



# Distinguishing Deficits in Emotional Regulation from Mood Disorders in Youth

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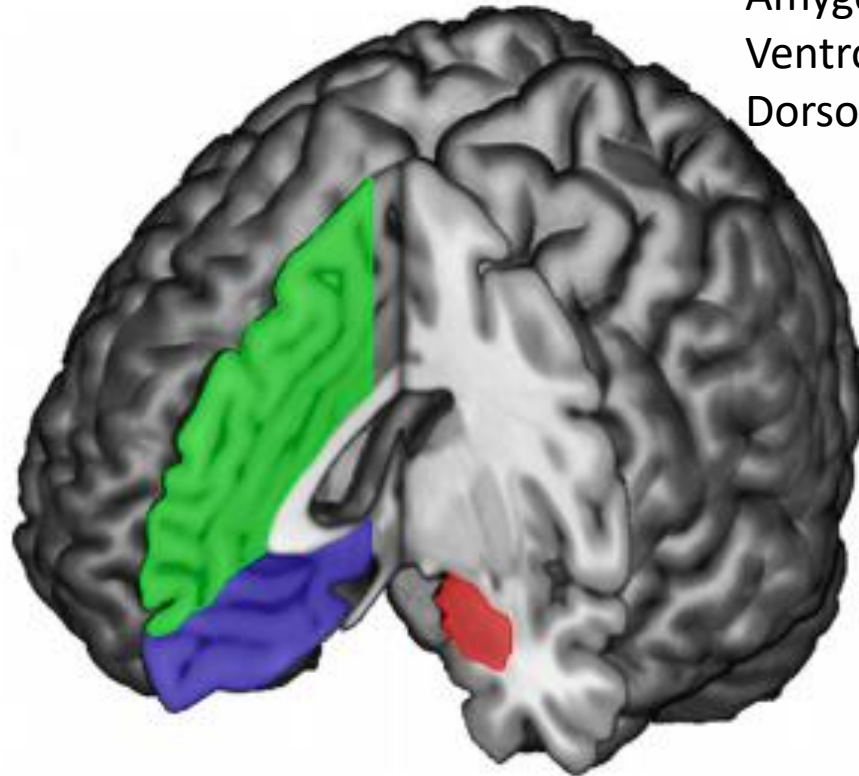
# Disclosures 2020-2021

My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:

- *Research support:* Genentech, Headspace Inc., Pfizer Pharmaceuticals, Roche TCRC Inc., Sunovion Pharmaceuticals Inc., Takeda/Shire Pharmaceuticals Inc., and Tris.
- *Consulting fees:* Akili, Avekshan LLC, Jazz Pharma, and Shire/Takeda
- *Honorarium for scientific presentation:* Tris
- *Royalties paid to the Department of Psychiatry at MGH, for a copyrighted ADHD rating scale used for ADHD diagnoses:* Biomarin, Bracket Global, Cogstate, Ingenix, Medavent Prophase, Shire, Sunovion, and Theravance
- Through Partners Healthcare Innovation, I have a partnership with MEMOTEXT to commercialize a digital health intervention to improve adherence in ADHD.



# Amygdala-Prefrontal Circuitry



Amygdala: Red

Ventromedial prefrontal cortex: Blue

Dorsomedial prefrontal cortex: Green

**Fig. 1.** Structural magnetic resonance image of the human brain highlighting the major components of the amygdala-prefrontal circuitry: amygdala (red), ventromedial prefrontal cortex (blue), and dorsomedial prefrontal cortex (green) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

(Kim 2011 Behavioral Brain Research)



# Types of Mood Disturbance

- Severe Mood Disturbance / Temper Dysregulation Disorder (Leibenluft et al., AJP 2003)
- DSM V Disruptive Mood Dysregulation Disorder (DMDD)
- ODD emotional items (DSM IV)
- Emotional Lability (many authors)
- Emotionality (Stringaris et al., JAACAP, 2010)
- Irritability (many uses)
- Dysphoric Conduct Disorder (CD disorder comorbid with BP disorder)
- Deficient Emotional Self-Regulation (DESR) (Barkley, JARD, 2010)
- Emotional Impulsivity (Biederman et al.)



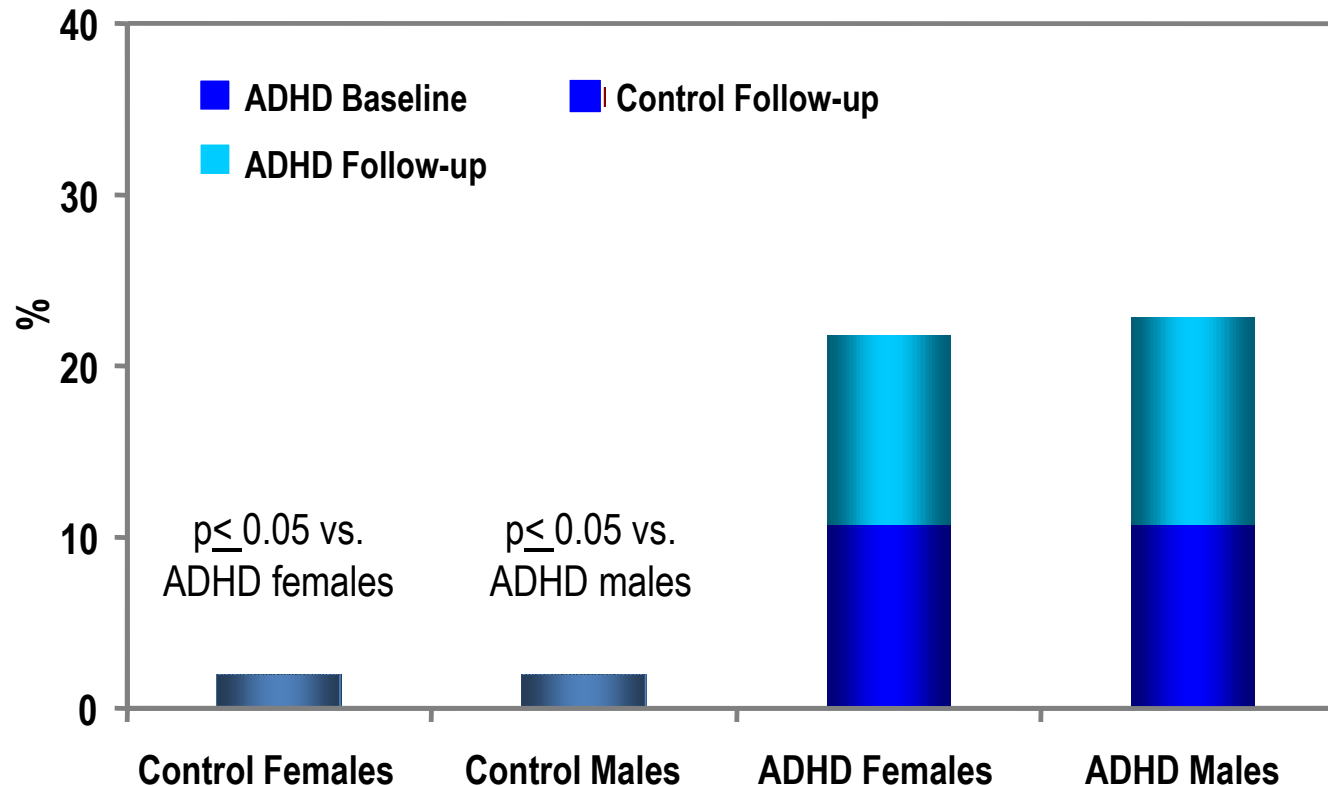


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# **ROBUST BIDIRECTIONAL ASSOCIATION BETWEEN BIPOLAR DISORDER AND ADHD IN CHILDREN AND ADULTS**



