Neurobiological basis of anxiety risk and resilience

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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
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.

“It’s critical to be able to intervene before a life is disrupted,”
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

Clauss & Blackford (2012). JAACAP
Clauss, Avery, Blackford (2015). Progress in Neurobiology
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

inhibited
shy, reserved, cautious, risk averse, avoids novelty

\[ \mu \]

uninhibited
outgoing, adventurous, risk taking, approaches novelty
Developmental trajectories

- Anxiety disorder
- Subsyndromal anxiety
- No anxiety

- Extremely inhibited
- Extremely uninhibited

- Inhibited
- Uninhibited
Psychological mechanisms

- Behavioral trait
- Psychological process
- Brain function

- Inhibited temperament
- ?
- ?
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

Anatomical Target → Sign of Fear/Anxiety

- lateral hypothalamus → tachycardia, galvanic skin response, paleness, pupil dilation, blood pressure elevation
- dorsal motor n of vagus
- nucleus ambiguus → ulcers, urination, defecation, bradycardia
- parabrachial nucleus → panting, respiratory distress
- ventral tegmental area
- locus coeruleus → behavioral and EEG arousal, increased vigilance, increased attention
- lateral dorsal tegmental n
- basal forebrain
- n reticularis pontis caudalis → increased startle
- periaqueductal grey → freezing, conflict test, CER, social interaction, hypoalgesia
- trigeminal, facial motor n → facial expressions of fear
- paraventricular n (hypothal.) → corticosteroid release (“stress response”)
Amygdala detects novelty

Novel faces task

Familiarization Phase

Test Phase

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familiar          novel
Amygdala response to familiar faces is sustained over time
Amygdala responses habituate quickly
Individual differences are likely

response

exposures

sustained response

habituation
Familiarization
Inhibited adults fail to habituate

Amygdala

Hippocampus
For the first part of the study, faces will appear in the middle of the screen. You will have the option to indicate whether the face is happy or sad. The faces will then randomly change.

Instructions | Baseline | Exposure phase | Baseline
---|---|---|---
0s | 10s | ~60s | 4m 51s
repeat 3 times/run (2 runs)

Repeated Faces Task *(each face is presented either...)*:

1 time | 3 times | 5 times | 7 times
Inhibited temperament is correlated with habituation across many brain regions.
Amygdala-visual cortex connectivity drives habituation
Replication

Schwartz (2012) Molecular Psychiatry

Bas-Hoogendam et al (2019). Depression and Anxiety
Risk mechanism #1

behavioral trait → psychological process → brain function

inhibited temperament → response to novelty → failure of neural habituation
Risk Mechanism #2
Threat Anticipation
inhibited temperament → increased negative arousal → exposure to novel or aversive stimulus → negative experience → negative anticipation → inhibited temperament
Children

shy, reserved, cautious, risk averse, avoids novelty

outgoing, adventurous, risk taking, approaches novelty
Threat anticipation task

1s cue  3 - 8s anticipation  1s cue  1s
image  image

Jacci Clauss, MD, PhD

Clauss, Benningfield, Rao, Blackford (2016). JAACAP.
Inhibited children fail to engage PFC during threat anticipation

Clauss, Benningfield, Rao, Blackford (2016). JAACAP.
PFC activation is delayed in inhibited children

Clauss, Benningfield, Rao, Blackford (2016). JAACAP.
Risk mechanism #2

- Behavioral trait
- Psychological process
- Brain function

- Inhibited temperament
- Threat anticipation
- Lack of prefrontal cortex activation
Risk Mechanism #3
Unpredictable Threat
The Bed Nucleus of the Stria Terminalis

Anatomical Target

- lateral hypothalamus
- dorsal motor n of vagus nucleus ambiguus
- parabrachial nucleus
- ventral tegmental area
- locus coeruleus
- lateral dorsal tegmental n
- basal forebrain
- n reticularis pontis caudalis
- periaqueductal grey
- trigeminal, facial motor n
- paraventricular n (hypothal.)

adapted from Davis (2001). Molecular Psychiatry
Amygdala vs BNST

amygdala

short-lived response
“fight or flight”

phobic stimuli
predictable threat

fear

BNST

sustained response
hypervigilance, avoidance

context stimuli
unpredictable threat

anxiety

Davis, LeDoux, Walker, Fanselow and others
Degree of threat

Avery, Clauss & Blackford (2016). Neuropsychopharmacology.
Imaging the BNST is challenging
Accurate localization of the BNST with ultra-high field imaging
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

