Research to Practice Series

Managing emotions in teens: Responding to dysregulation and challenging behaviors

THE NEUROBIOLOGY OF ADOLESCENT MOOD

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Disclosure Information
University of Minnesota
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⇒ I have no financial relationships to disclose.
⇒ I will not discuss off label use and/or investigational use in my presentation.
The transition through adolescence is accompanied by transformations:

- Physical
- Psychological
- Social

Silk, Steinberg, & Morris, 2003

These changes are associated with experiences that elicit novel and intense emotional arousal requiring emotion regulation.

Silk, Steinberg, & Morris, 2003

Stressful Contexts
Emotion Regulation

In adolescence there is continued maturation of multiple systems that underlie emotion (stress regulation)

- Neural systems
- Physiological systems

Silk, Steinberg, & Morris, 2003; Paus, Keshavan, & Giedd, 2008

OBJECTIVES

- How does the neurobiological stress regulatory system develop?
  - Maturation of the brain and physiological systems
- How might development go awry?
  - Contributing Factors (distal and proximal)
  - Example of Adolescent Depression
- How do these advances provide hope for effectively intervening?
  - Preliminary Evidence
1. How does the neurobiological stress regulatory system develop?

- Brain
  - Frontal Lobe
  - Limbic Lobe
- Physiological Response
  - Hypothalamic-Pituitary-Adrenal (HPA) axis

Neurobiological Stress Model

- Nervous system
  - Central nervous system
    - Brain
  - Peripheral nervous system
    - Sensory
    - Motor
    - Autonomic
      - Sympathetic
      - Parasympathetic
- Physiological Response
  - Hypothalamic-Pituitary-Adrenal (HPA) axis

http://servingnature.blogspot.com/2013/03/ans-pharmacology.html

Brain Development:
Prenatal Brain Development and Organization

Brain Structures

Brain Functions

Frontal Lobe
(Control)
- Motor Cortex
- Prefrontal Cortex – Cognitive Processes
  - Planning
  - Control

Limbic Lobe
(Emotion)
- Amygdala
  - Attention to Stress (Threat)
- Hippocampus
  - Memory

Frontal Lobe:
- Control
- Cognitive Processes
  - Planning
  - Executive

Limbic Lobe:
- Emotion
- Stress Response
  - Attention
  - Memory
Physiological Stress System: Basal

Physiological Stress System: Stress

Stress Test

- TSST
  - Prepare a speech for 5 minutes.
  - Deliver 5 minute speech (job interview)
  - Arithmetic, 5 minutes

Kirschbaum, Pirke, & Hellhammer, 1993
II. How might development go awry?

Example: Adolescent Depression

Plasticity & Brain Development

- **Plasticity**: extent to which the brain can respond to new experience or recover from injury
  - Typically decreases with age (nervous system becomes specialized)
  - Not limited to infancy/childhood—new synapses (and some new neurons) are formed throughout life
Sensitive Period & Brain Development

- **Sensitive period**: an optimal time interval during which a specific type of experience is necessary for proper development of brain systems and corresponding behavioral skills.

Adverse Events
Psychopathology

Interaction of biology and environment

Factors that Promote or Interfere with Emotion Regulation

Distal Factors
- Genetic Factors (temperament)
- Environmental Factors (learning history)

Proximal Factors
- Available Resources
  - Social Support
  - Lifestyle

Genetics
Genetic Contributions

Genetically engineered mice (mice lacking in the gene for GABA receptor component – delta subunit) showed signs of depression (lithargy, less pleasure seeking), shunned their pups and failed to make proper nests.

Maquire et al, 2008

Environmental Contributions

Early Life Stress Hypothesis

**RODENT RESEARCH:**

- In laboratory animal studies show that ELS leads to heightened stress reactivity and alterations in relevant neurocircuitry.
  - Adults rats separated from dams for 180min/day on postnatal days 2-14 exhibit three-fold increase in Cort responses to psychological stressors that control adults.

Ladd, et al, 2000; Plotsky & Meaney, 1993

Epigenetic Effects

Differential Gene Expression

The CORT receptor gene (GR) is important in regulating stress reactivity.

- In the mouse, maternal behavior affects gene expression.
- GR expression is highly plastic in the days immediately after birth.

