advance of changing environmental conditions [10,11]. This converging evidence suggests that the insula is part
of a neural network that allows particular individuals to excel in extreme situations.

The insula is critically important for interoception – that is, monitoring the physiological condition of the body, the integration of body state and emotion [12,13], and in anticipatory processing [14–17]. In previous work, we have suggested that optimal performance relates to the capacity of the insula to maintain an interoceptive balance in the presence of significant physiological perturbations [18,19]. Specifically, we have proposed that elite performance depends on the capacity to adapt to changing situations in the most efficacious way such that utilization of resources is situationally determined [6].

In this study, we sought to determine the degree to which elite warfighters, that is, Navy SEALs, would show an optimized capacity for situational adaptation to an anticipatory stressor, as evidenced by more activation in the insula when switching an interoceptive set. To investigate this, we used functional MRI and compared brain activation in off-duty male Navy SEALs relative to that in healthy male volunteers during a performance of an anticipatory anxiety task that specifically assesses brain activation during anticipation of affective set-shifting. Through this work we aim to continue to build a neural model that would provide a signature of elite performance.

**Methods**

**Participants**

All participants provided written informed consent and were interviewed with a structured diagnostic interview [20]. Only healthy participants who did not meet the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria for posttraumatic stress disorder (PTSD) were included in this study. Ten Navy SEALs (age, 28.7 ± 4.2) and 11 age-matched healthy male volunteers (age, 26.1 ± 2.7, t(19) = 1.705, P = 0.104) performed the anticipatory anxiety task in the scanner. This study was approved by the internal review board of the University of California, San Diego.

**Task**

In this task, participants were asked to press the left button when they saw a circle and the right button when they saw a square. Shapes were presented every 2 s, simultaneously with a short 500 Hz tone. Impending positive images were signaled by green shapes and a 250 Hz tone. Negative images were signaled by red shapes and a 1000 Hz tone. Seventeen positive images were taken from the International Affective Picture System, and 17 negative images were selected that displayed individuals in combat situations without graphic violence or open wounds.

There were 17 instances when anticipatory periods were preceded by a condition of a matched valence – that is, nonshifting trials (e.g., positive anticipation followed by positive anticipation or negative anticipation followed by negative anticipation) – and 16 instances when anticipatory periods were preceded by a condition of an opposite valence – that is, affective set-shifting trials (e.g., positive anticipation followed by negative anticipation or negative anticipation followed by positive anticipation). As positive-to-negative and negative-to-positive set-shifting required the same theoretical distance of regulation in the interoceptive state, they were combined to maximize detection power, as we have done before [10,11].

Behavioral data were collected and scored for accuracy and latency of response during the continuous performance task (CPT). Task performance was compared between the groups for: (a) baseline CPT (blue shapes), (b) positive-anticipation CPT (green shapes), (c) negative-anticipation CPT (red shapes), (d) set-shifting CPT (change from green to red shapes and vice versa), and (e) nonshifting CPT (change from green to green and from red to red shapes). No response from participants was required when a picture stimulus was presented on the screen.

**Analysis**

**Acquisition of images**

All scans were performed on a 3 T GE scanner (General Electric Medical Systems Inc., Waukasha, Wisconsin, USA). Each session consisted of a spoiled gradient recalled sequence (field of view = 25 cm; matrix = 192 × 256; 172 × 1 mm sagittal slices; time of repetition = 8 ms; time of echo = 3 ms; flip angle = 12°) and a T2*-weighted echoplanar image (EPIs; field of view = 23 cm, matrix = 64 × 64; 30 × 2.6 mm axial slices with 1.4 mm gap; time of repetition = 2000 ms; time of echo = 32 ms; flip angle = 90°).

**Image processing (shared)**

Structural and functional image processing was carried out using the Analysis of Functional Neuroimages (AFNI) software package (http://afni.nimh.nih.gov/afni). EPIs were coregistered using a three-dimensional coregistration algorithm that has been developed to minimize the amount of image translation and rotation relative to all other images. All slices of the EPI scans were temporally aligned following registration. The multivariate regressor approach detailed below was used to relate changes in EPI intensity to differences in task characteristics.