# Bipolar Disorder in Girls and Boys With and Without ADHD

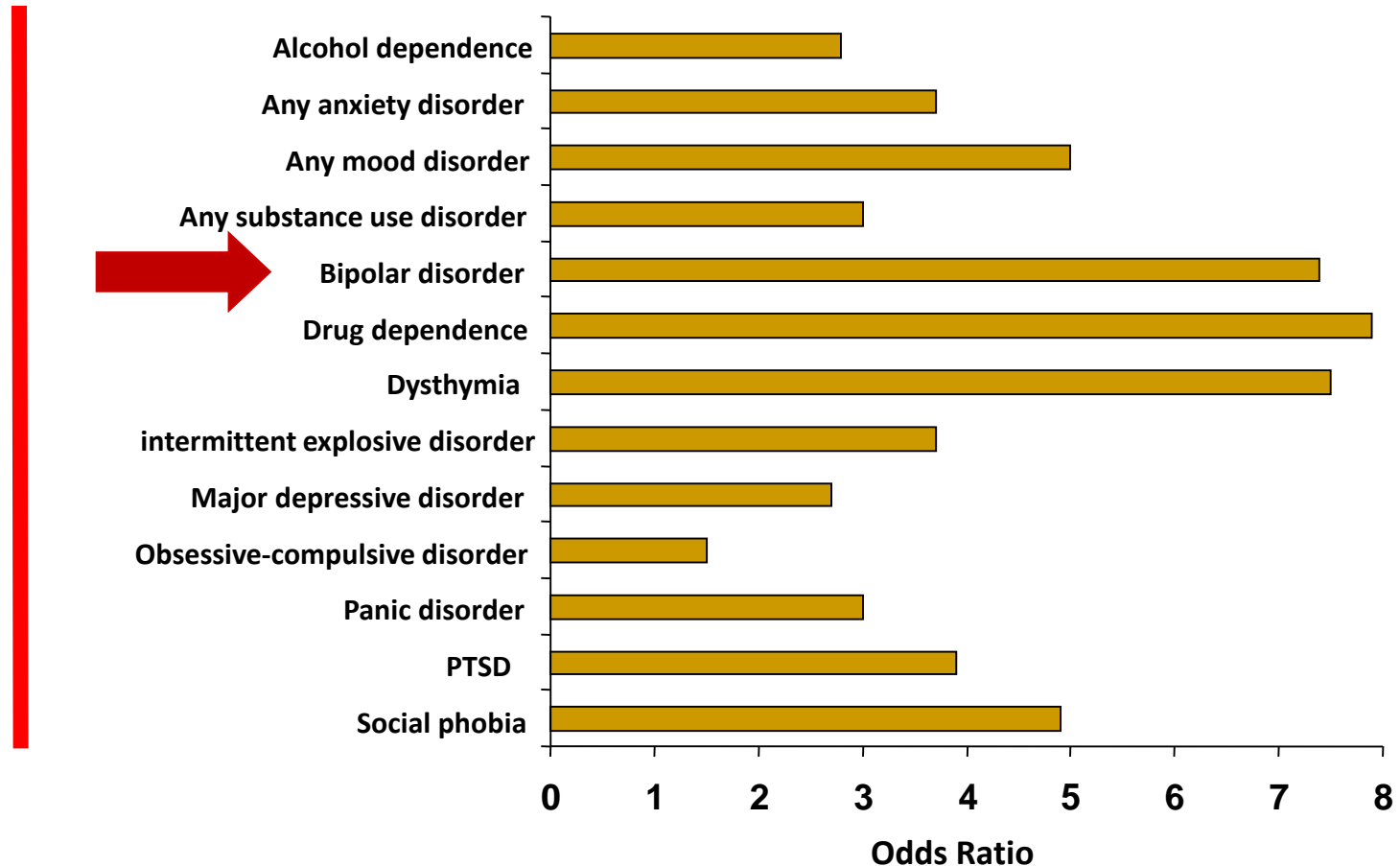


Biederman et al. *Psychological Medicine*. 2006; 36: 167-179.

Biederman et al. *Biological Psychiatry*. 2006; 60: 1098-1105.



# Patterns of Comorbidity in ADHD Adults





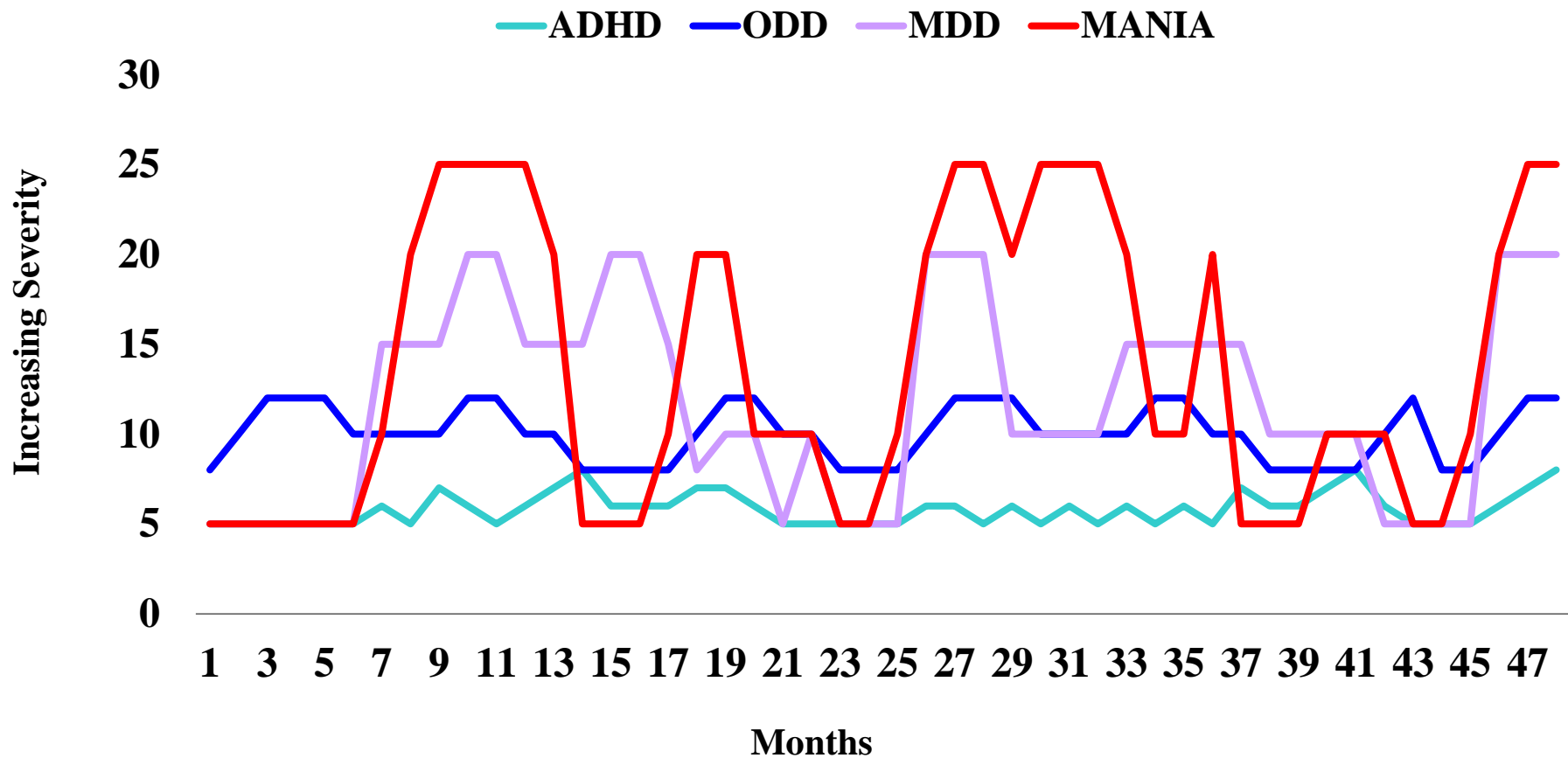


# Are All Forms of Irritability the Same?

Heterogeneity of Irritability



# Heterogeneity of Irritability in Children





# Juvenile Mania

- The type of irritability observed in manic children is very severe, persistent, and often violent
- The outbursts often include threatening or attacking behavior towards others, including family members, other children, adults, and teachers



