

Biology, Puberty, Stress, & Development

Discussion of summary by David Brent, MD

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NIMH
National Institute
of Mental Health

Outline

- **Part I: *Reiterating points from David***
 - *The “development” in developmental psychopathology*
 - *Therapeutics*
- **Part II: *Moving Forward***
 - *Integrating circuitry-based neuroscience approaches*
 - *Serotonin (5-HT) and development*

Points from David Brent, MD

Developmental Perspectives

- Major Depressive Disorder (MDD) is a Developmental Disorder
 - *Infants and child offspring of MDD parents*
 - *Early childhood precursors*
 - *Effects of risk factors operating during childhood (e.g. stress)*
 - *Initial MDD symptoms during adolescence*
 - *Prediction from adolescence onward*

Association between Any Adolescent Anxiety Disorder & Any Adult Mood/Anxiety Disorder

	Disorder as Adults?		
Disorder as Adolescents?	No	Yes	
No	390	36	426
Yes	191	62	253
	581	98	679

Pine et al. 1998, 1999; 2001, 2002

Therapeutics

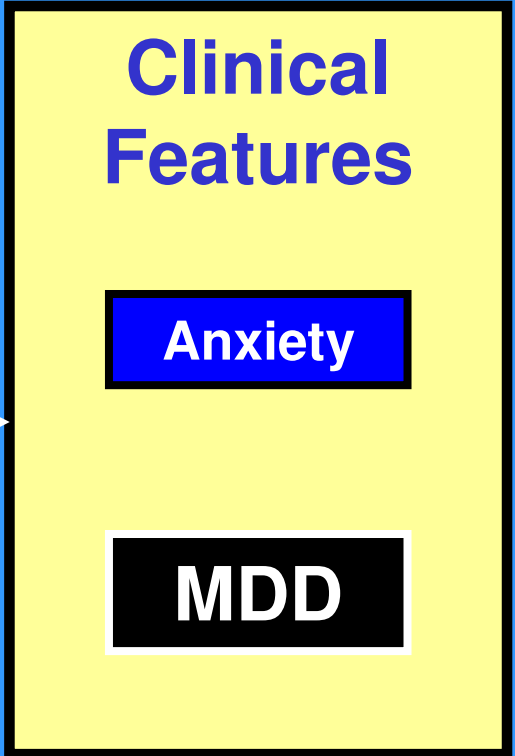
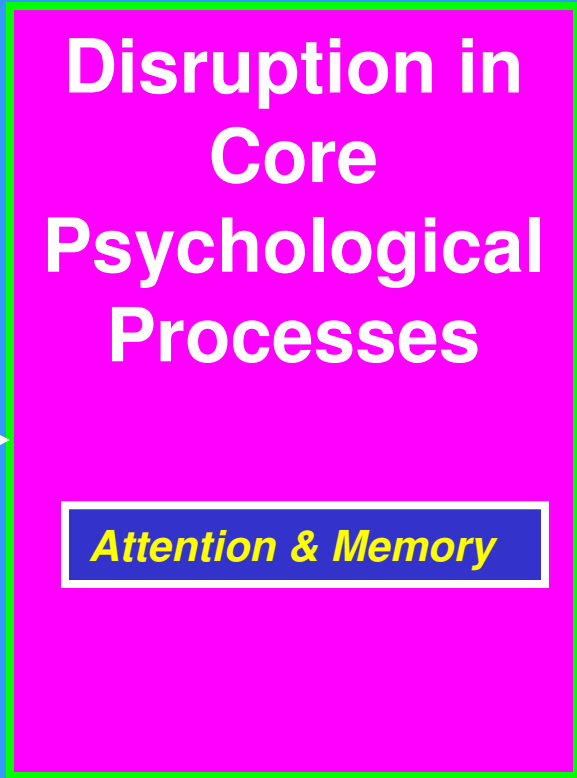
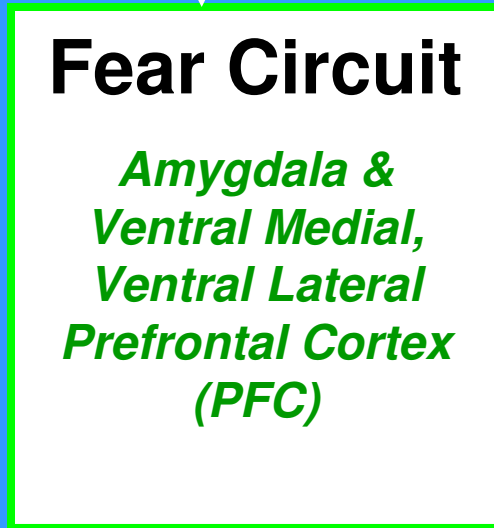
- *Antidepressants*
 - *A range of positions; not enough data*
 - *My “take”*
- *Psychotherapies*
- *The need for better treatments*

