

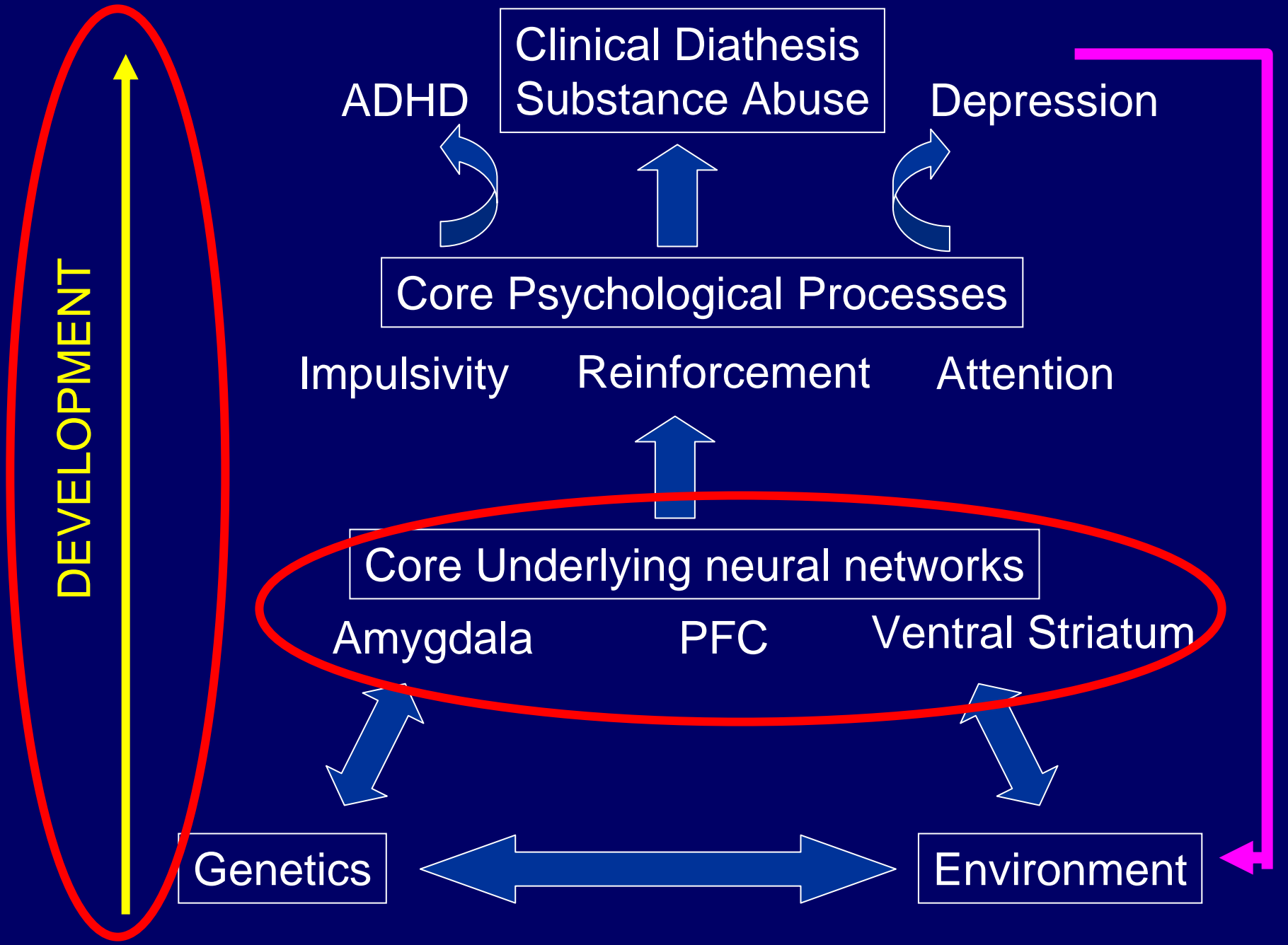
What is the directionality of the onset of comorbid substance use and  
other psychiatric disorders  
APA 2007

# Developmental Model To Explain Onset And Directionality Of Comorbid Disorders

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Emotional Development and Affective Neuroscience  
National Institute of Mental Health  
NIH / DHHS