# Heterogeneity of Irritability

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- Labile mood/hot temper: ODD
- Severe irritability: MDD
- Explosive/violent irritability: BPD





**IRRITABILITY IS ALSO A KEY  
FEATURE OF JUVENILE MDD**



# Irritability of ODD vs. Furiosity of Mania

- The irritable child with oppositional defiant disorder (ODD) is hypersensitive to provoking stimuli from **authority figures** and may or may not be able to self-regulate
- The furious bipolar child is hypersensitive and experiences **extremes of emotion** that are **impossible to self-regulate**



# Deficits in Emotional Regulation vs. Mood Disorder

- Deficits in emotional regulation (or Emotional Impulsivity) do not necessarily lead to extreme moods but always leads to poor self-regulation of mood
- Deficits in emotional regulation subside relatively rapidly and do not form a distinct protracted episode of the type that would qualify for a mood disorder



# Deficits in Emotional Regulation vs. Mood Disorders

- Deficits in emotional regulation are phenomenologically distinct from mood disorders, which are characterized by the experience of strong emotions, not their self-regulation (Thus, emotional impulsivity)
- Unlike deficits in emotional regulation , mood disorders require the presence of non-mood criteria including somatic and behavioral impairments
- Mood disorders show dysregulated mood throughout each episode, not only in response to provoking stimuli



# Important Caveat

- **Deficits in emotional regulation and Mood Disorders are not mutually exclusive and can co-exist**





# **The MGH Study of Deficient Emotional Self Regulation (DESR) in Pediatric ADHD**



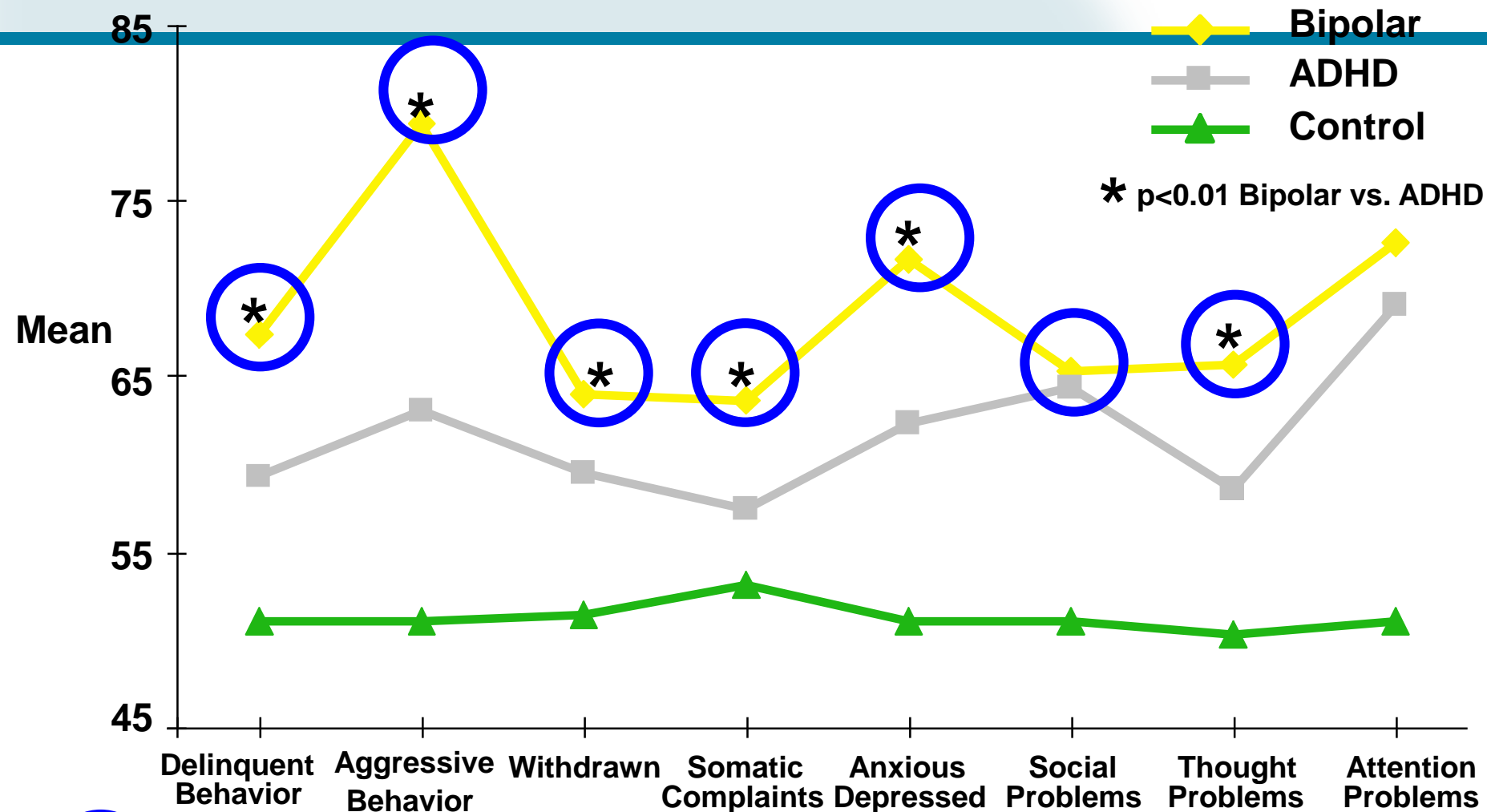
# DESR in Pediatric ADHD Study

- **Study Population**
  - **242 Youth with ADHD**
  - **224 Controls without ADHD**



# CBCL Clinical Scales

(Biederman et al., JAACAP, 1995)



Significantly elevated in children of BPD parents (Wals et al., JAACAP, 2001)



# CBCL Mood Dysregulation Profiles

- **CBCL-DESR** was operationalized using an aggregate score  $\geq 180$  and  $< 210$  in the Anxious/Depressed, Attention, and Aggression scales (AAA profile) of the CBCL
- **CBCL-Bipolar** profile was defined as  $\geq 210$  on the CBCL-AAA scale



