Chronic irritability in youth that may be misdiagnosed as bipolar disorder

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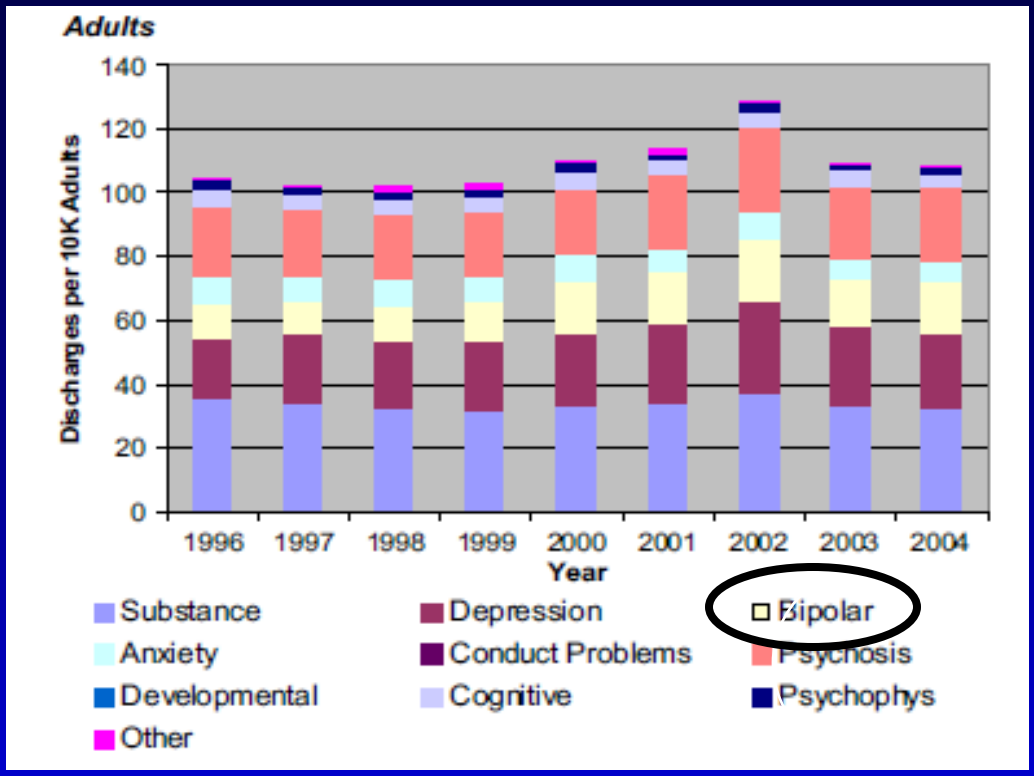
Talk Outline

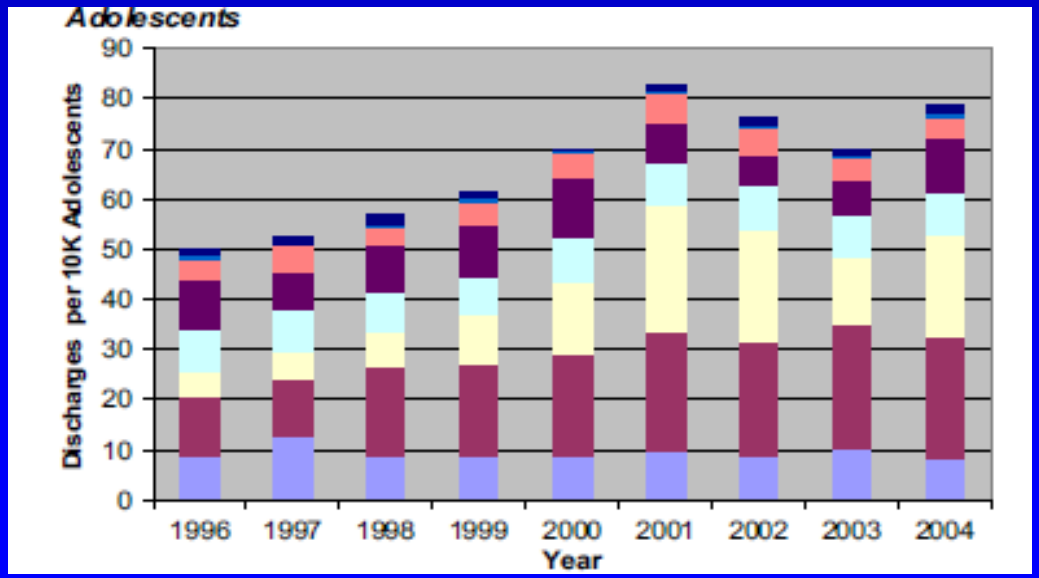
- Controversy about diagnosing pediatric BD in youth
  - Irritability: an important and neglected clinical phenomenon
  - Defining severe mood dysregulation (SMD)
  - Comparing BD and SMD
    - Outcome and family history

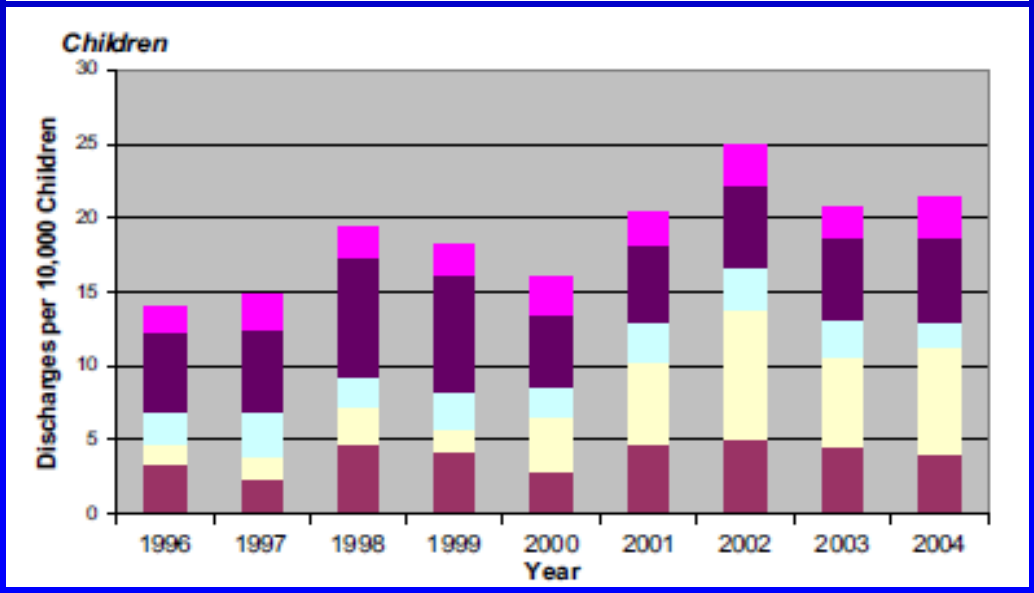
- fMRI studies
    - Face emotion processing
    - Frustration

Hospital discharge diagnoses in the U.S., 1996-2004

Rate of increase in d/c's for BD:
In adults, 56%
In adolescents, 400%
In children, 1.3 to 7.3 per 10,000 (~600%)







Blader and Carlson, 2007

Diagnosing pediatric bipolar disorder: The controversy

Is severe irritability and ADHD,
without distinct manic episodes,
a developmental form of bipolar disorder?

DSM-IV Criteria for Manic Episode: Unique features

A. Distinct period of elevated, expansive, or irritable mood ≥ 1 week

B. Symptoms (3, or 4 if irritable) at the same time as "A"

(1) grandiosity

(2) decreased need for sleep

(3) pressured speech

(4) flight of ideas, racing thoughts

(5) distractibility

(6) increased goal-directed activity, psychomotor agitation

(7) excessive pleasurable activities

C. Marked impairment, hospitalization, or psychosis

DSM-IV Criteria for Manic Episode: Overlap with ADHD

A. Distinct period of elevated, expansive, or irritable mood ≥ 1 week

B. Symptoms (3 of the following, or 4 if mood only irritable)
(1) inflated self-esteem, grandiosity
(2) decreased need for sleep
(3) pressured speech
(4) flight of ideas, racing thoughts
(5) distractibility
(6) increased goal-directed activity, psychomotor agitation
(7) excessive, pleasurable activities with potential for painful consequences

ADHD-like symptoms

C. Marked impairment, hospitalization, or psychotic features

Irritability in DSM-IV Childhood-Onset Disorders

- Major depressive episode
- Manic episode
- Dysthymic disorder
- Post-traumatic stress disorder
- Oppositional defiant disorder
- Generalized anxiety disorder
- PDD-spectrum disorders
- ADHD
- Conduct disorder

An important positive outcome of the controversy about the diagnosis of pediatric bipolar disorder

- Highlights that irritability is a common, yet relatively understudied, clinical presentation in children

- Regarding irritability, we need to know much more about:
  - clinical correlates
  - outcomes
  - treatment
  - measurement
  - pathophysiology and pathogenesis
    - impact of genes, environment, G X E interactions and correlations
    - neural circuitry

Three strands of research on irritability in youth

- From pediatric bipolar disorder to severe mood dysregulation
- Oppositional defiant disorder has two dimensions
  - Headstrong predicts to conduct disorder
  - Irritable predicts to unipolar depressive and anxiety disorders

  (Stringaris and Goodman 2009, Rowe et al 2010, Burke et al, 2010)
- Increased interest in emotional dysregulation in youth with ADHD (Martel, 2010; Sobanski et al, 2010)

Diagnosing pediatric bipolar disorder: The controversy

Is severe irritability and ADHD,
without distinct manic episodes,
a developmental form of bipolar disorder?

Research to address the controversy

- One can identify youth (including prepubertal youth) who meet “classic” (DSM-IV) criteria for BD.

- To demonstrate that an alternative phenotype is a developmental presentation of mania, recruit such children and compare them to those with the classic presentation

Severe Mood Dysregulation (SMD)

- Chronic presentation (vs. episodes of BD)

- Irritability clearly defined, with high bar:
  - baseline anger or sadness
  - ⬆ reactivity to negative emotional stimuli ≥ 3x/week

- Irritability impairing in ≥ 2 settings (home, school, peers)
  - SMD children should be as impaired as BD

- ADHD symptoms that overlap with "B" mania criteria

- SMD = most severely impaired ADHD + ODD
  - Don't fit well in DSM-IV!
  - DMDD= SMD without hyperarousal sx's.

Leibenluft et al, 2003

Interviewing tips

- Direct observation has the greatest weight
- Get lots of examples
- Interview parent and child separately and together
- Elevated mood, grandiosity are the trickiest
  - E.g. What is grandiosity in a 5, 10, 15, 25, 35 year old?
  - "The episode is your friend"….each children his/her own baseline.
- Ascertain episodes: worst mania, worst depression, euthymia
- ADHD etc. are diagnosed based on symptoms during euthymia.

Is SMD a developmental phenotype of BD?