# ADOLESCENCE PEAK ONSET OF PSYCHOPATHOLOGY

- MOOD DISORDERS
- ANXIETY DISORDERS
- SUBSTANCE ABUSE DISORDERS

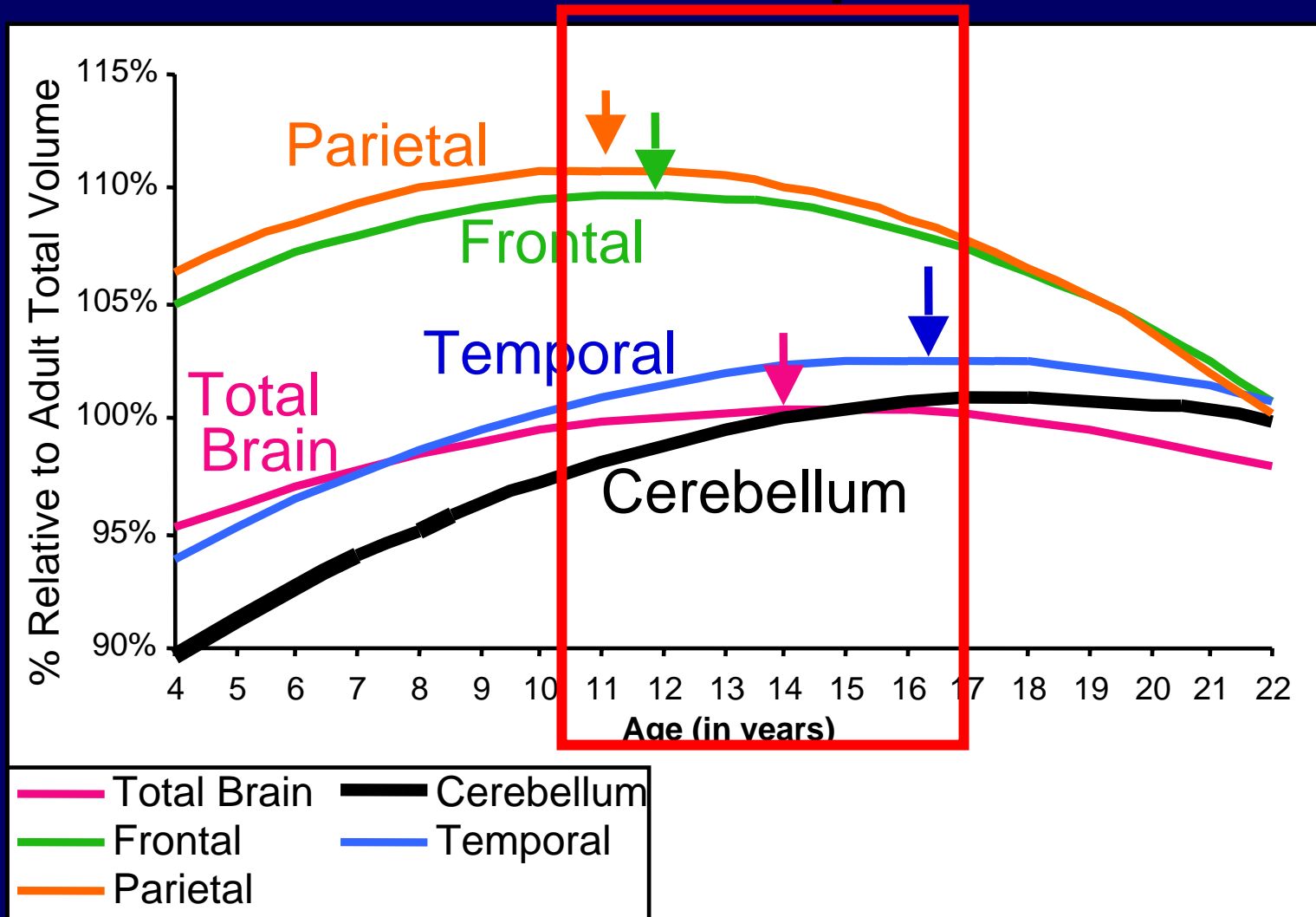
# ADOLESCENCE: UNIQUE COGNITIVE/AFFECTIVE ARCHITECTURE

COGNITIVE IMPULSIVITY

RISK SEEKING

AFFECTIVE INTENSITY

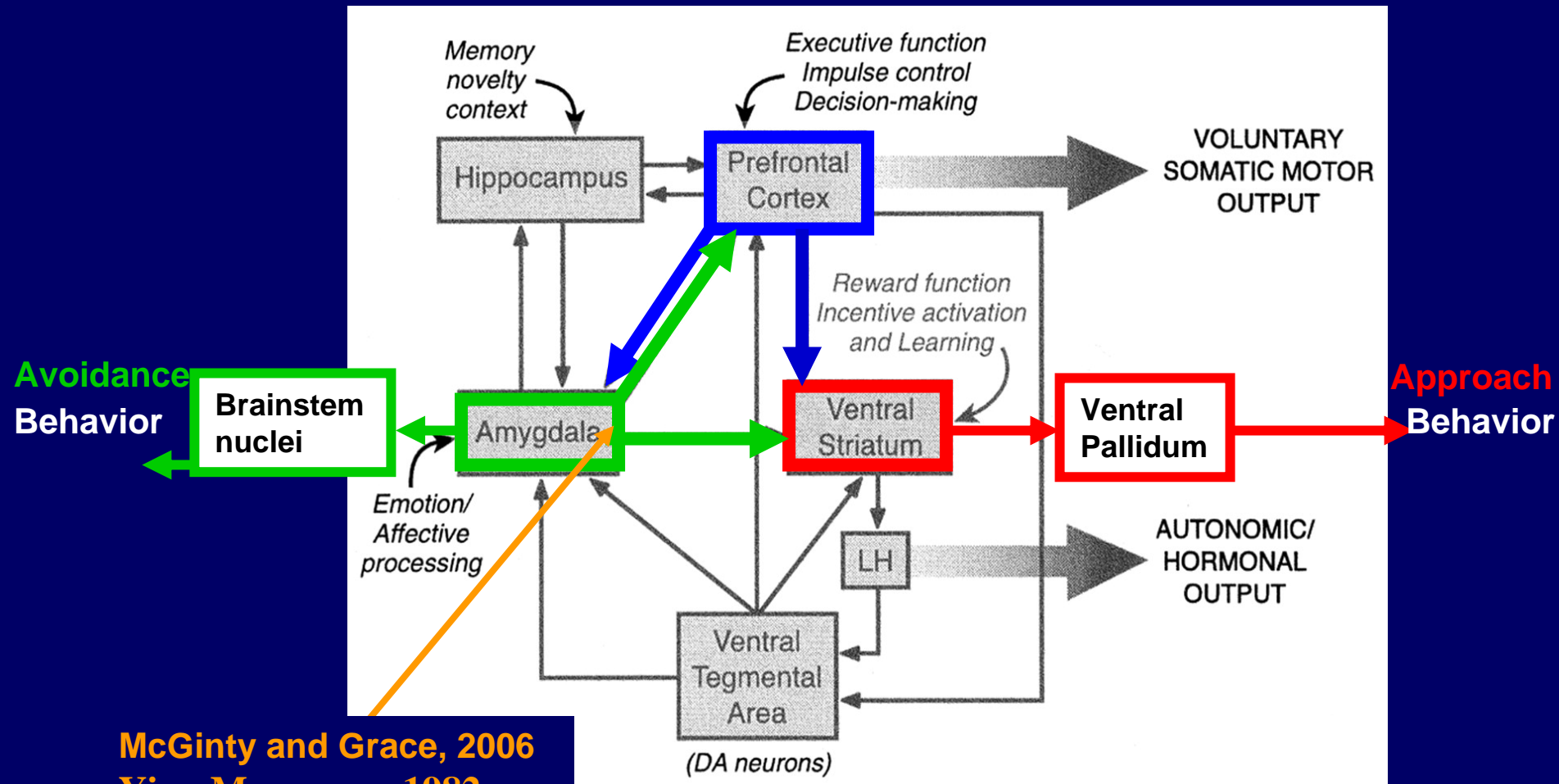
# Brain Development



Based on 243 Brain MRI Scans of 145  
Children and Adolescents

Giedd et al., 1999

# Decision-Making Circuits



McGinty and Grace, 2006  
Yim, Mogenson, 1982  
*Modulatory Control*

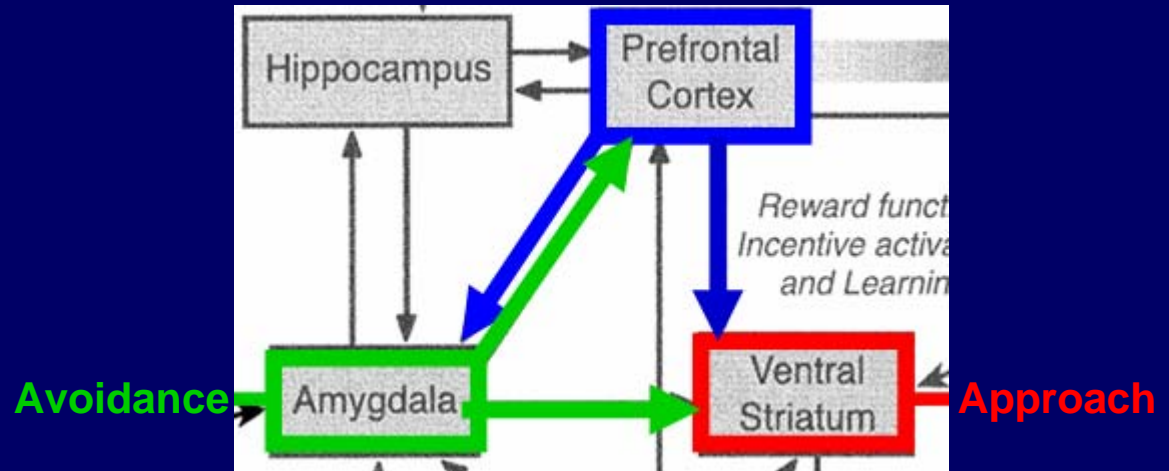
*From Kelley et al., 2004*

# ADOLESCENT BEHAVIOR

COGNITIVE IMPULSIVITY

RISK SEEKING

AFFECTIVE INTENSITY



- Imbalance between maturation of emotional systems and cognitive systems
- Imbalance among approach behavioral system, avoidance behavioral system, and self-regulation

# NUCLEUS ACCUMBENS (Ventral Striatum)

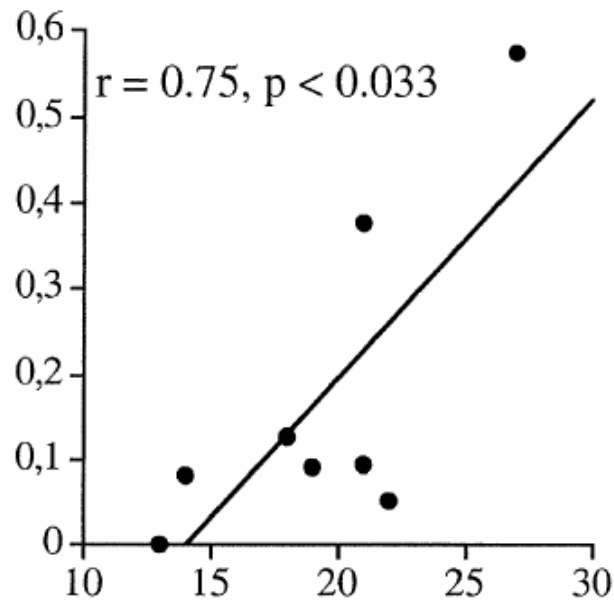
- Involved in responses to appetitive stimuli and approach behavior
- Indexed by changes in dopamine release in the striatum



