The neurological 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 emotion-related fMRI paradigms and repeated waves of smartphone experience-sampling and internalizing symptom assessments—acquired from an ethnically diverse, risk-enriched sample of emerging adults (n = 217-230) followed for 2.5 years.

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 the high levels of adverse health outcomes, including elevated risk for future anxiety and depression. Yet it remains unclear what drives these longitudinal links. Here, we used Taylor's big-end robust regression to test prospective associations between baseline N/NE and longitudinal changes in Dysphoria scores (p < 0.04). Results showed that baseline N/NE was associated with longitudinal increases in Dysphoria (p = 0.04; see Results for further information on this finding). In addition, baseline N/NE was also associated with future IDAS Dysphoria scores (p < 0.04). These findings support the hypothesis that baseline N/NE confers risk for future trajectories of anxiety and depression.

2. Variation in the N/NE phenotype is uniquely associated with heightened BST reactivity to Uncertain Threat perception, and 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 amygdala (Ce), including the bed nucleus of the amygdala (BST) and central nucleus of the amygdala (Ce). Yet the relevance of these tautological discoveries to the complexities of the human brain & human N/NE remains unclear.

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 relationship of the risk-conferring N/NE phenotype to emotion in daily life. To understand the relationship of N/NE to real-world momentary distress, we used fMRI 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, fMRI 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 (p = 0.02; t(215) = 2.27, p = 0.03). fMRI Ce reactivity to uncertainty (p = 0.02; t(215) = 2.27, p = 0.03; Fig. B), and reactive (p = 0.02; t(215) = 2.27, p = 0.03; Fig. C) NA. Using HLA, Negative Affect can be modeled as β0 + β1 × HLA + β2 × N/NE + β3 × N/NE × HLA + β4 × ε (relations between N/NE and tonic (stressor-independent) affect β0, β1, β2; relations between N/NE and reactive (stressor-dependent) affect β3, β4); these findings.

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 fMRI to examine whether threat-related EAC reactivity was associated with momentary NA (n = 217; gray box, below). Results showed that baseline N/NE and BST reactivity to Uncertain Threat was associated with reactive (p = 0.06; t(215) = 2.27, p = 0.03). fMRI Ce, and not tonic (p = 0.02; t(215) = 2.27, p = 0.03). NA when controlling for BST reactivity to Certain Threat. In contrast, Ce reactivity to each Uncertain or Certain Threat, BST reactivity to Certain Threat, and Ce or BST reactivity to emotional faces (p = 0.05).

The DISCUSSION & CONCLUSIONS

The present research demonstrates 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 suggest that BST reactivity to novel psychiatric therapies

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. 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.