The neural systems and real-world mood dynamics underlying dispositional risk for internalizing illness

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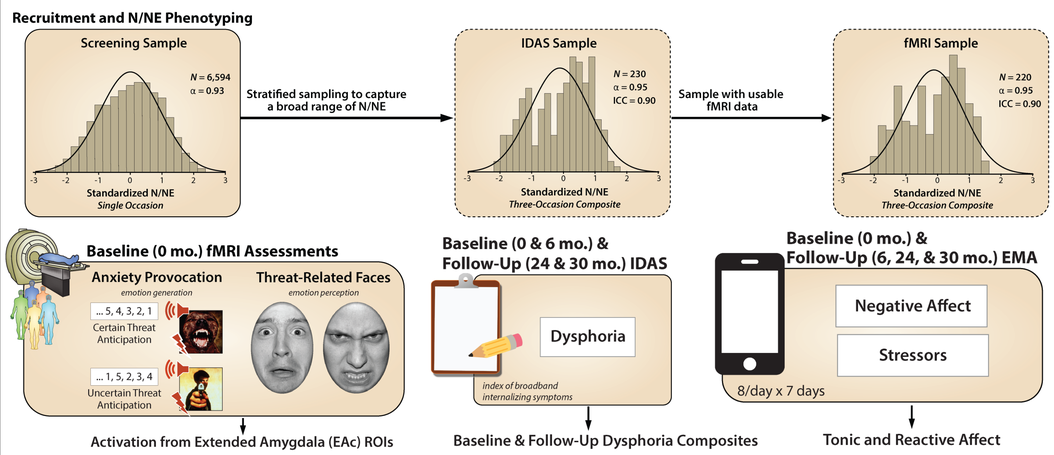
OVERARCHING AIM

- Internalizing disorders—anxiety, depression, and trauma disorders—impose a staggering burden on public health. Existing interventions are inconsistently effective, underscoring the need to understand the psychological and biological mechanisms that confer risk.
- Neuroticism/negative emotionality (N/NE) is a well-established temperamental risk factor for future anxiety and depression symptoms.
- Yet, the neural systems and real-world psychological processes underlying these prospective-longitudinal trajectories remain unclear.
- Here, we addressed these questions using a novel combination of data—including threat-anticipation and emotional-face fMRI paradigms and repeated waves of smartphone experience-sampling and internalizing symptom assessments—acquired from an ethnoracially diverse, risk-enriched sample of emerging adults (*n*s=217-230) followed for 2.5 years.

CONCEPTUAL OVERVIEW & METHOD

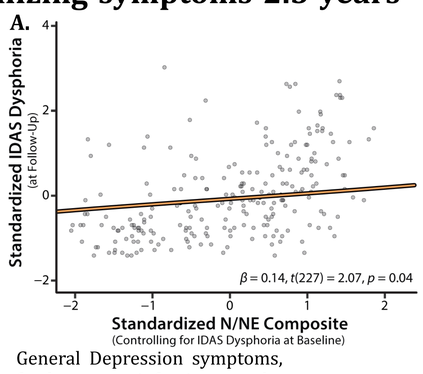


- 230 emerging adults (50.0% female; 60.9% White, 18.3% Asian, 9.1% Black/African American, 4.8% Hispanic/Latinx, 0.4% Native Hawaiian or Other Pacific Islander, 6.5% Multiracial/Other; *M*=18.7 years, *SD*=0.4 years) were selectively recruited from a pool of 6,594 phenotyped individuals to capture a broad spectrum of internalizing risk (N/NE; 50% high, 25% medium, 25% low; **above, top row**) and followed for 2.5 year (30 months).
- All participants were free from a lifetime history of psychotic and bipolar disorders; a current diagnosis of a mood, anxiety, or trauma disorder (past 2 months); severe substance abuse; active suicidality; and on-going psychiatric treatment as determined by an experienced, masters-level diagnostician using the Structured Clinical Interview for DSM-5.
- N/NE was assessed at initial screening, 0 months, and 6 months using Big Five Inventory Neuroticism & International Personality Item Pool Trait Anxiety.
- At baseline (0 months), we used two neuroimaging neuroimaging paradigms to probe circuits sensitive to threat processing and anxiety. Our well-established Maryland Threat Countdown fMRI paradigm (**above, far left bottom**) was used to quantify neural reactivity to the Uncertain and Certain anticipation of Threat (i.e., aversive stimulation). To provide a more direct link with on-going biobank research, reactivity to a popular emotion-perception paradigm ('threat-related' emotional faces) was also assessed (**above, far left bottom**). Both tasks recruit the extended amygdala (EAc), which has been linked to N/NE in prior work.
- At 0, 6, 24, and 30 months, self-reported broadband internalizing symptoms were assessed using the Inventory of Depression and Anxiety Symptoms (IDAS; **above, middle bottom**). Participants also completed one week of intensive smartphone-based ecological momentary assessment (EMA; 8 surveys/day x 7 days), allowing us to capture moment-by-moment fluctuations in *tonic* (stressor-independent) and *reactive* (stressor dependent) negative affect; **above, far right bottom**).
- Diagnoses and negative life events were assessed using 'gold-standard' clinical interviews at 0, 15, and 30 months, but were not examined in the present set of analyses.