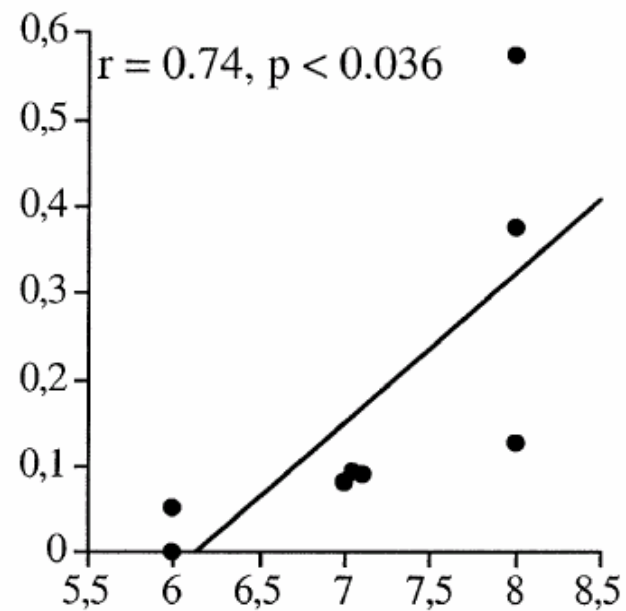
# Nucleus Accumbens-- Approach

Extracellular Dopamine

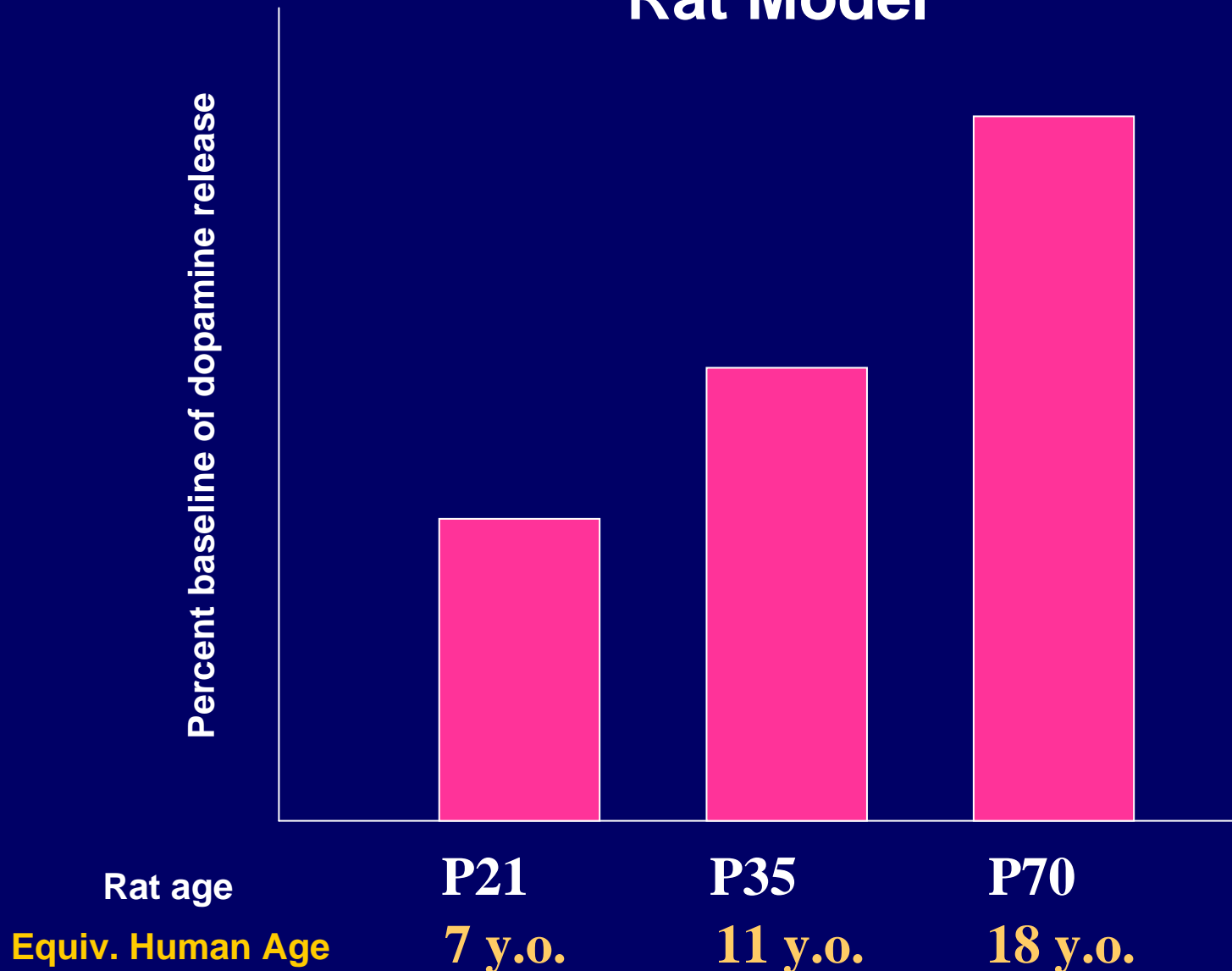
Novelty Seeking



Exploratory-Excitability



# 5mg/kg ip amphetamine Rat Model

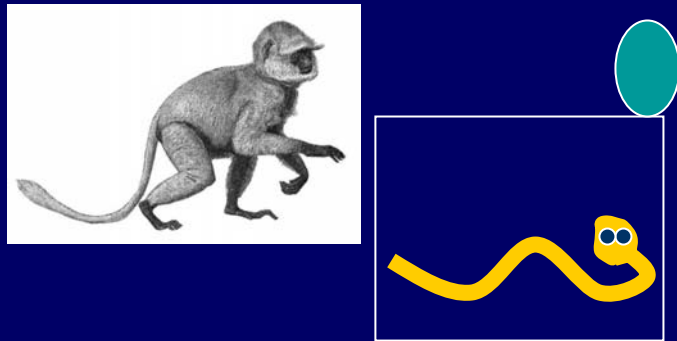


# AMYGDALA

- 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



snake

Neutral Trial

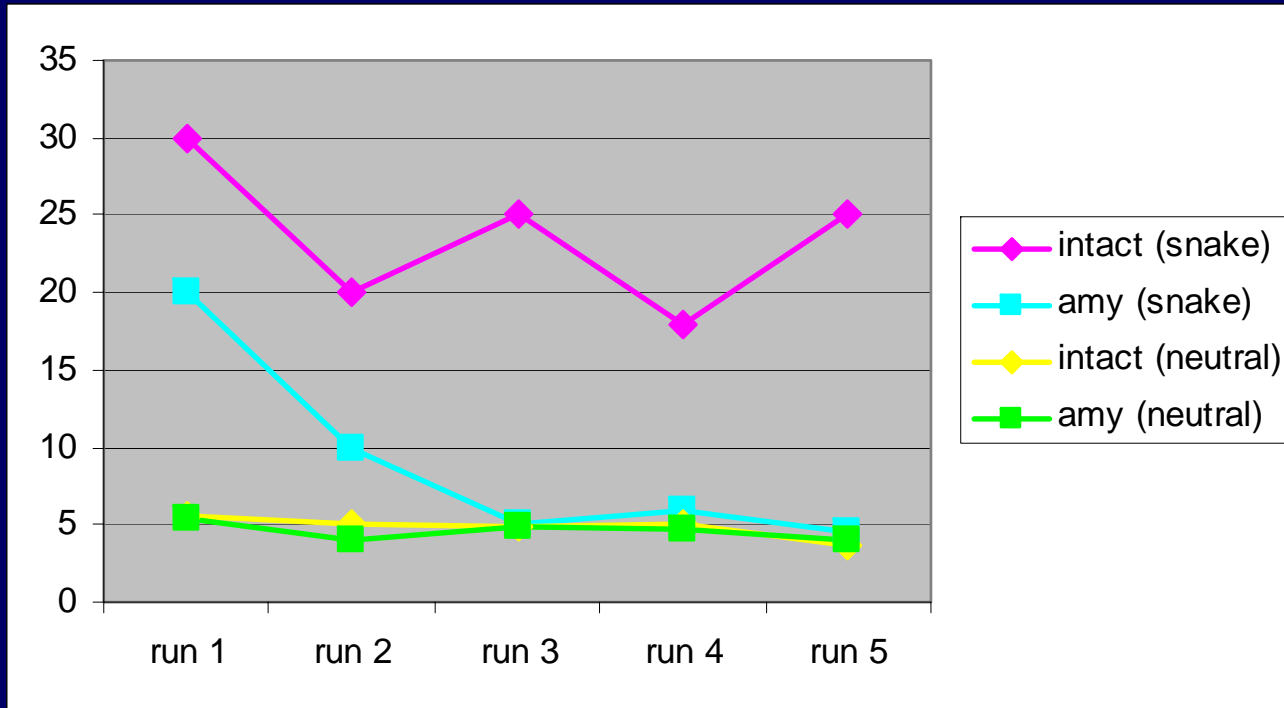


neutral

# APPROACH / AVOIDANCE AMYGDALA LESIONS

Avoidance

Mean latency (s)



Approach

# 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
  3. Disappearance of DA autoreceptors, loss of buffering capacity (Dumont et al, 2004)

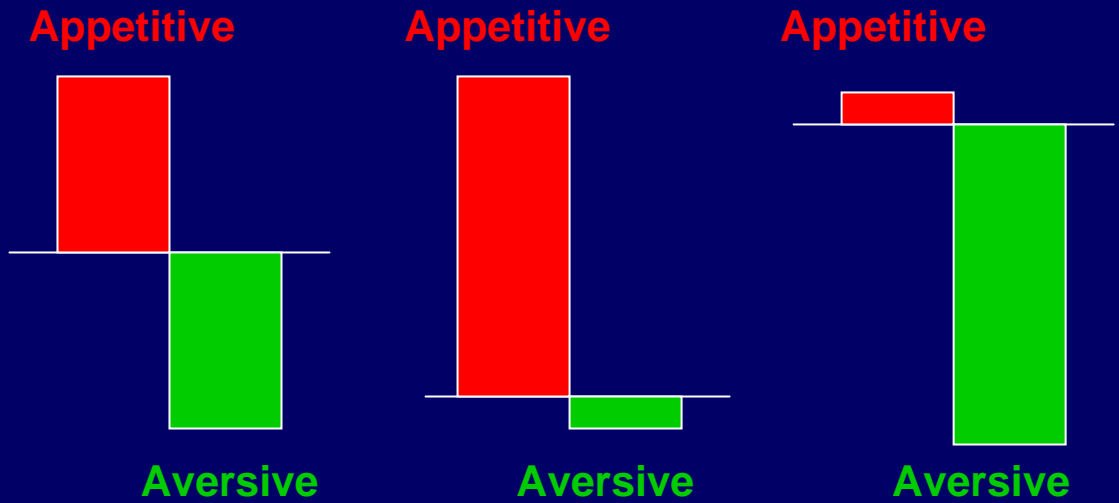
# VALENCE RESPONSE IN ADULTS

## Appetitive vs. Aversive

[Appetitive – Aversive]

fMRI BOLD signal change

0



Reactivity to:

