Neuroticism/negative emotionality is associated with increased reactivity to uncertain threat in the bed nucleus of the stria terminalis, not the amygdala

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AUTHOR CONTRIBUTIONS

A.J.S., K.A.D., and J.F.S. designed the overall study. S.E.G. and A.J.S. envisioned the present project. J.F.S. and A.J.S. developed and optimized the imaging paradigm. K.A.D. managed data collection and study administration. K.A.D., J.F.S., A.S.A, S.I., and R.M.T. collected data. J.F.S. and M.K. developed data processing and analytic software for imaging analyses. J.H., J.F.S., H.C.K., and R.M.T. processed imaging data. S.E.G., J.F.S., and A.J.S. analyzed data. S.E.G., M.G.B., and A.J.S. developed the analytic strategy. S.E.G., A.S.F., J.F.S., and A.J.S. interpreted data. S.E.G. and A.J.S. wrote the paper. S.E.G. created figures and tables. A.J.S. funded and supervised all aspects of the study. All authors contributed to reviewing and revising the paper and approved the final version.

PREREGISTRATION

Our general approach and hypotheses were preregistered (https://osf.io/wzhdm).

RESOURCE SHARING

Raw data and select materials are publicly available at the National Institute of Mental Health Data Archive (https://nda.nih.gov/edit_collection.html?id=2447). Processed data are available at the Open Science Framework (https://osf.io/w5cdk). Key neuroimaging maps are available at NeuroVault.Org (https://neurovault.org/collections/13109).

ABSTRACT

Neuroticism/Negative Emotionality (N/NE)—the tendency to experience and express more frequent, intense, or persistent negative affect—is a fundamental dimension of childhood temperament and adult personality, with profound consequences for health, wealth, and wellbeing. Elevated N/NE is associated with a panoply of adverse outcomes, from reduced socioeconomic attainment and divorce to mental illness and premature death. Yet our understanding of the underlying neurobiology remains surprisingly speculative. Work in animals suggests that N/NE reflects heightened reactivity to uncertain threat in the central extended amygdala (EAc)—including the central nucleus of the amygdala (Ce) and bed nucleus of the stria terminalis (BST)—but the relevance of these discoveries to the complexities of the human brain and temperament have remained unclear. Here we used a combination of psychometric, psychophysiological, and neuroimaging approaches to understand the relevance of the EAc to individual differences in N/NE in a racially diverse sample of adults selectively recruited to capture a broad spectrum of N/NE. A series of cross-validated, robust regression analyses demonstrated that trait-like individual differences in N/NE are uniquely associated with heightened BST activation during the uncertain anticipation of a genuinely distressing threat. In contrast, N/NE was unrelated to BST activation during the certain anticipation of threat, Ce activation during the anticipation of either threat, or activation in either region during the presentation of threat-related faces. While the BST is often associated with anxiety, analyses showed that heightened BST reactivity to uncertain threat is broadly associated with the internalizing facets of N/NE, including depression. Implicit in much of the neuroimaging literature is the assumption that different threat paradigms are quasi-interchangeable probes of individual differences in circuit function, yet our analyses revealed negligible evidence of convergence between popular threat-anticipation and threat-perception (emotional faces) tasks in the EAc. These observations provide a framework for conceptualizing emotional traits and the development of emotional disorders; for guiding the design and interpretation of biobank and other neuroimaging studies of psychiatric risk, disease, and treatment; and for informing mechanistic research in humans and animals.

INTRODUCTION

Neuroticism/Negative Emotionality (N/NE)—the tendency to experience and express more intense, persistent, or frequent negative affect—is a fundamental dimension of childhood temperament and adult personality with profound consequences for health, wealth, and wellbeing[1,2]. Individuals with a more negative disposition show diminished socioeconomic attainment[3-6]. They are more likely to experience interpersonal conflict, unemployment, and divorce; to have difficulty adjusting to major life transitions; to feel lonely, dissatisfied, and burned out; to engage in unhealthy behaviors; to develop chronic disease; to be hospitalized; and to die prematurely[3,4,7-18]. The deleterious consequences of N/NE are especially robust in the sphere of mental health[19]. Individuals with a negative disposition are more likely to develop pathological anxiety and depression; and, among those who do, to experience more severe, recurrent, and treatment-resistant symptoms[13,20-32]. Despite this burden, the neural systems underlying variation in this risk-conferring phenotype remain incompletely understood, impeding the development of more effective or tolerable biological interventions.

It is widely believed that N/NE reflects a neurobiological tendency to overreact to novelty, threat, and other 'trait-relevant' challenges, increasing the likelihood or intensity of distress, arousal, and defensive behaviors when stressors or potential threats are encountered[33-37]. While a number of neural systems have been implicated[1,38,39], the central extended amygdala (EAc) has received the most empirical scrutiny and occupies a privileged position in most theoretical models of N/NE[3,40,41]. The EAc is a neuroanatomical macrocircuit encompassing the dorsal amygdala in the region of the central nucleus (Ce) and the neighboring bed nucleus of the stria terminalis (BST)[42]. Mechanistic studies demonstrate that the EAc is critical for orchestrating adaptive defensive responses to a wide variety of threats in rodents, monkeys, and humans[3,43]. Neuroimaging studies in monkeys show that Ce and BST reactivity to uncertain threat

covaries with trait-like variation in anxious temperament and behavioral inhibition, core biobehavioral facets of N/NE[44,45]. But the relevance of these discoveries to the complexities of the human brain and temperament remains unclear. In stark contrast to animal studies, only a handful of human neuroimaging studies have used genuinely distress-eliciting threats to examine relations between N/NE and EAc function and nearly all have focused exclusively on the amygdala proper (**Table S1**). Studies focused on the acute presentation of aversive photographs and Pavlovian threat cues have yielded inconsistent results. Even less is known about the BST, the other major division of the EAc. Only one small-scale (*N*=50) study has directly addressed this question, providing preliminary evidence that individuals with a more negative disposition show heightened BST activation during the uncertain anticipation of aversive stimulation[46]. Although modest sample sizes, limited neuroanatomical resolution, and a lack of attention to the BST preclude decisive inferences, these observations motivate the hypothesis that N/NE reflects heightened recruitment of the BST, and possibly the dorsal amygdala (Ce), during the anticipation of aversive stimulation and suggest that these associations may be more pronounced when threat is uncertain in timing or likelihood.

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Study	*N* (% Male)	Neuroticism/Negative Emotionality (N/NE)	MRI Field Strength (T)	EPI Voxel Size (mm^3)	Normalization[a]	Trait-Relevant Challenge(s)	Analysis Type	Summary of EAc Results
Present Study	220 (49.5%), stratified sampling to capture a broad spectrum of N/NE; screened to exclude current internalizing illness	Multi-Scale, Multi-Occasion Composite	3	10.5	BBR and Diffeomorphic	Anticipation of Uncertain/Certain Aversive Shock, Auditory Clips, and Photographs; Negative Emotional Faces vs. Place Scenes	ROIs, Voxelwise	See the main report
Brinkmann et al., 2018[47]	93 (35.5%), screened to exclude any internalizing illness in the past five years	STAI	3	15.3	Affine and Manual TT	Aversive Photographs	NR	***NS***
Indovina et al., 2011[48]	23 (43.5%), screened to exclude lifetime internalizing illness	STAI	3	18.0	"SPM5"	Pavlovian Threat Cue (Auditory UCS; Uninstructed)	Amygdala ROI	***Positive relations*** *between the magnitude of amygdala reactivity and N/NE*
Kirlic et al., 2019[49]	83 (42.2%), 43 of whom had depression or anxiety disorder diagnoses	Multi-Scale Composite	3	18.1	"AFNI" and Diffeomorphic	Anticipation of Uncertain Shock	Voxelwise	***NS***
Klumpers et al., 2017[50]	108 (100%), screened to exclude lifetime internalizing illness	STAI	1.5	38.1	"SPM8"	Anticipation of Uncertain Shock	Amygdala and BST ROIs	***NS***
Schuyler et al., 2012[51]	127 (36.2%), screened to exclude past-year internalizing illness	BFI-N	3	56.25	Affine	Aversive Photographs	Amygdala fROI	***Positive relations*** *between the persistence of amygdala reactivity and N/NE*
Sjouwerman et al., 2020[52]	113 (61.1%), screened to exclude lifetime internalizing illness	STAI	3	8.0	"SPM8"	Pavlovian Threat Cue (Shock UCS; Uninstructed)	Amygdala SVC	***Positive relations*** *between amygdala reactivity and N/NE*
Somerville et al., 2010[46]	50 (44%), screened to exclude lifetime internalizing illness	Multi-Scale Composite	3	31.5	"SPM2"	Anticipation of Uncertain Shock	Amygdala and BST fROIs, Voxelwise	***Positive relations*** *between the magnitude of BST reactivity and N/NE* ***NS Amygdala***
Visser et al., 2021[53]	98 (30.6%), screened to exclude lifetime internalizing illness	STAI	3	8.0	BBR and Diffeomorphic	Pavlovian Threat Cue (Shock UCS; Uninstructed)	Amygdala SVC	***NS Amygdala***

