Neurodevelopmental Approach to Affective Disorders

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US Health Statistics underscore importance of understanding psychopathology from a neurodevelopmental viewpoint

Adolescents is the most common time of life for psychiatric illness to emerge (Kessler et al., 2005) reported anxiety reaching its lifetime peak at this time (Abe & Suzuki, 1986) and suicide being the fourth leading cause of death (Eaton et al., 2008).
Overarching Question

How is the brain changing during developmental periods of increased risk such as adolescence?
-Differential development of limbic subcortical relative to prefrontal control regions leads to imbalance in brain systems that may favor incentive/emotion driven over rational behaviors.
Frontolimbic Circuitry
MRI Data shows Cortical Development across Childhood

Gogtay et al 2004 PNAS
Dramatic developmental changes in prefrontal and subcortical limbic regions during adolescence

Focus has typically been on prefrontal cortex (PFC)

Subcortical limbic regions involved in fight, flight

Sowell et al 1999
Nature Neuroscience
Most affective disorders reflect aberrant learning/unlearning of cues/contexts that signal safety or danger.
Facial Expressions as Conditioned Cue in the Environment – implies learning across development
Development of the amygdala response to facial expressions

Thomas et al., 2001
Amygdala response to Neutral Faces decreases with Age
Amygdala response to Fear faces increase with Age
Childhood Anxiety and Amygdala

Thomas, et al. (2001)
Archives of General Psychiatry, 58, 1057

Child Reported SCARED Score

% Signal Change in R. Amygdala

$r = 0.787$
$p < 0.001$
Signals of Safety or Threat (emotional cues) can bias Behavior

Repeated exposure to “empty threat”

Hare et al 2005 Bio Psychiatry
Emotional Cues Bias Behavior

![Graph showing reaction time for different emotional cues: Fearful, Neutral, Happy. The Fearful cue has a significantly higher reaction time with an asterisk indicating statistical significance.](image-url)
Neuroanatomical Correlates of Behavioral Bias

Hare et al 2008 Bio Psychiatry
Strength of Frontolimbic Connections is correlated with Emotion Regulation (DTI)
Sensitivity to emotional cues (Emotional Reactivity) is exaggerated in adolescents.

Consistent with work by Thomas, Monk, Baird, etc.

Hare et al. 2008 Bio Psychiatry
Amygdala Activity to Repeated Exposures of Emotional Cues (Habituation)

Hare et al. 2008 Bio Psychiatry
Habituation of Amygdala Response to repeated exposures of empty threat correlated with ratings of Trait Anxiety (i.e., decrease in activity from early to late trials)

Note: female pattern Thomas et al 2001
Functional Coupling of Ventromedial Prefrontal Cortex and Amygdala associated with Habituation of Amygdala Response

Stress on these systems
Anxious Individual

Less Anxious
Environmental & Genetic Risk Factors

- Exposure to adversity
- Genetic predisposition
THE AFTERMATH OF 9/11
Effects of proximity and repeated trauma on emotional centers of the brain (amygdala).

Ganzel, Casey et al 2007 *Emotion*
THE AFTERMATH OF 9/11
Effects of proximity and repeated trauma on emotional centers of the brain (amygdala).

Ganzel, Casey et al 2007 *Emotion*
Effects of Trauma on Amygdala response to threatening stimuli (Rauch et al., 2000)

Current models: Hyper-responsiveness of amygdala inadequate top-down governance by mPFC
Prefrontal dendritic complexity in rodents and functional connectivity in humans decreases with stress

Liston, McEwen, Casey (in press) *PNAS*
Genetic Factors:
BDNF Val66Met mouse model
(insertion not deletion)
Anxious phenotype
Slower Extinction of fear response

Chen et al 2006 Science
BDNF Polymorphism associated with greater anxiety

HUMAN

分离焦虑

MOUSE

皮质醇对压力的反应

Casey, Bath, Tottenham, Altemus & Lee
Genetic Factors:
BDNF Val66Met mouse model
(insertion not deletion)
Anxious phenotype
Slower Extinction of fear response
Altered Extinction

**Rodent**

- % Freeze to Cue
- Blocks (3 trials)
- Genotypes: +/+, +/M, M/M

**Human**

- Galvanic Skin Response To CS+ relative to CS-
- Blocks (3 trials)

Soliman, Pattwell, Glatt, Lee, Casey
Implications

Early identification and intervention of individuals at risk for anxiety, depression and suicide based on imaging and genetic measures.
Changes in behavior during adolescence are paralleled by differential development of subcortical limbic regions relative to prefrontal control regions leading to **imbalance**.

Individual differences in sensitivity to motivational and emotional cues suggest environmental and genetic factors feed into risk and resilience during this period.