Neuroscience and Moving Forward

- Information Processing, Brain Circuit Function, and Pathology
 - *The “fear” circuit*
 - *The “reward” circuit*
- “Sensitive” periods in development and serotonin (5-HT)

Information Processing and Brain Circuitry

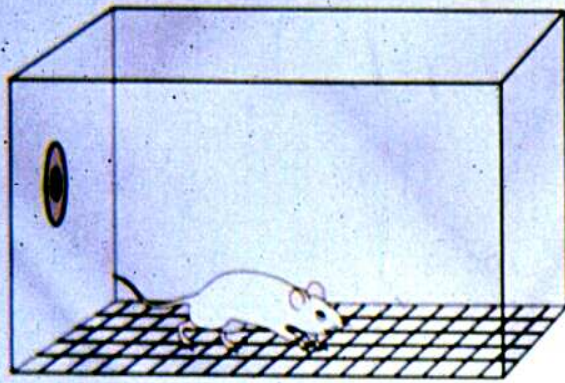
Genetic influences



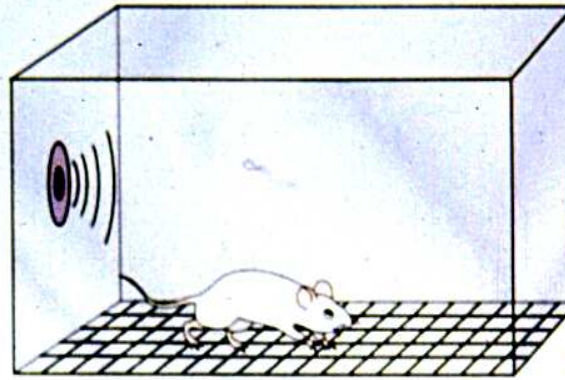
Environmental influences



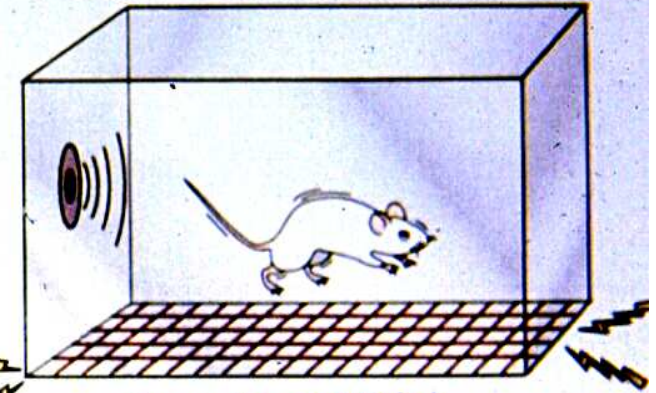
TRAINING



Exposure to context (2 min)

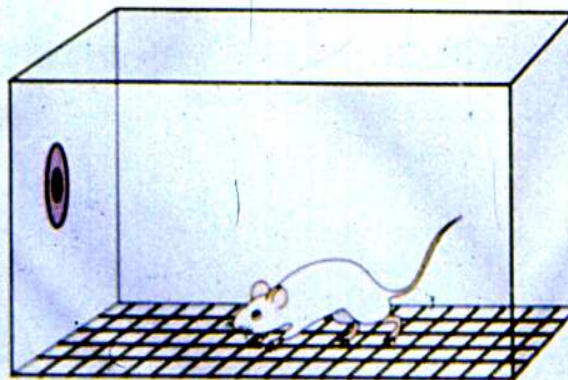


Onset of sound (CS: 30 s)