RESULTS

1. Elevated N/NE at baseline portends a worsening of internalizing symptoms 2.5 years later

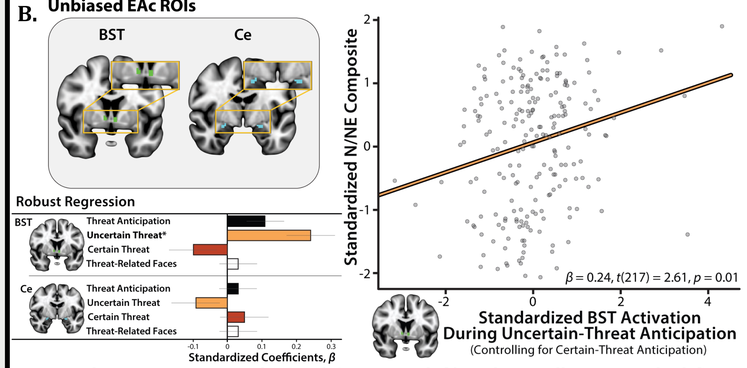
Meta-analyses suggest that high N/NE—the tendency to experience anxiety and other negative emotions—confers risk for a panoply of adverse health outcomes, including elevated risk for future anxiety and depression. Yet it remains unclear what drives these longitudinal links. Here, we used Tukey's biweight robust regression to test prospective associations between N/NE at baseline and IDAS Dysphoria score at follow-up in 230 risk-enriched emerging adults. Results showed that elevated baseline N/NE was associated with longitudinal increases in dysphoria (β=.14, t(227) = 2.07, p=.040; **Fig. A.**), controlling for dysphoria at baseline. Heightened baseline N/NE was also associated with future IDAS General Depression symptoms, further reinforcing the hypothesis that N/NE serves as a common root cause or 'diathesis' for the chronically elevated broadband distress that cuts across the internalizing disorders.



For further methodological details:

2. Variation in the N/NE phenotype is uniquely associated with heightened BST reactivity to Uncertain Threat anticipation, but not BST/Ce reactivity to Certain Threat or faces

Mechanistic work in animals and neuroimaging work in primates suggest that N/NE reflects heightened reactivity to threat in the central extended amygdala (EAc), including the bed nucleus of the stria terminalis (BST) and central nucleus of the amygdala (Ce). Yet the relevance of these tantalizing discoveries to the complexities of the human brain & human N/NE remains unclear.



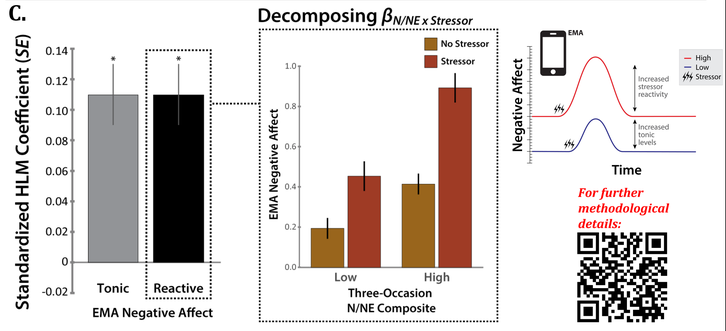
We used *a priori* anatomical ROIs (**Fig. B.**, top left) and spatially unsmoothed fMRI data (n=220) to test the hypothesis that individuals with a more negative disposition will show exaggerated recruitment of the EAc (BST and/or Ce) during threat anticipation, and test whether this association is more evident when the timing of the threat encounter is uncertain. Robust regression revealed that individuals with higher N/NE showed greater BST activation during Uncertain-Threat anticipation, controlling for Certain Threat (β=.24, t(217)=2.61, p=.010). This association remained significant in models that *included* Ce reactivity to threat, *included* Ce reactivity to just *Uncertain* Threat, *included* BST reactivity to emotional faces, or *excluded* BST reactivity to *Certain* Threat (ps<.05). These null effects are consistent with prior work and make it clear that the acute perception of threat-related faces and the anticipation of aversive stimulation are statistically distinct probes of individual differences in EAc function.

For further methodological details:

3. N/NE is associated with elevated tonic (stressor-independent) and reactive (stressor-dependent) negative affect in daily life

Yet the aforementioned results do not address the relevance of the risk-conferring N/NE phenotype to emotion in daily life. To understand the relevance of N/NE to real-world momentary distress, we hierarchical linear models (HLMs) to test associations between our baseline N/NE composite, on the one hand, and tonic and reactive negative affect (NA) assessed via smartphone EMA across the 30-month follow-up period (**gray box**, below). Unlike traditional ANOVA approaches, HLM naturally handles the nested dependency and variable number of EMAs contributed by each subject (n=217). Results revealed that, as expected, baseline N/NE was associated with heightened levels of both tonic (β=.12, t(215)=5.93, p<.001; **Fig. C.**) and reactive (β=.12, t(215)=5.57, p<.001; **Fig. C.**) NA.