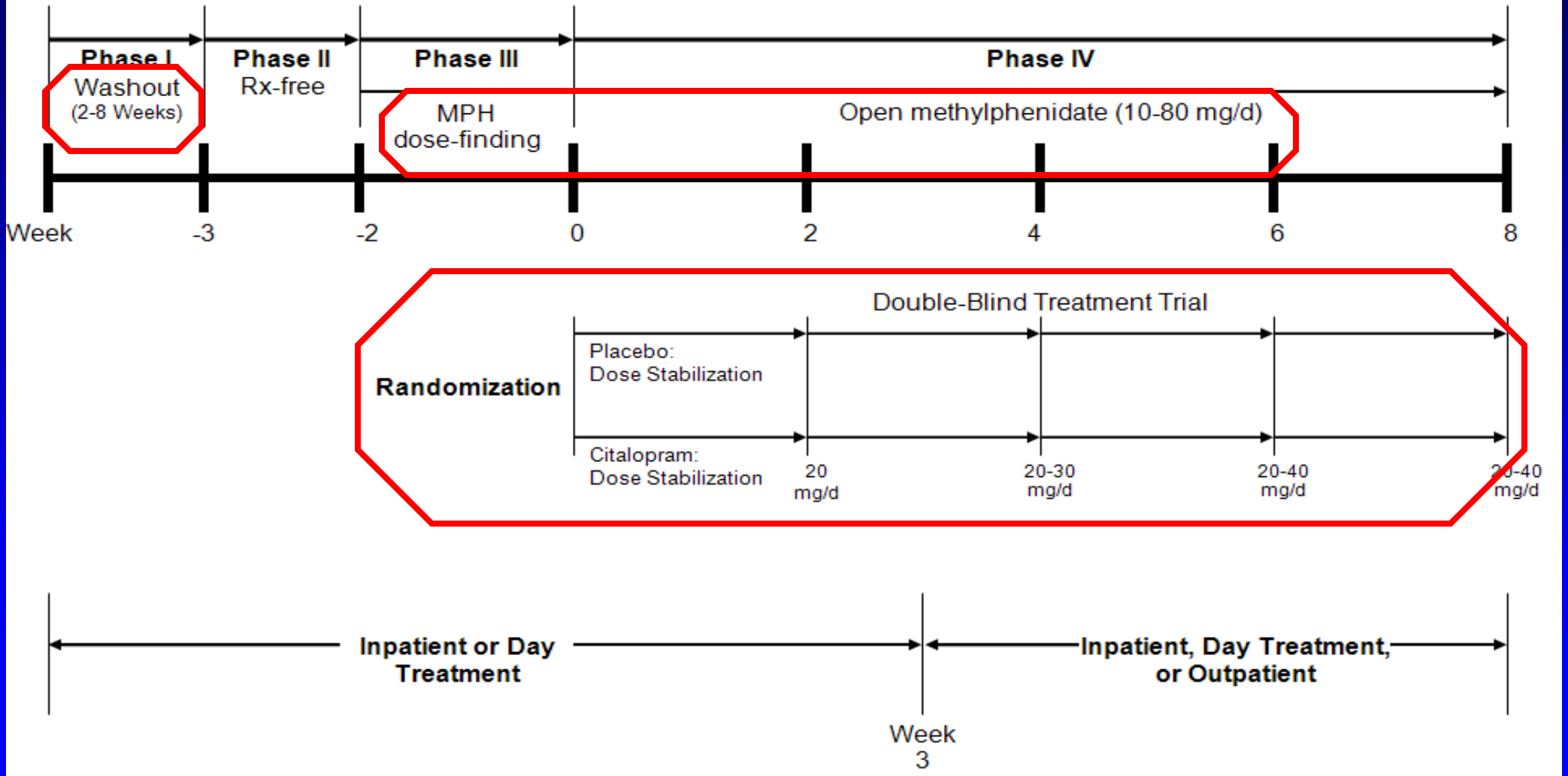
- Longitudinal course (epidemiological studies)
- Family history
- Neural circuitry dysfunction

Caveat: “bipolar” is not really a categorical variable

Why does it matter whether SMD is a form of BD?

- Treatment!!!
- If SMD = BD, then antipsychotic medication, anticonvulsants
- If SMD = ADHD + anxiety and/or depression, then stimulants and SRI's
  - Ongoing trial at NIMH

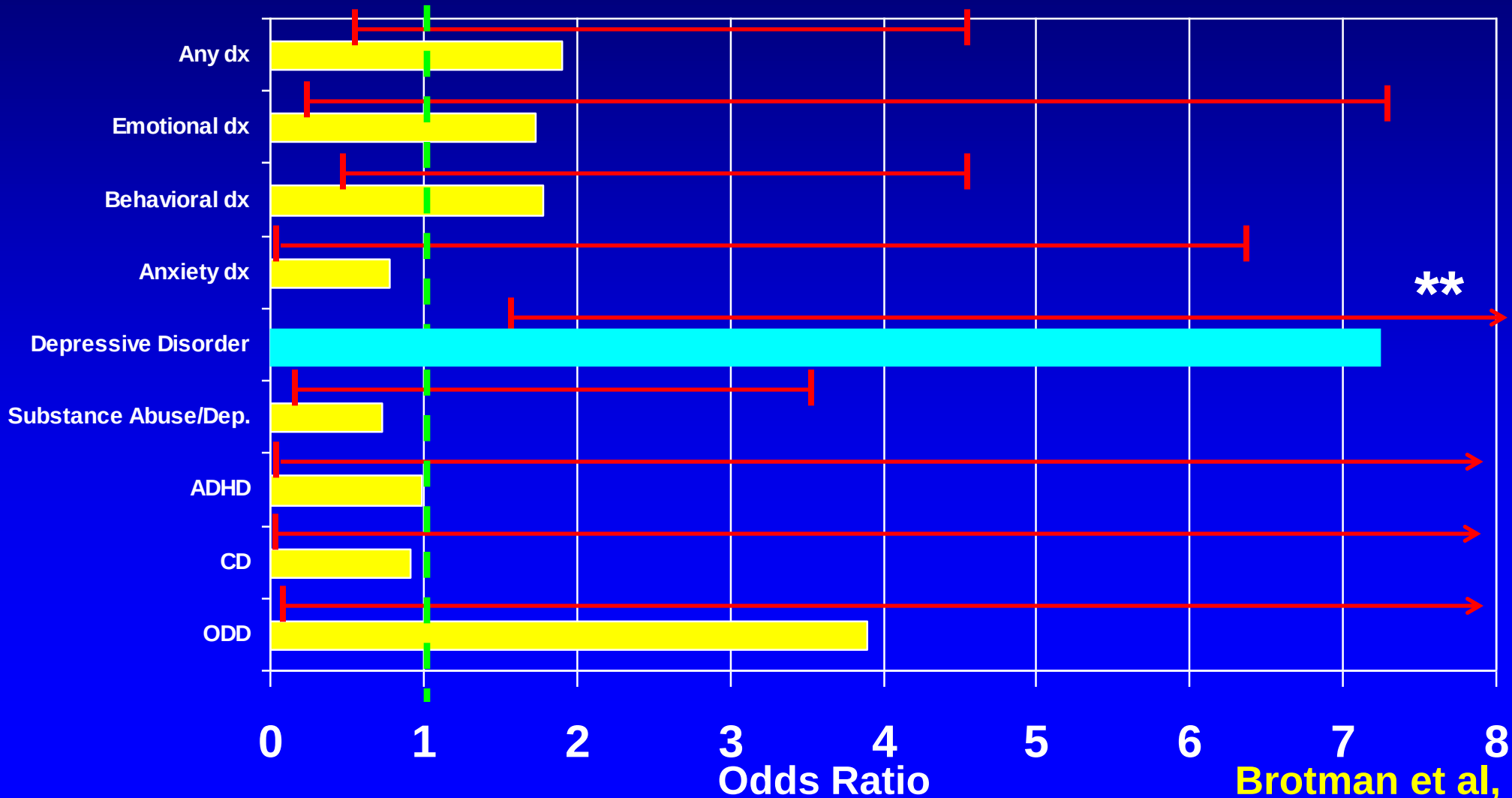
Citalopram + MPH vs. Placebo + MPH: Clinical Trial



Longitudinal Outcome and Family History

Last wave diagnoses:
SMD vs. non-SMD youth (mean age=18.3 ± 2.1 y)

N=1366 non-SMD, 54 SMD at age 10.6 ± 1.4 y (3.2%)



Brotman et al, 2006

Chronic irritability in youth predicts MDD, dysthymia, anxiety at f/u

	N	Age at baseline	Age at f/u	MDD	GAD	Dysth	MDD & GAD
Children in the Community	776	13.8	33.2	1.33 (1.0-1.8)	1.72 (1.0-2.9)	1.81 (1.1-3.1)	n/a

Chronic irritability did not predict mania or Axis II Disorders.

Stringaris et al, 2009

Three strands of research on irritability in youth

- From pediatric bipolar disorder to severe mood dysregulation
- **Oppositional defiant disorder has two dimensions**
  - Headstrong predicts to conduct disorder
  - **Irritable predicts to unipolar depressive and anxiety disorders**

  (Stringaris and Goodman 2009, Rowe et al 2010, Burke et al, 2010)
- Increased interest in emotional dysregulation in youth with ADHD (Martel, 2010; Sobanski et al, 2010)

Genetic associations between depression and irritability

- Twins (N=2651, ages 12-19), studied at 8 and 33 months post baseline (Eley et al.)

- Two dimensions of oppositional behavior (Stringaris and Goodman, 2009) with different longitudinal predictions:
  - irritable ⟶ depression
  - headstrong ⟶ antisocial behavior

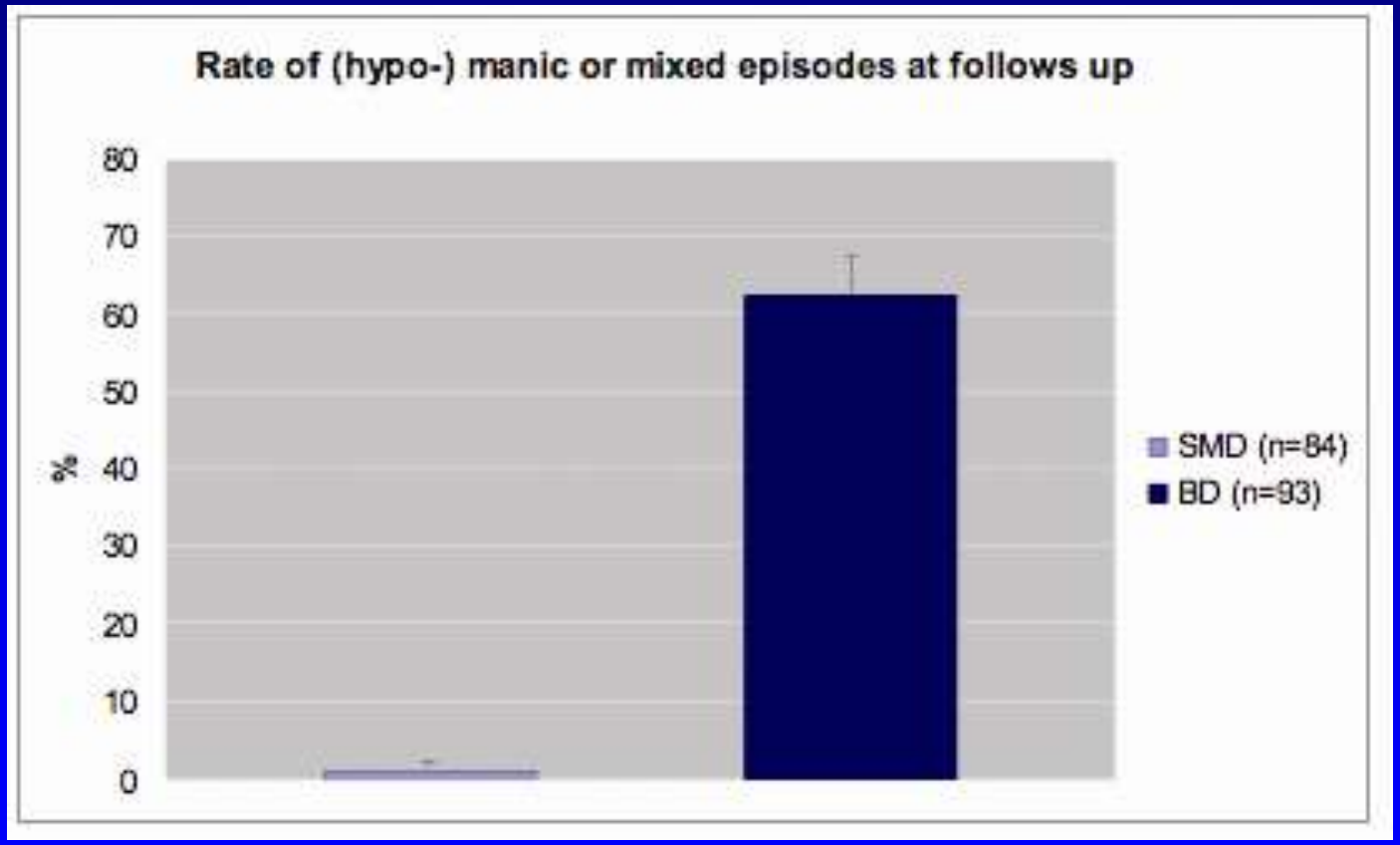
- Heritability of irritability= 0.31

- Cross-sectional genetic correlations between
  - irritability and depressed mood (0.70, CI: 0.59-0.82)
  - headstrong and delinquency (0.80, CI: 0.72-0.86)