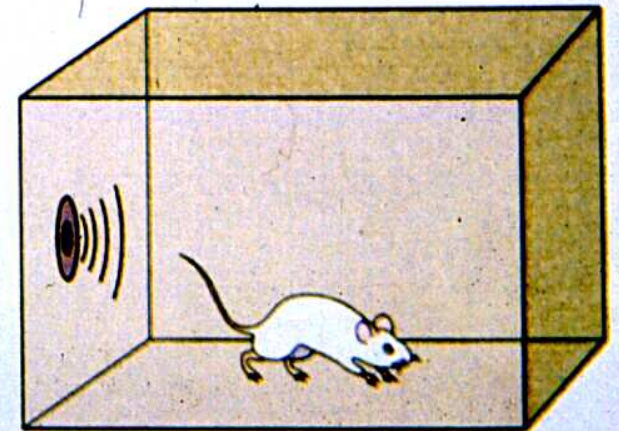
Onset of shock (US: 2 s)

TESTING: Context
Test at 1 hour
and 24 hours

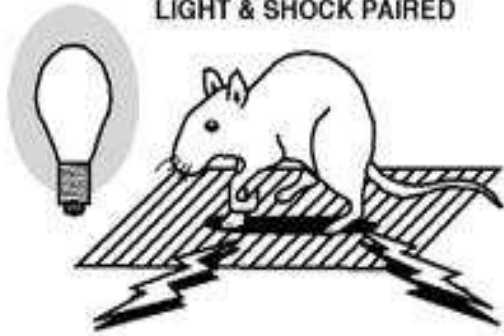
