Human Bed Nucleus of the Stria Terminalis Indexes Hypervigilant Threat Monitoring

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Background: Though a key symptom underlying many anxiety disorders is hypervigilant threat monitoring, its biological bases in humans remain poorly understood. Animal models suggest that anxious processes such as hypervigilant threat monitoring are distinct from cued fear-like responses and mediated by the bed nucleus of the stria terminalis (BNST). Here, we applied psychophysiological and neuroimaging methodologies sensitive to sustained arousal-based responses to test the role of the human BNST in mediating environmental threat monitoring, a potential experimental model for sustained anxiety symptoms.

Methods: Healthy participants ($n = 50$) with varying trait anxiety performed an environmental threat-monitoring task during functional magnetic resonance imaging where a stimulus line continuously fluctuated in height, providing information relevant to subsequent risk for electric shocks. Skin conductance was collected in a separate cohort ($n = 47$) to validate task-evoked modulation of physiological arousal.

Results: A forebrain region consistent with the BNST showed greater overall recruitment and exaggerated tracking of threat proximity in individuals with greater anxiety. The insular cortex tracked threat proximity across all participants, showed exaggerated threat proximity responding with greater anxiety, and showed enhanced recruitment when threat proximity was ostensibly controllable.

Conclusions: Activity in the BNST and insula continuously monitored changes in environmental threat level and also subserved hypervigilant threat-monitoring processes in more highly trait anxious individuals. These findings bridge human and animal research informing the role of the BNST in anxious-related processes. In addition, these findings suggest that continuous functional magnetic resonance imaging paradigms offer promise in further elucidating the neural circuitries supporting sustained anticipatory features of anxiety.

Key Words: Anxiety, bed nucleus of stria terminalis, emotion, fMRI, insula, vigilance

A primary aspect of anxious behavior, and a key symptom of anxiety disorders, is chronic, nonspecific apprehension and arousal related to the potential occurrence of future threats (1,2). In clinical populations, levels of apprehension are often inappropriate given environmental demands, leading to tension, worry, behavioral impairments, and distress (3,4). Anxious apprehension is distinct from exaggerated cue-evoked responses to potential threats such as a phobic individual encountering their most feared stimulus (5,6). Such cued responses are triggered readily and exaggerated in magnitude but tend to subside over time when the fear-evoking stimulus is no longer present. Anxious apprehension, by contrast, can fluctuate in magnitude over an extended time scale and be triggered in the absence of discrete, fear-evoking cues. One manifestation of anxious apprehension is hypervigilance, defined as an enhanced state of arousal and readiness to deal with potential threats, often accompanied by negative affect states and activation of the autonomic nervous system (7). Psychologically, hypervigilance is characterized by heightened monitoring of the environment for cues related to one's future level of threat or safety (8,9).

Seminal work using the animal model has dissociated profiles of transient and sustained threat processing that map onto the constructs of fear and anxiety (10,11). In rodents, the presence of an unambiguous, proximal predator elicits the classically characterized fear response (12,13). As the distance from a predator increases or if the predator's presence is ambiguous, these discrete behaviors give way to sustained risk assessment and vigilance (12). Neurobiologically, cued threat processing is initiated by the amygdala, whereas sustained vigilance associated with ambiguous or distant threat cues is represented by tonic engagement of the bed nucleus of the stria terminalis (BNST), a ventral basal forebrain structure located superior, medial, and rostral to the amygdala (11,14–18). Recently, elevated resting metabolism within the BNST has been identified to mediate trait anxious temperament in primates (19,20) and BNST lesions disrupt individual variability in rodent anxiety-like behavior (21). Taken together, these data motivate the hypothesis that the neurobiological bases of hypervigilant threat monitoring in humans may also be more BNST-dependent and less amygdala-dependent, distinguishing this form of affective processing from the extensive literature implicating the amygdala in cued responses to discrete threats.

Presently, human neuroimaging experiments poised to inform our understanding of hypervigilant threat monitoring are rare, as most experimental paradigms evaluate responses to discrete stimuli. Meta-analyses have identified a network of brain regions including the amygdala, insular cortex, medial prefrontal cortex, and anterior cingulate that are consistently engaged while processing discrete affective cues including facial expressions, negative images, and conditioned stimuli (22,23). Additionally, individuals with anxiety disorders elicit exaggerated responses in several of these regions when encountering discrete affective cues (24,25).

By contrast, we developed a task in which arousal is continuously modulated along temporally slow parameters while subjects monitor the environment for cues signaling risk for a forthcoming aversive event. During functional magnetic resonance imaging (fMRI) scanning and skin conductance recording, participants viewed a stimulus line that fluctuated in height, and if the line exceeded a marked threshold, they would accumulate an electric shock that they believed would be administered later. This rendered the experiment free of cued, transient affective

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events. Variation in the height of the line comprised a dynamic representation of future environmental threat level, validated with skin conductance data to evoke greater arousal with increasing proximity to the shock threshold. We targeted the ventral basal forebrain (VBF), which includes the human BNST, to test whether responses increased with greater threat level and were biased toward exaggerated activity in anxious individuals. Finally, we assessed whether controllability modulated these effects (17,26) by including one condition where participants believed the line represented their physiological responding and a second line was thought to be outside of their volitional control.