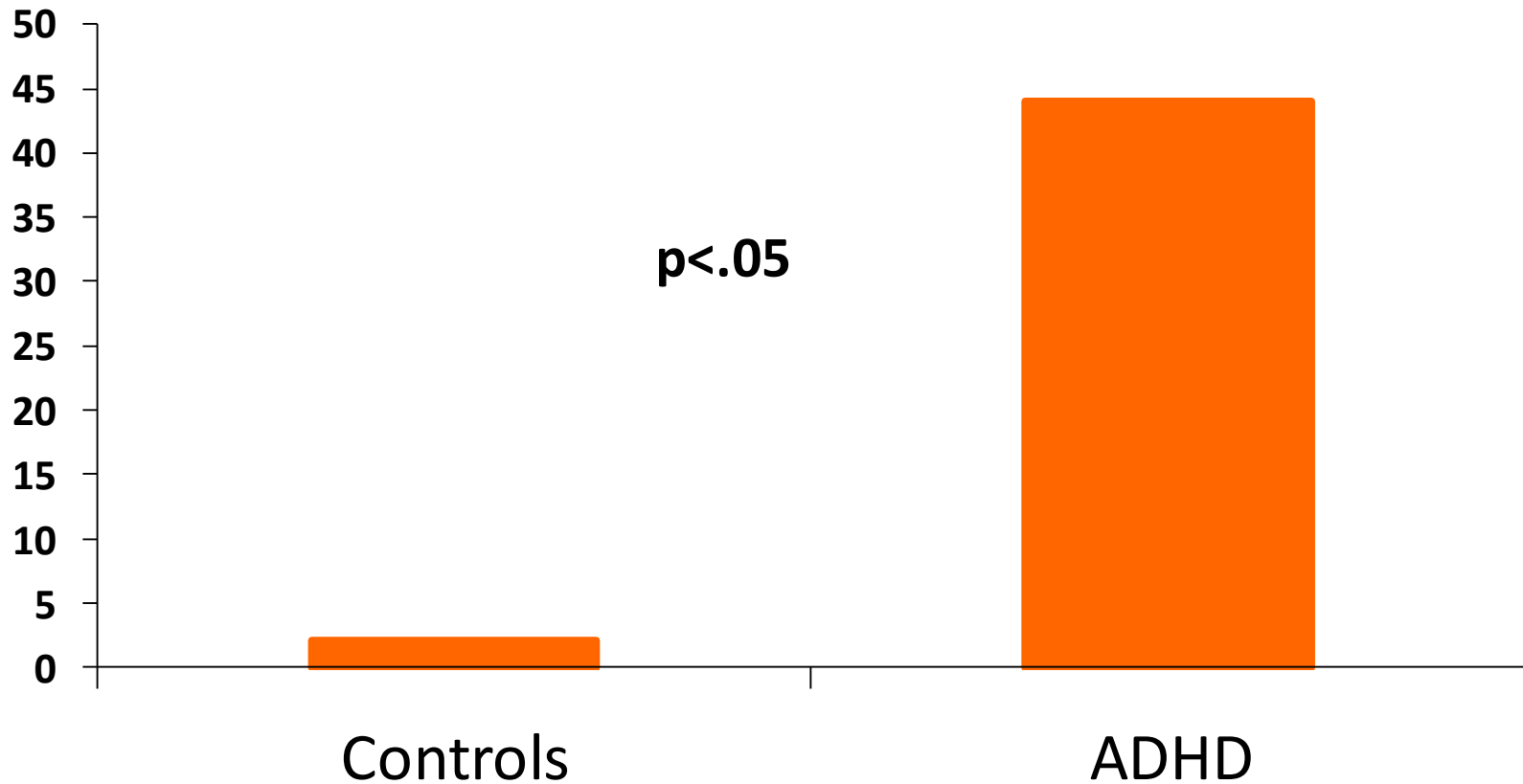
# CBCL-DESR Profile

- CBCL-DESR profile was selected because of its conceptual congruence with the clinical concept of DESR or Emotional Impulsivity
- Its extreme (>210) form had been previously associated with BP-I disorder



# Rates of DESR in ADHD and Control Youth

(Spencer et al., Postgrad Med 2012)



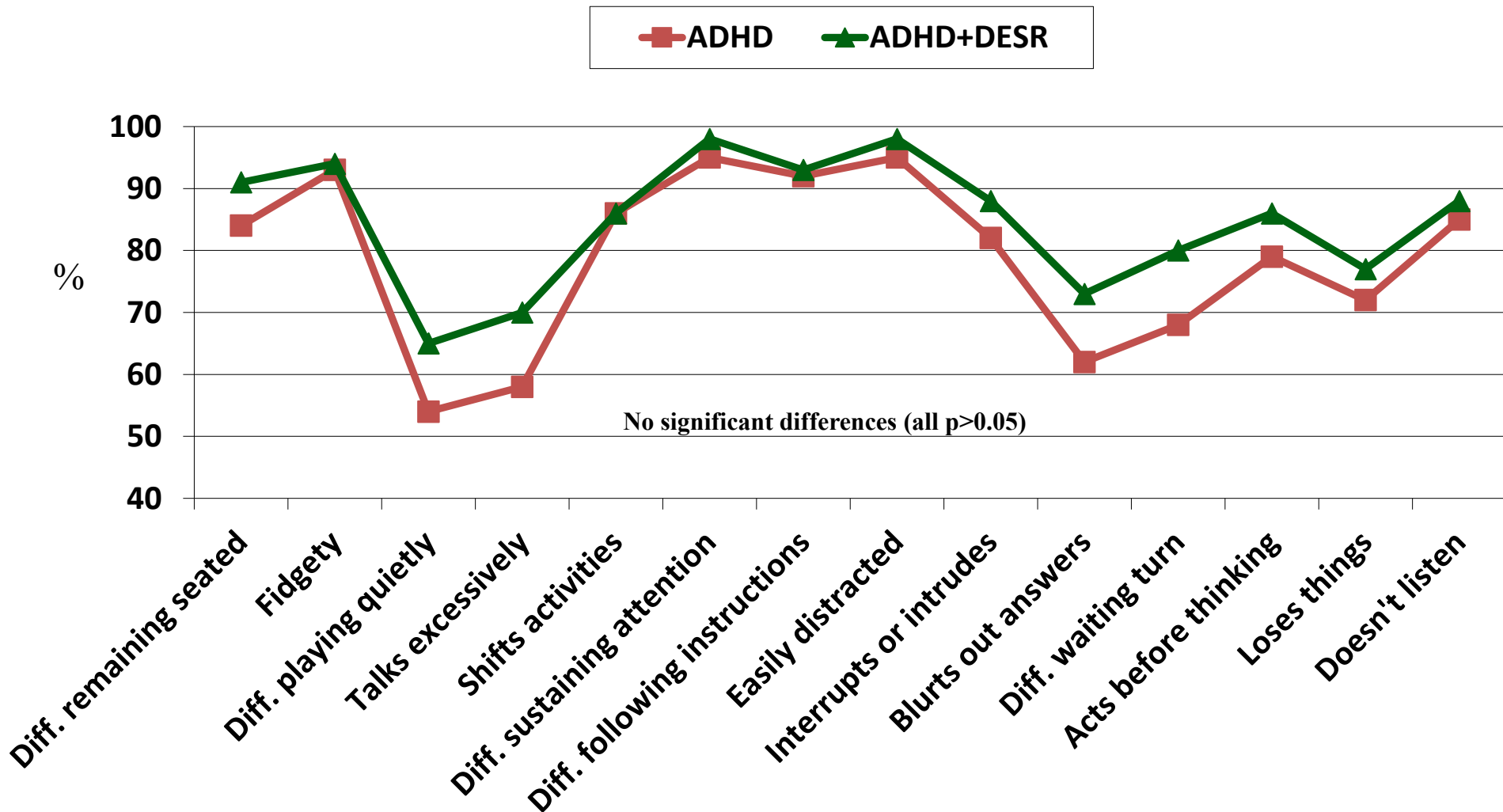


# Main Findings

- 44% of ADHD children had a + CBCL-DESR profile vs. 2% of controls ( $p < 0.001$ )
- The CBCL-DESR profile was associated with elevated rates of anxiety disorders, depression, CD and ODD
- The CBCL-DESR profile was associated with more impairments in psychosocial functioning