From Sapolsky, 2004
Neurobiological Stress Model

Current models of adult depression have implicated the frontal-limbic neurocircuitry in the HPA axis.


Structural Connectivity Results

White matter connectivity between the subgenual ACC and the amygdala
Lower Fractional Anisotropy in MDD group

F=7.1, p=0.01, Effect size = 1.0
Cullen, Klimes-Dougan, Mazur, et al, 2010

Functional Connectivity Results

Seed: Subgenual ACC (BA25)

Controls
Depressed
Group Difference

p < 0.05, corrected
Cullen, Gee, Klimes-Dougan et al, 2009
Functional Differences

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Physiological Stress System: Stress

http://upload.wikimedia.org/wikipedia/en/b/b1/Basic_HPA_Axis.jpeg

“Why Zebras Don’t Get Ulcers”

Robert Sapolsky

- Mobilizes energy
- Raises HR/BP
- Slows digestion
- Slows growth
- Slows reproduction
- Blunts pain
- Speeds up aging
- Suppresses immune functions
Neurotoxic Effect of Stress

- Key Receptors
  - GR - glucocorticoid
  - MR - mineralcorticoid
- Receptor Regions of Concentration
  - Amygdala
  - Hippocampus
  - Lateral Septum
  - VMPFC

HPA axis functioning in Depressed Adults

- Burke, Davis, Ottie, & Mohr, 2005
- In infants (4 mo) from the NC group, low cortisol levels regardless of whether they received high sensitivity (HS) parenting or low sensitivity (LS) parenting. Infants in the DX group had significantly higher cortisol levels if they received LS parenting, but not if they received HS parenting.

Children at Risk for Depression

- Importance of Maternal Sensitivity
- Kaplan, Evans, & Monk, 2007
- Infants of mothers in the NC group had low cortisol levels regardless of whether they received high sensitivity (HS) or low sensitivity (LS) parenting. Infants in the DX group had significantly higher cortisol levels if they received LS parenting, but not if they received HS parenting.
Children at Risk for Depression
Prepubertal

Saliva cortisol in normal children compared with children of parents with MDD under basal conditions (A) and after 5 mg dexamethasone (dex) (B).
Elevated cortisol in the children of MDD parents (B).

Young, Vazquez, Jiang & Pfeffer, 2006

TSST - HPA Axis
Adolescents with Emotional/Behavioral Problems

Klimas-Dragan, Hastey, Granger et al., 2001; DeRose, Klimas-Dragan, Shirtcliff et al., 2009

III. How do these advances provide hope for effectively intervening?
Example: Adolescent Depression
Adolescent Depression

- Major Depressive Disorder (MDD)
  - Is a leading cause of disability worldwide
    - Ranked 3rd as global burden of disease
  - Onset is common in adolescence
  - An early onset in adolescence carries a particularly poor prognosis
    - Risk for morbidity
    - Risk for mortality

www.sdchip.org/work_teams/wt_na/wt_na_pdfs/F-depression
Brent & Kolko, 1990

Adolescent Depression

- Growing interest in addressing the problem early in the disease course
  - It is thought to be critical to take advantage of the malleability of brain and physiological systems
    - prior to maturity
    - before detrimental processes become entrenched (scarring)

Available Evidence Based Treatments (EBTs)

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<tr>
<th>Mild</th>
<th>Mild to moderate</th>
<th>Moderate to Severe</th>
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| • Psycho-education  
  • Supportive Therapy | • Cognitive Behavioral Therapy (CBT)  
  • Interpersonal Therapy (IPT) | • Medication (fluoxetine & escitalopram)  
  • Medication + CBT or IPT |
Hypothetical model of functional changes in amygdala and the main prefrontal areas involved in anxiety disorders and major depressive disorder.

Quide, Witteveen, El-Hage et al., 2011

Current Treatment Response Rates

TADS Team (2004)


Response defined as CGI = 1 or 2 ("much improved" or "very much improved")

About 30% did not benefit from COMB
A Promising Approach: Personalizing Interventions

- The next step: to move beyond determining what interventions work to identifying which interventions work for whom

- Identifying patient characteristics that interact with, or moderate, intervention can guide clinicians in selecting an intervention that more rapidly and efficiently manages depression

Insel, 2009; National Institute of Mental Health Strategic Plan, 2008

Thank you!