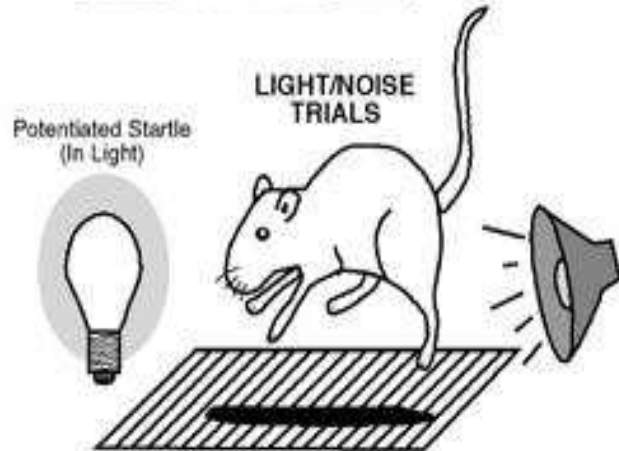
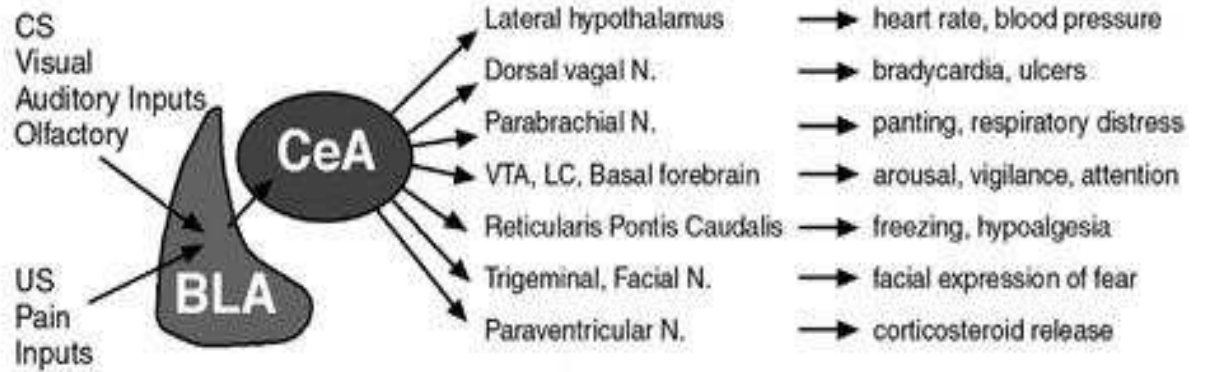
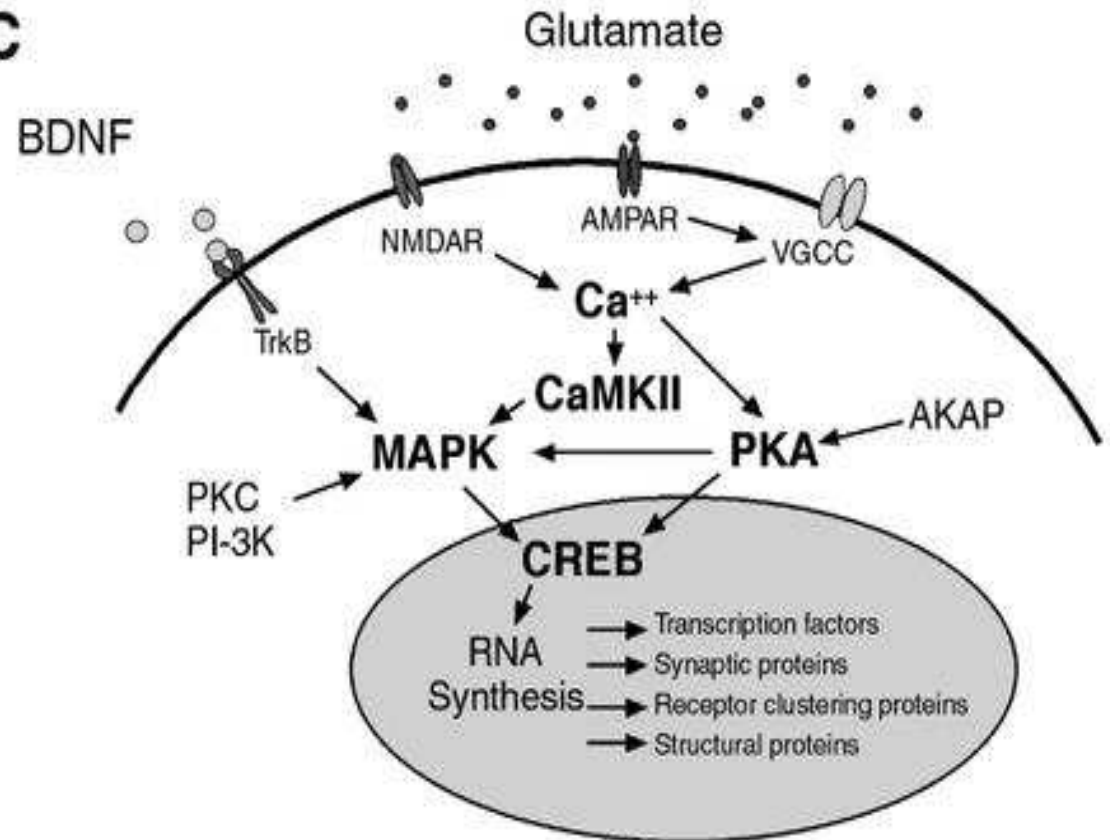