- Longitudinal association between irritability and depression due to genetic association

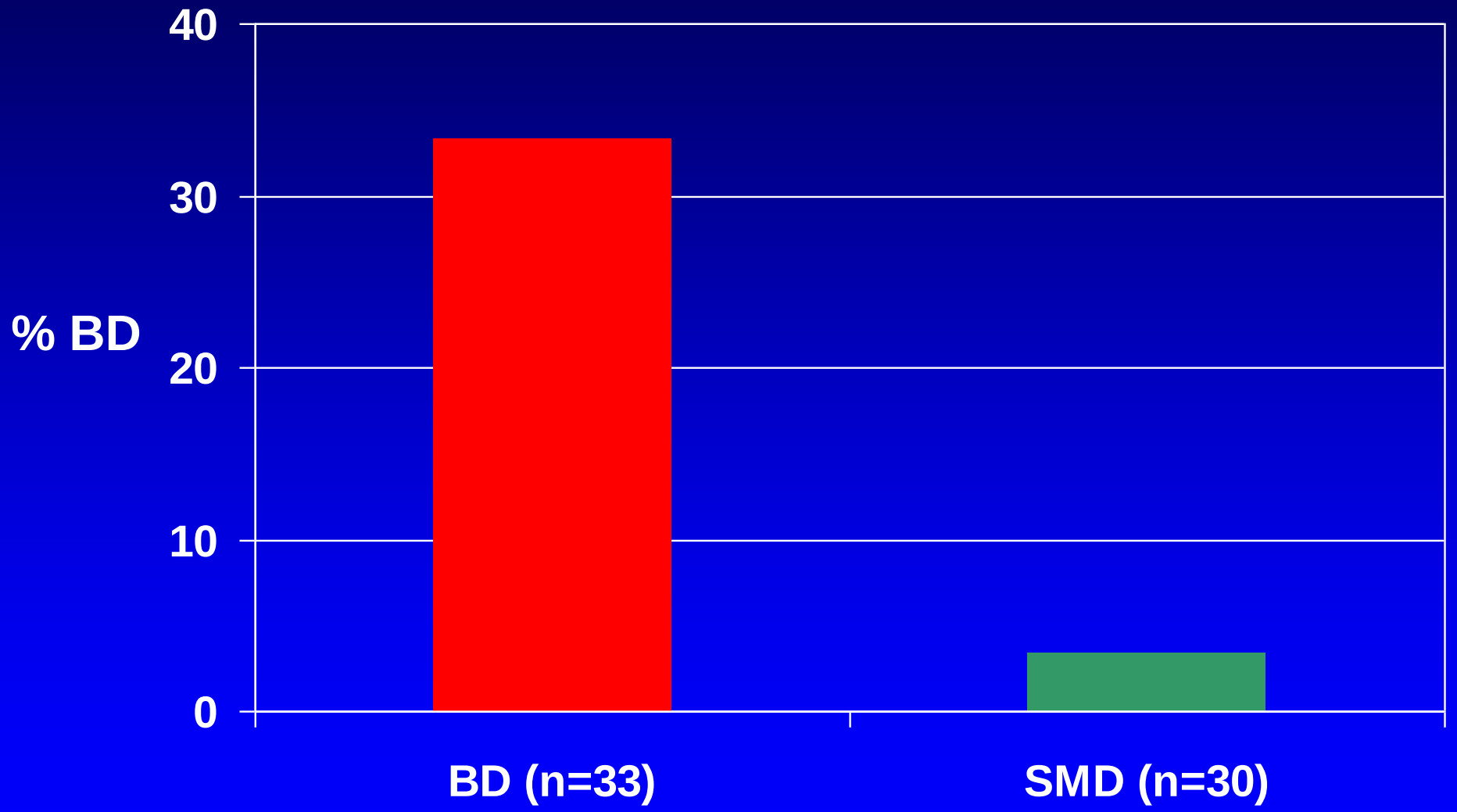
Stringaris et al, 2012

Longitudinal follow-up of BD vs. SMD (median=28.4 months)



Stringaris et al, 2010

Parents of BD youth more likely to have BD than are parents of SMD children



OR 17.96, CI 1.89-170.77, p≤.01; Chi-square= 6.32

Brotman et al, 2007

Neuroimaging studies

Goals:

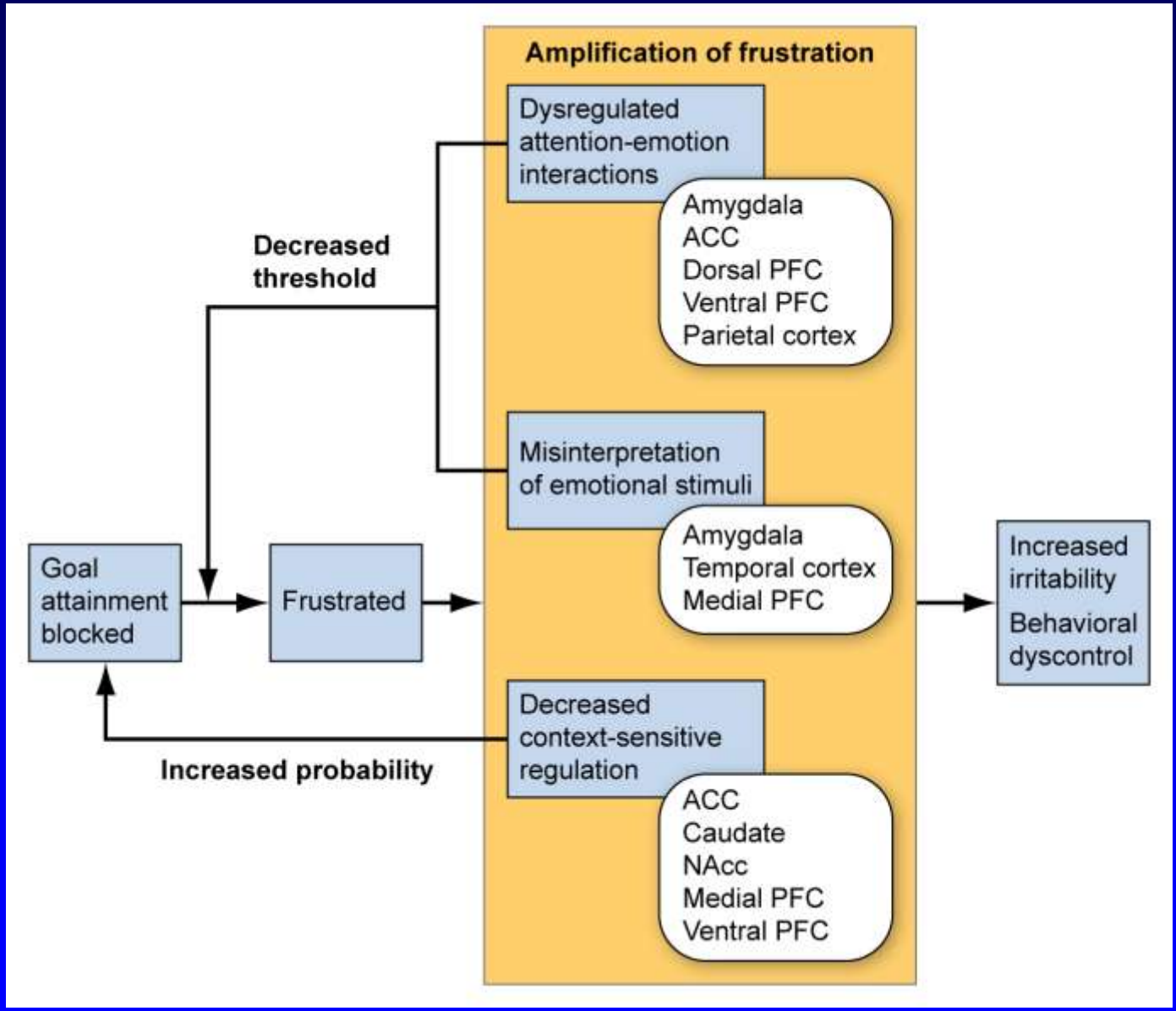
1) **Differentiate SMD and BD pathophysiologically**
2) **Elucidate the neural mechanisms mediating irritability**

Domains:

1) **Face emotion processing**
2) **Frustration**

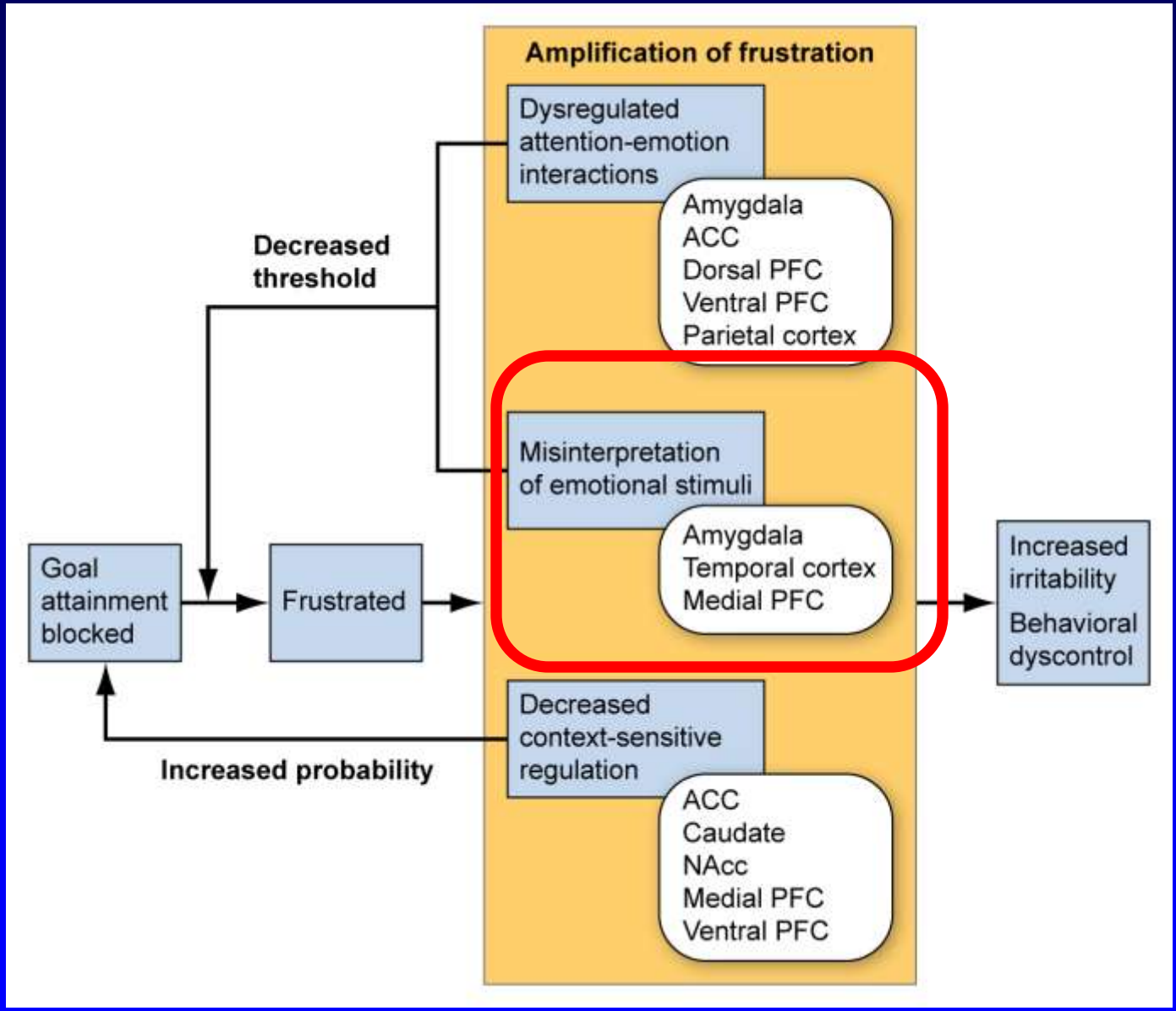
Clinical characteristics	BD (N=118)	SMD (N= 134)
Age	12.9 ± 2.8	12.0 ± 2.0
Age of onset	9.8 ± 3.5	5.6 ± 2.2
Gender (% male)	52.0	69.7
% ADHD	57.0	85.3
% ODD	36.0	84.4
% Anxiety d/o	56.0	52.3
Number meds	2.4 ± 1.70	1.37 ± 1.45
% hospitalized	63.0	40.4
Children's Global Assessment Scale	51.1 ± 10.8	47.4 ± 9.0