Predictable Condition

Unpredictable Condition
Region of interest approach

BNST

amygdala
BNST selectively responds to unpredictable threat cues

Clauss, Avery, Benningfield, Blackford (2019) Depression and Anxiety
Amygdala responds to threat images

Predictable Images

Percent Signal Change

BNST
Amygdala

* *

Threat Image Safe Image

Images following Predictable Cues

Clauss, Avery, Benningfield, Blackford (2019) Depression and Anxiety
Social anxiety correlates with stronger BNST activation to unpredictable threat.

Clauss, Avery, Benningfield, Blackford (2019) Depression and Anxiety
Risk mechanism #3

behavioral trait
psychological process
brain function

social anxiety
response to unpredictability
heightened BNST activation
Children

full continuum of anxiety severity
Unpredictable threat task

Predictable Condition

- 1 sec cue
- 3-8 sec anticipation
- 1 sec face
- 3-8 sec anticipation
- 1 sec cue
- 3-8 sec anticipation
- 1 sec face
- 3-8 sec anticipation
- 1 sec cue
- 3-8 sec anticipation
- 1 sec face
- 3-8 sec anticipation

Uncertain
- Uncertain face
- Certain neutral face
- Certain neutral object

Unpredictable Condition

- 1 sec cue
- 3-8 sec anticipation
- 1 sec face
- 3-8 sec anticipation
- 1 sec cue
- 3-8 sec anticipation
- 1 sec face
- 3-8 sec anticipation

Uncertain
- Uncertain

Brandee Feola, PhD  Jacci Clauss, MD, PhD  Sir Norman Melancon, MD
Amygdala selectively responds to unpredictable threat cues
Amygdala response to images is insensitive to unpredictability

Predictable Images

- BNST
- Amygdala

Unpredictable Images

- BNST
- Amygdala

Images following Predictable Cues

Images following Unpredictable Cues

Feola et al (2021) Developmental Psychobiology
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

- Behavioral trait
  - Psychological process
    - Brain function
      - Anxiety response to unpredictability
        - Heightened amygdala activation
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

![Brain Image]

**Adults**

- BNST (Blue)
- Amygdala (Red)

Percent Signal Change

Unpredictable Threat | Predictable Threat | Predictable Neutral

**Children**

- BNST (Blue)
- Amygdala (Red)

Percent Signal Change

Unpredictable Threat | Predictable Threat | Predictable Neutral

**Cognitive Neuroscience of Development and Aging Center**
Anxiety Resilience Mechanisms
Anxiety resilience

- Anxiety disorder
- Subsyndromal anxiety
- No anxiety

Extremely inhibited

Extremely uninhibited

Early childhood

Late adolescence

Development
Resilience Mechanism #1
Preparation for Threat
Adults

Inhibited
- shy, reserved, cautious
- risk averse, avoids novelty

Uninhibited
- outgoing, adventurous
- risk taking, approaches novelty
Threat anticipation task

1 sec cue 4 - 9.5 sec anticipation 1 sec face 4 - 9.5 sec

fear trial

1 sec cue 4 - 9.5 sec anticipation 1 sec face 4 - 9.5 sec

neutral trial

Jacci Clauss, MD, PhD
Inhibited adults have a heightened PFC response during threat anticipation

dorsolateral prefrontal cortex

anterior cingulate cortex

Clauss et al (2014). Depression and Anxiety
Stronger PFC response is associated with amygdala suppression

Clauss et al (2014). Depression and Anxiety
Individual differences in anxiety and coping

- Social anxiety
- Emotion regulation

Clauss et al (2014). Depression and Anxiety
Medial PFC engagement during threat anticipation is associated with resilience

Clauss et al (2014). Depression and Anxiety
behavioral trait

psychological process

brain function

inhibited temperament

preparation for threat

stronger prefrontal cortex activation
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

[Logos of Vanderbilt University, University of Nebraska Medical Center, University of Wisconsin-Madison, NIH, National Institute of Mental Health, U.S. Department of Veterans Affairs]
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