Both

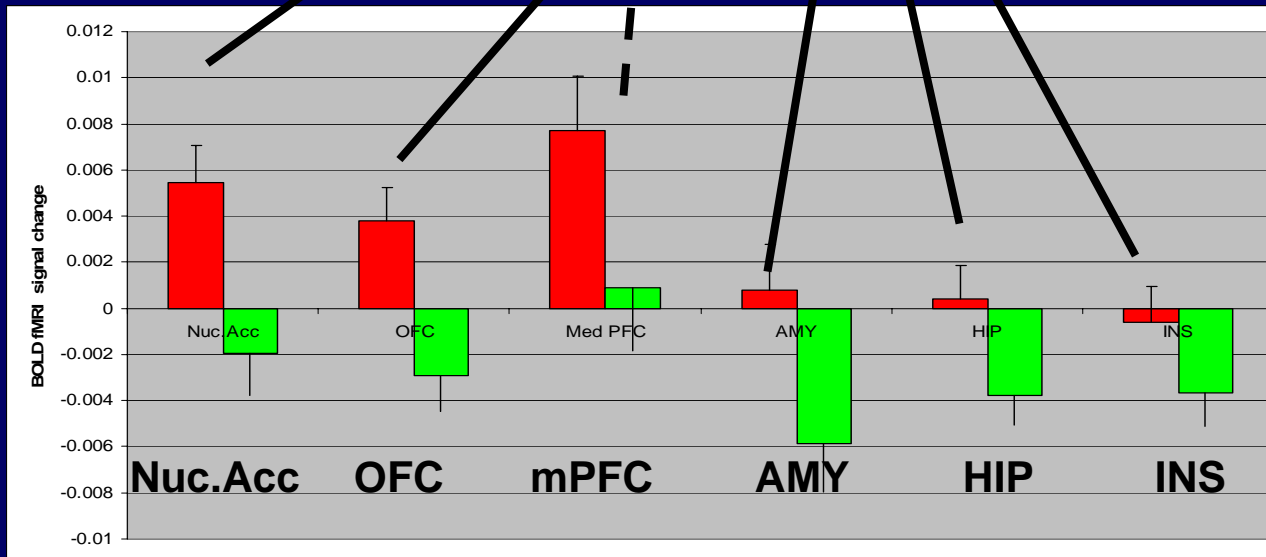
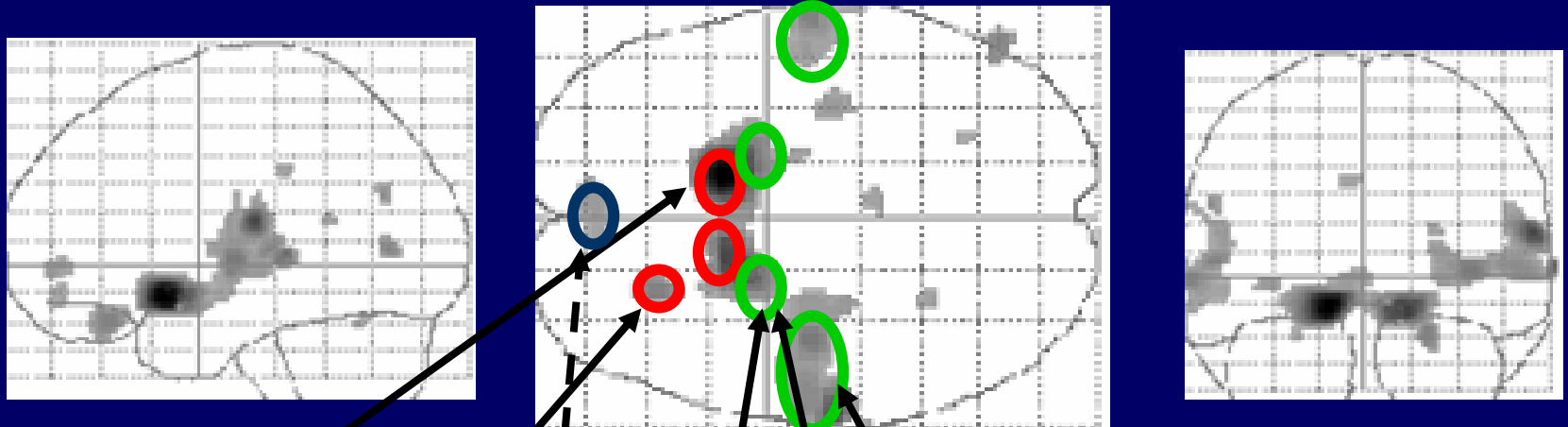
Appetitive