Neural mechanisms of frustration



Leibenluft, 2011

Neural mechanisms of frustration



Leibenluft, 2011

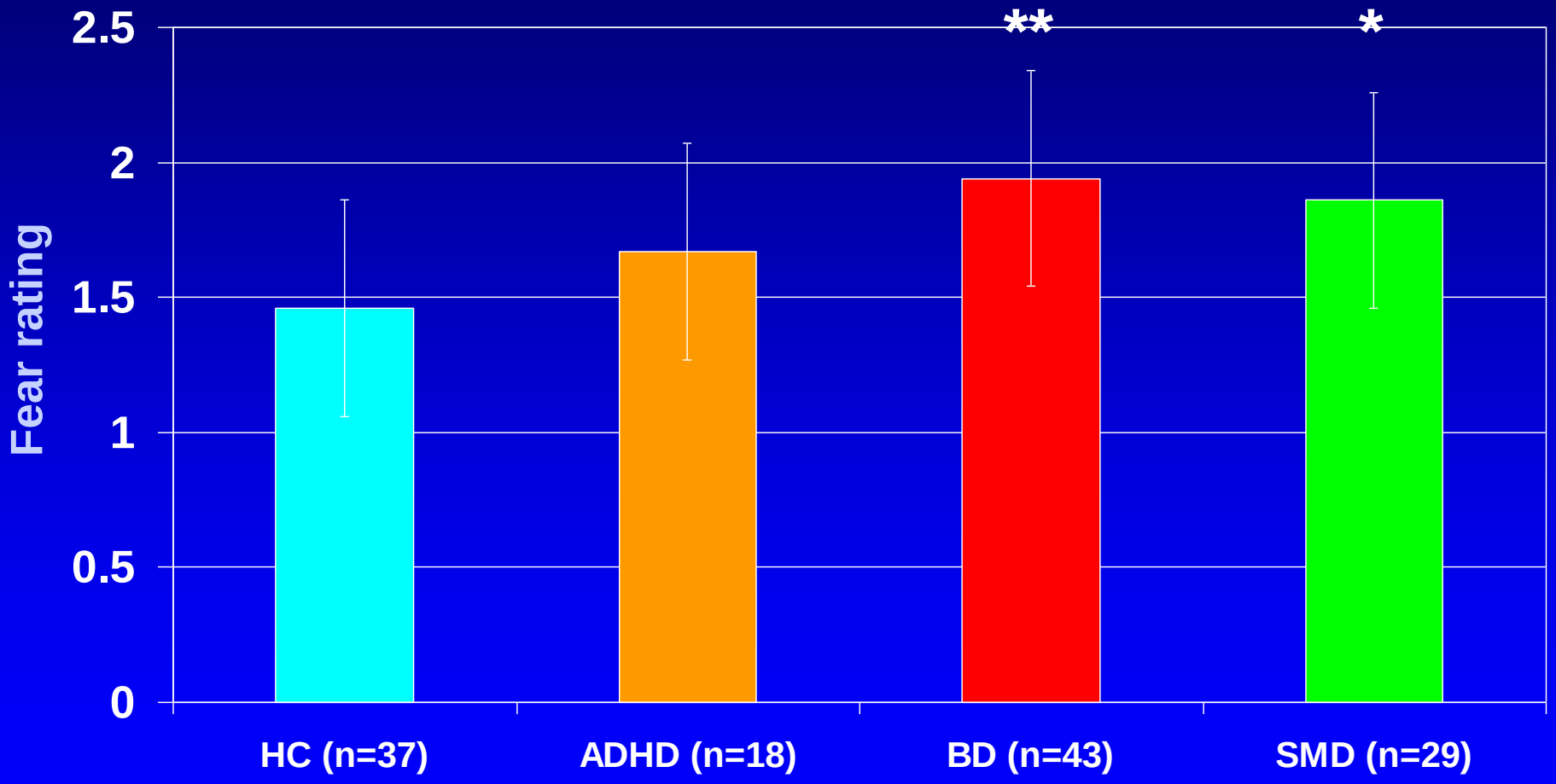
Faces fMRI task design

How hostile is this person?

How afraid are you?

How wide is the nose?

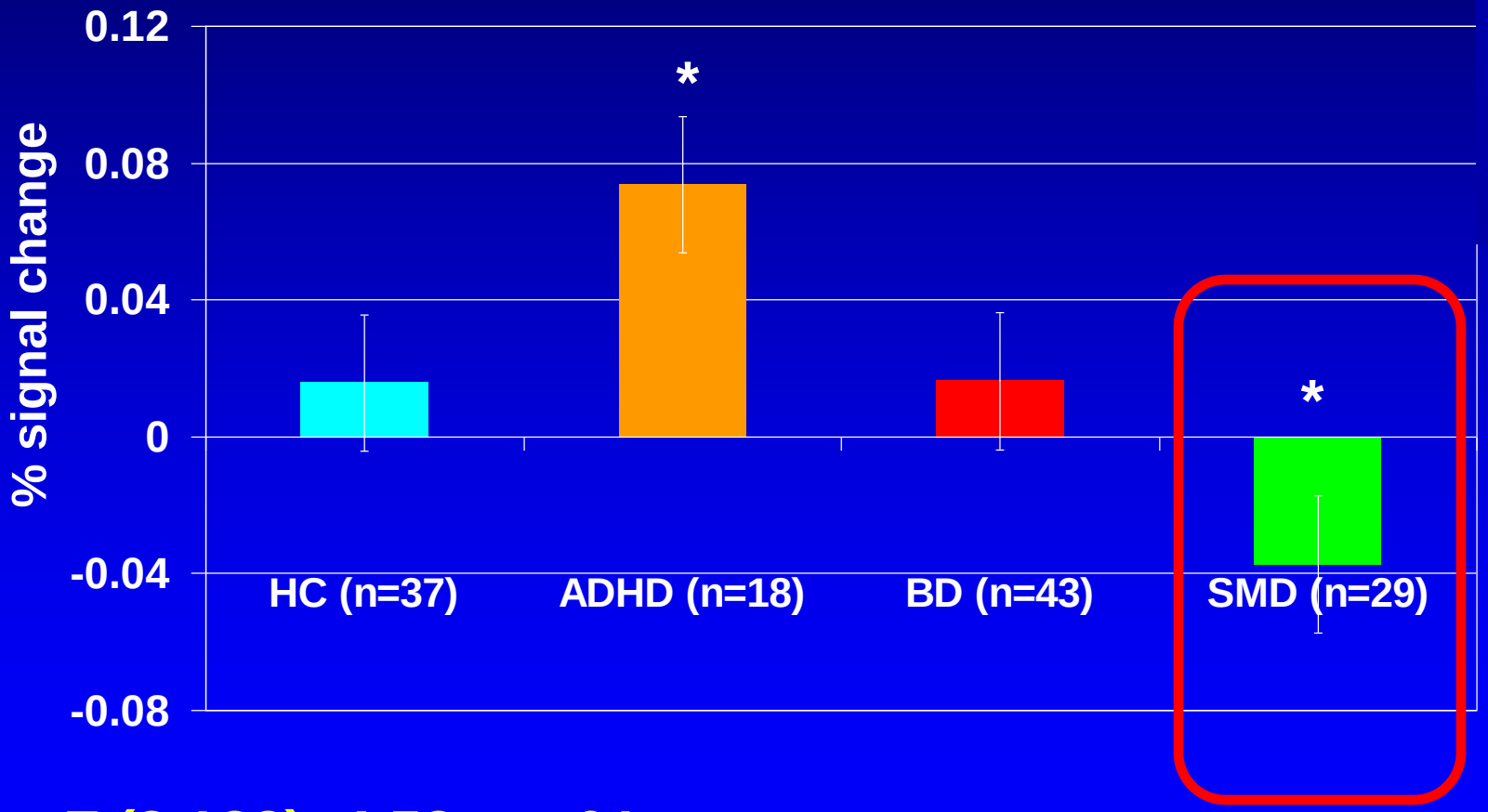
Neutral faces: How afraid are you?



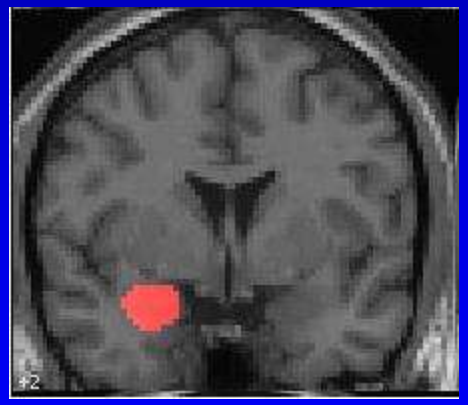
F(3,122)=3.11, p=.029
BD vs. controls p=.006
SMD vs. controls p=.020

Brotman et al, 2010

How afraid are you vs. How wide is nose
Left amygdala ROI, Neutral faces



ADHD > HC (p=.047)
ADHD > SMD (p<.001)
ADHD > BD (p=.046)
SMD < ADHD (p<.001)
SMD < HC (p=.037)
SMD < BD (p=.035)



F (3,122)=4.53, p<.01
*p<.05 vs. all other groups

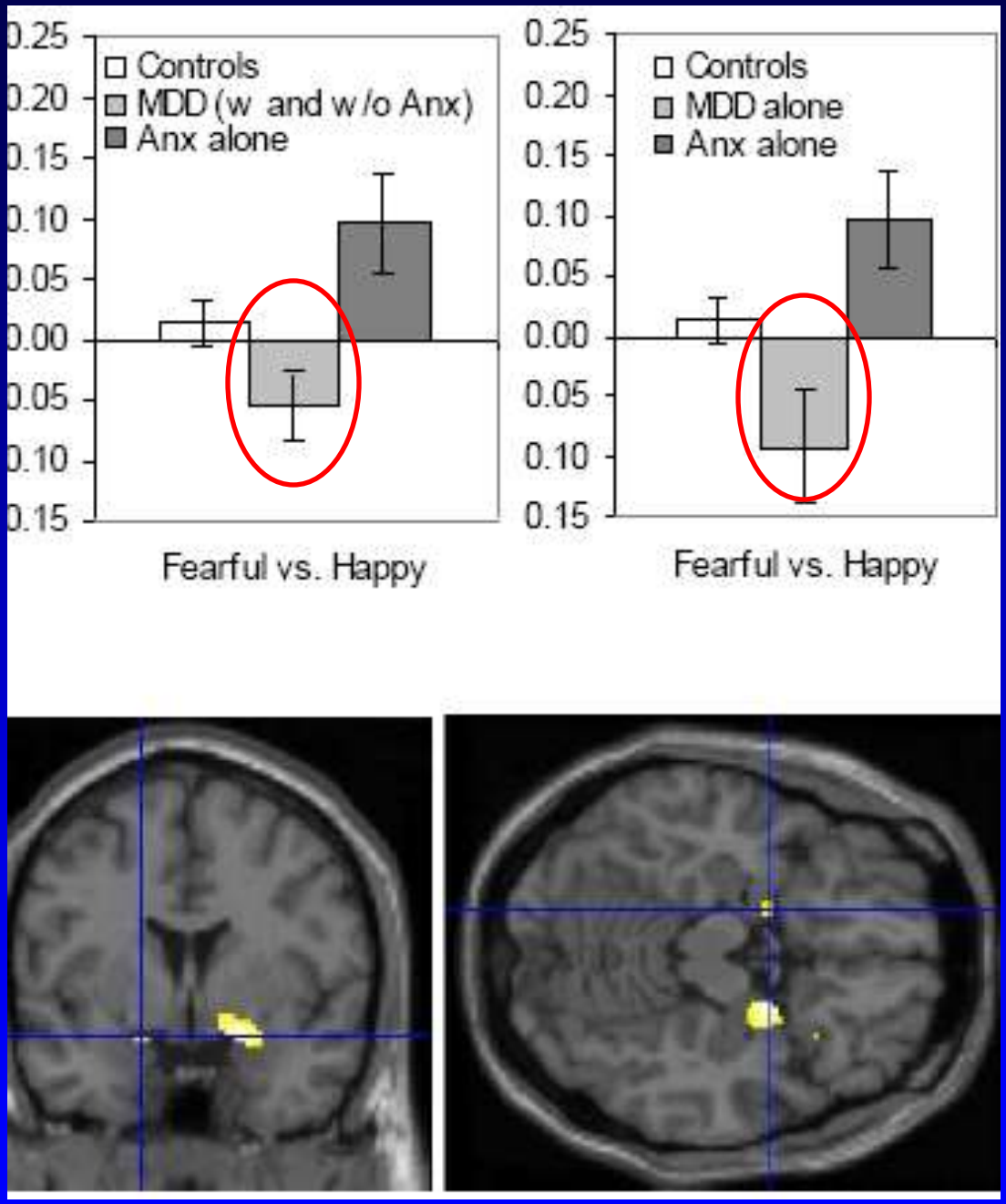
Brotman et al, 2010

Like SMD, MDD have decreased amygdala activation during face processing

Passive viewing of fearful vs. happy faces

N= 27 MDD, 17 ANX, 47 controls

Beesdo et al, 2009



The developmental psychopathology of bipolar disorder: Focus on face emotion processing