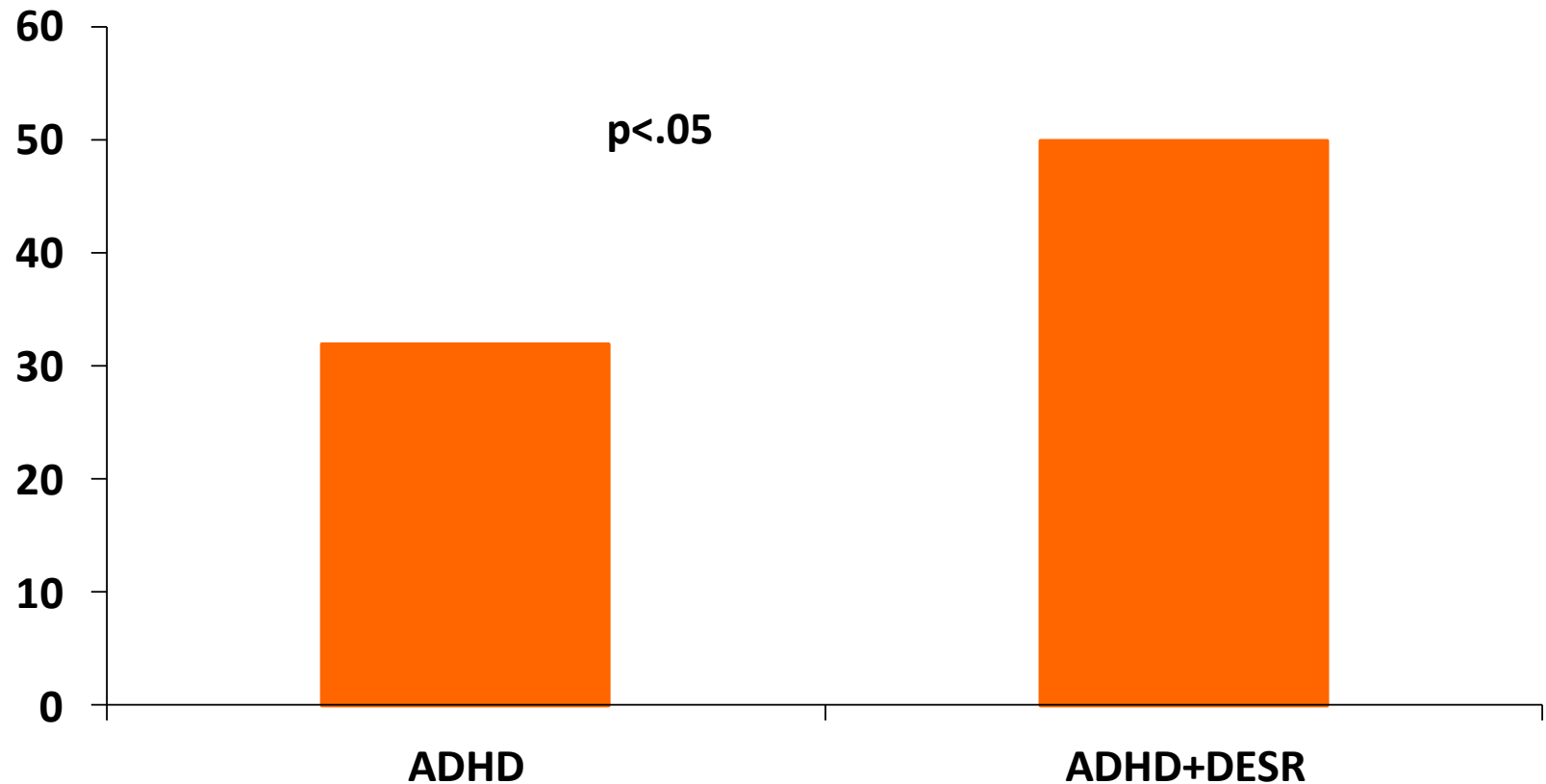


# ADHD Symptoms





# Percent of subjects with ADHD-Associated Severe Impairment

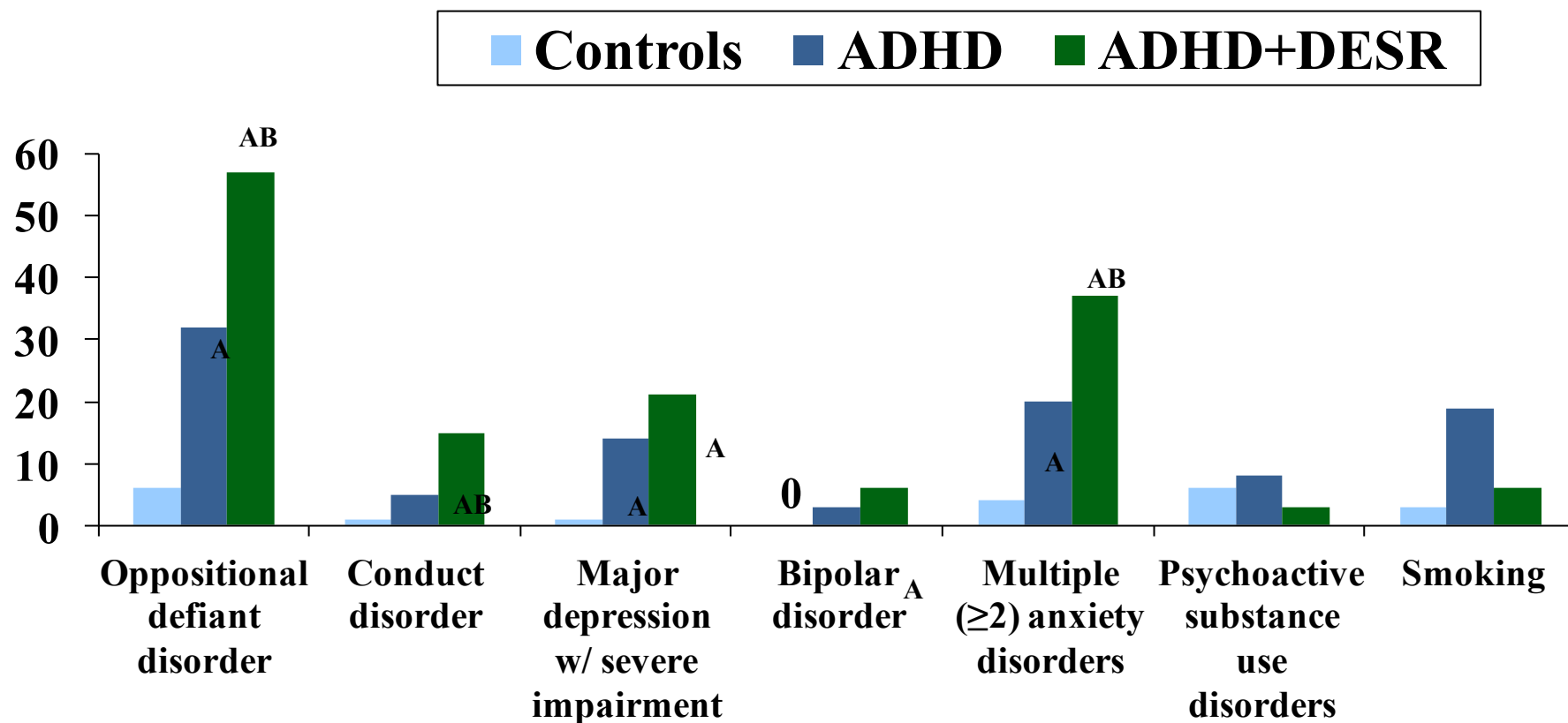


(Spencer et al., Postgrad Med 2012)



