Background and Significance
Anxiety disorders are extremely common, debilitating, and challenging to treat, underscoring the importance of understanding the development, maintenance, and treatment of these conditions.

Threats differ along several major dimensions—probability, imminence, and duration—yet we know remarkably little about how the brain represents and responds to them. Conceptual progress has been slowed by neuroimaging paradigms that confound these key dimensions (e.g., fast vs. slow threat will occur; brief cues vs. prolonged contexts) or other perceptual characteristics (e.g., emotional faces vs. threat-of-shock; Shackman & Fox 2016).

Here, we present results from an ongoing study using a novel task and multiband fMRI to identify neuroimaging signatures related to the brain's representation of key anxiety dimensions (e.g., probability, imminence) in healthy young adults.

Competing Hypotheses
1. Functional Segregation: It is widely believed that phasic responses to certain-imminent threat (‘fear’) are organized by the central extended amygdala (Ce), whereas sustained responses to uncertain threat (‘anxiety’) are organized by the neighboring bed nucleus of the stria terminalis (BST; e.g., Somerville et al., 2013).

2. Functional Integration: Recent work in humans, monkeys, and rodents suggests that these two regions represent a tightly interconnected neural system, one that assembles states of fear and anxiety in response to a broad spectrum of dangers, including both certain and uncertain threat (Shackman & Fox, 2016).

Method
A total of 42 healthy young adults (20 F, M = 22.9 years, SD = 2.4) provided usable datasets. All procedures were approved by the University of Maryland Institutional Review Board.

Imaging data were collected on a 3T Siemens TIM Trio scanner equipped with a 32-channel head coil. A total of 578 oblique-axial EPI volumes were collected during each functional scan (multiband acceleration = 6, TR = 1 s, TE = 39.4 ms, 60 2.2-mm slices, 2.18 x 2.18 mm in-plane resolution). Images were collected at an angle of 5° relative to the AC-PC plane to minimize susceptibility artifacts. Image preprocessing was done using an in-house mix of software packages including ANTS, AFNI, and FSL. See the Detailed fMRI Method section in the lower-right corner for details. Statistical analyses were conducted with SPm12 and results are reported at FDR < 0.05 whole-brain corrected for multiple comparisons.

MultiThreat Countdown Task (2 x 2 Factorial Design)
In the Certain-Threat condition, trials consisted of a 18-s countdown followed by a 4-s exposure to one of the following threat images: Certain-Threat or Uncertain-Threat.

Results
Threat increases subjective anxiety, indexed by on-line ratings
- Threat was associated with significantly greater anxiety than Safe, p < 0.001.
- Consistent with prior work (Somerville et al., 2013), the threat x Certainty interaction was significant, p < 0.01.
- Follow-up analyses revealed that Uncertain-Threat was associated with greater anxiety than Certain-Threat, p < 0.005.

The Amygdala and BST both show phasic responses during the final 4-s of Certain-Threat
- Threat was associated with significantly greater electrodermal activity (EDA) than Safe, p < 0.001.
- The threat x Certainty interaction was significant, p < 0.001.
- Follow-up analyses revealed that Uncertain-Threat was associated with greater anxiety thanCertain-Threat, p < 0.01.

The BST shows sustained responses across the 18-s of Uncertain-Threat
- Threat increases objective arousal, indexed by EDA during the countdown
- Threat was associated with significantly greater electrodermal activity (EDA) than Safe, p < 0.001.

Discussion and Future Directions
Contrary to the Functional Segregation hypothesis, both the amygdala and BST show phasic responses to clear-and-imminent threat. Contrary to the Functional Integration hypothesis, only the BST exhibited sustained activation during Uncertain-Threat. These results are broadly consistent with recent work in monkeys showing that although both regions play a role in orchestrating responses to acute threat, the BST plays a role in organizing persistent responses to more diffuse or uncertain dangers (Shackman et al., Molecular Psychiatry, in press). A key challenge for future research will be to formally assess the Region x Condition interaction.

Our results also highlight a set of cortical regions—the MCC and AI—regions not typically considered in the rodent literature, that show both phasic and sustained responses to threat. Collectively, these results showcase the value of the MultiThreat Countdown Task and provide a novel framework for understanding the neurobiology of fear and anxiety.

References