Supplementary Table S1. Human studies of N/NE and distress-eliciting neuroimaging paradigms. [a]Older normalization techniques (e.g., affine) can introduce substantial spatial smoothing and registration error, which is a concern for work focused on small subcortical structures, such as the Ce and BST. Abbreviations—AFNI, Analysis of Functional NeuroImages software package; BBR, boundary-based registration of the T1- and T2-weighted images; EAc, central extended amygdala; fROI, functionally defined region-of-interest (all others are anatomically defined); NEO-FFI, Neuroticism/Extraversion/Openness Five-Factor Inventory-3; NR, not reported or indeterminate; NS, not significant; SPM#, Statistical Parametric Mapping software package (# indicates version); STAI, Spielberger State-Trait Anxiety Inventory; SVC, Small-Volume Corrected; TT, piecewise linear Talairach-Tournoux transformation; UCS, Unconditioned Stimulus.

Here we used fMRI to quantify EAc reactivity to the Maryland Threat Countdown task—a well-established and genuinely distressing threat-anticipation paradigm—and test its relevance to variation in N/NE in a racially diverse (38.6% BIPOC) sample of 220 emerging adults (**Figure 1** and **Figure S1**). A best-practices fMRI pipeline and spatially unsmoothed data enhanced our ability to resolve the Ce and BST relative to earlier studies (**Table S1**). Participants were selectively recruited from a pool of 6,594 pre-screened individuals, ensuring a broad spectrum of N/NE and addressing a key limitation of prior work focused on self-selected convenience samples[54]. We focused on 'emerging adulthood' because it is a time of profound, often stressful transitions[55]. Indeed, more than half of undergraduate students report moderate-to-severe symptoms of anxiety and depression, with many experiencing the first emergence or recurrence of frank internalizing illness (pathological anxiety or depression) during this turbulent developmental chapter[56-58]. Prior neuroimaging studies of N/NE have relied on analytic approaches that produce overly optimistic estimates of brain-phenotype association[59]. Here we instead rely on *a priori* anatomically defined EAc (Ce and BST) regions-of-interest (ROIs) and cross-validated robust estimates of brain-temperament associations (**Figure 1**). To further enhance power, we used a composite measure of N/NE—aggregated across two scales and three measurement occasions—minimizing state-like fluctuations in responding ('noise') that can attenuate brain-phenotype associations (**Figure S2**)[60,61]. Study hypotheses and general approach were pre-registered as a further guard against questionable research practices[62].

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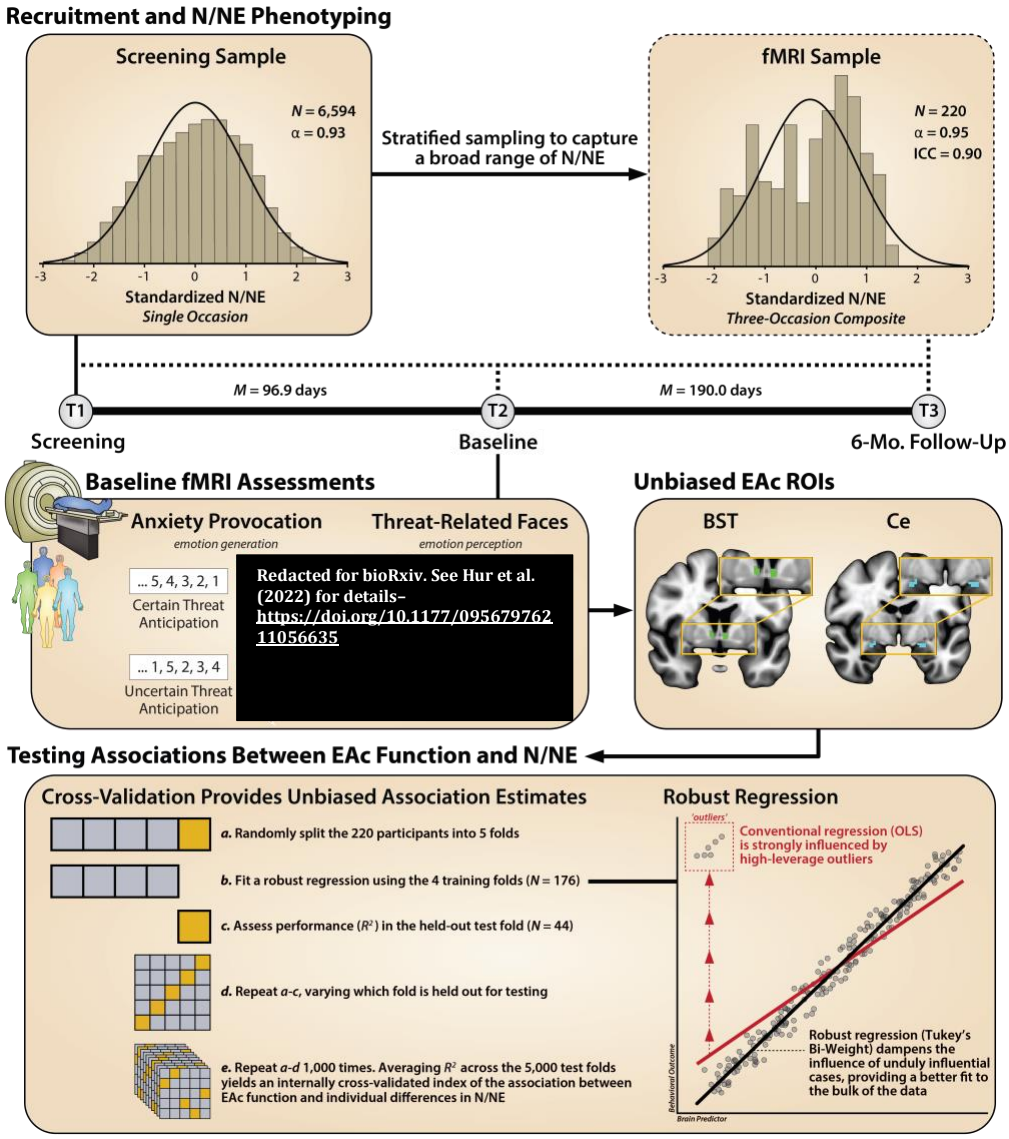
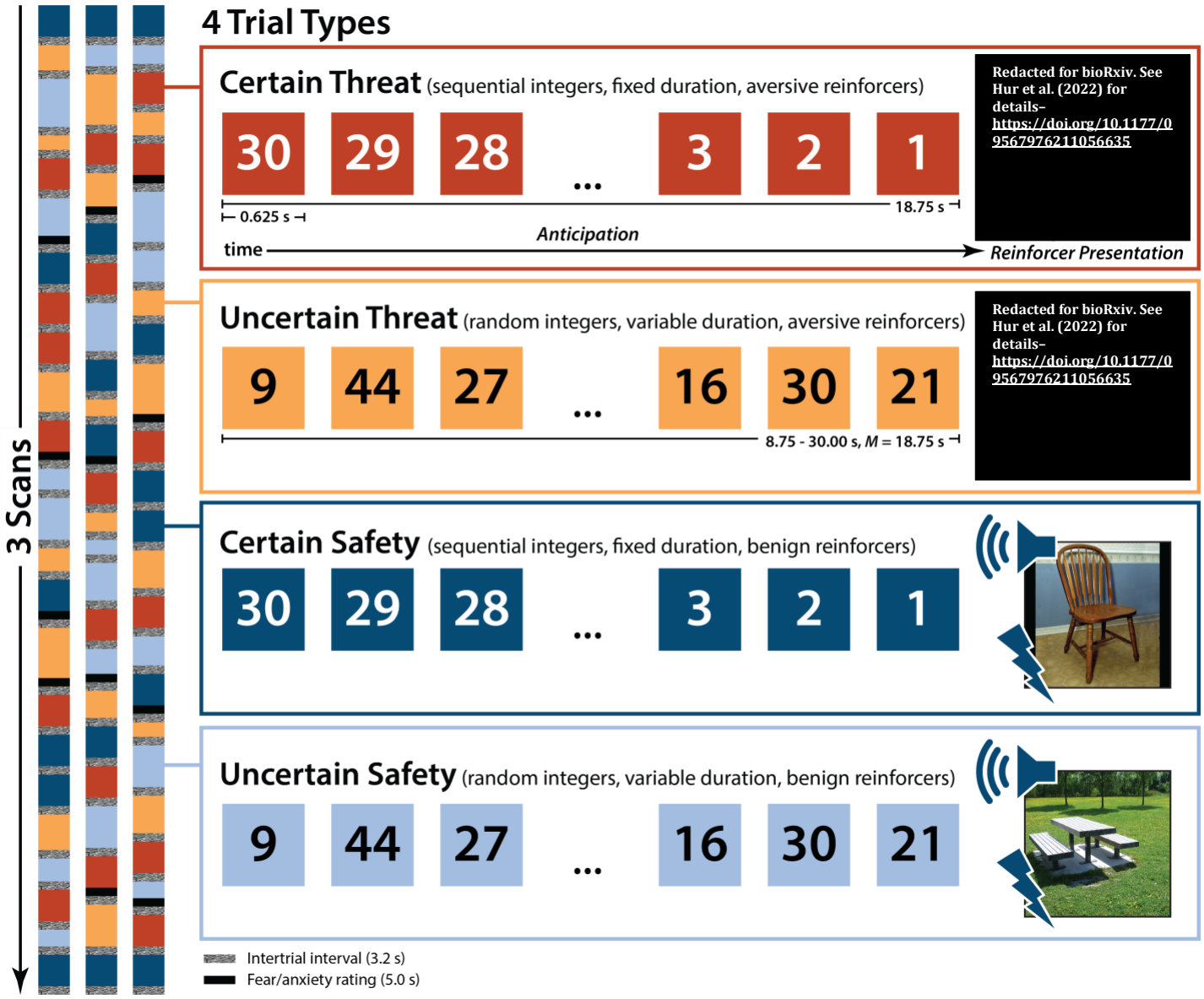