# DESR and Lifetime Psychopathology

(Spencer et al., Postgrad Med 2012)



**A:  $p < 0.05$  vs. Controls; B:  $p < 0.05$  vs. ADHD**



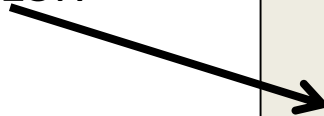
# ADHD predicts DESR

## Independent of Lifetime History of Comorbidity

(Spencer et al., Postgrad Med 2012)

**Regression model included individual comorbid disorders and ADHD  
as DESR predictors**

**RED**= association with DESR



**ADHD remained associated  
with DESR when covaried  
with each comorbidity**

**Oppositional Defiant Disorder**  
**Conduct Disorder**  
**Multiple Anxiety Disorders**  
Bipolar Disorder  
Major Depression  
Substance Use Disorders



# Severity of the Aggression/Anxiety-Depression/Attention Child Behavior Checklist Profile Discriminates Between Different Levels of Deficits in Emotional Regulation in Youth With Attention-Deficit Hyperactivity Disorder

Joseph Biederman, MD,\*† Carter R. Petty, MA,\* Helen Day, BA,\* Rachel L. Goldin, BA,\* Thomas Spencer, MD,\*† Stephen V. Faraone, PhD,‡§ Craig B. H. Surman, MD,\*† Janet Wozniak, MD\*†

**ABSTRACT:** *Objective:* We examined whether severity scores (1 SD vs 2 SDs) of a unique profile of the Child Behavior Checklist (CBCL) consisting of the Anxiety/Depression, Aggression, and Attention (AAA) scales would help differentiate levels of deficits in children with attention-deficit hyperactivity disorder (ADHD). *Study Design:* Subjects were 197 children with ADHD and 224 without ADHD. We defined deficient emotional self-regulation (DESR) as an aggregate cutoff score of >180 but <210 (1 SD) on the AAA scales of the CBCL (CBCL-DESR) and Severe Dysregulation as an aggregate cutoff score of  $\geq 210$  on the same scales (CBCL-Severe Dysregulation). All subjects were assessed with structured diagnostic interviews and a range of functional measures. *Results:* Thirty-six percent of children with ADHD had a positive CBCL-DESR profile versus 2% of controls ( $p < .001$ ) and 19% had a positive CBCL-Severe Dysregulation profile versus 0% of controls ( $p < .001$ ). The subjects positive for the CBCL-Severe Dysregulation profile differed selectively from those with the CBCL-DESR profile in having higher rates of unipolar and bipolar mood disorders, oppositional defiant and conduct disorders, psychiatric hospitalization at both baseline and follow-up assessments, and a higher rate of the CBCL-Severe Dysregulation in siblings. In contrast, the CBCL-DESR was associated with higher rates of comorbid disruptive behavior, anxiety disorders, and impaired interpersonal functioning compared with other ADHD children. *Conclusion:* Severity scores of the AAA CBCL profiles can help distinguish 2 groups of emotional regulation problems in children with ADHD.

(*J Dev Behav Pediatr* 33:236–243, 2012) **Index terms:** affective symptoms, CBCL, bipolar disorder, severity of illness index.





# **The MGH Study of Deficient Emotional Self Regulation in Adult ADHD**



# DESR in Adults with ADHD Study

- **Study Population**
  - **206 Adults with ADHD**
  - **123 Controls**



# Deficient Emotional Self Regulation (DESR) in Adults with ADHD

- **Methods**
  - **Barkley's Current Behavior Scale**
  - **SCID / KSADS modules for Axis I disorders**
  - **Quality of Life, Enjoyment, Satisfaction Scale-Short Form**
  - **Social Adjustment Scale - Self Report**
  - **Functional outcomes questionnaire**



# Deficient Emotional Self Regulation Inventory Items (From Barkley Scale)

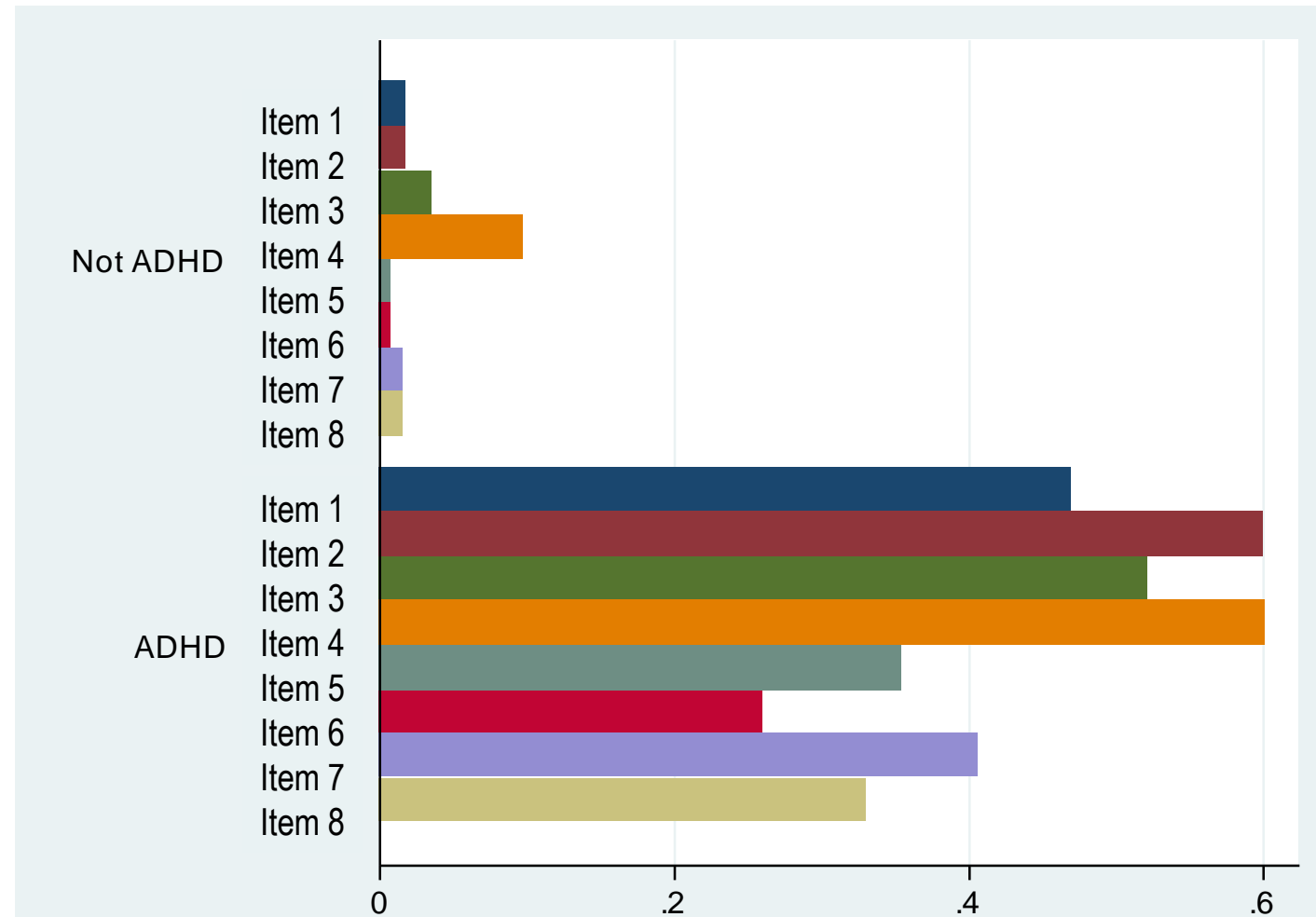
1. Quick to get angry or become upset
2. Easily Frustrated
3. Over-react emotionally
4. Easily excited by activities going on around me
5. Lose my temper
6. Argue with others
7. Am touchy or easily annoyed by others
8. Am angry or resentful