Same context (5 min)

TESTING: Cued
Test at 1 hour
and 24 hours



Onset of sound (CS: 3 min)

A**CONDITIONING:
LIGHT & SHOCK PAIRED****TESTING:
NOISE-ALONE
TRIALS****LIGHT/NOISE
TRIALS****B***Ressler & Davis 2003***C**

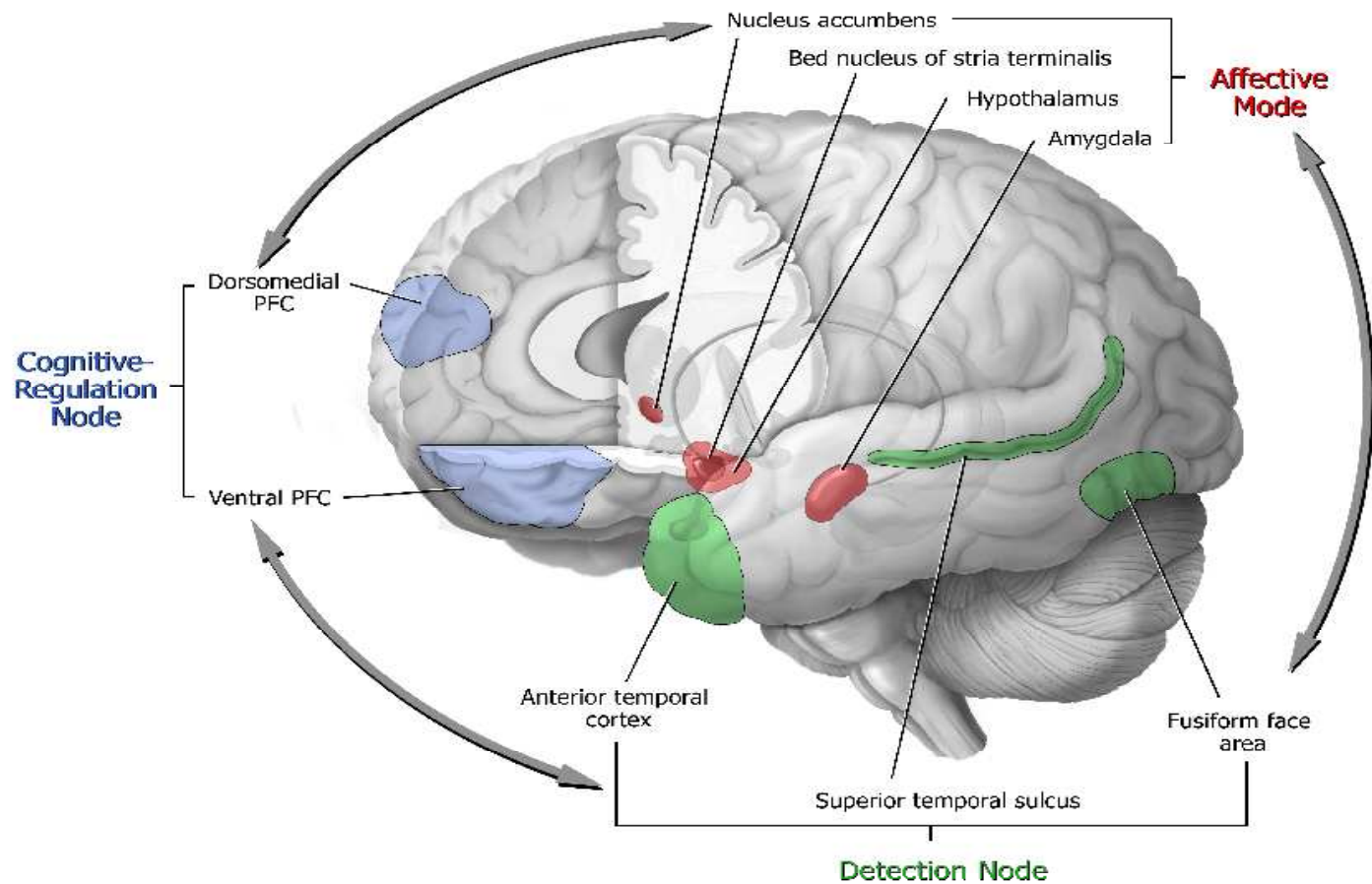
VISUAL
CORTEX

VISUAL THALAMUS

AMYGDALA



LeDoux. *Sci Am.* 1994;270:50.



The Brain, Reward Function, and Adolescence: *The Social Information Processing Network Model*