**Anticipation regressors**

The task behaviors were modeled using the four regressors of no interest: (a) anticipation of a positive image, (b) anticipation of a negative image, (c) the positive image phase, and (d) the negative image phase (for results see Supplementary Table 2, Supplemental digital content 1, http://links.lww.com/WNR/A173).

**Set-shifting regressors**

Nonshifting trials were not regressed as the combination of shift and nonshift would create colinear matrices once...
the task regressors were included. The four anticipation regressors were entered in addition to control for main effects of anticipation.

**Regression analysis (shared)**

In addition, six more nuisance regressors were entered into the linear regression model: three movement-related regressors used to account for residual motion (in the roll, pitch, and yaw direction), a white matter regressor, and regressors for baseline and linear trends used to eliminate slow signal drifts. Percentage signal change of contrasts of interest in both analyses was calculated by dividing the $\beta$-weight for the regressor of interest by the baseline $\beta$-weight. A Gaussian filter with full-width at half-maximum 6 mm was applied to the voxel-wise percentage signal change data to account for individual variations in the anatomical landmarks.

Data from each participant were normalized to the Talairach coordinates as defined by preexisting atlases. Voxel-wise percentage signal change data for the whole brain were analyzed using two-sample $t$-tests contrasting SEALs and healthy controls. A threshold adjustment method based on Monte-Carlo simulations was used to guard against identifying false-positive areas of activation [21]. A priori voxel-wise probability of $P$ less than 0.05 in a cluster of 1408 $m^3$ resulted in an a posteriori probability of $P$ less than 0.05. Finally, the average percentage signal difference was extracted from regions of activation that were found to survive this threshold/cluster method. Second level analyses were carried out using the Analysis of Functional Neuroimages or statistiXL (Nedlands, Western Australia, Australia). As set-shifting is still a relatively novel analysis, the effects of task in the combined group are also presented to draw a parallel with our previous work [10].

**Results**

**Behavioral results**

Two repeated-measures analysis of variance with set-shifting condition as a repeated factor (set-shifting, nonshifting) and group as a between-participants factor for (a) latency and (b) accuracy of responses were used to inspect behavioral performance during set-shifting compared with nonshifting trials. There was a significant slowing down during set-shifting anticipatory trials in contrast to nonshifting trials [$F(1,16) = 6.319, P = 0.024$] that occurred primarily in the control group, leading to a significant group-by-task interaction [$F(1,16) = 9.710, P = 0.007$]. There were no significant task [$F(2,15) = 1.434, P = 0.269$], group [$F(1,16) = 0.349, P = 0.563$], or group-by-task differences [$F(2,15) = 0.920,$]

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**Fig. 1**

Brain activation in SEALs versus healthy controls for the (a) task effect (aversive to nonaversive) and (b) group contrast during aversive anticipation task.
Anticipatory group effect

The SEALs showed less activation in the right insula [cluster volume (cm³); centroid at x/y/z: 3584/35/–20/10], left medial frontal gyrus (8064;–8/46/35), left middle occipital gyrus (5184;–22/–49/10), left middle frontal gyrus (3904;–44/7/40), and right cingulate gyrus (2304;22/6/22) compared with healthy controls for the negative-anticipation versus positive-anticipation condition. No significant clusters were found where SEALs activated more for this contrast (Fig. 1).

Set-shifting task effect

When we investigated the blood-oxygen-level dependent response during affective set-shifting in the combined group, the right insula (2432;–29/–86/–7), the left cuneus (2432;–3/–88/14), and the left lingual gyrus (1728;–14/–93/–5) showed more activation, whereas the bilateral medial frontal gyrus (15872;13/57/3 and 2368;–14/4/51), the right paracentral lobule (3392;15/–33/50), the left cerebellum (2688;–1/–48/4), the left thalamus (2048;–8/–18/7), and the left middle frontal gyrus (1792;–32/57/7) showed less activation during set-shifting trials (Fig. 1).