Using HLM, Negative Affect can be modeled as $\beta_i + \beta_{N/NE} + \beta_{Stressor} + \beta_{Stressor\ x\ N/NE} + e$
$\beta_{N/NE}$ — relations between N/NE and *tonic* (stressor-independent) affect
$\beta_{N/NE\ x\ Stressor}$ — relations between N/NE and *reactive* (stressor-dependent) affect



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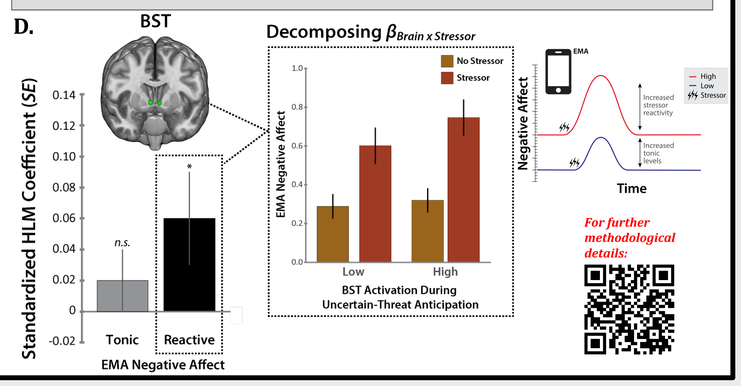
4. BST reactivity to Uncertain Threat is selectively associated with heightened reactivity to real-world stressors

At-risk individuals (high N/NE) experience pervasively elevated distress and are hyper-reactive to stressors. However, the relevance of these findings to traditional threat circuitry remains unknown. Here, we used HLMs to examine whether threat-related EAc reactivity was associated with momentary NA (n=217; **gray box**, below). Results showed that baseline BST reactivity to Uncertain Threat was associated with reactive (β=.06, t(214)=2.27, p=.023; **Fig. D.**), but *not* tonic (β=.02, t(214)=.63, p=.53), NA when controlling for BST reactivity to Certain Threat. In contrast, null relations were found in models examining Ce or BST reactivity to threat, Ce reactivity to either *Uncertain* or *Certain* Threat, BST reactivity to *Certain* Threat, and Ce or BST reactivity to emotional faces (ps>.05).

Using HLM, Negative Affect can be modeled as $\beta_i + \beta_{Brain} + \beta_{Stressor} + \beta_{Stressor\ x\ Brain} + e$
β_{Brain} — relations between brain function and *tonic* (stressor-independent) affect
$\beta_{Brain\ x\ Stressor}$ — relations between brain function and *reactive* (stressor-dependent) affect



For further methodological details:

DISCUSSION & CONCLUSIONS

- The present results demonstrate the individuals with elevated N/NE experience greater future broadband internalizing symptoms and show heightened BST activation during temporally uncertain—but not certain—threat anticipation, even after controlling for either BST reactivity to Certain Threat or Ce reactivity to Uncertain Threat.
- Our results further show that N/NE is associated with momentary distress even in the absence of stressors, whereas BST reactivity to Uncertain Threat was selectively associated with heightened stressor reactivity, but not tonic distress.
- This suggests that elevated levels of N/NE phenotype reflect exaggerated BST threat-reactivity, which manifests as potentiated reactivity to everyday stressors and challenges.
- N/NE was unrelated to Ce activation during threat anticipation and to EAc (BST/Ce) activation during 'threatening' face presentation.
- Collectively, these observations:
  - provide a first glimpse at the neural and momentary affective processes that link a prominent dispositional risk factor to the emergence of internalizing illness.
  - reinforce the hypothesis that the BST is a central component of the distributed neural system governing N/NE and its facets
  - motivate the hypothesis that exaggerated BST reactivity to uncertain threat is an active ingredient (i.e., diathesis) that helps mediate the association between N/NE and internalizing illnesses
  - caution against relying on a single task to understand the role of EAc in internalizing illness, and against muddling 'threat-related' faces (emotion perception) and genuinely distress-eliciting stimuli (emotion generation), a practice which is routine in experimental studies of novel psychiatric therapeutics
  - provide a neurobiologically grounded framework for conceptualizing internalizing illnesses and prioritizing mechanistic work focused on the BST
  - A relatively large, carefully phenotyped sample, well-controlled fMRI tasks, a 2.5-year follow-up period, and a best-practices approach (e.g., spatially unsmoothed, *a priori* ROIs, and a robust regression framework) enhances confidence in the robustness and translational relevance of these findings.

This work was supported by the ASAP Foundation; California National Primate Center; NIH (DA040717, MH107444, MH121409, MH121735, MH128336, MH129851, OD011107, MH131264, MH132280); National Research Foundation of Korea (2021R1F1A1063385 & 2021S1A5A2A03070229); UC Davis; UMD; and Yonsei Signature Research Cluster Program (2021-22-0005). Authors declare no conflicts of interest. ***Hungry to learn more about our work? Check out:*** **https://shackmanlab.org/**