Nelson, McClure, Leibenluft, & Pine 2005

Sensitive Periods and 5-HT

Development, Anxiety, & 5-HT1a R

Gross et al. Nature 2002

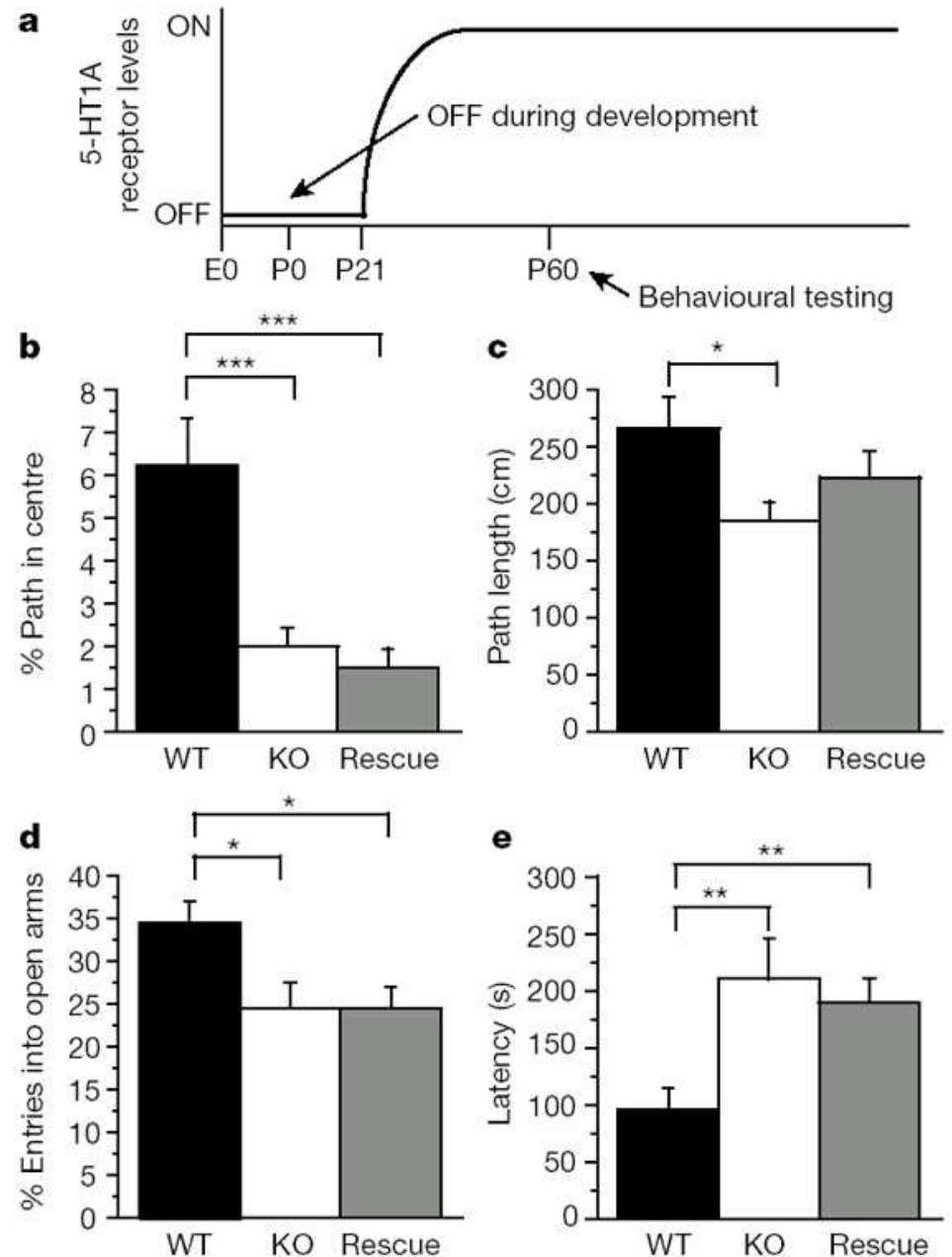
5-HT1a receptor must be present pre-adolescence to “rescue” anxious phenotype.

Relevance for humans

pharmacology

5-HT changes

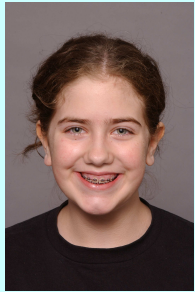
effects of stress



Conclusions

- **Part I: *Reiterating points from David Brent***
 - *The “development” in developmental psychopathology*
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Engaging Ventral Striatum and Fusiform Face Area During Social Interactions



...



...

HOW MUCH DO YOU WANT
TO CHAT WITH THIS PERSON?

Block 1: Motivation



...

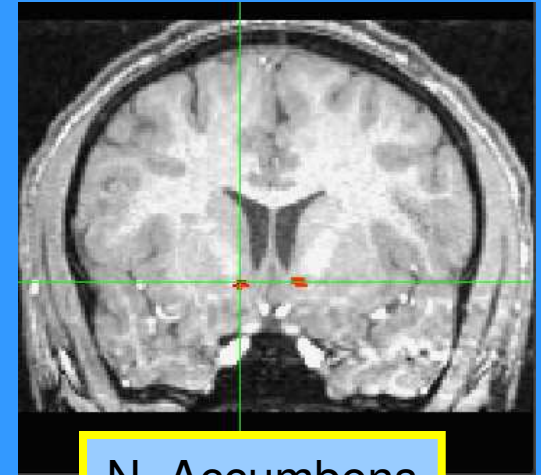


...