**Severity: None (0), Sometimes (1) Often (2), Very Often (3)**

Items from Barkley's Current Behavior Scale



# Rate of subjects endorsing DESR symptoms as “Often” or “Very Often”

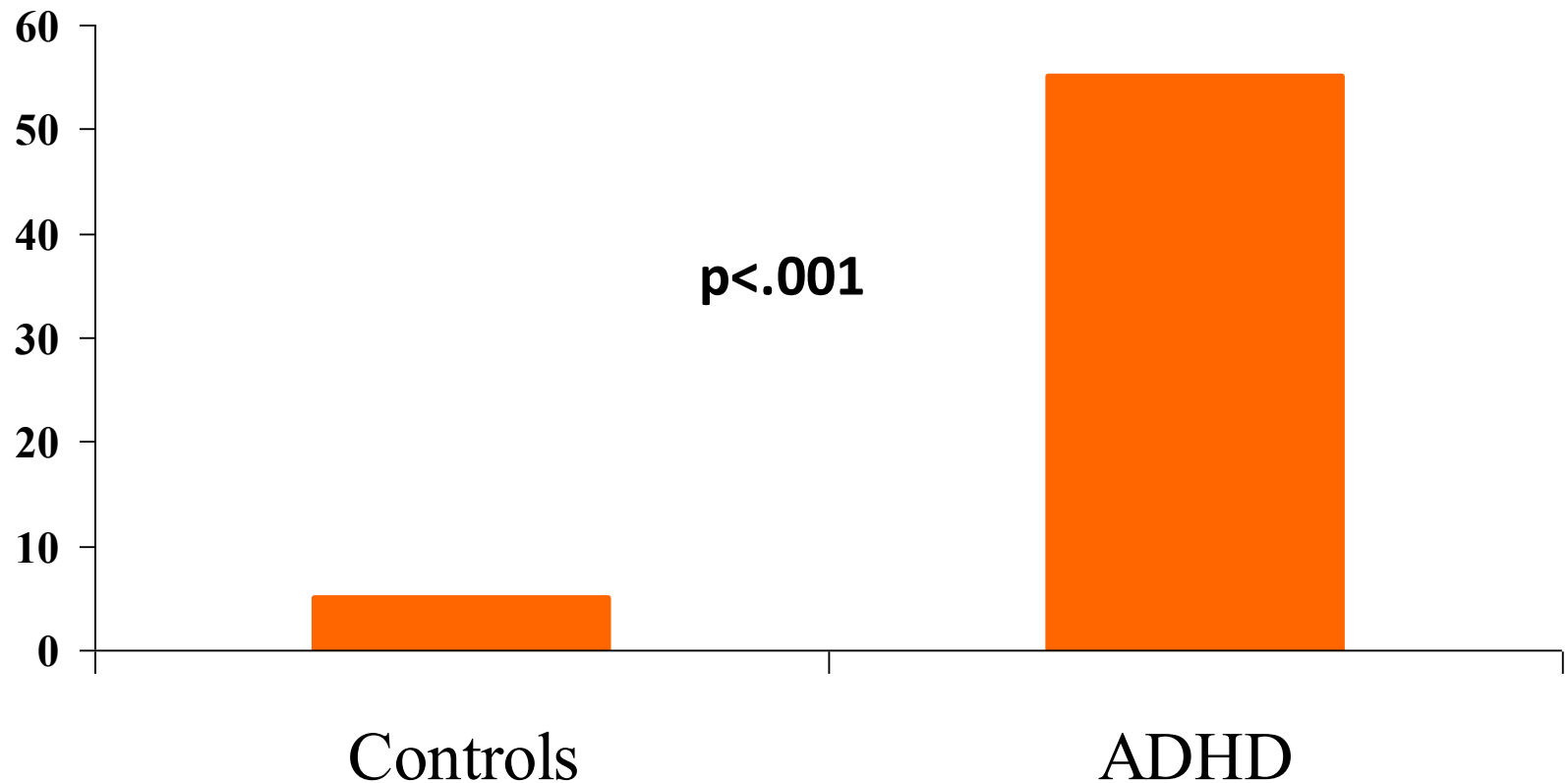


Internal Consistency of Items (Cronbach's alpha: 0.90)



# DESR in ADHD and Control Adults

(Surman et al., American J Psychiatry, 2011)





# ADHD predicts DESR

## Independent of Lifetime and Current Comorbidity

(Surman et al., American J Psychiatry, 2011)

Regression model included individual comorbid disorders and ADHD as DESR predictors

**RED** = association with DESR

**ADHD remained associated with DESR when covaried with each comorbidity**

**Disruptive Behavior Disorders**

**Major Depression**

**Anxiety Disorders**

**Alcohol Abuse**

**Substance Dependence**

Bipolar Disorder

Substance Abuse

Alcohol Dependence



# Quality of Life Enjoyment / Satisfaction in ADHD+DESR Probands

|  | Correlation | z     | P       |
|--|-------------|-------|---------|
| 1. Work  | -0.32       | -3.53 | < 0.001 |
| 2. Household activities                          | -0.43       | -7.43 | < 0.001 |
| 3. Social relationships                          | -0.46       | -8.31 | < 0.001 |
| 4. Family relationships                          | -0.45       | -7.58 | < 0.001 |
| 5. Leisure time activities                       | -0.44       | -8.22 | < 0.001 |
| 6. Ability to function in daily life             | -0.54       | -8.40 | < 0.001 |
| 7. Sexual drive, interest, and/or<br>performance | -0.43       | -7.65 | < 0.001 |
| 8. Economic status                               | -0.40       | -6.62 | < 0.001 |
| 9. Living or housing situation                   | -0.38       | -9.08 | < 0.001 |