The developmental trajectory of bipolar disorder:

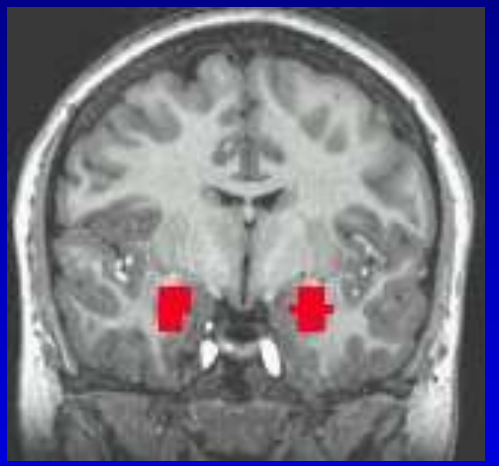
- Children at risk
- Child probands
- Adult probands

All three groups have face emotion labeling deficits.

Amgydala dysfunction??

Faces morph fMRI task (Blair et al)

- Three face expressions:
  - Neutral
  - Fearful: 50%, 100%, 150%
  - Angry: 50%, 100%, 150%



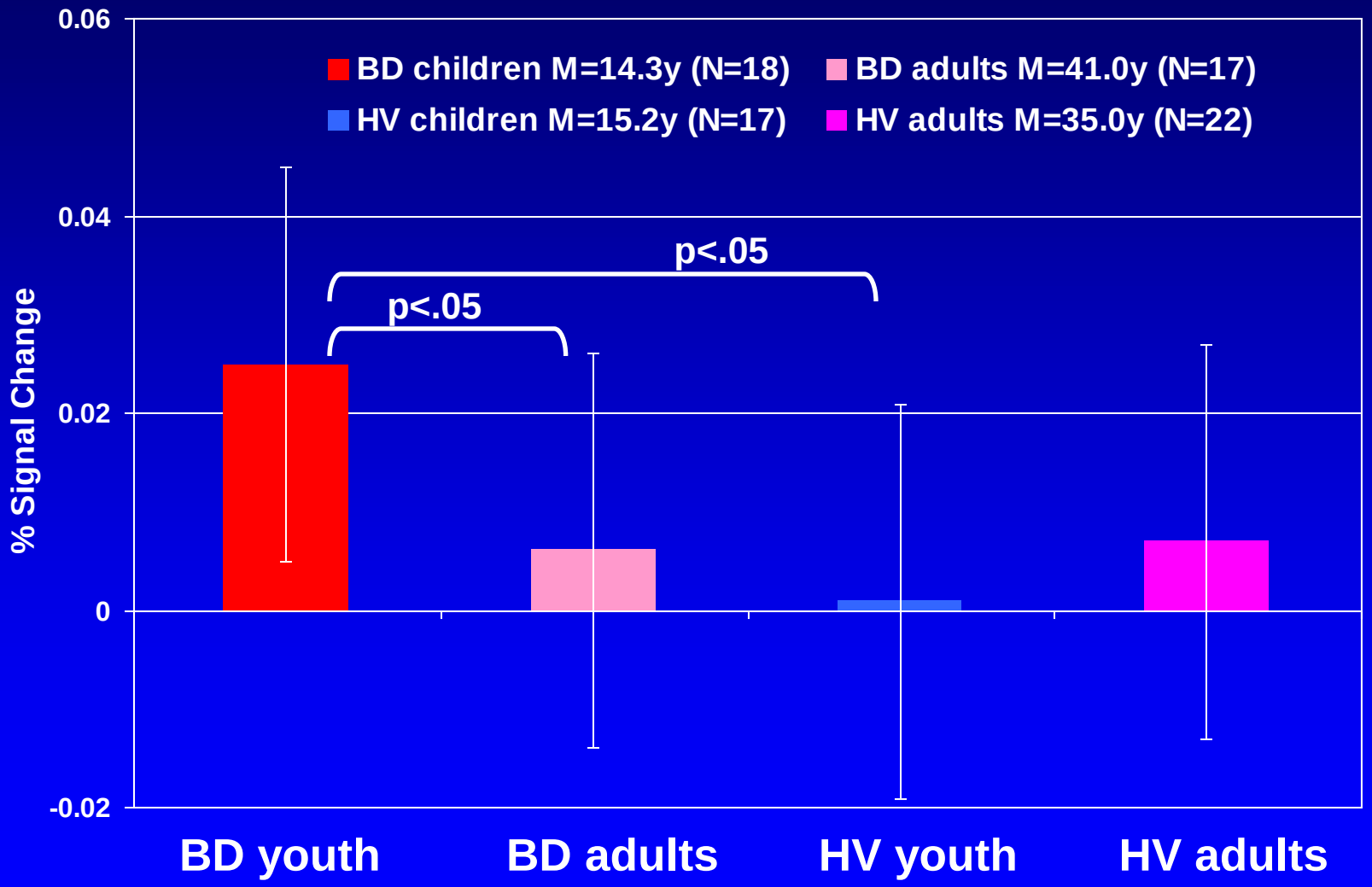
- Implicit processing: gender identification

- 4 groups:
  - child BD (N=18), adult BD (N=17)
  - child HV (N=17), adult HV (N=22)

- ANOVA: age group (child, adult) x diagnosis (BD, HV) x emotion (neutral, fearful, angry) on BOLD signal in anatomical ROI of amygdala

Kim et al, submitted

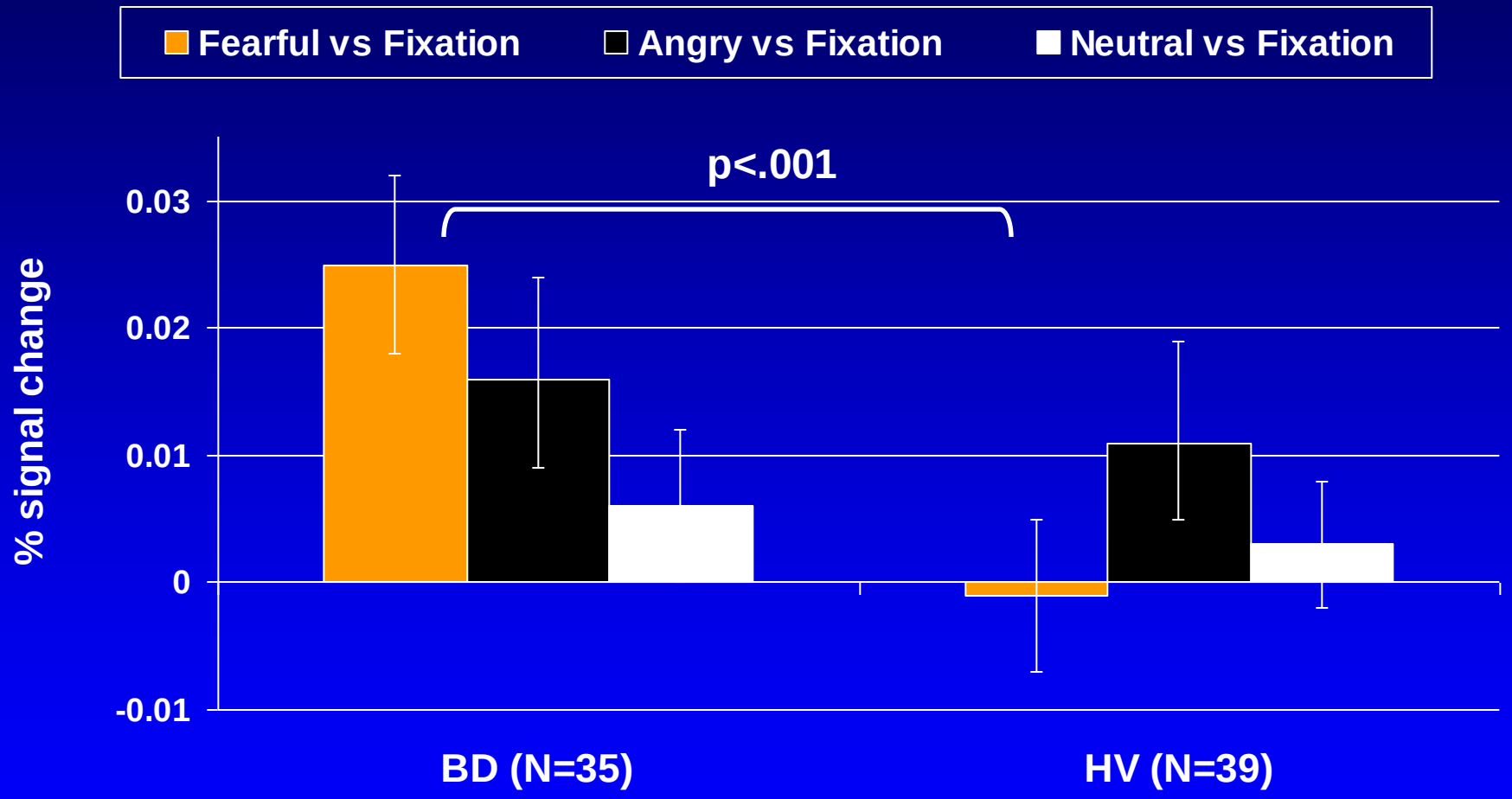
Across emotions, children with BD have ↑ amygdala activation vs. adults with BD and healthy children



age X diagnosis interaction: F= 4.43, df= 1,66, p=.04

Kim et al, in press

Compared to controls, adults and children with BD have ↑ amygdala activation in response to fearful, but not neutral or angry, faces