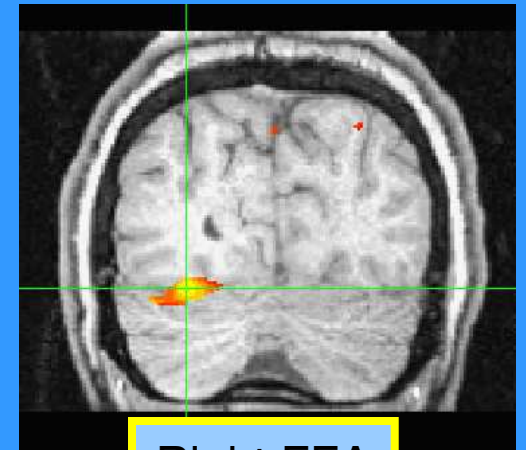
Interested

Not Interested

Block 2: Feedback



N. Accumbens

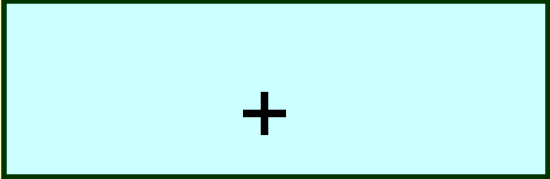

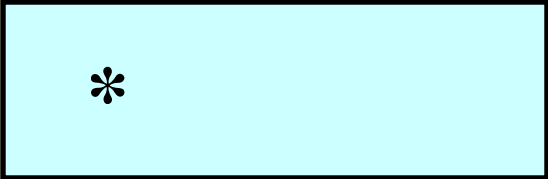


Right FFA

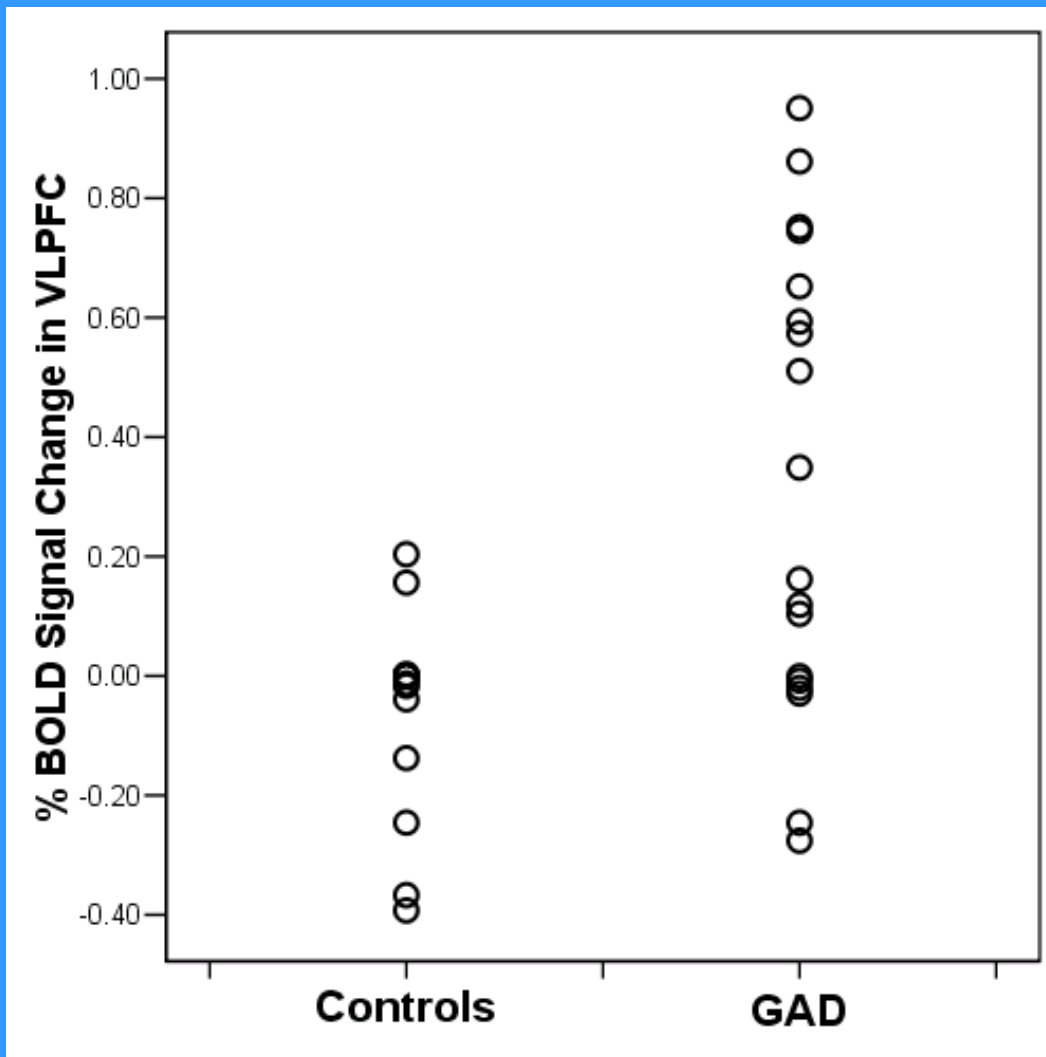
t-values > 5.0; p < .0001

fMRI Contrast:
high motivation D1, INTERESTED –
high motivation D1, NOT INTERESTED