Figure 1. Study overview. ***Recruitment and N/NE Phenotyping.*** To ensure a broad spectrum of N/NE, participants were selectively recruited from an ethno-racially diverse pool of 6,594 pre-screened individuals. N/NE was assessed at screening (T1), at the baseline laboratory session (T2), and at the 6-month follow-up session (T3). To maximize reliability and power, analyses leveraged a composite measure of N/NE that was aggregated across 2 scales and 3 measurement occasions (see also **Supplementary Figure S2**). Upper inset panels indicate the distribution (histogram), internal-consistency reliability (α), and test-retest reliability of N/NE in the screening (*left*) and fMRI (*right*) samples. Timeline indicates the interval between assessments. ***Baseline fMRI Assessments. Anxiety Provocation.*** Following the baseline laboratory assessment (T2), participants completed an fMRI assessment. All participants completed the Maryland Threat Countdown task, a well-established anxiety-provocation paradigm. As detailed in **Supplementary Figure S1**, the MTC takes the form of a 2 (*Valence:* Threat/Safety) × 2 (*Temporal Certainty:* Certain/Uncertain) factorial design. On threat trials, subjects saw a stream of integers that terminated with the temporally certain or uncertain presentation of a noxious electric shock, unpleasant photograph, and thematically related audio clip. Safety trials were similar, but terminated with the delivery of benign stimuli. Hypothesis testing focused on neural activation associated with the anticipation of temporally certain and uncertain threat, relative to safety. A total of 220 individuals provided usable imaging data. ***Threat-Related Faces.*** A subset of 213 participants also completed a 'threat-related' (fearful/angry) faces fMRI paradigm. As detailed in **Supplementary Figure S3**, participants viewed short blocks of photographs, alternating between blocks of faces and benign everyday scenes (e.g. park, office). Hypothesis testing focused on activation associated with threat-related faces, relative to scenes. ***Unbiased EAc ROIs.*** Anatomically defined regions-of-interest (ROIs) enabled us to rigorously test the central hypothesis that N/NE reflects heightened recruitment of the BST (*green*), and potentially the Ce (dorsal amygdala; *cyan*), during aversive anticipation and explore the possibility that these associations are more evident when the timing of threat encounters is uncertain. Unlike conventional whole-brain voxelwise analyses—which screen thousands of voxels for statistical significance and yield optimistically biased associations—anatomically defined ROIs 'fix' the measurements-of-interest *a priori*, providing statistically unbiased estimates of brain-phenotype associations. Standardized regression coefficients were extracted and averaged across voxels for each combination of ROI, task contrast, and participant. ***Testing Associations Between EAc Function and N/NE. Cross-Validation Provides Unbiased Association Estimates.*** Conventional regression approaches use all available data for model fitting ('training'), yielding optimistically biased estimates of model performance (R^2) that do not generalize well to unseen data ('overfitting'). As shown in the bottom-left panel, we used a well-established cross-validation framework (i.e. repeated 5-fold) to compute unbiased associations. ***Robust Regression.*** As shown in the bottom-right panel, conventional regression is sensitive to high-leverage outliers (*red*). Here we used robust regression (Tukey's bi-weight) to reduce the influence of unduly influential cases, providing a better fit to the bulk of the data, and reducing volatility across the cross-validated training (N=176) and test (N=44) folds. The same analytic framework was used for the faces dataset. Abbreviations—α, Cronbach's alpha (internal-consistency reliability); BST, bed nucleus of the stria terminalis; Ce, dorsal amygdala in the region of the central nucleus; EAc, central extended amygdala; ICC, intraclass correlation (test-retest reliability); *M*, mean; Mo., months; *N*, number of observations; N/NE, neuroticism/negative emotionality; OLS, ordinary least squares; ROI, region of interest.



Supplementary Figure S1. ***Threat-Anticipation paradigm.*** The Maryland Threat Countdown task takes the form of a 2 (*Valence:* Threat/Safety) × 2 (*Temporal Certainty:* Certain/Uncertain) repeated-measures, randomized event-related design. Participants were completely informed about the task design and contingencies prior to scanning. The task was administered in 3 scans, with short breaks between scans. On Certain-Threat trials, participants saw a descending stream of integers ('count-down') for 18.75 s. To ensure robust anxiety, this anticipation epoch always terminated with the presentation of a noxious electric shock, unpleasant photograph, and thematically related audio clip (e.g. scream). Uncertain-Threat trials were similar, but the integer stream was randomized and presented for an uncertain and variable duration (8.75-30.00 s; *M*=18.75 s). Participants knew that something aversive was going to occur, but they had no way of knowing precisely *when*. Safety trials were similar, but terminated with the delivery of benign reinforcers (e.g., just-perceptible electrical stimulation). White-noise visual masks (3.2 s) were presented between trials to minimize persistence of visual reinforcers in iconic memory. Participants were periodically prompted to rate the intensity of fear/anxiety experienced a few seconds earlier, during the anticipation ('countdown') epoch of the prior trial. Participants were promoted to rate each condition once per scan. Skin conductance was continuously acquired.