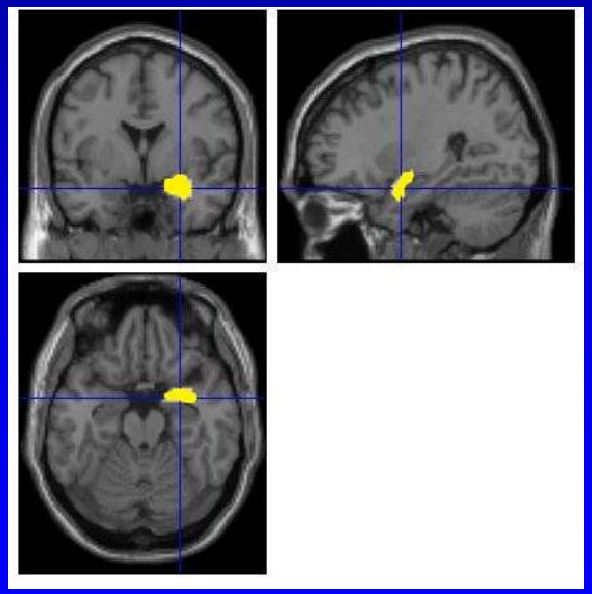


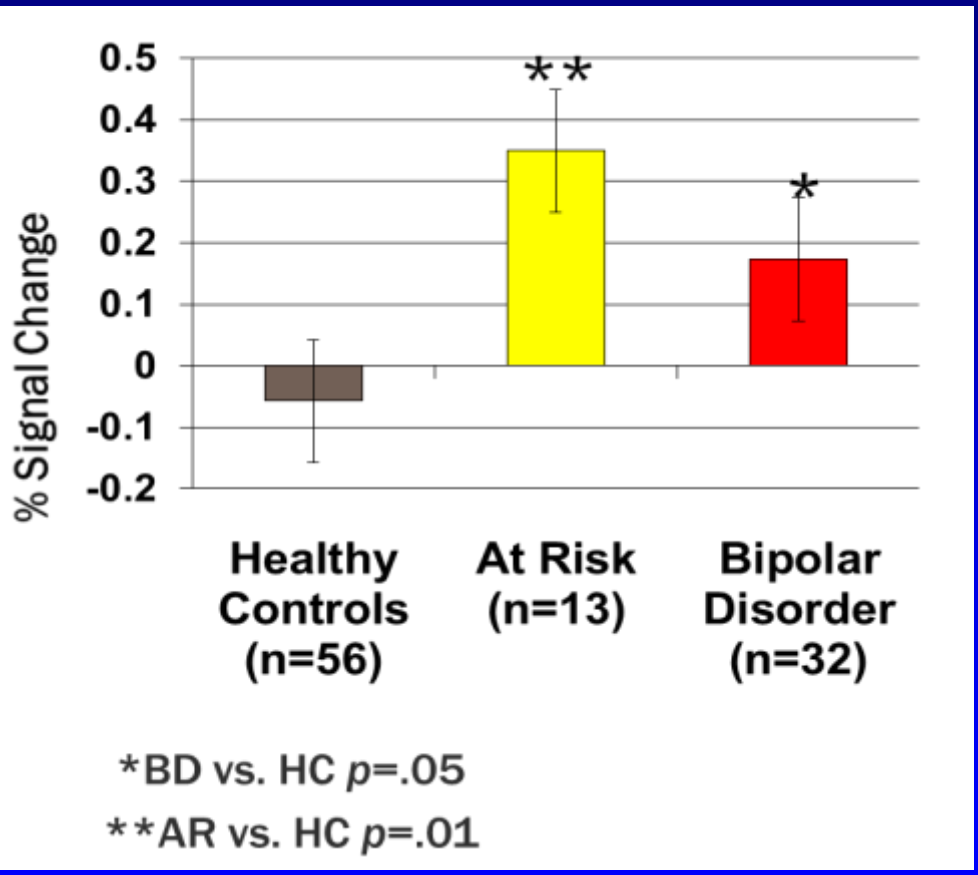
Emotion x diagnosis interaction: F= 5.40, df= 2,132, p=.006

Kim et al, in press

Amygdala activity in unaffected children at risk for BD

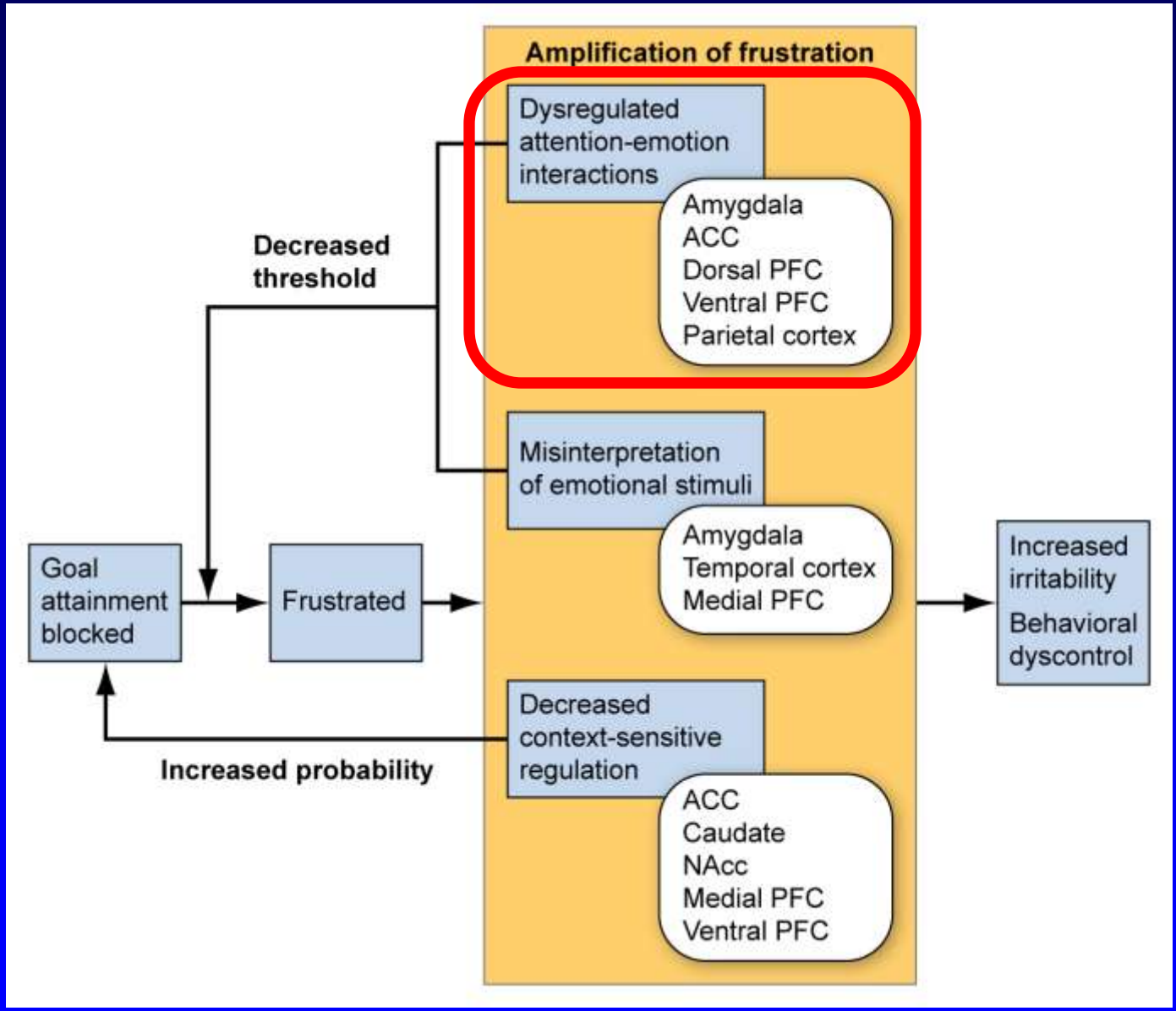
Viewing fearful faces:
How afraid are you?





Olsavsky et al, 2012

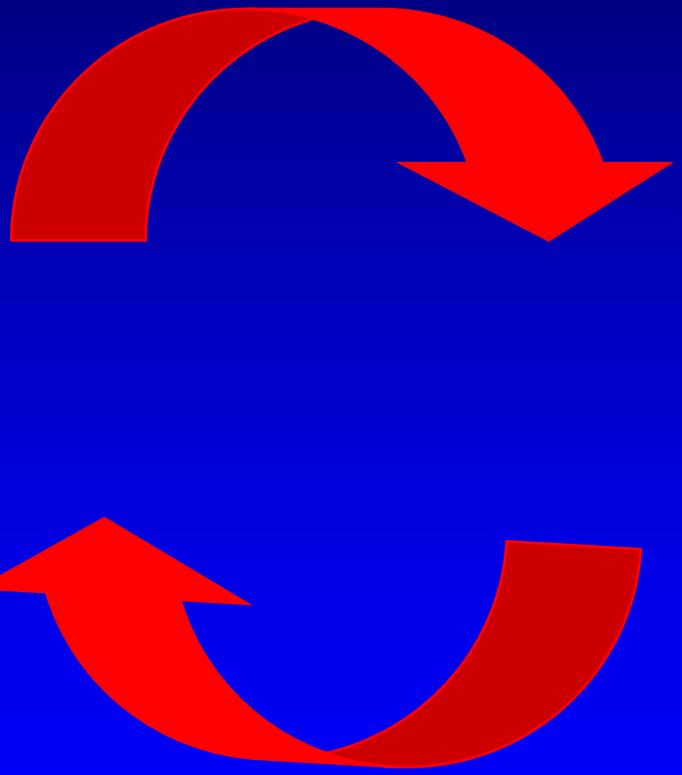
Neural mechanisms of frustration



Leibenluft, 2011

Attention-emotion interactions

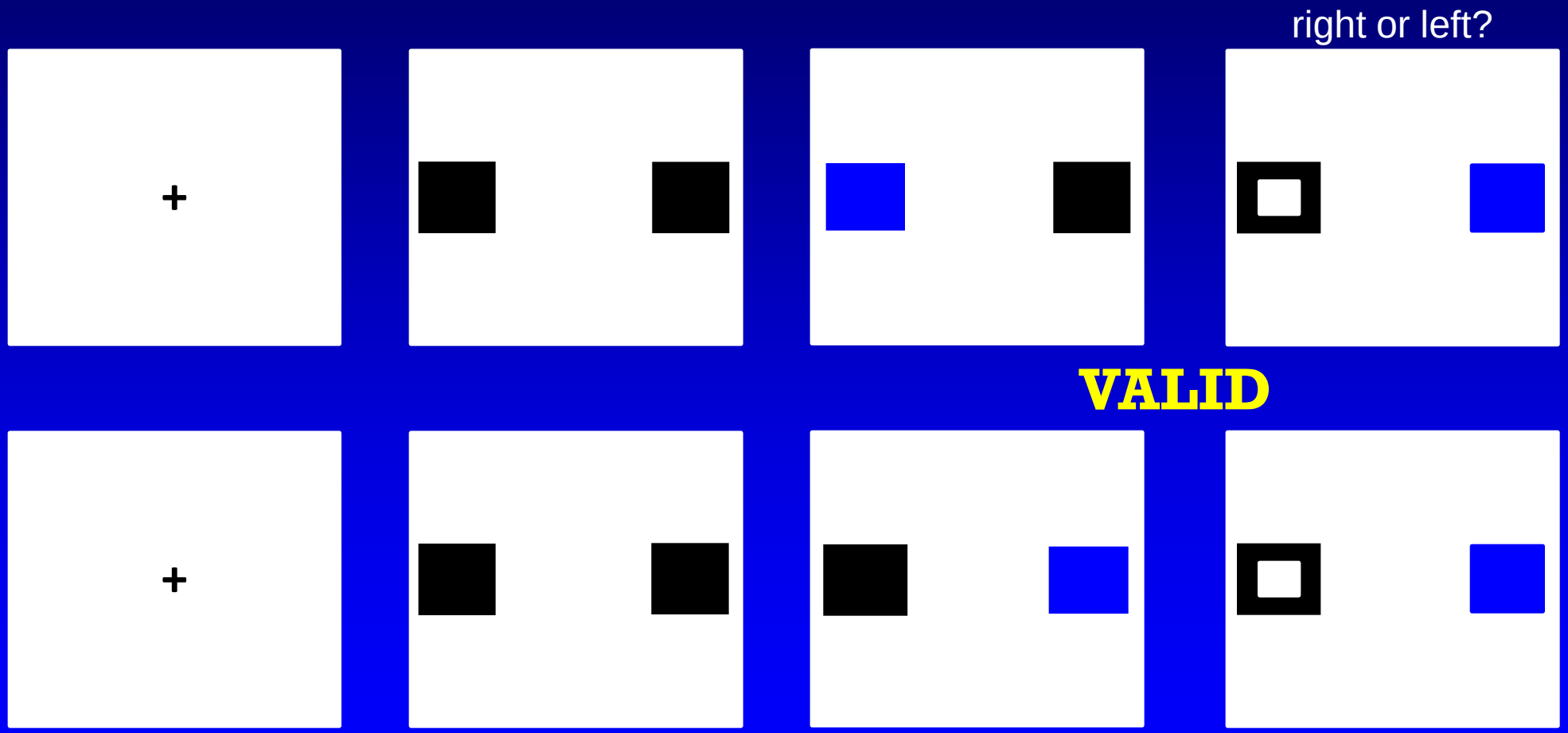
When you're upset, it's hard to "think straight."