Aversive



# VALENCE RESPONSE IN ADULTS

## Appetitive vs. Aversive

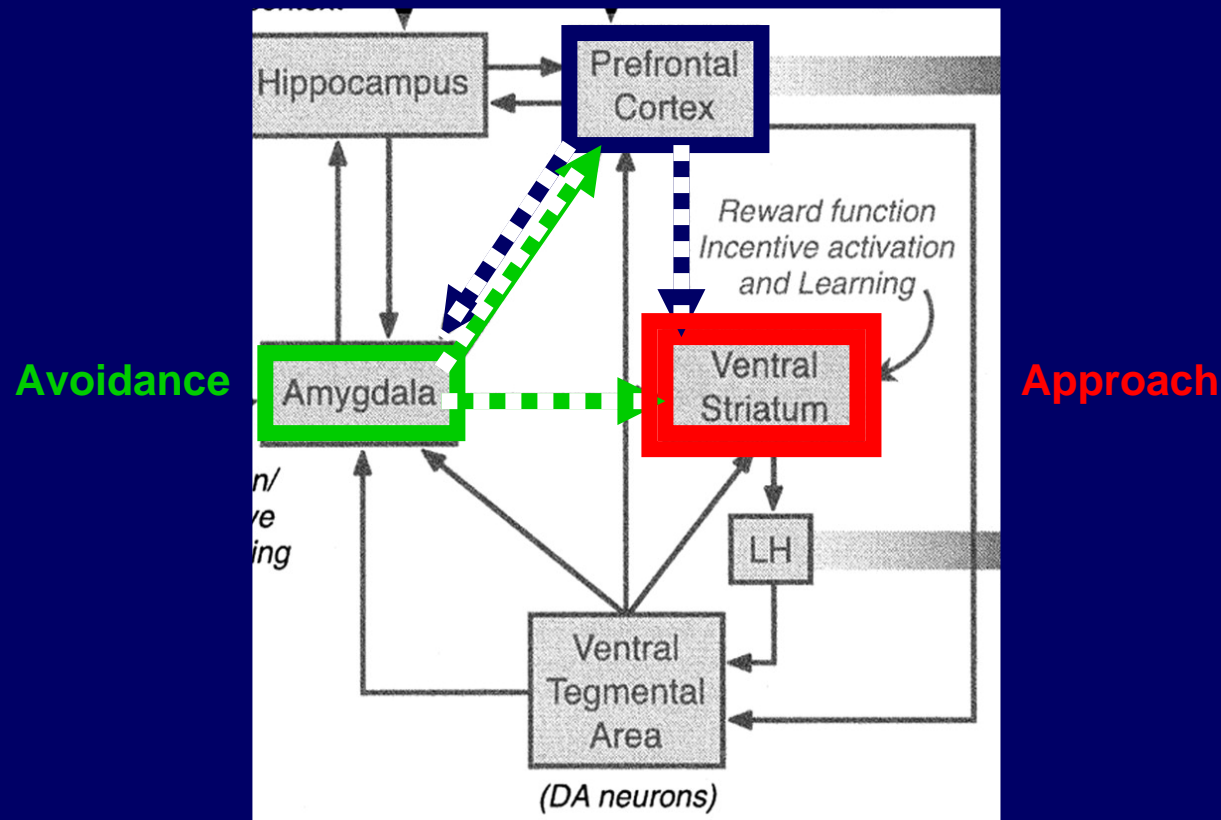


**Appetitive**  
GAIN > NO-GAIN

**Aversive**  
NO-LOSS > LOSS

# Adolescent Balance

## Risk-taking proclivity

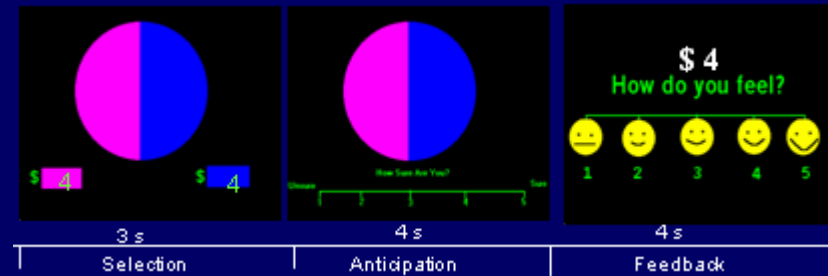


*From Kelley et al., 2004*

# PARADIGMS

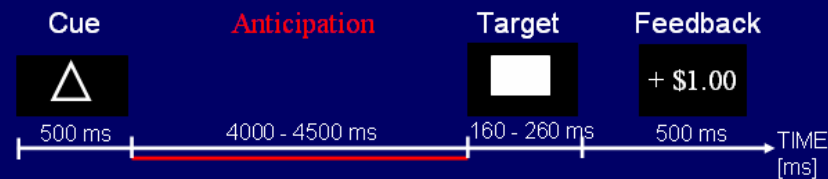
## Wheel of Fortune (Ernst et al., 2003)

Selection-Action  
Anticipation  
Feedback



## Monetary Incentive Delay (Knutson et al., 2001)

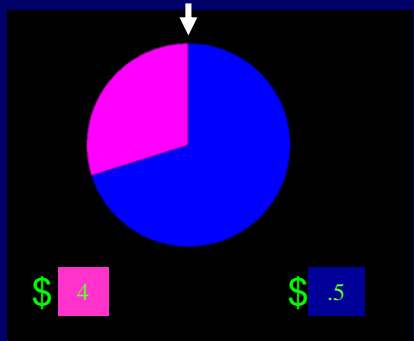
Anticipation-Action  
Feedback



# Wheel of Fortune Task

Stages:

