

Neurobiological basis of anxiety risk and resilience

Jenni Blackford, PhD Hattie B. Munroe Professor and Director of Research Munroe-Meyer Institute University of Nebraska Medical Center



Anxiety disorders are characterized by excessive fear and avoidance of stimuli that causes significant distress and functional impairment.



Anxiety disorders are common



Data from Kessler (2005). Archives of Gen Psychiatry

Anxiety disorders start early



Anxiety disorders create substantial burden

- early onset
- chronic course
- significant impairment
- lack of treatment seeking
- later depression, substance use
- heightened risk for suicide

The New York Times

All Children 8 and Older Should Be Screened for Anxiety, U.S. Task Force Says

A panel of experts says the latest research supports early intervention for younger kids.

🛱 Give this article 🔗 🗍 🖵 246



What causes anxiety risk?

Biology

- inhibited temperament
- negative affective
- stress reactivity

Environment

- child maltreatment
- bullying
- overprotective parenting

Inhibited temperament

is a behavioral phenotype characterized by wariness and avoidance of novel people and situations



Inhibited temperament confers heightened risk for anxiety



Inhibited temperament is heritable

50 -80%

Inhibited temperament is stable across development







Inhibited temperament is conserved across species



What are the neurobiological basis of inhibited temperament?



Conceptual approaches

Extreme phenotype



Developmental trajectories



Psychological mechanisms



Anxiety Risk Mechanisms

Risk Mechanism #1 Novelty and Habituation

The amygdala



The amygdala detects threat



The amygdala produces fear



adapted from Davis (2001). Molecular Psychiatry

Amygdala detects novelty



Novel faces task



Familiarization Phase



Test Phase



Amygdala response to familiar faces is sustained over time



Blackford, Avery, Cowan, Shelton & Zald (2011) Social, Cognitive, and Affective Neuroscience.

Amygdala responses habituate quickly

response



exposures

Individual differences are likely



exposures

Familiarization



_+_MINININ_ +_MINININ_ +_MINININ_ +_MINININ_ +_

Inhibited adults fail to habituate









Suzanne Avery, PhD

Inhibited temperament is correlated with habituation across many brain regions



Avery and Blackford (2016) SCAN

Amygdala-visual cortex connectivity drives habituation



Replication



Schwartz (2012) Molecular Psychiatry



Bas-Hoogendam et al (2019). Depression and Anxiety

Risk mechanism #1



Risk Mechanism #2 Threat Anticipation


Children



shy, reserved, cautious, risk averse, avoids novelty

outgoing, adventurous, risk taking, approaches novelty

Threat anticipation task





Jacci Clauss, MD, PhD

Clauss, Benningfield, Rao, Blackford (2016). JAACAP.

Inhibited children fail to engage PFC during threat anticipation



PFC activation is delayed in inhibited children









Clauss, Benningfield, Rao, Blackford (2016). JAACAP.

Risk mechanism #2



Risk Mechanism #3 Unpredictable Threat

The Bed Nucleus of the Stria Terminalis

Anatomical Target



adapted from Davis (2001). Molecular Psychiatry

Amygdala vs BNST

amygdala

short-lived response

"fight or flight"

phobic stimuli predictable threat **BNST**

sustained response

hypervigilance, avoidance

context stimuli unpredictable threat

anxiety

fear

Davis, LeDoux, Walker, Fanselow and others

Degree of threat



Imaging the BNST is challenging

BNST



amygdala











3 mm

Accurate localization of the BNST with ultra-high field imaging





Avery, Clauss, Winder, Woodward, Heckers & Blackford (2014). NeuroImage. Theiss, Ridgewell, McHugo, Heckers, Blackford. (2018). NeuroImage