Mogg & Bradley Task

Sample Trial	Duration (ms)	Event
	500	Fix
	500 msec	Angry/Neutral
	1100	Probe (button press)

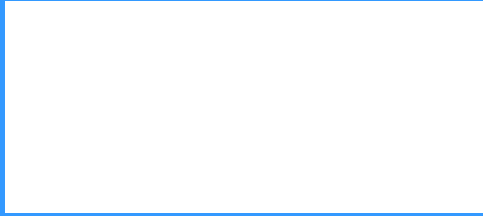
Engaging the *Cortical* Circuit in GAD/SoPh



GAD/SoPh vs. Healthy



- $t(28) = 3.9$ $p < .001$ uncorrected
- $p < .05$ corrected for ventral frontal region (Monte Carlo Sim)



“Clear”

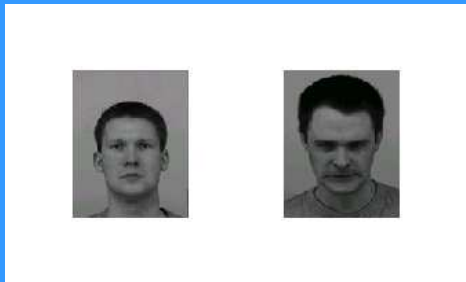
32



“Symmetrical”

32 x 3

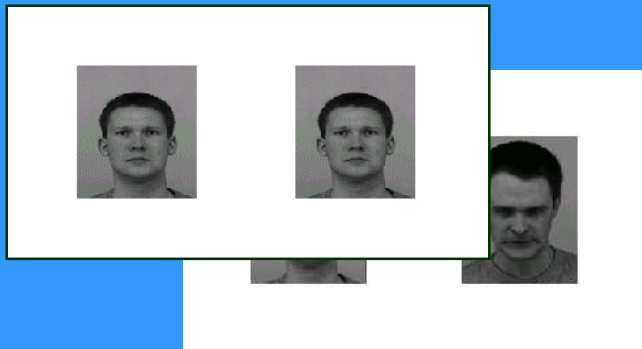
angry, happy, neutral



“Unmasked”

64 x 2

angry, happy



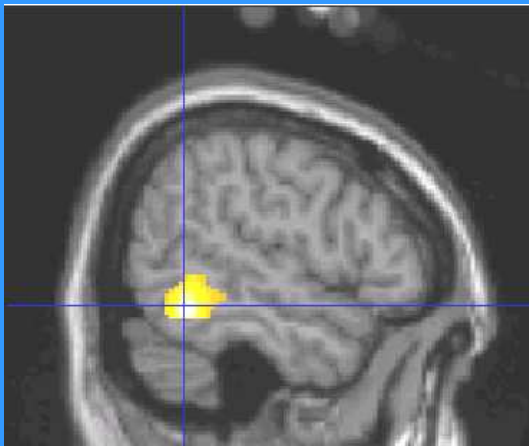
“Masked”

64 x 2

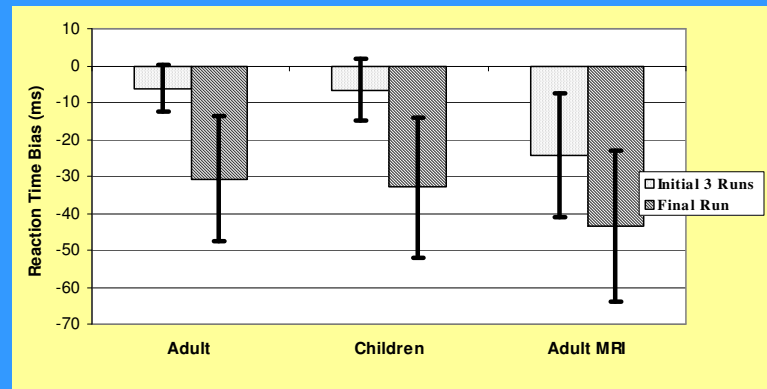
angry, happy

384 Probe Trials

Changes in Attention Bias to Threat



Changes in brain activation over time
 $t=7.8$; $p<.05$



Changes in attention bias over time