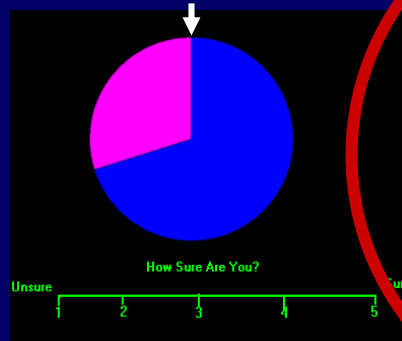
1- Selection



3 s

Selection

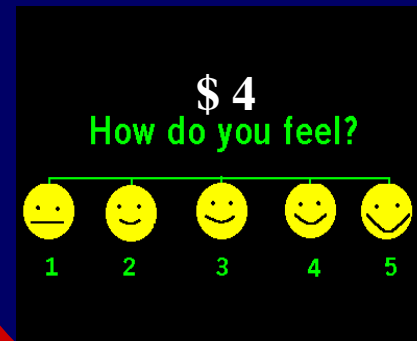
2- Anticipation



4 s

Anticipation

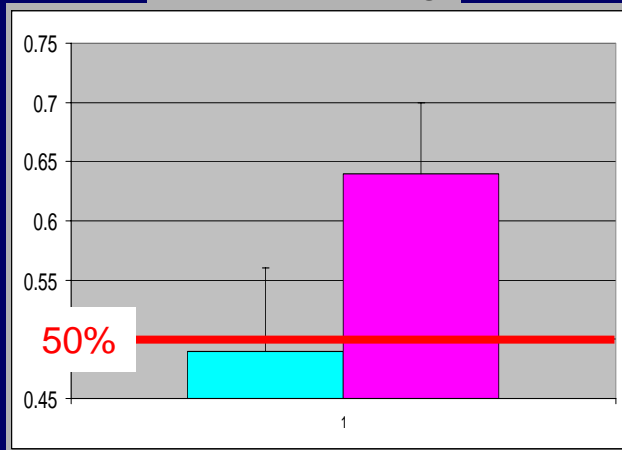
3- Feedback



4 s

Feedback

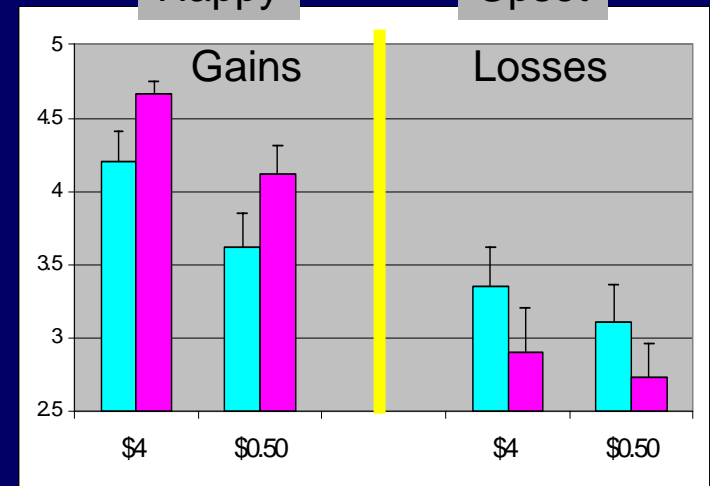
% Risk-Taking



Adults  
Adolescents

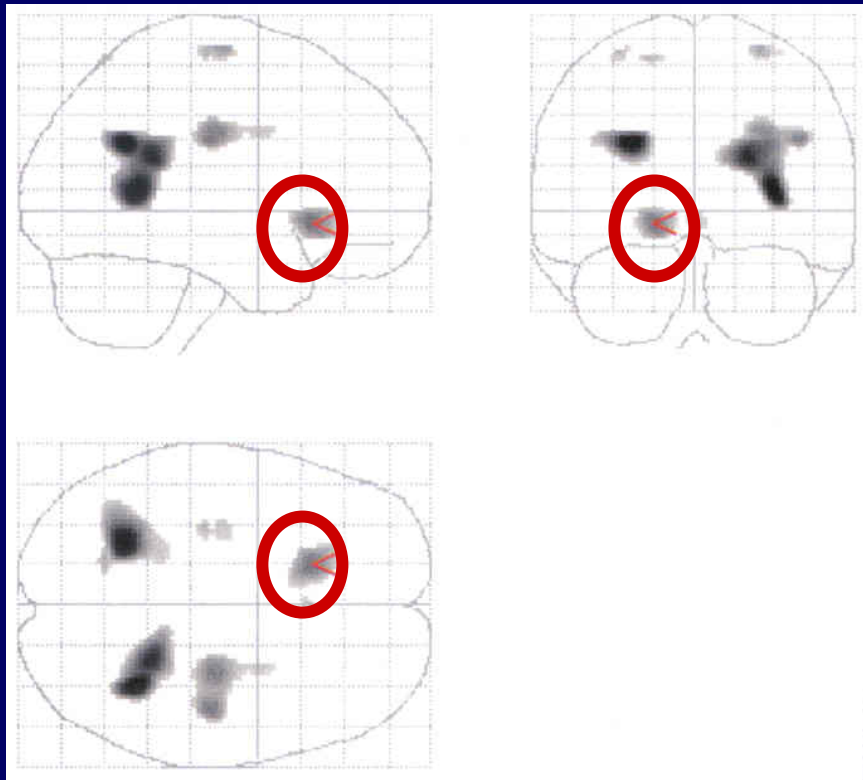
Happy

Upset



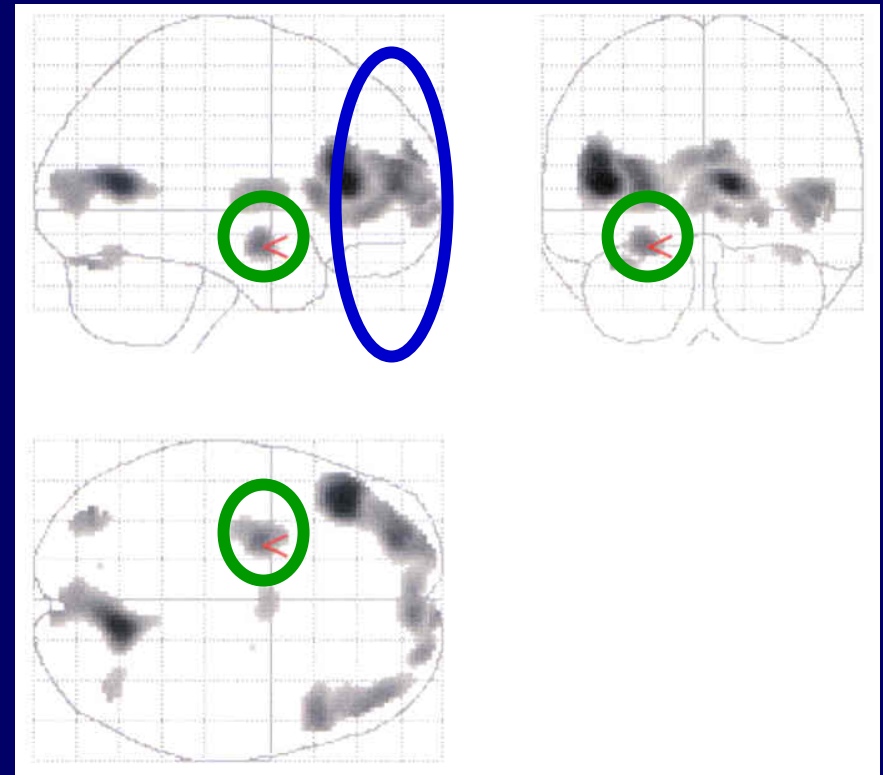
# Win \$4.00 vs. No-Win \$4.00

ADOLESCENTS > ADULTS



Nucleus Accumbens

ADULTS > ADOLESCENTS

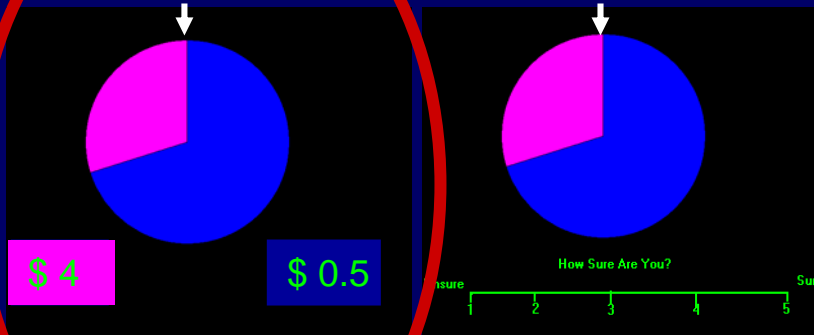


Amygdala

# Wheel of Fortune Task

Stages:

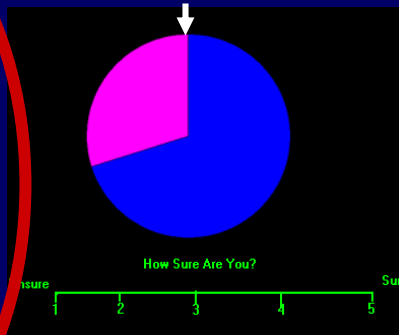
1- Selection



3 s

Selection

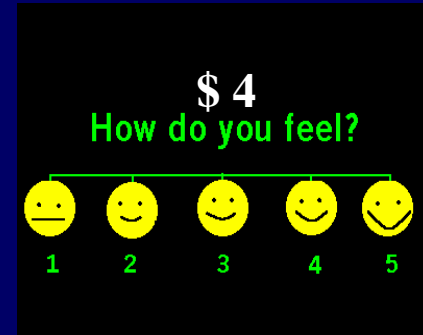
2- Anticipation



4 s

Anticipation

3- Feedback

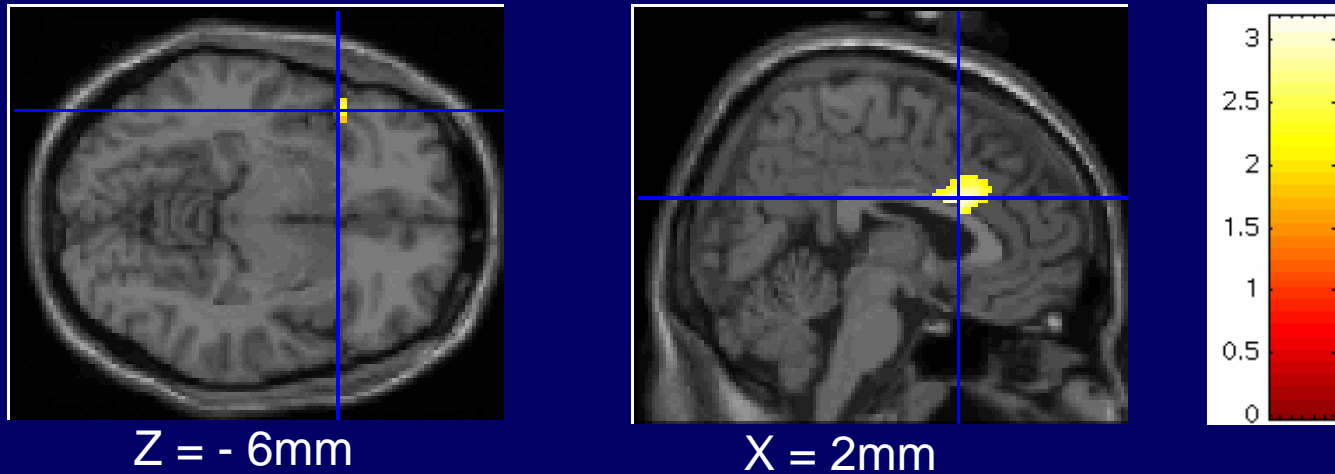


4 s

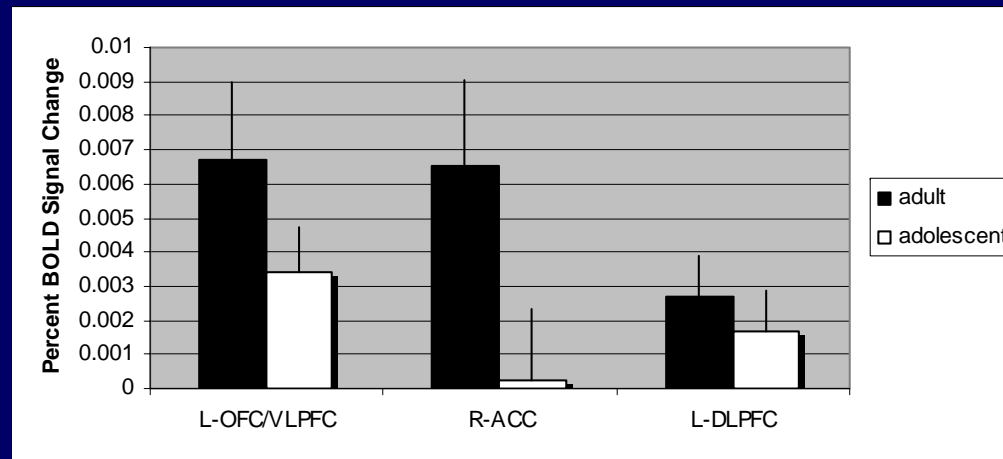
Feedback

# PREFRONTAL ACTIVATION ADOLESCENTS < ADULTS

A.