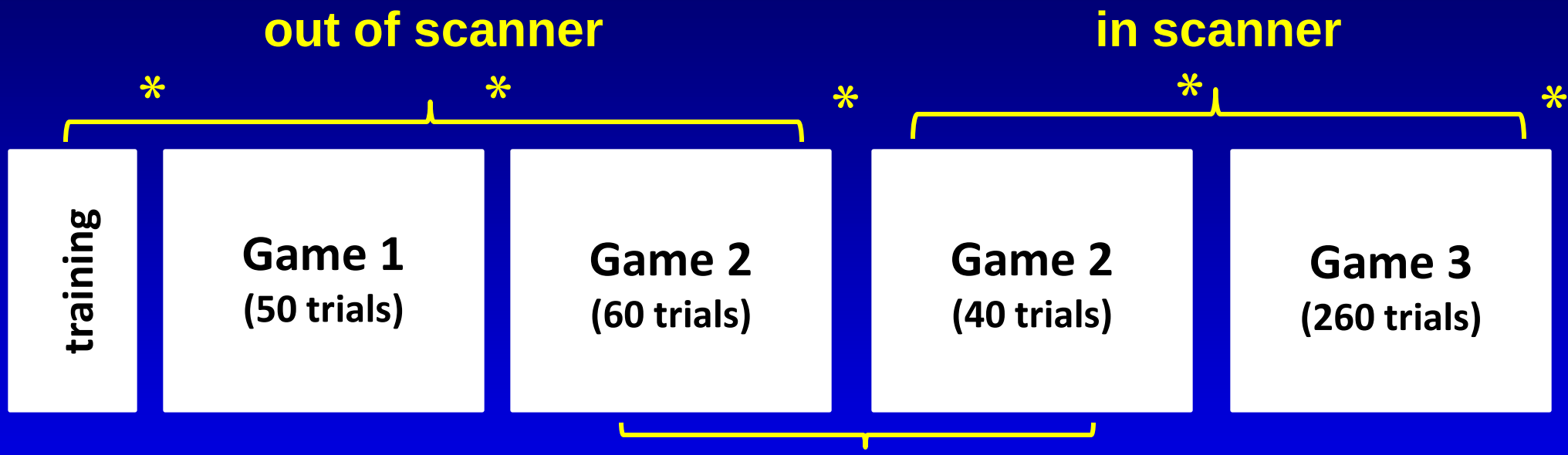
Children learn to regulate emotion by regulating attention

Affective Posner frustration task

Posner task

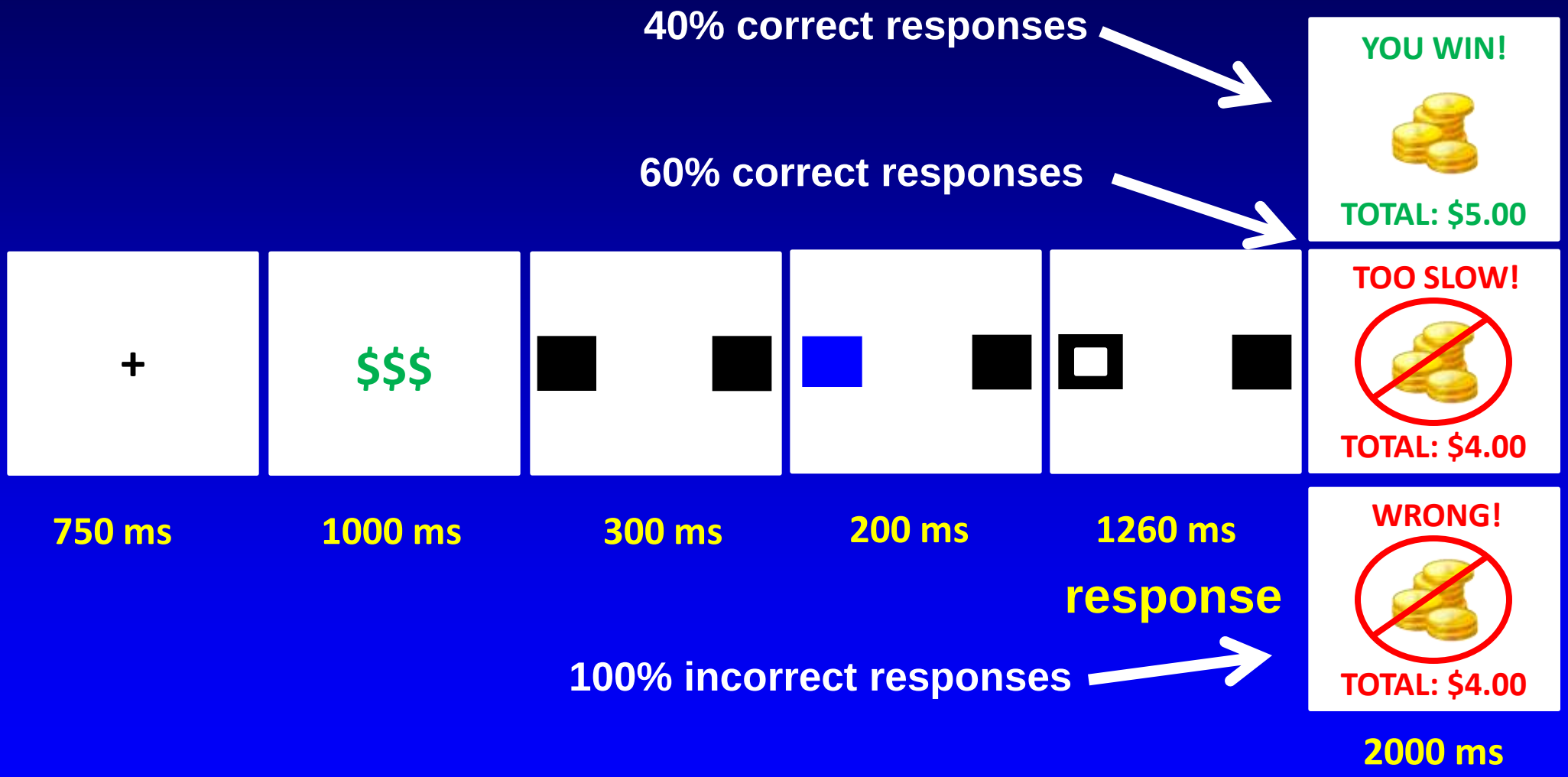


fMRI study design



*state valence, arousal, and frustration ratings

Rigged reward trials (Game 3)



Participants

	SMD N=19	NV N=23
Age	13.6	14.3
IQ	104	110
Gender*	15M/4F	11M/12F

*p<.05

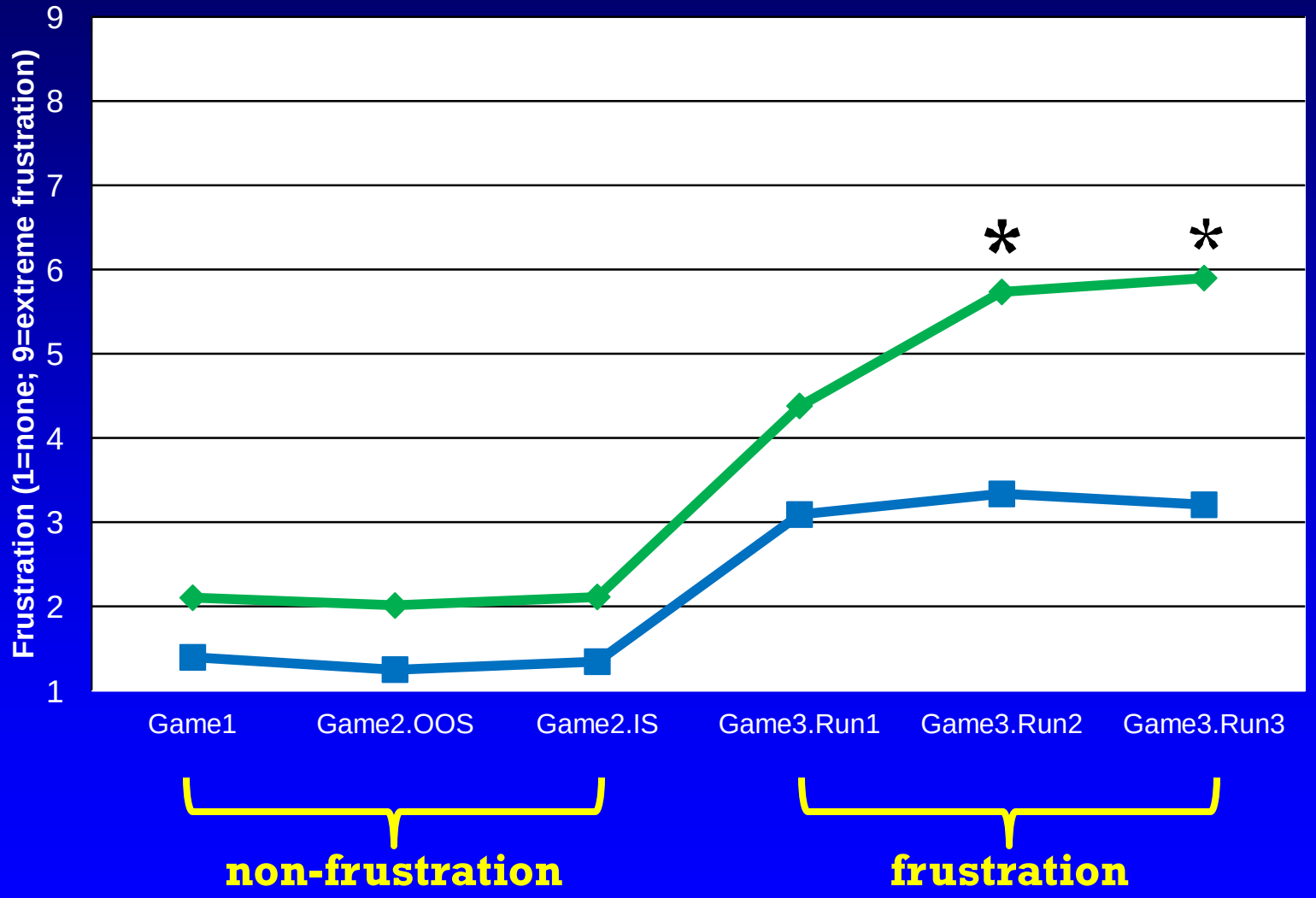
Clinical features in SMD

DSM-IV diagnoses:

ADHD: 78.9%
ODD: 84.2%
Anxiety: 63.2%

Medicated: 63.2%

Frustration



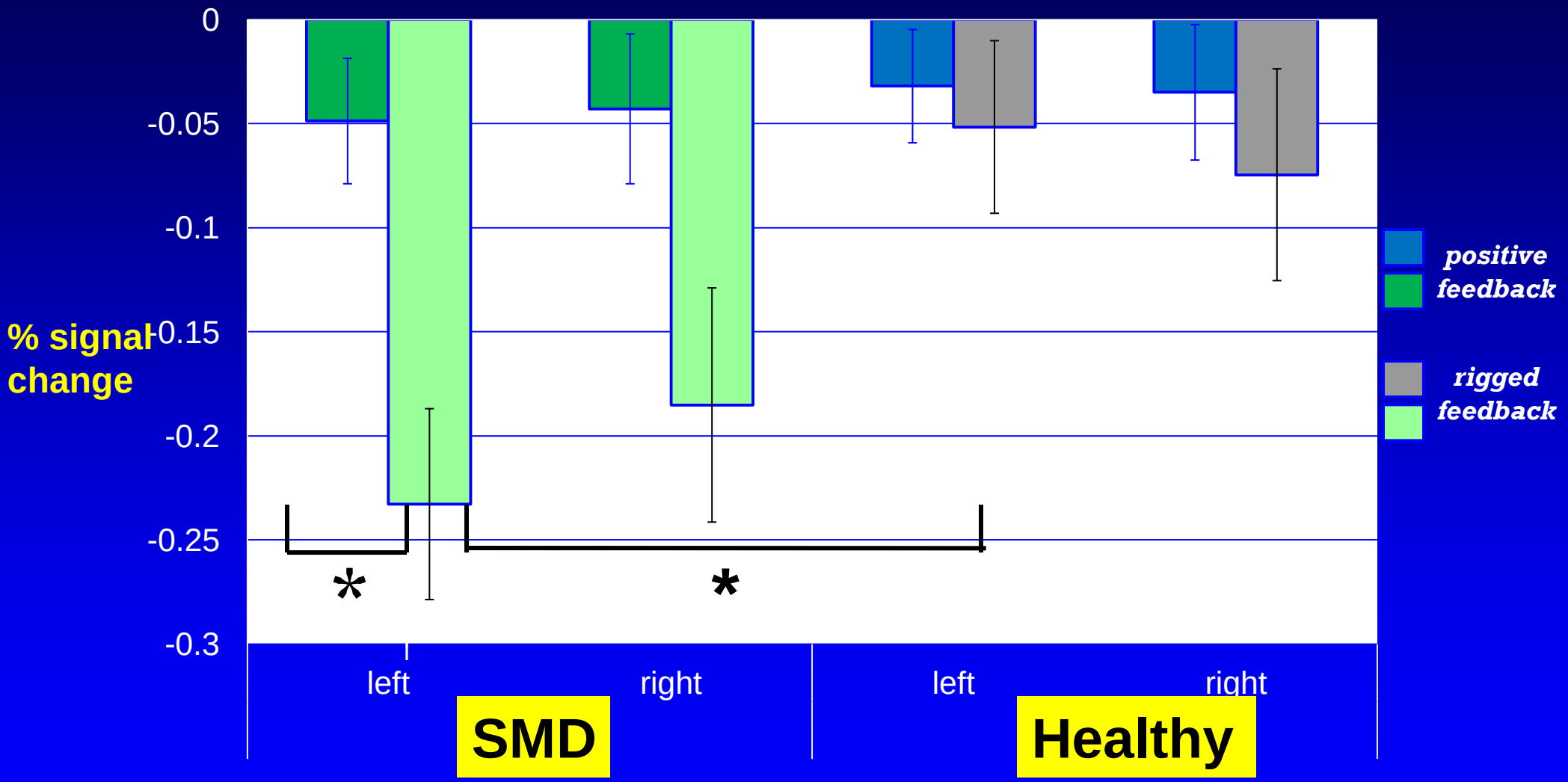
***Group x Game* interaction (*F*(5,190)=3.42, *p*<.05)**