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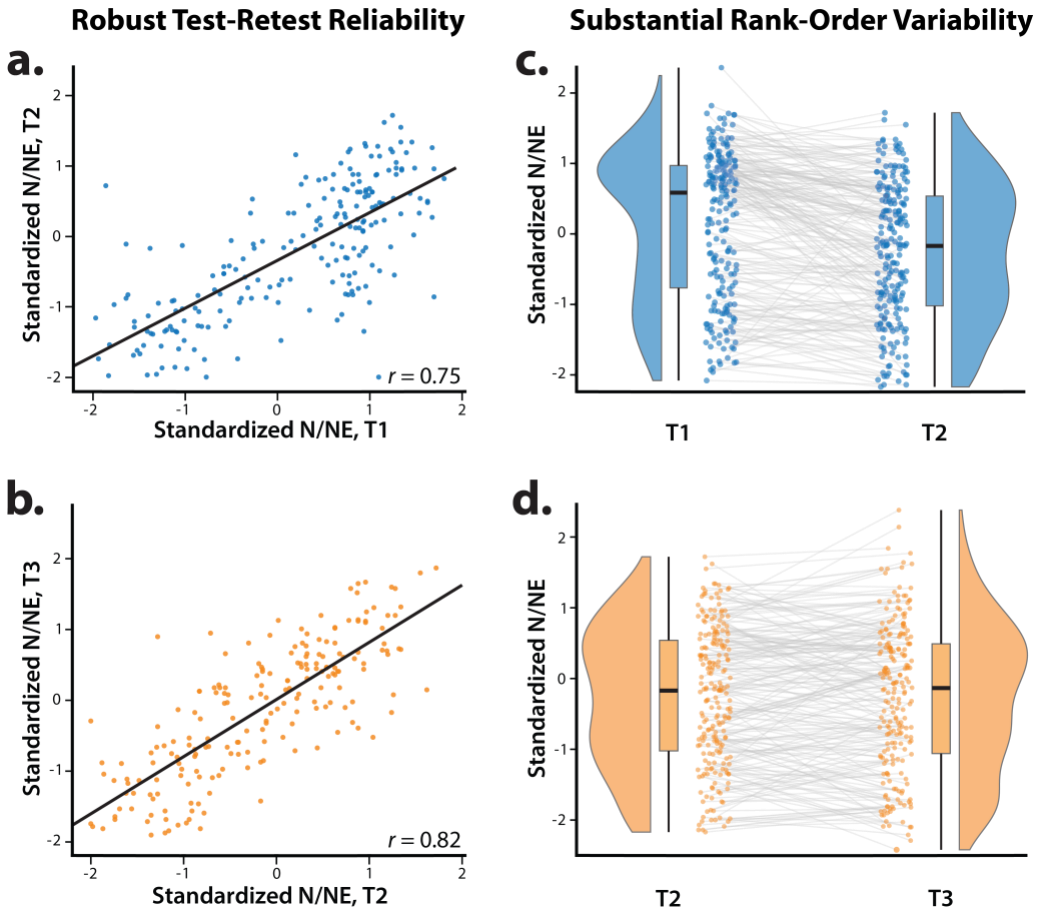

Supplementary Figure S2. ***Robust test-retest reliability belies substantial rank-order variability in N/NE.*** A voluminous literature underscores the reliability of questionnaire measures of personality and temperament[63]. Indeed, as shown in panels *a* and *b*, our multiscale measure of N/NE showed robust test-retest reliability across successive measurement occasions (see **Figure 1** for details). Nevertheless, inspection of the raincloud plots depicted in panels *c* and *d* revealed notable variability in the rank order of participants, with 46.4% of the sample showing at least a 0.5 *SD* change between T1 (Screening) and T2 (Baseline), 41.4% between T2 and T3 (6-Month Follow-Up), and 55.9% between T1 and T3. In short, even highly reliable single-occasion ('one-shot') measurements of N/NE contain considerable state and error variance. Consistent with recent methodological recommendations[60], we addressed this issue by creating a composite measure of N/NE that was aggregated across 2 scales and 3 measurement occasions (T1-T3), maximizing reliability and power to detect brain-trait associations. Raincloud plots depict the smoothed density distributions (i.e. 'bean' or 'half-violin') of standardized N/NE. Box-and-whisker plots indicate the medians (*horizontal lines*) and interquartile ranges (*boxes*). Whiskers depict 1.5× the interquartile range. Colored dots connected by gray lines indicate changes in standardized N/NE for each participant.

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To provide a more direct link with on-going research, we performed parallel analyses using data from a subset of 213 participants who also completed an emotional-faces fMRI paradigm. Variants of the emotional-faces paradigm are widely used as probes of amygdala function—often in the guise of quantifying variation in Research Domain Criteria (RDoC) 'Negative Valence Systems'[64]—and have been incorporated into many prominent biobank studies (e.g., ABCD, UK Biobank). Although there is abundant evidence that photographs of 'threat-related' (fearful/angry) facial expressions robustly recruit the amygdala[65], they do not elicit substantial distress in typical adults and, therefore, are better conceptualized as a measure of threat perception, rather than the experience or expression of negative emotion[3]. Here, we tested whether EAc (Ce and BST) reactivity to threat-related faces is associated with variation in N/NE.

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Supplementary Figure S3. Threat-perception (*emotional faces) paradigm.* The emotional-faces paradigm took the form of a pseudo-randomized block design and was administered in 2 scans, separated by a short break. During each scan, participants viewed standardized photographs of adults (half female) modeling prototypical angry faces, fearful faces, happy faces, or places (i.e. emotionally neutral everyday scenes; 7 blocks/condition/scan). Blocks consisted of 10 briefly presented photographs of faces or places (1.6 s) separated by fixation crosses (0.4 s). To further minimize potential habituation, each photograph was only presented a maximum of two times.

The inclusion of two neuroimaging tasks also afforded the opportunity to determine whether they are statistically interchangeable. It is often tacitly assumed that different experimental tasks targeting a common psychological function (e.g., 'threat') are quasi-equivalent probes of individual differences in circuit function (i.e., threat-of-shock ≈ threat-related faces). Yet this assumption of rank-order fungibility has rarely been examined empirically, never in a large sample, and never in the BST[66]. Here, we formally quantified the degree to which the threat-anticipation and threat-perception tasks show statistical interchangeability ('convergent validity') in the EAc (Ce and BST).

N/NE has been conceptualized as the single most important psychological risk factor in public health, yet the underlying neurobiology remains surprisingly speculative[2]. Addressing this fundamental question has the potential to refine basic scientific and clinical models of temperament and personality; inform the design, use, and interpretation of biobank data; and guide mechanistic work aimed at developing improved biological interventions for extreme N/NE[19].

RESULTS

Threat anticipation amplifies subjective distress and objective arousal

We used a series of repeated-measures general linear models (GLMs) to confirm that the threat-anticipation paradigm had the intended impact on anxious distress and arousal. Mean-centered N/NE was included as a fully crossed dimensional covariate, allowing us to explore the possibility that N/NE alters reactivity to this well-controlled emotional challenge[1].

As shown in **Figure 2a**, fearful and anxious feelings were significantly elevated during the anticipation of Threat compared to Safety, and this was particularly evident when the timing of aversive encounters was

uncertain (*Valence: F*(1,218)=1,135.06, *p*<0.001; *Certainty: F*(1,218)=212.95, *p*<0.001; *Valence × Certainty: F*(1,218)=31.75, *p*<0.001; *Threat, Uncertain vs. Certain: F*(1,218)=148.90, *p*<0.001; *Safety, Uncertain vs. Certain: F*(1,218)=78.78, *p*<0.001).

As shown in **Figure 2b**, the same general pattern was evident for skin conductance, an objective psychophysiological index of arousal (*Valence: F*(1,216)=790.55, *p*<0.001; *Certainty: F*(1,216)=138.95, *p*<0.001; *Valence × Certainty: F*(1,216)=661.63, *p*<0.001; *Threat, Uncertain vs. Certain: F*(1,216)=455.78, *p*<0.001; *Safety, Uncertain vs. Certain: F*(1,216)=270.03, *p*<0.001). These observations confirm the validity of the threat-anticipation paradigm as an experimental probe of fear and anxiety, replicating and extending prior work using the Maryland Threat Countdown task[67-69].