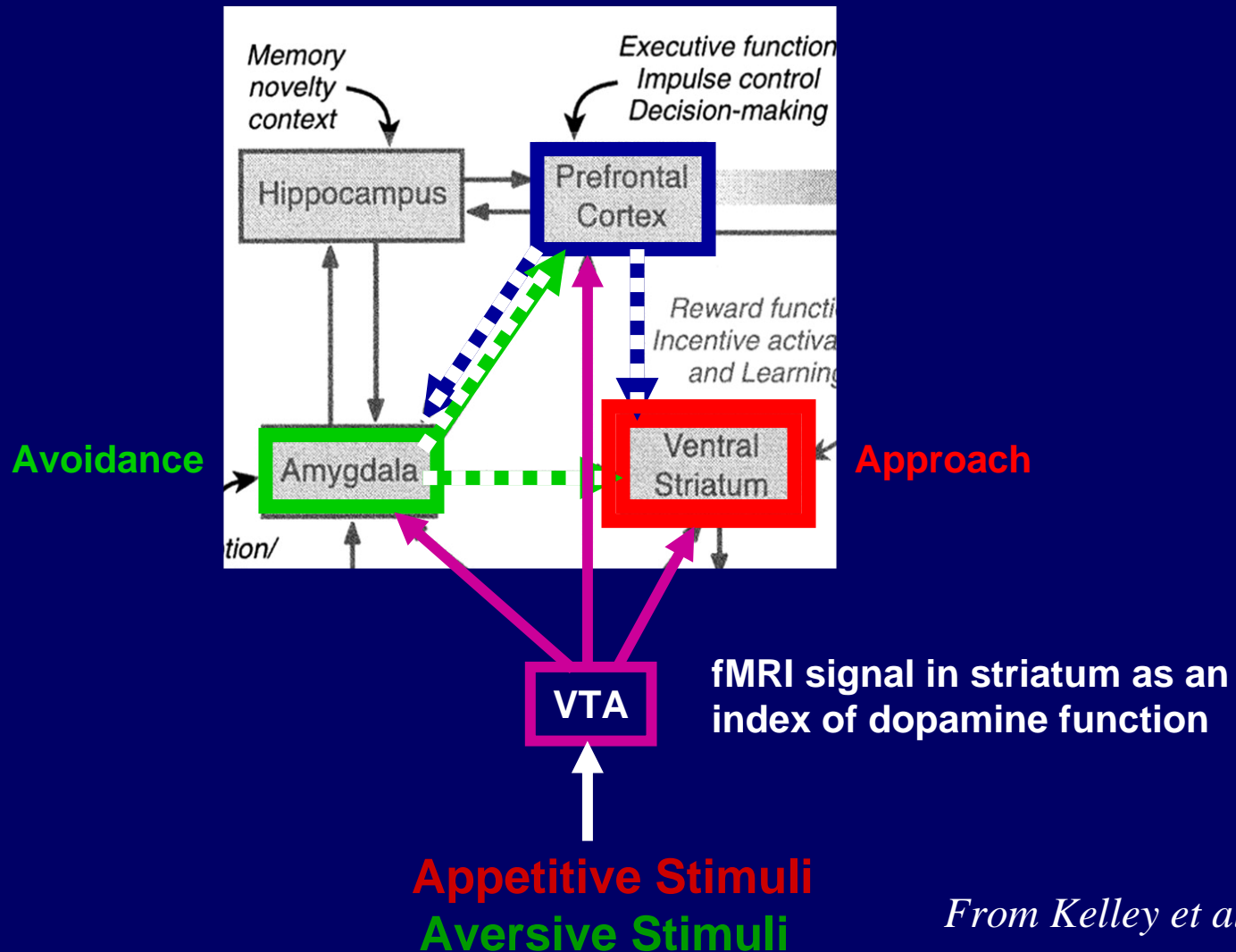


B.



