Developmental Model To Explain Onset And Directionality Of Comorbid Disorders

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What is the directionality of the onset of comorbid substance use and other psychiatric disorders
APA 2007
Clinical Diathesis
Substance Abuse
Genetics
Environment

DEVELOPMENT

Core Psychological Processes
Impulsivity
Reinforcement
Attention

ADHD
Depression

Core Underlying neural networks
Amygdala
PFC
Ventral Striatum

Genetics
Environment
ADOLESCENCE PEAK ONSET OF PSYCHOPATHOLOGY

- MOOD DISORDERS
- ANXIETY DISORDERS
- SUBSTANCE ABUSE DISORDERS
ADOLESCENCE: UNIQUE COGNITIVE/AFFECTIVE ARCHITECTURE

COGNITIVE IMPULSIVITY

RISK SEEKING

AFFECTIVE INTENSITY
Brain Development

Based on 243 Brain MRI Scans of 145 Children and Adolescents

Giedd et al., 1999
Decision-Making Circuits

From Kelley et al., 2004

McGinty and Grace, 2006
Yim, Mogenson, 1982
Modulatory Control
• Imbalance between maturation of emotional systems and cognitive systems

• Imbalance among approach behavioral system, avoidance behavioral system, and self-regulation
NUCLEUS ACCUMBENS
(Ventral Striatum)

- Involved in responses to appetitive stimuli and approach behavior
- Indexed by changes in dopamine release in the striatum
Nucleus Accumbens--Approach

Leyton et al., 2002

Extracellular Dopamine

Novelty Seeking

$\text{r} = 0.75, p < 0.033$

Exploratory-Excitability

$\text{r} = 0.74, p < 0.036$

Leyton et al., 2002
5mg/kg ip amphetamine
Rat Model

Percent baseline of dopamine release

Rat age
P21  P35  P70
7 y.o. 11 y.o. 18 y.o.

Equiv. Human Age
7 y.o. 11 y.o. 18 y.o.

Andersen et al., 1997
AMYGDALA

- Involved in responses to aversive stimuli and avoidance behavior: Amygdala lesions
- Developmental changes: Early gene expression in response to stress
APPROACH / AVOIDANCE AMYGDALA LESIONS

Active Trial

Neutral Trial

Izquierdo and Murray, 2004
APPROACH / AVOIDANCE AMYGDALA LESIONS

Izquierdo and Murray, 2004
Amygdala Response in Rats
After 15 min. restraint

Adults

Adolescents

Adolescents: **less** Fos expression in amygdala

Kellogg et al., 1998
MEDIAL PREFRONTAL CORTEX

• Involved in Executive Function, higher level of behavioral control

• Unique changes in adolescence (animal work)
  1. DA input to PFC peaks in adolescence (Rosenberg & Lewis, 1995).
  2. DA concentrations (Leslie et al, 1991) and DA fiber density (Benes et al, 2000) rise throughout adolescence
VALENCE RESPONSE IN ADULTS

Appetitive vs. Aversive

[Appetitive – Aversive]

fMRI BOLD signal change

Reactivity to:

Both

Appetitive

Aversive

Appetitive

Aversive

Appetitive

Aversive
VALENCE RESPONSE IN ADULTS

Appetitive vs. Aversive

BOLD fMRI signal change

Appetitive
GAIN > NO-GAIN

Aversive
NO-LOSS > LOSS
Adolescent Balance

Risk-taking proclivity

From Kelley et al., 2004
PARADIGMS

Wheel of Fortune
(Ernst et al., 2003)

Selection-Action
Anticipation
Feedback

Monetary
Incentive Delay
(Knutson et al., 2001)

Anticipation-Action
Feedback

Cue
Anticipation
Target
Feedback

500 ms
4000 - 4500 ms
180 - 260 ms
500 ms

TIME (ms)

3 s
4 s
4 s

Selection
Anticipation
Feedback

How do you feel?
1
2
3
4
5

$4

+ $1.00
Wheel of Fortune Task

Stages: 1- Selection  2- Anticipation  3- Feedback

<table>
<thead>
<tr>
<th>Selection</th>
<th>Anticipation</th>
<th>Feedback</th>
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<tbody>
<tr>
<td>3 s</td>
<td>4 s</td>
<td>4 s</td>
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<tr>
<td>$ 4</td>
<td>$ 0.50</td>
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How do you feel?

1  2  3  4  5

Happy  Upset

% Risk-Taking

Gains  Losses

$4  $0.50  $4  $0.50

50%

Adults  Adolescents
Win $4.00 vs. No-Win $4.00

ADOLESCENTS > ADULTS

Nucleus Accumbens

ADULTS > ADOLESCENTS

Amygdala

Ernst et al., 2005

P<0.05
Wheel of Fortune Task

Stages:
1- Selection
2- Anticipation
3- Feedback

Selection

Anticipation

Feedback

$4

$0.5

3 s

4 s

4 s

How do you feel?

1 2 3 4 5
PREFRONTAL ACTIVATION
ADOLESCENTS < ADULTS

A.

Z = - 6mm

X = 2mm

B.

Eshel et al., Neuropsychologia, 2007
Adolescent Balance

Risk-taking proclivity

From Kelley et al., 2004
Dopamine Models

DOPAMINE IN REWARD FUNCTION

DOPAMINE → Salience/valence → Action → Outcome Response

DOPAMINE IN RISK-TAKING

DOPAMINE

HE

High

Low

Need State

Incentive Salience Model (Berridge & Robinson, 1998)

Action

Feedback

High

High

High-Efficiency Model (HE)

Low

High
MONETARY INCENTIVE DELAY MID Task

Knutson et al., 2001
ADOLESCENTS VS. ADULTS

Bjork JM, Knutson B, Fong GW, Caggiano DM, Bennett SM, Hommer DW.
EXUBERANT TEMPERAMENT

(J. Neuroscience 2006)
Attention Deficit Hyperactivity Disorder

Scheres A., Milham MP, Knutson B, Castellanos FX
(Biol Psychiatry, 2006)

ADHD ADOLESCENTS

CONTROL ADOLESCENTS
Developmental Model of Reward Systems

RISK FOR PSYCHOPATHOLOGY
COMORBIDITY (SUBSTANCE ABUSE, ADHD, DEPRESSION…)

High-Efficiency Model (HE)

High-Efficiency Model (HE)

Avoidance

Approach

Action

Feedback

Low

High

Appetitive Stimuli

Aversive Stimuli
CLINICAL IMPLICATIONS

• Evolutionary fitness:
  – Highly conserved behavior across species

• Policy making:
  – Age limit for driving license
  – Age limit for alcohol consumption

• Risk for psychopathology - comorbidity:
  – Predictive value of the model
  – Parameters specific to distinct disorders
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<th>NIMH</th>
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