Mapped the BNST circuit

diffusion tensor imaging structural connectivity



resting state imaging functional connectivity





Unpredictable threat task

predictable threat "fear"





predictable safe





unpredictable threat "anxiety"





or

Adults



full continuum of social anxiety severity

Task design



Clauss, Avery, Benningfield, Blackford (2019) Depression and Anxiety

Region of interest approach



BNST selectively responds to unpredictable threat cues



Amygdala responds to threat images

Predictable Images



Clauss, Avery, Benningfield, Blackford (2019) Depression and Anxiety

Social anxiety correlates with stronger BNST activation to unpredictable threat



Risk mechanism #3



Children



full continuum of anxiety severity

Unpredictable threat task







Brandee Feola, PhD Jacci Clauss, MD, PhD Sir Norman Melancon, MD

Amygdala selectively responds to unpredictable threat cues



Cue Type

Amygdala response to images is insensitive to unpredictability



Predictable Images

Unpredictable Images



Images following Unpredictable Cues

BNST vs amygdala correlated with anxiety and age





Anxiety scores are positively correlated with BNST > amygdala response to unpredictable threat cues. BNST relative to amygdala activation to cues is higher for the older children.

Risk mechanism #3 children



Risk mechanism #1

Failure of multiple brain regions to habituate to repeated exposure to stimuli. Prevention Implication: Exposure therapy

Risk mechanism #2

Lack of prefrontal cortex activation during threat anticipation. Prevention Implication: Training to increase the use of cognitive resources during threat anticipation.

Risk mechanism #3

Heightened brain responses during unpredictable situations, such as a possible upcoming threat.

Prevention Implication: Training to increase tolerance to unpredictability.

Developmental shifts in responses to unpredictable threat







Cognitive Neuroscience of Development and Aging Center



Anxiety Resilience Mechanisms

Anxiety resilience



Resilience Mechanism #1 Preparation for Threat





shy, reserved, cautious risk averse, avoids novelty outgoing, adventurous, risk taking, approaches novelty

Threat anticipation task





Jacci Clauss, MD, PhD

Inhibited adults have a heightened PFC response during threat anticipation

dorsolateral prefrontal cortex





anterior cingulate cortex





Stronger PFC response is associated with amygdala suppression



Individual differences in anxiety and coping


Medial PFC engagement during threat anticipation is associated with resilience







Take-home points

Anxiety is highly prevalent and impairing and inhibited temperament confers risk for anxiety.

Risk mechanism #1: Failure to habituate to novel stimuli in the amygdala, hippocampus, and visual cortex.

Resilience mechanism #2: Lack of prefrontal cortical engagement during threat anticipation.

Risk mechanism #3: Hyper-responsivity to unpredictable threat, although this brain regions involved are different for children (amygdala) vs adults (BNST).

Resilience mechanism #1: Stronger prefrontal cortical engagement during threat anticipation.

Other projects

Adaptive Brains Learning about Emotion (ABLE) Study

Transdiagnostic studies of the BNST and anxiety



National Institute on Alcohol Abuse and Alcoholism



National Institute of Mental Health



U.S. Department of Veterans Affairs









Current Lab Members

Nikki Zabik, PhD Katelyn Kelley Jessica Stump Marshall Biven Brandon Wallroff Izzy Vargas

Previous Lab Members

Suzanne Avery, PhD Jacci Clauss, MD, PhD Kale Edmiston, PhD Justin Theiss April Seay, MD Marina Zaky, MD Erin Miller Ariane Huet Adaora Mgboh

Brandee Feola, PhD Manesh Gopaldas, MD Lizzie Flook, MD, PhD Cara Bedock Hannah Gardner, MSN Madison Noall

Vanderbilt University Medical Center

Meg Benningfield, MD Stephan Heckers, MD Ron Cowan, MD, PhD Baxter Rogers, PhD David Zald, PhD Neil Woodward, PhD Uma Rao, MD Maureen McHugo, PhD

Vanderbilt University

Bunmi Olatunji, PhD Danny Winder, PhD

Harvard/McLean Marisa Silveri, PhD