# Adolescent Balance

## Risk-taking proclivity

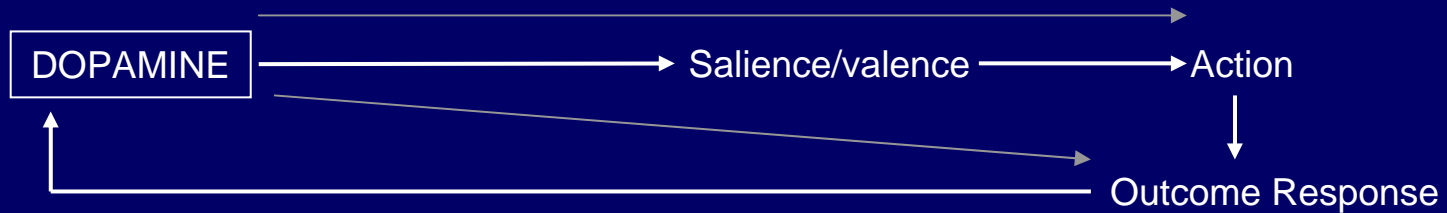


From Kelley et al., 2004

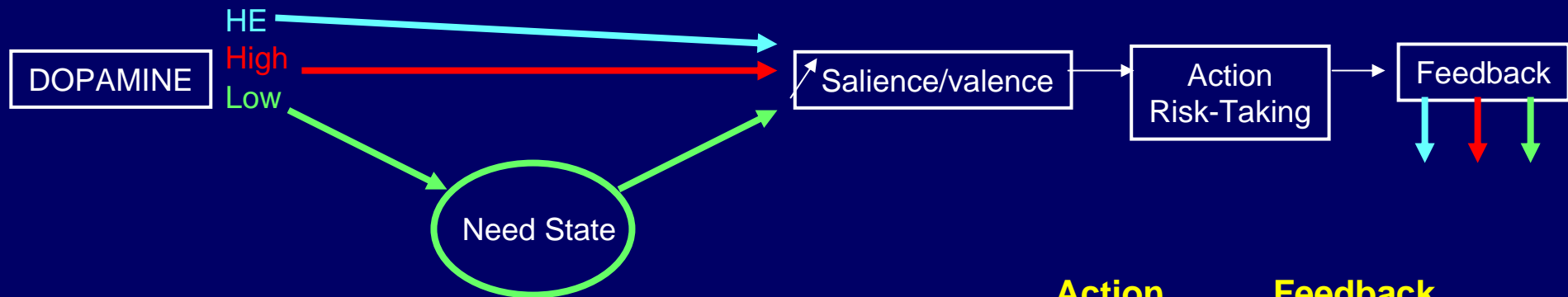


# Dopamine Models

## DOPAMINE IN REWARD FUNCTION



## DOPAMINE IN RISK-TAKING



**Incentive Saliency Model (Berridge & Robinson, 1998)**

**Action**

**Feedback**

High

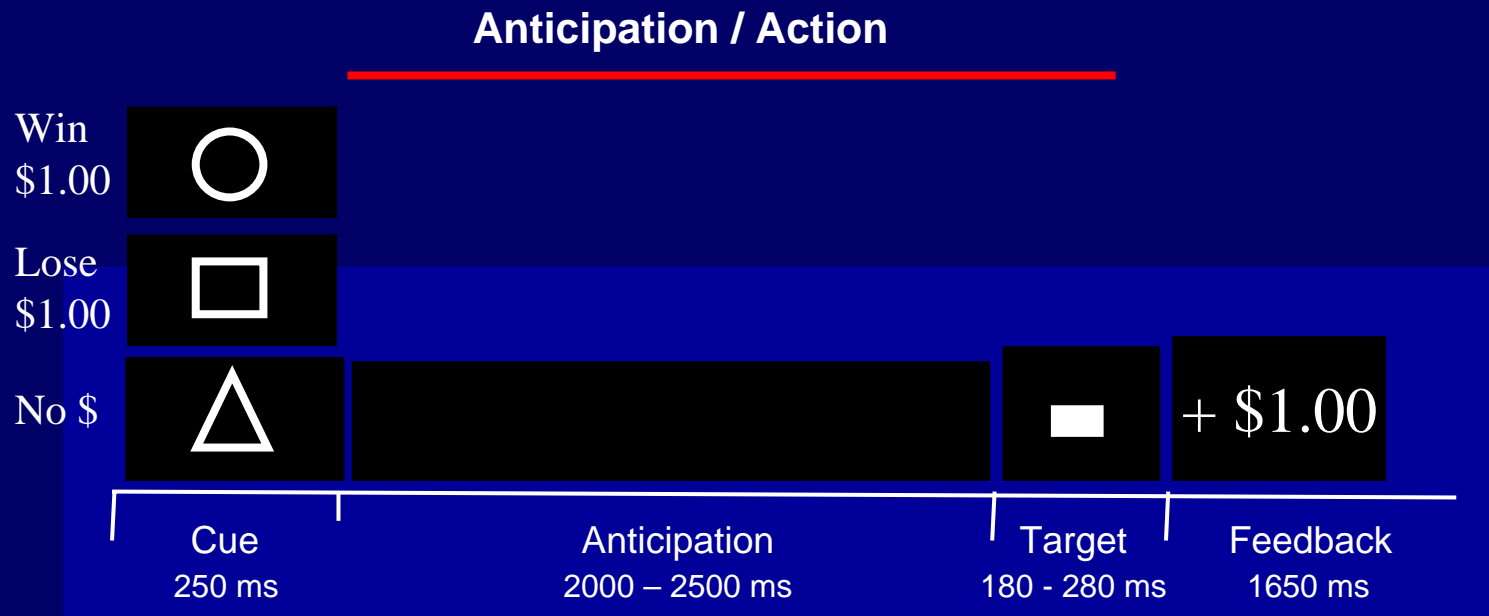
High

**High-Efficiency Model (HE)**

Low

High

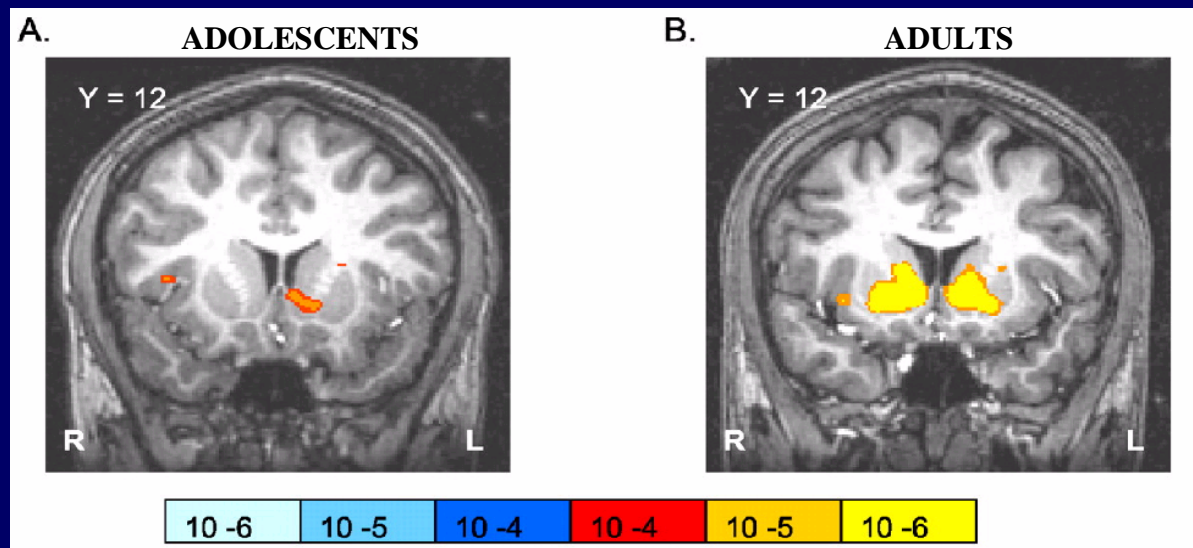
# MONETARY INCENTIVE DELAY MID Task



# ADOLESCENTS VS. ADULTS

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

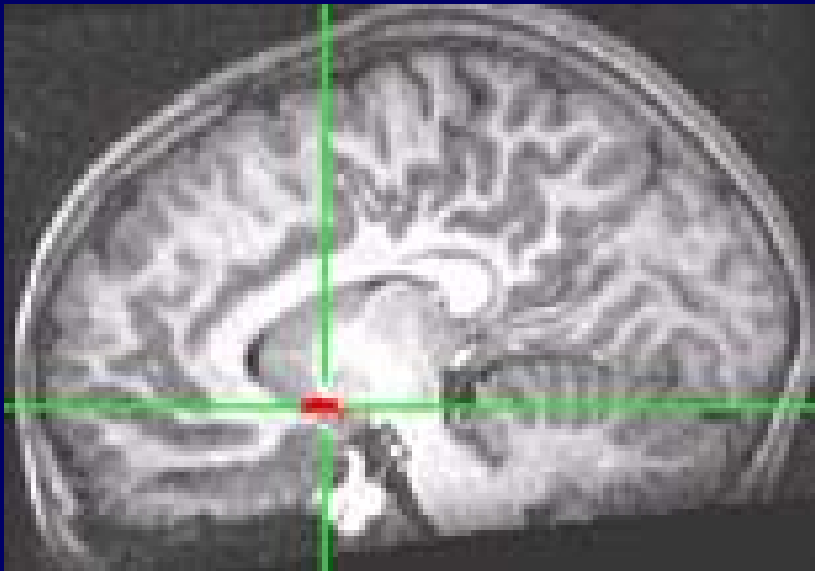
J Neurosci. 2004 Feb 25;24(8):1793-802



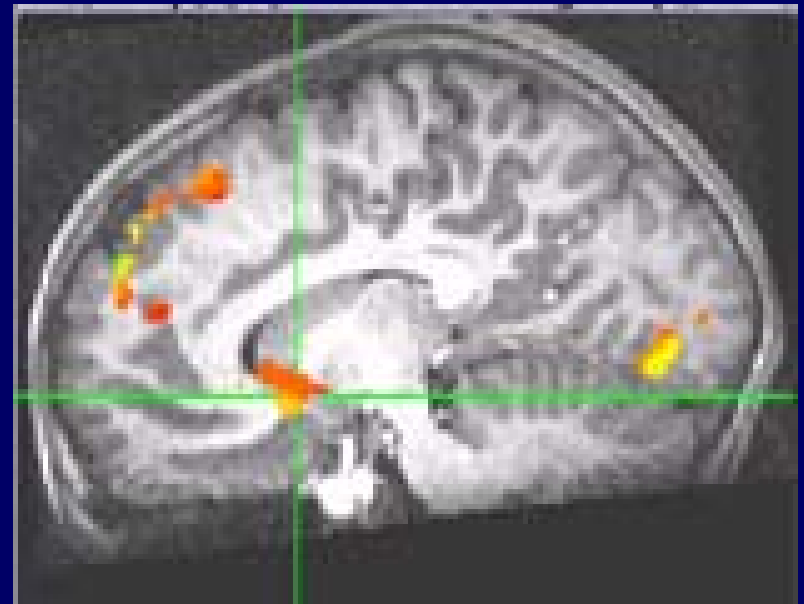
# EXUBERANT TEMPERAMENT

Guyer, A., Nelson, E., Hardin, M., Perez-Edgar, K., Bjork, J., Fox, N., Pine, D., Ernst, M.  
(J. Neuroscience 2006)

EXUBERANT ADOLESCENTS



CONTROL ADOLESCENTS



# Attention Deficit Hyperactivity Disorder

Scheres A., Milham MP, Knutson B, Castellanos FX

(Biol Psychiatry, 2006)

ADHD ADOLESCENTS



CONTROL ADOLESCENTS



# Developmental Model of Reward Systems

Action

Feedback

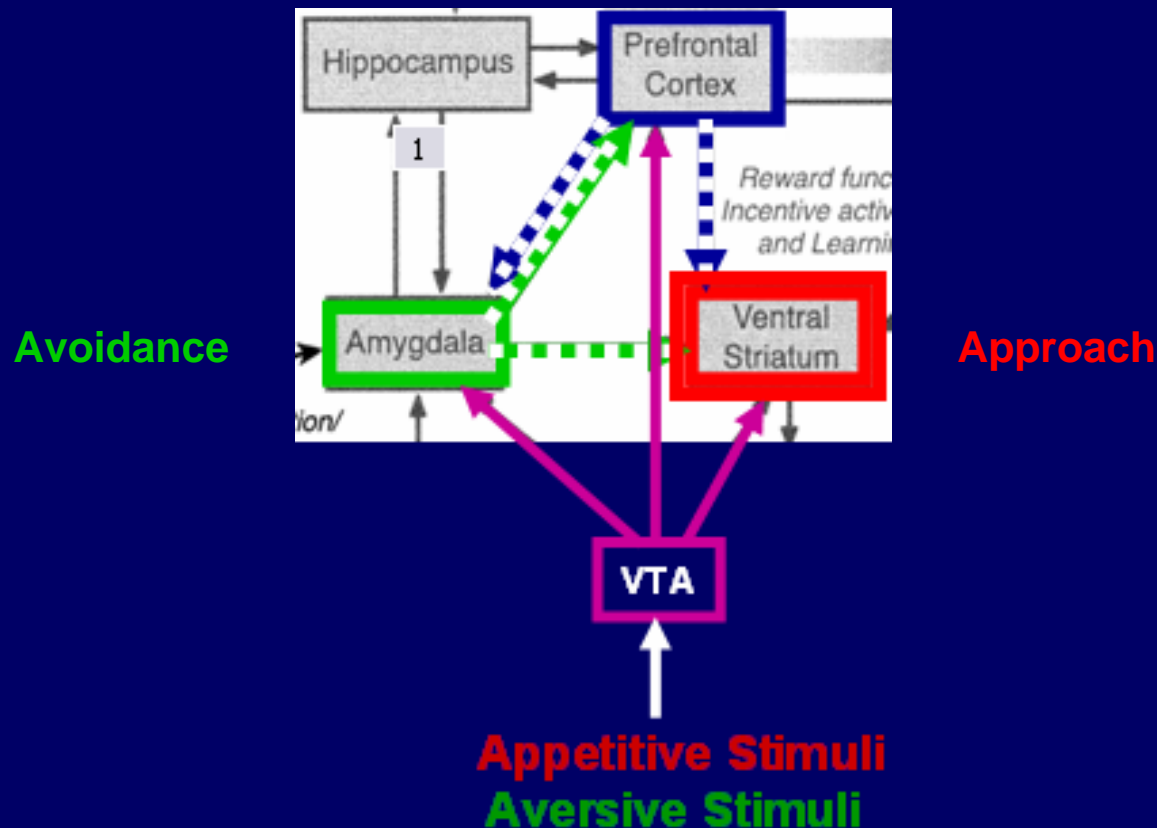
RISK FOR PSYCHOPATHOLOGY

COMORBIDITY (SUBSTANCE ABUSE, ADHD, DEPRESSION...)

High-Efficiency Model (HE)

Low

High



# 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

# THANKS

## NIMH

**Daniel Pine**

**Eric Nelson**

**James Blair**

**Neir Eshel**

**Michael Hardin**

**Amanda Guyer**

**Ellen Leibenluft**

## University of Maryland

**Nathan Fox**

**Koraly Perez-  
Edgar**

## NIAAA

**Daniel Hommer**

**James Bjork**