Methods and Materials

Participants

One hundred seven subjects participated in one of two experiments. Forty-eight subjects underwent skin conductance recording and 59 separate subjects completed fMRI scanning. In the fMRI sample, seven participants were excluded for movement exceeding 2 mm and/or signal artifacts, and two participants were excluded for suspicion of the cover story (disbelief they could be shocked), leaving a final sample of $n = 50$ (22 male participants, mean age = 19.1). One participant from the skin conductance sample was excluded due to suspicion of the cover story, leaving a final sample of $n = 47$ (22 male participants, mean age = 18.9). Setup, recording, and analysis of the skin conductance sample are reported in Supplement 1. This research was conducted in accordance with guidelines of the Committee for the Protection of Human Subjects at Dartmouth College and all participants provided informed written consent.

Prescreening

Participants were verified to be absent of clinically diagnosable levels of current anxiety disorders and current or past mood disorders using the Structured Clinical Interview for DSM-IV Axis I Disorders (27) and no participant was using psychotropic medications. The potential for covarying mood effects was minimized by excluding any participant scoring greater than 10 on the Beck Depression Inventory (28). The fMRI participants reported no abnormal neurological history, were native speakers of English, and were verified right-handed with the Edinburgh Handedness Inventory (29).

Anxiety Characterization

Participants completed several self-report indexes including the Spielberger State-Trait Anxiety Inventory (30), Behavioral Inhibition/Activation Scale (31), NEO Personality Inventory Neuroticism and Extraversion subscales (32), Intolerance of Uncertainty (33), Penn State Worry Questionnaire (34), Anxiety Symptom Index (35), and Beck Depression Inventory (28). It was reasoned that several scales assessing a range of anxiety symptoms would more comprehensively represent participants' general anxiety level than any scale alone. When evaluating the range of anxiety scores against population norms using the Spielberger State-Trait Anxiety Inventory Trait scale (30), scores in the fMRI cohort ranged from the 1st to 85th percentile with a mean percentile of 39 (SD = 22.7; median = 38) and the galvanic skin response (GSR) cohort ranged from the 1st to 99th percentile with a mean percentile of 38 (SD = 27.56; median = 40). A principal components analysis was conducted with standard parameters (36), inputting self-report measures, to identify latent metavariables representing general anxiety. Results identified two factors (Table S1 in Supplement 1). Scales indexing general anxiety loaded on the first factor, which explained 45.13% of variance in the overall dataset. Component scores were extracted and used as a single representation of participants' dispositional anxiety in subsequent analyses. The second factor explained 13.3% of variance representing extraversion and was not analyzed further.

Task

During fMRI scanning, participants viewed videos of a line fluctuating in height over time, which they believed represented either their own real-time physiological state (self line [SELF]), ostensibly recorded via a pulse oximeter attached to their finger (Supplementary Methods in Supplement 1 for details regarding stimuli and setup). To test for effects of whether the threat was supposedly controllable, we included a passive line-viewing condition where subjects ostensibly viewed a prerecorded physiological time course of another subject who had previously completed the experiment (other line [OTHER]). Lines were, in fact, created by experimenters but appeared to resemble physiological responses using actual recording software (Figure S1 in Supplement 1). For both conditions, participants were instructed they would accumulate electric shocks that would be delivered after the task whenever the line exceeded a certain threshold (horizontal blue line). An updated tally of the number of accumulated shocks was viewable on the right side of the screen (Figure 1).

Participants were instructed that during one scan (SELF), they would passively view their own physiological responses in real time and should try to stay calm and avoid accumulating shocks. When viewing the other line (OTHER), they were to passively view the other person's performance, realizing that any shocks accrued by the prior subject would also be delivered at the conclusion of the experiment. To circumvent the use of discrete threat, we stated that we would measure how much time they spent above the blue line and would give them the shocks they

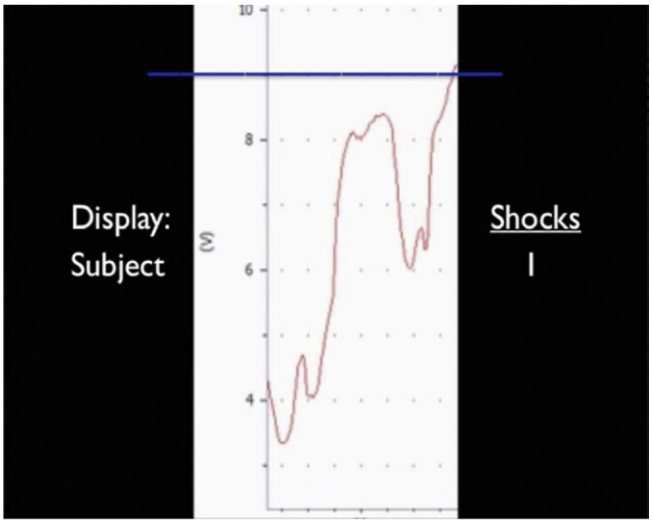

Figure 1. Representative screenshot of task stimulus. Stimuli consisted of a fluctuating line (red) that continuously advanced across the screen from right to left. The stationary blue line represented the height above which participants would accumulate an electric shock to be delivered later. On the right is a continuous tally of how many shocks had been accumulated. On the left is a label of whether the presented ostensibly represented the participant's own internal state information (Subject) or a prerecording of another individual's internal state information (Other), which the participant was to passively view.