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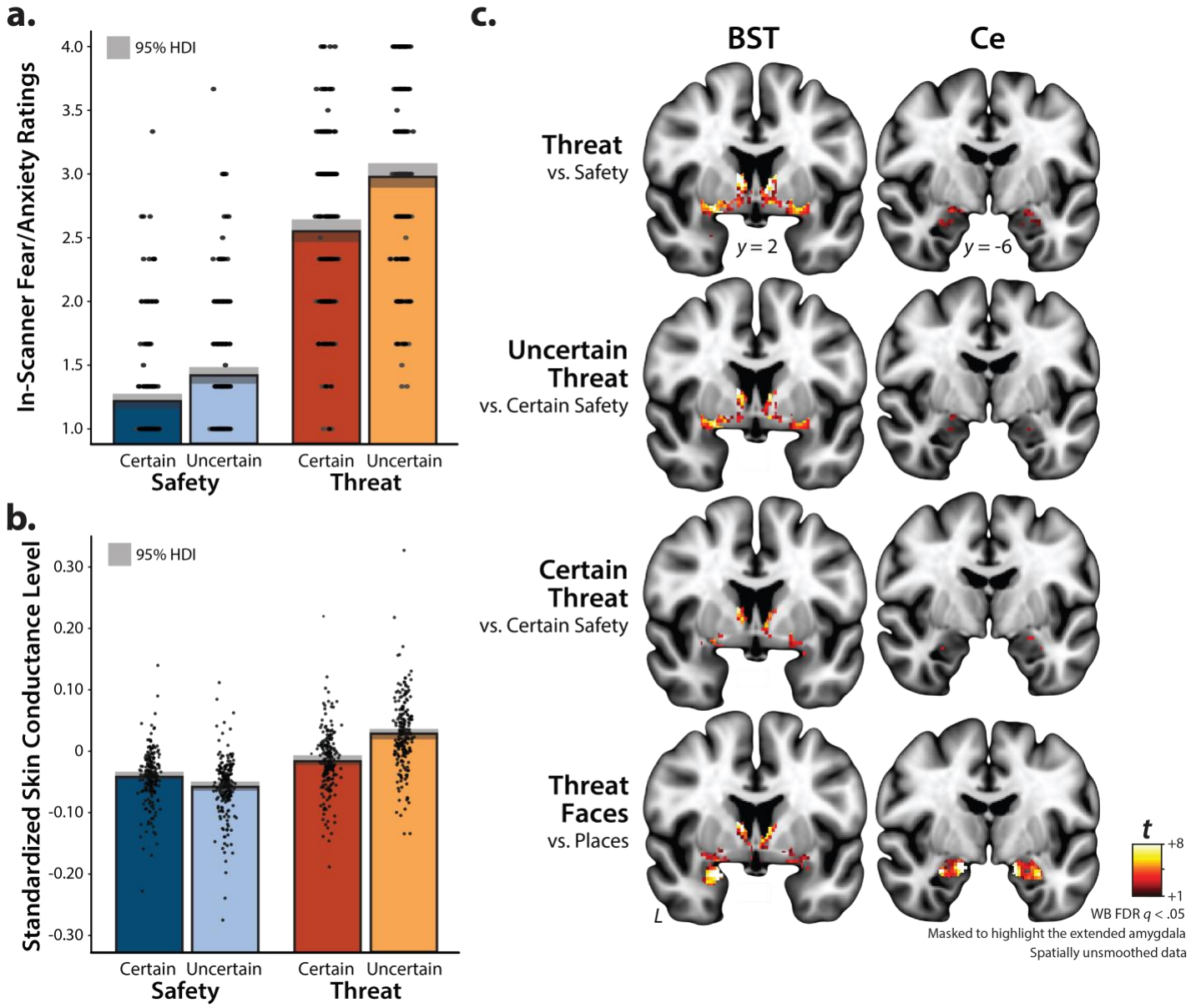

Figure 2. The threat-anticipation and threat-perception tasks are valid probes of EAc function. a. ***Threat anticipation evokes subjective distress.*** Fear and anxiety were increased during the anticipation of Threat compared to Safety, and this was particularly evident for Uncertain Threat (p<0.001). **b.** ***Threat anticipation evokes objective signs of arousal.*** A similar pattern was evident for skin conductance level (p<0.001). **c.** ***Threat-anticipation and threat-perception recruit the EAc.*** As shown in the top three rows, the anticipation of Threat, Uncertain Threat, and Certain Threat activated the BST and the dorsal amygdala in the region of the Ce, when compared to their respective reference conditions (q<0.05, corrected). As shown in the bottom row, the acute presentation of threat-related faces was also associated with significant activation in the region of the BST and the dorsal amygdala (Ce), relative to the reference condition. See the **Supplement** for complete whole-brain voxelwise results. Bars indicate the means (*colored bars*), Bayesian 95% highest density intervals (*gray bands*), and individual participants (*black points*). Abbreviations—BST, bed nucleus of the stria terminalis; Ce, dorsal amygdala in the region of the central nucleus; FDR, false discovery rate; HDI, highest density interval; *t*, Student's *t*; WB, whole-brain-corrected.

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N/NE amplifies distress evoked by the threat-anticipation paradigm

Exploratory analyses demonstrated that individuals with a more negative disposition experienced pervasively elevated distress across the four conditions of the threat-anticipation paradigm—both aversive and benign ($F(1,218)=33.56$, $p<0.001$)—and modestly potentiated reactivity to the anticipation of Threat compared to Safety, and to the anticipation of Uncertain compared to Certain outcomes (*N/NE × Valence:* $F(1,218)=6.35$, $p=.01$; *N/NE × Certainty:* $F(1,218)=6.03$, $p=.02$; **Figure S4**). No other moderator effects were significant for either subjective distress or objective arousal ($p>0.57$). In short, individuals with a more negative disposition show a combination of indiscriminately elevated ('overgeneralized'), threat-potentiated, and uncertainty-potentiated anticipatory distress, in broad accord with prior work[1,70].

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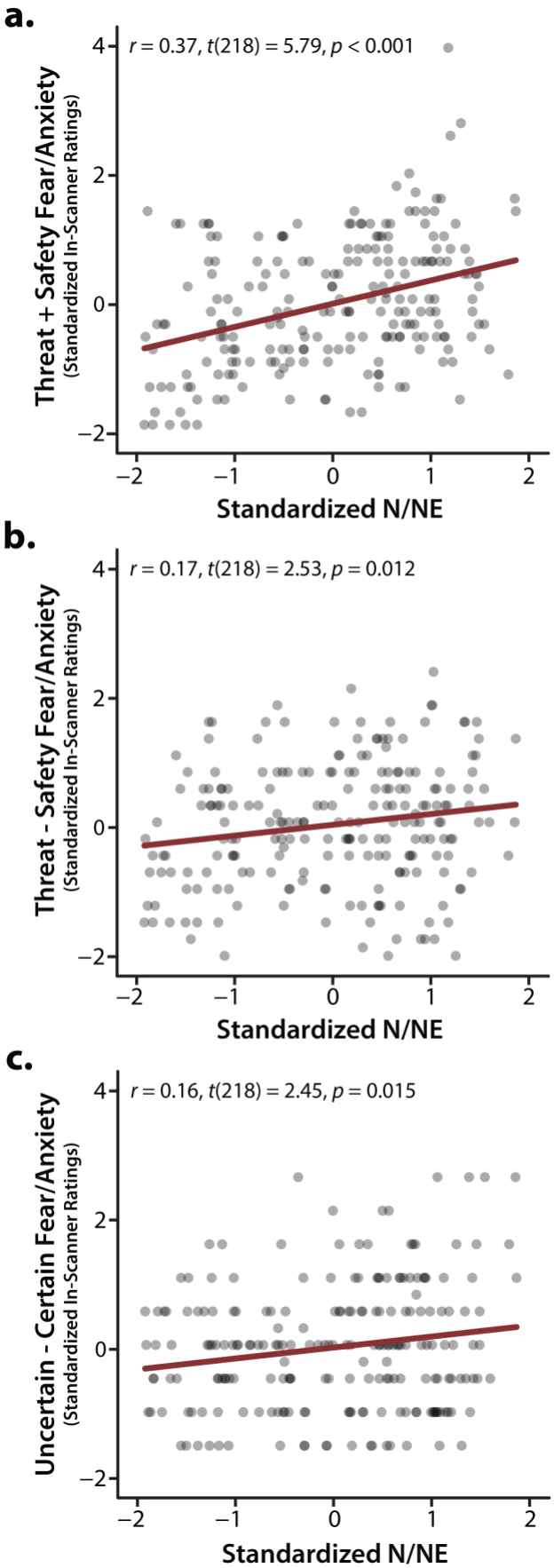


