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%)
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 $\geq 1$ 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

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

<table>
<thead>
<tr>
<th>Age at baseline</th>
<th>MDD</th>
<th>GAD</th>
<th>Dysth</th>
<th>MDD &amp; GAD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children in the Community</strong></td>
<td>776</td>
<td>13.8</td>
<td>33.2</td>
<td>1.33 (1.0-1.8)</td>
</tr>
</tbody>
</table>

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
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• 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 $\rightarrow$ depression
  - headstrong $\rightarrow$ 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, \( p \leq .01 \); 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
<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>BD (N=118)</th>
<th>SMD (N= 134)</th>
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<tbody>
<tr>
<td>Age</td>
<td>12.9 ± 2.8</td>
<td>12.0 ± 2.0</td>
</tr>
<tr>
<td>Age of onset</td>
<td>9.8 ± 3.5</td>
<td>5.6 ± 2.2</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>52.0</td>
<td>69.7</td>
</tr>
<tr>
<td>% ADHD</td>
<td>57.0</td>
<td>85.3</td>
</tr>
<tr>
<td>% ODD</td>
<td>36.0</td>
<td>84.4</td>
</tr>
<tr>
<td>% Anxiety d/o</td>
<td>56.0</td>
<td>52.3</td>
</tr>
<tr>
<td>Number meds</td>
<td>2.4 ± 1.70</td>
<td>1.37 ± 1.45</td>
</tr>
<tr>
<td>% hospitalized</td>
<td>63.0</td>
<td>40.4</td>
</tr>
<tr>
<td>Children’s Global</td>
<td>51.1 ± 10.8</td>
<td>47.4 ± 9.0</td>
</tr>
<tr>
<td>Assessment Scale</td>
<td></td>
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</table>
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

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

Brotman et al, 2010

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

Amygdala 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 increased 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

right or left? 

VALID

INVALID
fMRI study design

out of scanner

training

Game 1
(50 trials)

standard
Posner

in scanner

Game 2
(60 trials)

Game 2
(40 trials)

Game 3
(260 trials)

*state valence, arousal, and frustration ratings

reward trials only
100% correct responses: win 50¢
100% incorrect responses: lose 50¢
accurate feedback

rigged feedback
reward & neutral
trials
Rigged reward trials (Game 3)

40% correct responses

60% correct responses

YOU WIN!
TOTAL: $5.00

TOO SLOW!
TOTAL: $4.00

WRONG!
TOTAL: $4.00

100% incorrect responses

response

750 ms 1000 ms 300 ms 200 ms 1260 ms
Participants

<table>
<thead>
<tr>
<th></th>
<th>SMD N=19</th>
<th>NV N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>13.6</td>
<td>14.3</td>
</tr>
<tr>
<td>IQ</td>
<td>104</td>
<td>110</td>
</tr>
<tr>
<td>Gender*</td>
<td>15M/4F</td>
<td>11M/12F</td>
</tr>
</tbody>
</table>

Clinical features in SMD

DSM-IV diagnoses:
- ADHD: 78.9%
- ODD: 84.2%
- Anxiety: 63.2%

Medicated: 63.2%

*p<.05
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
  • $k \geq 37$, $p<.001$ 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

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.

BiPOLARKids RESEARCH STUDIES at NIMH CALL TO PARTICIPATE

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

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

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