Set-shifting group effect

When we compared blood-oxygen-level dependent response during the affective set-shifting between the groups, the right insula (2624;50/3/43), the right cingulate gyrus (2880;8/3/43), the bilateral parietal lobule (1984;–43/–44/29), and the bilateral middle frontal gyrus (1536;29/35/28 and 1536;–31/–6/40) showed more activation in SEALs compared with healthy control participants. There were no regions in which SEALs showed significantly less activation (Fig. 2b).

Brain–behavior relationships

After controlling for multiple comparisons, no significant correlations between the degree of activation to affective set-shifting and either response latency or response accuracy were observed in the SEAL group.
Discussion
The primary finding in this study is that Navy SEALs activated the middle insula and bilateral frontal lobes more during shifting of anticipatory valence compared with healthy participants. This suggests that, rather than being reactive to anticipatory stressors, Navy SEALs show more engagement of brain systems involved in modulating emotional and interoceptive processing when they are aware of a change in the anticipated situation. These findings provide further evidence that elite warfighters show neural tuning such that energy is expended on adaptation to new changes in their environment. Taken in conjunction with previous work displaying neurophysiological inertia in PTSD [10] and depression [11], as well as increased neural tuning [6] and vagal suppression [9] in Navy SEALs, the current results forward the notion that elite warfighters may be able to reduce the impact of previous events through modulation of their physiological homeostasis. Potentially, this capacity may indicate how and why these elite performers are capable of pushing themselves physically and emotionally beyond the capacities of others.

In our recently published work, we hypothesized that Navy SEALs would show a unique ability to adapt to changes in their environment in a modulatory way [6]. This neural tuning, or capacity to show directed rather than global energy expenditures, may be a key aspect that allows them to perform at a high level. This hypothesis of neural tuning and directed physiology would suggest that these individuals would be likely to use information before a stimulus to optimize the integration of physiological information, and thus they would use set-shifting cues to appropriately modulate their neurophysiology. Such tuning mechanisms seem to be absent or impaired in individuals with PTSD and major depressive disorder (MDD) [10,11].

In two previous studies investigating the neurophysiology of anticipatory affective set-shifting, we found that such set-shifting engaged the right anterior insula and prefrontal cortices. In addition, those with PTSD or MDD showed a marked and specific decrease in their response within the right insula [10,11]. This finding was consistent across populations (PTSD vs. MDD) and stimuli (images vs. pain). We conceptualized a potential mechanism in which distressed individuals were highly reactive, showing increased anticipatory activation [17,22]. Increased emotional reactivity subsequently hindered modulation of the insula in response to the conditional shift. In contrast, frontal systems that are less subservient to homeostatic demands could adapt more rapidly. We choose to replicate these findings in the current sample because of our prior evidence that Navy SEALs should be more capable of discrete efficacious interoceptive focus [6]. Although this initial study is in a small sample and needs replication, we successfully confirmed the hypothesis that Navy SEALs displayed less activation to aversive anticipation in insula and more insula activation to situational interoceptive shifts. This study highlights the insula as an important region for neurophysiological tuning. Of specific relevance is the role of insula in emotional [23] and anticipatory processing [16,24]. These models would predict that the insula, which is part of the interoceptive network, would have an important role in interoceptive modulation in this anticipatory set-shifting analysis.

This study further extends work on optimal performance and on Navy SEALs in particular and suggests that optimal performance is achieved through discrete focus of attention – potentially facilitated by greater physiological control. The capacity to quickly and effectively shift interoceptive state during the anticipation of a changing stimulus allows elite performers to respond rapidly with minimal interference from immediately prior experiences. The ultimate goal of these studies is to better understand the role of these circuits to develop more targeted training interventions that further improve performance in extreme environments.

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Conflicts of interest
There are no conflicts of interest.

References