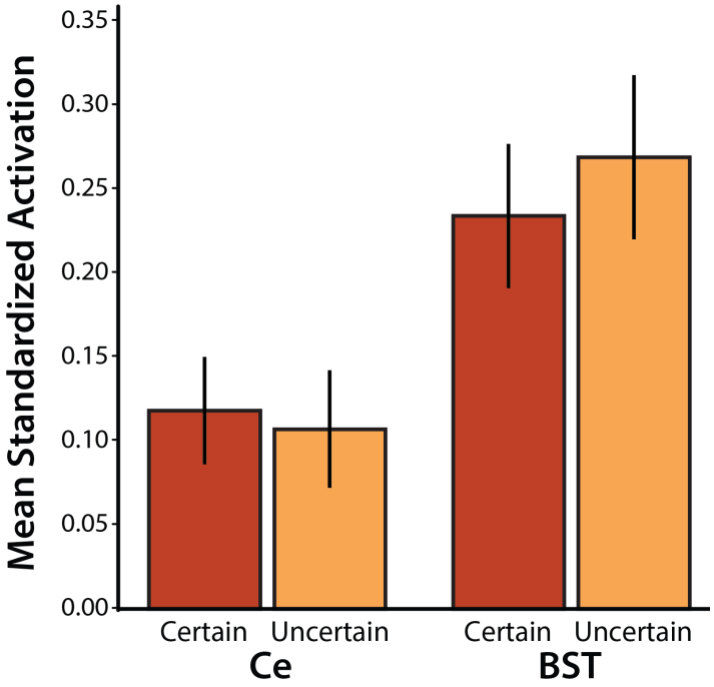
Supplementary Figure S4. ***N/NE amplifies subjective fear and anxiety elicited by the threat-anticipation paradigm.*** Individuals with higher levels of N/NE exhibited a mixture of **(a)** indiscriminately elevated ('overgeneralized') distress across Threat and Safety trials, **(b)** potentiated distress when anticipating aversive relative to benign stimulation, and **(c)** potentiated distress when anticipating temporally uncertain stimulation. *Red lines* indicate regression slopes. *Gray dots* depict individual participants.

Threat anticipation and perception robustly recruit the EAc

We used whole-brain voxelwise GLMs to confirm that the threat-anticipation and threat-perception (emotional-faces) paradigms had the intended consequences on brain function. As expected, the anticipation of Threat, Uncertain Threat, and Certain Threat significantly recruited both the BST and the dorsal amygdala in the region of the Ce (FDR q<.05, whole-brain corrected; **Figure 2c**). Beyond the EAc, each of these contrasts was associated with significant activation across a widely distributed network of regions previously implicated in the expression and regulation of human fear and anxiety[71], including the midcingulate cortex, anterior insula/frontal operculum, dorsolateral prefrontal cortex, and periaqueductal grey (**Tables S3-S4**). Analyses focused on the presentation of threat-related faces revealed significant activation in the BST and the dorsal amygdala, consistent with prior work (**Figure 2c** and **Table S5**)[43]. Together, these observations demonstrate that both tasks are both robust probes of EAc function.

N/NE is uniquely associated with BST activation during the uncertain anticipation of threat

We used statistically unbiased anatomical ROIs and spatially unsmoothed fMRI data to test the hypothesis that individuals with a more negative disposition will show exaggerated recruitment of the EAc (BST and/or Ce) during threat anticipation, and test whether this association is more evident when the timing of the threat encounter is uncertain (**Figure 1**). As a precursor to hypothesis testing, we used a series of *t*-tests to confirm that the anatomically defined BST and Ce ROIs are recruited by the threat-anticipation and threat-perception (emotional-faces) tasks. Consistent with the voxelwise results (**Figure 2c**), both anatomically defined ROIs evinced nominally significant activation ($ts(219)>3.10$, $ps<0.002$, uncorrected; **Figure S5** and **Tables S6-S7**).



Supplementary Figure S5. ***Exploratory analysis of EAc reactivity to threat anticipation.*** The anatomically defined BST ROI was more strongly recruited during the anticipation of threat, relative to the Ce (p=0.002). Neither the main effect of Certainty nor the critical Region × Certainty ('double dissociation') interaction was significant (p>0.18). Furthermore, the focal contrast of Certain versus Uncertain Threat was not significant in either anatomical ROI (p>0.40, $|d|$<0.07, BF_{10}<0.20). For additional details, see **Supplementary Tables S6-S7**. Bars depict mean standardized activation during the anticipation of Certain or Uncertain Threat relative to baseline for each ROI. Whiskers depict standard errors. Abbreviations—BST, bed nucleus of the stria terminalis ROI; Ce, central nucleus of the amygdala ROI; ROI, region of interest.

As shown schematically in **Figure 1**, cross-validated robust GLMs were used for hypothesis testing. Results revealed that general EAc threat reactivity—aggregating across the anticipation of certain and uncertain aversive stimulation—was unrelated to individual differences in N/NE (*BST:* β=0.12, t(218)=1.57, p=0.12; *Ce:* β=0.02, t(218)=0.32, p=0.75; **Figure 3a**). Prior work suggests that relations between N/NE and EAc function may be magnified when threat encounters are uncertain in their timing or likelihood[46]. To test this, we computed robust regressions between N/NE and EAc reactivity to *un*certain threat, separately for each region. To clarify specificity, models controlled for activation during *certain* threat anticipation. Results demonstrated that heightened BST activation during uncertain-threat anticipation was significantly and selectively associated with trait-like variation in N/NE (*Uncertain:* β=0.24, t(217)=2.61, p=0.01; *Certain:* β=-0.09, t(217)=-1.00, p=0.32; **Figures 3a-3b**). Leveraging a simpler bivariate model, we estimated that BST reactivity to uncertain threat explained, on average, 5.1% of the variance in N/NE in out-of-sample test folds (β=0.19, t(218)=2.59, p=0.01, R^2_{CV}=0.051). BST reactivity was unrelated to individual differences in task-related distress (p>0.21; **Table S8).**

In contrast to the BST, Ce reactivity to the threat-anticipation task was unrelated to variation in N/NE, regardless of threat certainty (*Certain:* β=0.04, t(217)=0.45, p=0.65; *Uncertain:* β=-0.10, t(217)=-0.99, p=0.32; **Figure 3a**). EAc reactivity to the threat-perception (emotional-faces) task was also unrelated to N/NE (*BST:* β=0.03, t(211)=0.37, p=0.72; *Ce:* β=0.03, t(211)=0.38, p=0.70; **Figure 3a**). Consistent with these nil effects, the association between BST reactivity to uncertain threat and N/NE remained significant in models that controlled for either BST reactivity to threat-related faces or Ce reactivity to uncertain-threat anticipation (t>2.59, p<0.02). In sum, individual differences in N/NE are uniquely associated with heightened BST activation during the uncertain anticipation of a genuinely distressing threat.