Deveney et al, unpub

fMRI analysis

- Included valid (75% of trials) & correct trials only
- Amygdala anatomical ROI
- Whole-brain analysis
  - k ≥ 37, *p*<.001 uncorrected= p<.05, whole brain corrected
- Three way interaction: Group x Trial Type (neutral, reward) x Feedback (rigged, positive), not significant
- Two way interaction Group x Feedback (rigged, positive), significant in amygdala and other brain regions (especially parietal)

Amygdala

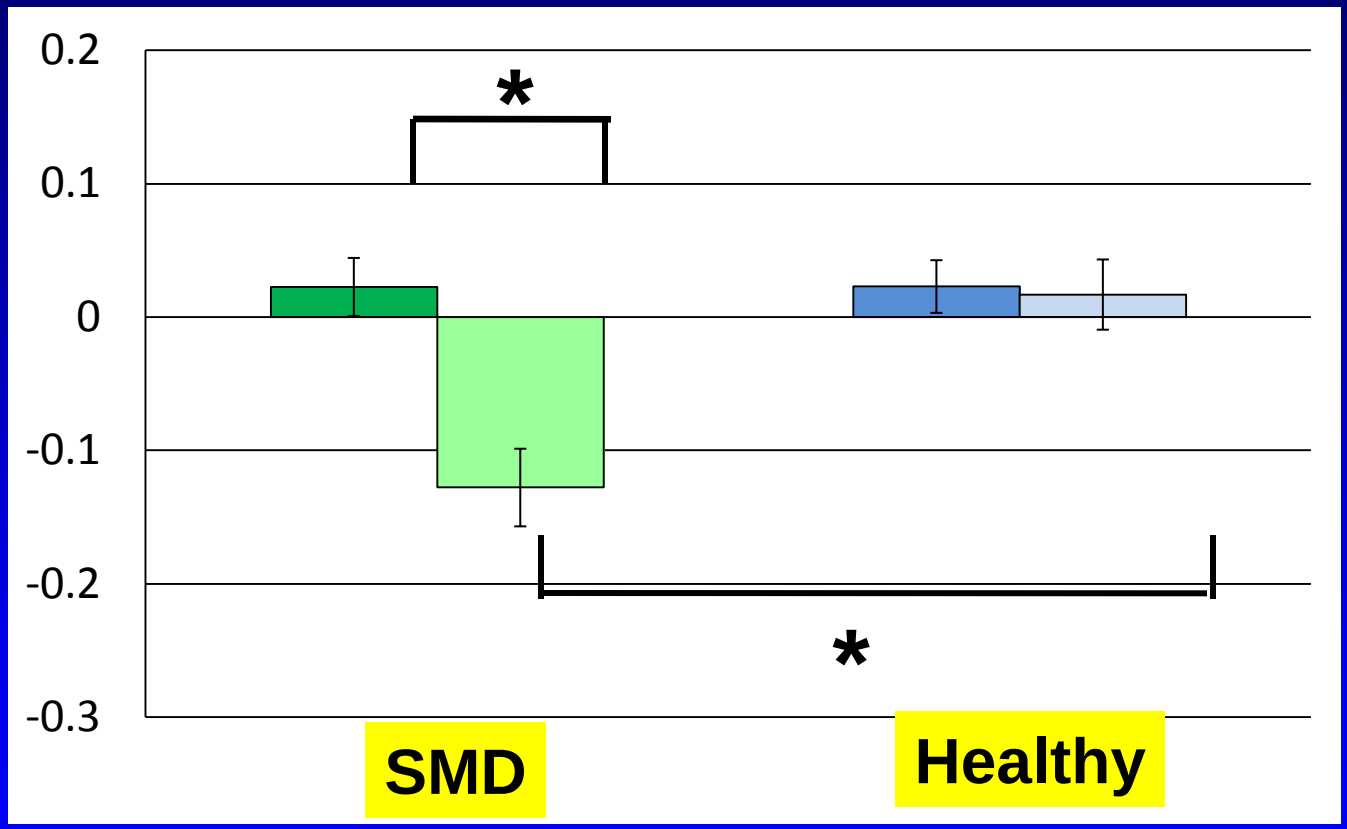


Group x Feedback on the left: F(1.39)=10.84, p<.005

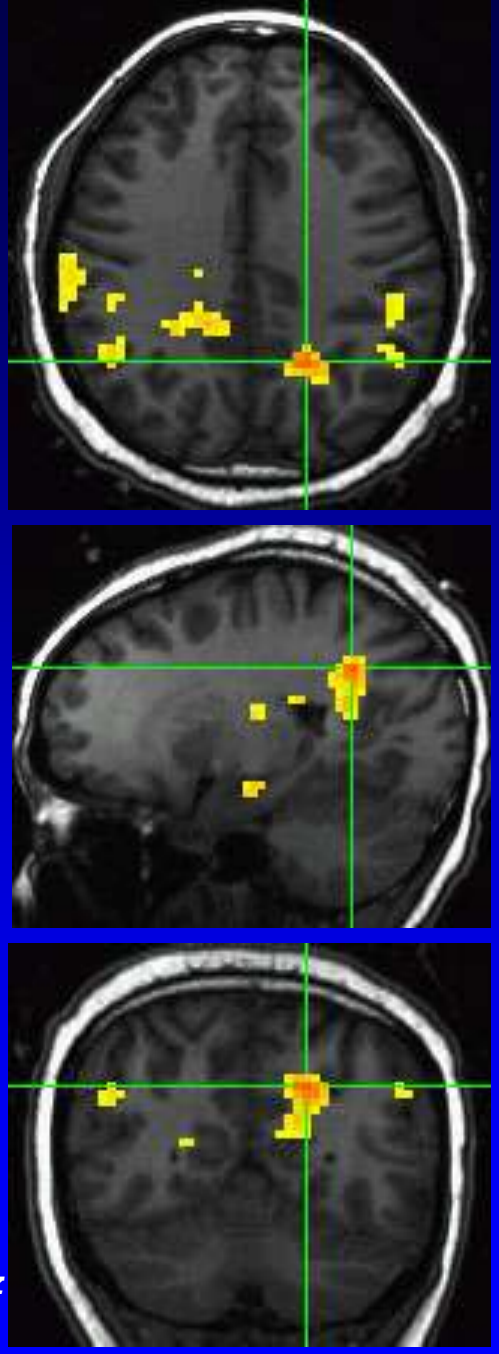
*** p<.01**

Deveney et al, unpub

Left posterior cingulate & precuneus



F (1,39)=14.62, p<.001
*p < .005



positive feedback

rigged feedback

Deveney et al, unpub

Summary

- Severe non-episodic irritability (SMD) differs from BD in:
  - longitudinal course: unipolar depression, anxiety in SMD
  - family history
  - amygdala dysfunction associated with face emotion processing deficits
- Therefore, the BD diagnosis should be reserved for youth with episodic symptoms.
- In SMD, frustration is associated with dysfunction in emotion-attention interactions mediated by amygdala and parietal cortex.
- More research should focus on the brain mechanisms mediating severe irritability in youth, and on its treatment.
- Future work: Dimensionalizing irritability

Thanks to:

- Danny Pine MD
- Ken Towbin MD
- Melissa Brotman PhD
- Argyris Stringaris MD
- Christen Deveney PhD
- Clinicians and research assistants

And our patients and their families!!

DO YOU HAVE A CHILD WITH Bipolar Disorder or *Severe Irritability?*

At the NIH Clinical Center in Bethesda, Maryland, several research studies are being conducted into the **causes of bipolar disorder or severe irritability.**

These studies seek children and adolescent participants ages 6-17 who have bipolar disorder or severe irritability.

All evaluations, research procedures, and inpatient/day hospital care are free of cost. Children and parents are compensated for participation.

Travel expenses are paid, and both parent and child must agree to the child's participation.

CAUSES OF BIPOLAR DISORDER

Participant Criteria:

- Ages 6-17 with bipolar disorder
- Able to perform research tasks that include: neuroimaging, computer tasks, and neuropsychological testing

A) Non-Treatment Study:

If stable on current medications:

- Receive annual outpatient visits

B) Two Different Treatment Studies:

If unstable on current medications, day or full hospitalization to discontinue medication

- Parent and clinician together choose either:

1) Perform research tasks while medication-free for 2 weeks, followed by standard medications.

2) Clinical trial of riluzole vs. placebo

- Ages 9-17 with bipolar disorder
- Have not done well on mood stabilizer and/or atypical antipsychotic drugs alone or in combination

Protocol #: 00-M-0198 & 09-M-0042

CAUSES OF SEVERE IRRITABILITY

Participant Criteria:

- Ages 7-17
- Have irritability symptoms that include: difficulty handling frustration (severe temper tantrums and rages) and "hyper" behavior (distractible, hyperactive, trouble sleeping)
- Able to perform research tasks that include neuroimaging, computer tasks and neuropsychological testing

A) Non-Treatment Study:

If stable on current medications:

- Receive annual outpatient visits

B) Treatment Studies:

If unstable on current medications:

- Receive day or full hospitalization to discontinue medication
- Parent and clinician together choose either:

1) Perform research tasks while medication-free for 2-weeks, followed by standard medications

2) Study the efficacy of methylphenidate plus citalopram, vs methylphenidate plus placebo, for decreasing irritability in children with severe mood and behavioral problems

- This study lasts 12 to 15 weeks
- If clinically appropriate, participants who received methylphenidate plus placebo will be offered the opportunity to receive methylphenidate plus citalopram at the end of the study

Protocol #: 02-M-0021 & 09-M-0034

BiPOLARKids
RESEARCH STUDIES at NIMH

CALL TO PARTICPATE **301-496-8381**

TTY: 1-866-411-1010

Ellen Leibenluft, M.D. or Kenneth Towbin, M.D. Email: bipolarkids@mail.nih.gov

NATIONAL INSTITUTE OF MENTAL HEALTH
NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH & HUMAN SERVICES

NIMH National Institute of Mental Health

1) BD
2) SMD
3) at risk for BD

Non-treatment studies (e.g., scans) and treatment studies

Definitions

- **Irritability**
  - **Clinical (as in SMD)**
    - **developmentally inappropriate outbursts**
    - **inter-outburst negative mood**
  - **Neuroscience: decreased threshold for, and maladaptive responses to, frustration**
- **Frustration: emotional response that occurs when goal attainment is blocked**