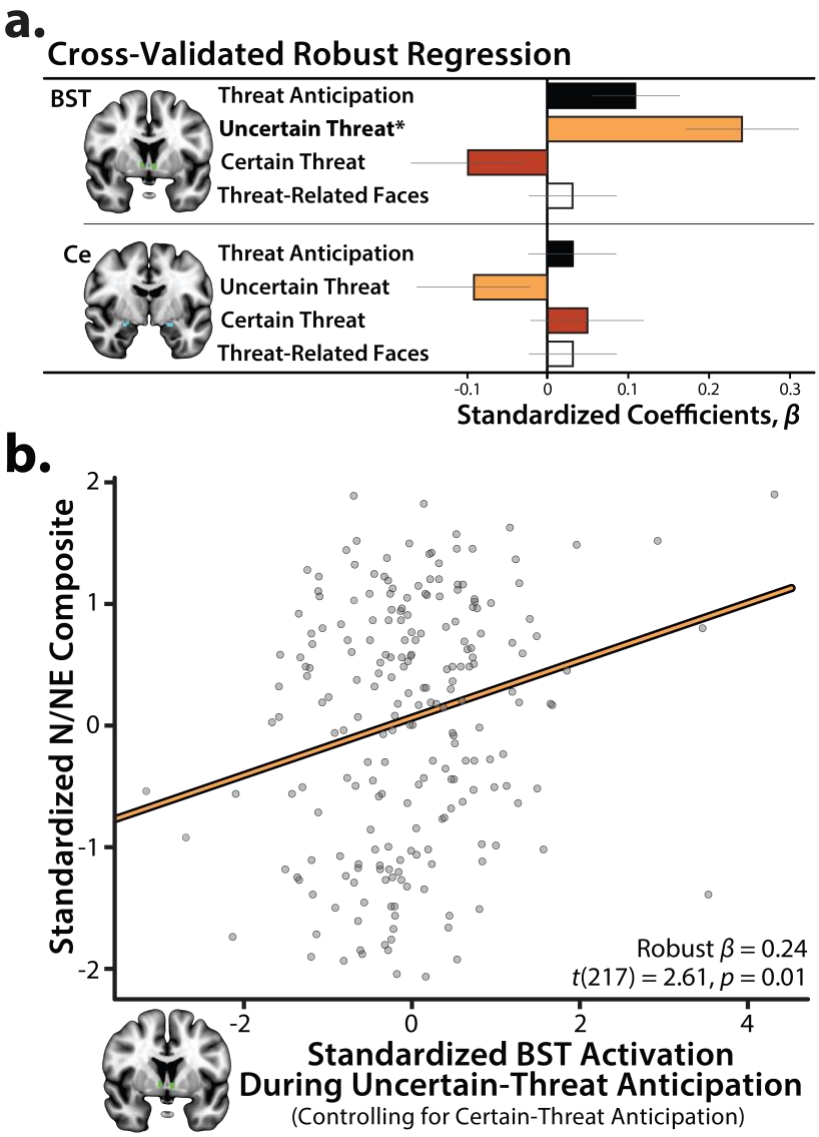


Figure 3. ***Individual differences in N/NE are uniquely associated with heightened BST activation during the uncertain anticipation of a genuinely distressing threat.*** **a.** ***Standardized robust regression coefficients.*** Heightened BST reactivity to uncertain-threat anticipation (*orange*) was associated with variation in N/NE (p=0.01). Other effects were not significant (p>0.11). Bars depict standardized coefficients for each robust regression model. Whiskers indicate standard errors. Significant associations are marked by an asterisk. **b.** ***Scatterplot.*** Orange line depicts the robust association (Tukey's bi-weight) between BST reactivity to uncertain-threat anticipation and variation in the composite measure of N/NE, while controlling for differences in BST reactivity to certain-threat anticipation. Abbreviations—BST, bed nucleus of the stria terminalis ROI; Ce, central nucleus of the amygdala ROI; N/NE, neuroticism/negative emotionality.

BST reactivity to uncertain threat is broadly associated with the internalizing facets of N/NE

Epidemiological, psychiatric, and biological studies typically focus on coarse 'broadband' measures of N/NE[1,3]. Yet it is clear that N/NE is a complex phenotype that subsumes several narrower traits—including dispositional anxiety, depression/sadness, and emotional volatility[63,72,73]—each characterized by a mixture of shared and unique psychological associations and biological correlates[39,74-76]. While our composite N/NE instrument has many psychometric strengths (**Figure 1**), it cannot address which of these traits is most relevant to BST function. To do so, we leveraged the revised Big Five Inventory (BFI-2), a well-established, hierarchically organized scale that was expressly constructed to enable rigorous facet-level analyses[63]. The BFI-2 was administered at the baseline (T2) and 6-month follow-up (T3) sessions (**Figure 1**). Paralleling the approach used for broadband N/NE, facet scores were averaged across assessments to minimize occasion-specific fluctuations ('noise'). Cross-validated robust GLMs were used to quantify associations between BST reactivity to uncertain-threat anticipation and each facet of N/NE, while controlling for BST reactivity to certain threat. Results revealed significant associations with dispositional Anxiety and Depression/Sadness, but not Emotional Volatility (*Anxiety:* β=0.20, t(217)=2.19, p=0.03; *Depression/Sadness:* β=0.22, t(217)=2.45, p=0.02; *Volatility:* β=0.10, t(217)=1.10, p=0.27). Consistent with the broadband results, BST reactivity to certain-threat anticipation was unrelated to the three narrow traits (p>0.21). In cross-validated bivariate models, variation in BST reactivity to uncertain-threat anticipation explained an average of ~4% of the variance in the Anxiety and Depression/Sadness facets of N/NE in out-of-sample test data (*Anxiety:* β=0.15, t(218)=2.13, p=0.04, R^2_{CV}=0.041; *Depression/Sadness:* β=0.16, t(218)=2.17, p=0.03, R^2_{CV}=0.040). While the BST is often conceptualized as playing a central role in anxiety-related states, traits, and disorders[43,71,77], these findings demonstrate that heightened BST reactivity to uncertain threat is more broadly associated with the 'internalizing' facets of N/NE. They also indicate that our major conclusions generalize across trait instruments.

EAc reactivity to the threat-anticipation and threat-perception tasks shows negligible convergence

It is often assumed that different experimental tasks targeting 'threat' are quasi-interchangeable probes of individual differences in circuit function (i.e., threat-of-shock ≈ threat-related faces). Yet this tacit assumption of convergent validity has never been tested in a larger sample or in the BST[66]. As shown in **Table S9**, robust GLMs revealed negligible associations between BST reactivity to the threat-anticipation and threat-perception (emotional faces) tasks (p>0.06). The same pattern of null associations was evident for the Ce (p>0.11). The absence of robust cross-task correlations raises important questions about the equivalence of two popular fMRI threat tasks—one centered on the cued anticipation of aversive stimulation, the other focused on the perception of angry and fearful facial expressions—and caution against relying exclusively on emotional-face paradigms to probe individual differences in threat-related EAc function.

DISCUSSION

N/NE is a fundamental dimension of mammalian temperament, with profound consequences for human health and wellbeing[1,3]. Yet our understanding of the underlying neurobiology remains far from complete. Mechanistic and neuroimaging research in rodents and monkeys suggests that N/NE reflects exaggerated EAc reactivity to uncertain dangers, but the translational relevance of this work has remained speculative[1,43]. Here we used a novel combination of psychometric, psychophysiological, and neuroimaging approaches to understand the relevance of the EAc to trait-like individual differences in N/NE in a racially diverse sample of 220 adults selectively recruited to capture a broad spectrum of N/NE (**Figure 1**). Results demonstrated that the threat-anticipation paradigm elicited robust symptoms of distress and signs of arousal, replicating work in smaller samples[67-69] (**Figure 2**). Fearful and anxious feelings were more intense and indiscriminate among individuals with a more negative disposition, with elevated distress evident while waiting to receive benign stimulation (**Figure S4**). Both the threat-anticipation and threat-

perception paradigms strongly recruited the Ce and BST (**Figure 2**). Leveraging statistically unbiased anatomical ROIs and spatially unsmoothed fMRI data, we used a series of cross-validated, robust GLMs to show that N/NE is uniquely associated with heightened BST activation during the uncertain anticipation of aversive stimulation (**Figure 3**). In contrast, N/NE was unrelated to variation in BST activation during the anticipation of certain threat, Ce activation during the anticipation of either threat, or EAc reactivity to threat-related faces. While the BST is often associated with anxiety[43,71,77,78], follow-up analyses showed that heightened BST reactivity to uncertain threat is broadly associated with the 'internalizing' facets of N/NE, including the tendency to feel depressed, sad, or insecure[63]. Implicit in much of the neuroimaging literature is the assumption that different threat paradigms are equivalent probes of individual differences in EAc function (i.e., threat-of-shock ≈ threat-related faces), yet our results revealed negligible evidence of cross-task convergence in the EAc (**Table S9**). In the section that follows, we outline the basic, clinical, and methodological implications of these observations.

Our results provide compelling evidence that individual differences in N/NE are associated with heightened BST reactivity to the uncertain anticipation of a genuinely distressing threat, replicating and extending prior neuroimaging observations in young monkeys and a comparatively small convenience sample of Dartmouth undergraduates[44-46]. Individual differences in N/NE are heritable, and work in monkeys suggests that individual differences in BST reactivity to uncertain threat may be particularly relevant to the heritable variance of this risk-conferring trait[3,44]. Invasive anatomical tracing studies in rodents and monkeys indicate that the BST is poised to assemble behavioral, psychophysiological, and neuroendocrine signs of negative affect via dense mono- and polysynaptic projections to brainstem and subcortical effector regions[79,80], with many of these regions also showing robust functional connectivity with the BST in human neuroimaging studies[81-83]. Collectively, these observations reinforce the hypothesis that the BST is a key component of the distributed neural circuitry governing N/NE. A key challenge for the

future will be to clarify causation. Although the mechanistic contribution of the BST to dispositional fear and anxiety has yet to be explored in humans or other primates, work in rodents provides compelling evidence that specific cellular populations in the BST exert bi-directional control over defensive behaviors elicited by a range of uncertain threats, consistent with a causal role[84-89]. Among humans, N/NE is stable, but not immutable, and can change in response to positive and negative life experiences, providing opportunities for enhancing mechanistic insight[1,3,19,90-93]. In a comprehensive meta-analysis of 199 studies, Roberts and colleagues found marked reductions in N/NE following psychosocial or pharmacological treatment for internalizing disorders(Cohen's *d*=0.59-0.69)[94]. It will be fruitful to determine whether this salubrious effect is associated with diminished BST reactivity to uncertain threat.

N/NE is a well-established risk factor for future internalizing illnesses. The magnitude of these associations is substantial and remains evident even when eliminating overlapping item content or adjusting for baseline symptoms[95,96]. For example, the Zurich Cohort Study (*N*=591) reported that a one standard-deviation increase in N/NE increased the odds of developing an anxiety disorder by 32% and a major depressive episode by 41% across the twenty-year follow-up period[97]. Likewise, a comprehensive meta-analysis revealed medium-to-large associations between N/NE and future symptoms and diagnoses, for both anxiety (Cohen's *d*=0.48-0.68) and depression (*d*=0.50-0.74)[96]. Our results provide a framework for understanding the mechanisms underlying this transdiagnostic liability[3,98]. Co-morbidity between anxiety and depression disorders is rampant and ~75% of patients with DSM-5 Major Depressive Disorder show clinically significant anxiety symptoms[98-101]. From a biological perspective, anxiety, depression, and N/NE show robust genetic correlations and overlapping pharmacological effects (e.g., respond to anti-depressants)[3,75,94,98,102-104]. While these findings are suggestive of a common neurobiological substrate[98], identifying the relevant neural systems has proven challenging[105]. Our observation that heightened BST reactivity to uncertain threat is associated with both the anxious and the depressive facets of N/NE

suggests that alterations in BST threat reactivity might contribute to this still-enigmatic shared substrate. While this hypothesis remains to be tested, the available circumstantial evidence is supportive. A recent meta-analysis demonstrated that the BST is hyper-reactive to unpleasant emotional challenges among individuals with anxiety disorders[71,106]. Both anxiety disorders and depression are often treated via chronic administration of selective serotonin reuptake inhibitors (SSRIs) or, in the case of anxiety, acute administration of benzodiazepines[103,104]. Both treatments have been shown to reduce defensive responses to uncertain threat in humans and rats and to dampen threat-evoked BST activity in rats[107,108]. From the standpoint of understanding the etiology of internalizing disorders, a key avenue for future research will be to use prospective-longitudinal data to determine whether exaggerated BST reactivity to uncertain threat increases the likelihood of experiencing pathological anxiety and depression.

Our results also have implications for the design and interpretation of neuroimaging studies of psychiatric risk, disease, and treatment development. Much of this work relies on emotional-face tasks as the sole probe of fear, anxiety, and related 'Negative Valence Systems'[64]. Yet our results indicate that EAc (Ce and BST) reactivity to 'threat-related' (fearful/angry) faces is unrelated to the risk-conferring N/NE phenotype, despite a relatively well-powered sample. Although there are a number of possible explanations, these null effects are not unprecedented. Three other recent well-powered studies failed to detect significant associations between amygdala reactivity to threat-related faces and individual differences in N/NE (Duke Neurogenetics Study, *N*=1,256; Human Connectome Project, *N*=319; Minnesota Twin Study, *N*=548)[109-111]. Our results also make it clear that the perception of threat-related faces and the anticipation of aversive stimulation are fundamentally distinct assays of individual differences in EAc function, in broad accord with prior work[66]. These observations highlight the hazards of continuing to rely on a single or small number of 'workhorse' neuroimaging paradigms to understand and predict emotion, temperament, and psychopathology[77,112,113]. Our results also caution against muddling the distinction between threat

perception and the actual experience and expression of fear and anxiety[114], a practice that has become routine in experimental therapeutics neuroimaging research[115-118].

The present results indicate that BST reactivity to uncertain-threat anticipation predicted 5.1% of the variance in N/NE in out-of-sample data. The size of this effect—while far too modest to be useful for screening, diagnostic, or treatment-development purposes—compares favorably with other psychiatrically relevant biological associations, including prospective associations between ventral striatum reward reactivity and depression (1%) and amygdala reactivity to threat-related faces and internalizing symptoms (2.7%)[105]. It exceeds the out-of-sample performance (1.5-4.2%) of polygenic scores derived from large-scale GWAS of N/NE, but is half that of the cross-validated association reported by Marek, Tervo-Clemmens and colleagues for the variance in general cognitive ability explained by activation in the dorsal-attention network during a working-memory task (11.6%)[59,119,120]. From a mechanistic or therapeutics-development perspective, the small-but-reliable 'hits' uncovered by adequately powered association studies are useful for prioritizing targets for perturbation and recording studies in animals and neuromodulation studies in humans. It merits comment that small-but-reliable brain-behavior associations do not preclude much larger effects with targeted biological interventions[121,122]. Indeed, EAc perturbations can have dramatic consequences for anxiety-related behaviors[43].

Our results also have implications for psychological theories of N/NE. Consider this fundamental question, *What does N/NE negativity do?* Decades ago, the influential theorist, Gordon Allport, answered by writing that, "traits are cortical [or] subcortical … dispositions having the capacity to gate or guide specific phasic reactions" [123]. Today, most theories remain rooted in the idea that differences in N/NE, behavioral

inhibition, and trait anxiety reflect hyper-sensitivity to novelty, threat, and other 'trait-relevant' challenges, amplifying the intensity of distress, arousal, and defensive behaviors when such challenges are encountered[2,33-36,124-126]. Consistent with this perspective, we found that high-N/NE experienced potentiated fear and anxiety when anticipating threat (R^2=2.9%; **Figure S4b**). But they also reported elevated distress when anticipating outcomes—whether aversive or benign—that were uncertain in timing (R^2=2.6%; **Figure S4c**), consistent with models emphasizing the centrality of uncertainty to typical and pathological anxiety[70]. But by far the strongest effect of N/NE was indiscriminately elevated distress across threat and safety trials (R^2=13.7%; **Figure S4a**). The latter observation is consistent with several recent reports of overgeneralized distress in cued threat-anticipation paradigms[127,128] and extend work focused on more naturalistic distress provocations[129,130] and self-report measures of daily experience[1,68,131]. Taken together, these observations provide compelling empirical support for conceptual models that emphasize the importance of pervasive, contextually inappropriate negative affect[1,132-135]. From a psychiatric perspective, overgeneralized responses to threat are particularly interesting, because have been shown to promote instrumental avoidance, a key sign of pathological anxiety[136-138]; to distinguish anxiety patients from controls[139]; and to confer heightened risk for future internalizing symptoms and disorders[140-142].

Clearly, a number of other important challenges remain for the future. First, our study was focused on a racially diverse sample of emerging adults. Moving forward, it will be useful to expand this to encompass more nationally representative samples[143]. Second, although our results highlight the importance of the BST, N/NE is a complex phenotype that likely reflects multiple distributed networks. Moving forward, it will be important to understand how functional interactions between the BST and other regions implicated in the expression and regulation of negative affect support trait-like variation in N/NE.

Elevated N/NE is associated with a multitude of practically important outcomes—from satisfaction and wealth to divorce and disease—and has been conceptualized as the single most important psychological risk factor in public health[2]. Yet the underlying neurobiology has remained surprisingly speculative. Our observations provide rigorous evidence that individual differences in N/NE are significantly and selectively associated with heightened activation during the anticipation of an uncertain, genuinely distressing threat in the BST, but not the Ce. EAc reactivity to threat-related faces was also unrelated to variation in N/NE. These observations provide a framework for conceptualizing N/NE and lay the groundwork for the kinds of prospective-longitudinal and mechanistic studies that will be necessary to determine causation and, ultimately, to develop improved intervention strategies for extreme N/NE. A comparatively large, diverse, and carefully phenotyped sample (**Table S1**); well-controlled tasks; and a pre-registered, best-practices approaches to data acquisition, processing, and analysis enhance confidence in the robustness and translational relevance of these results.

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