ADHD/NOS n = 206; Control n =123



# Social Adjustment Scale in ADHD+DESR Probands

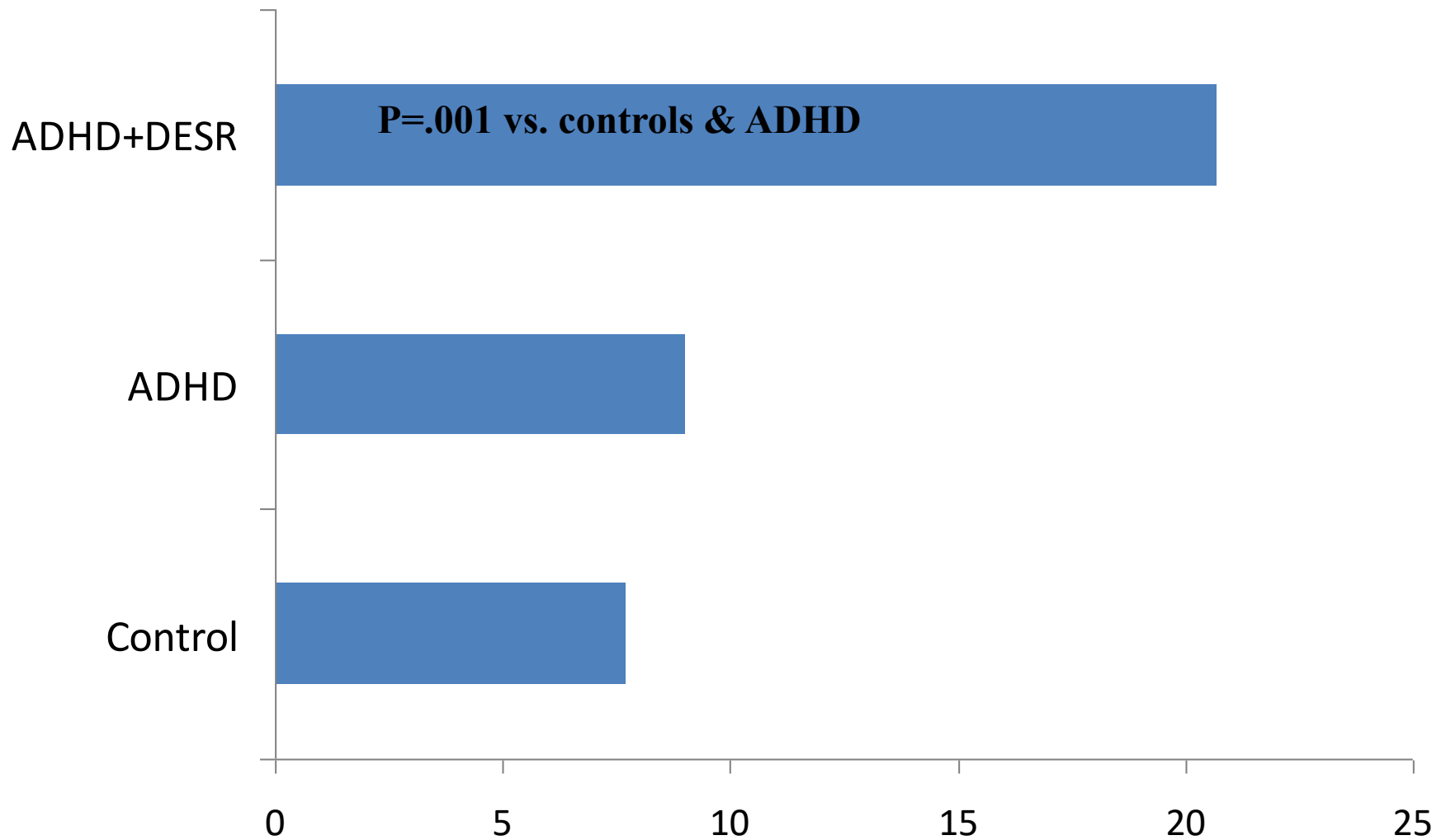
| Functioning Domain              | Correlation Coefficient | Z     | p       |
|---------------------------------|-------------------------|-------|---------|
| 1. Work                         | 0.45                    | 4.56  | < 0.001 |
| 2. Social/Leisure               | 0.58                    | 11.01 | < 0.001 |
| 3. Extended Family              | 0.49                    | 8.26  | < 0.001 |
| 4. Primary Relationship         | 0.50                    | 5.16  | < 0.001 |
| 5. Parenting                    | 0.06                    | 1.33  | 0.19    |
| 6. Family Unit                  | 0.49                    | 5.75  | < 0.001 |
| 7. <b>Total SAS Scale Score</b> | 0.66                    | 11.75 | < 0.001 |

ADHD/NOS n = 206; Control n =123



# Rates of Divorce by Proband Diagnosis

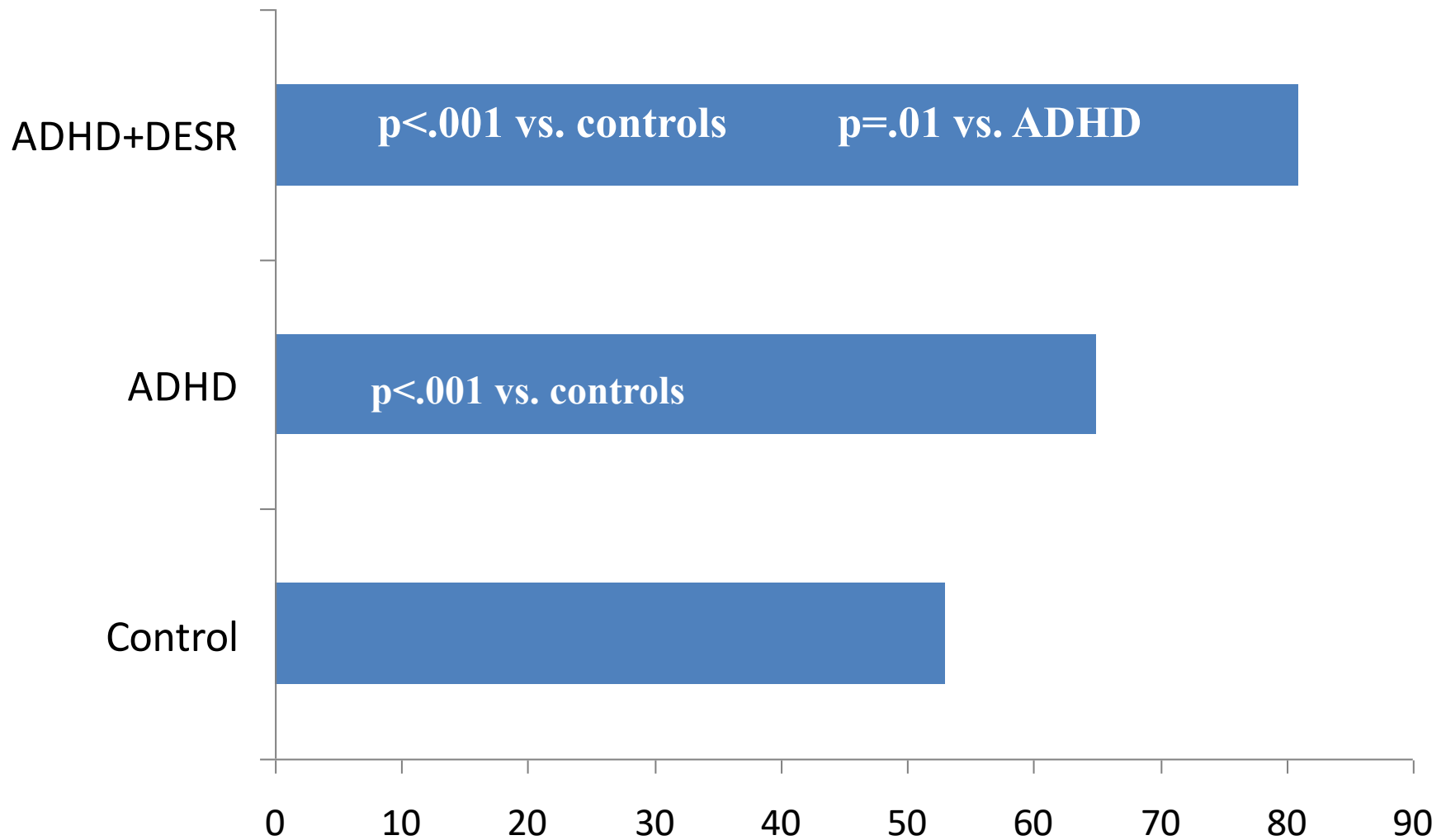
(Surman et al., American J Psychiatry, 2011)





# Percent of Subjects who Ever Had an Auto Accident

(Surman et al., American J Psychiatry, 2011)



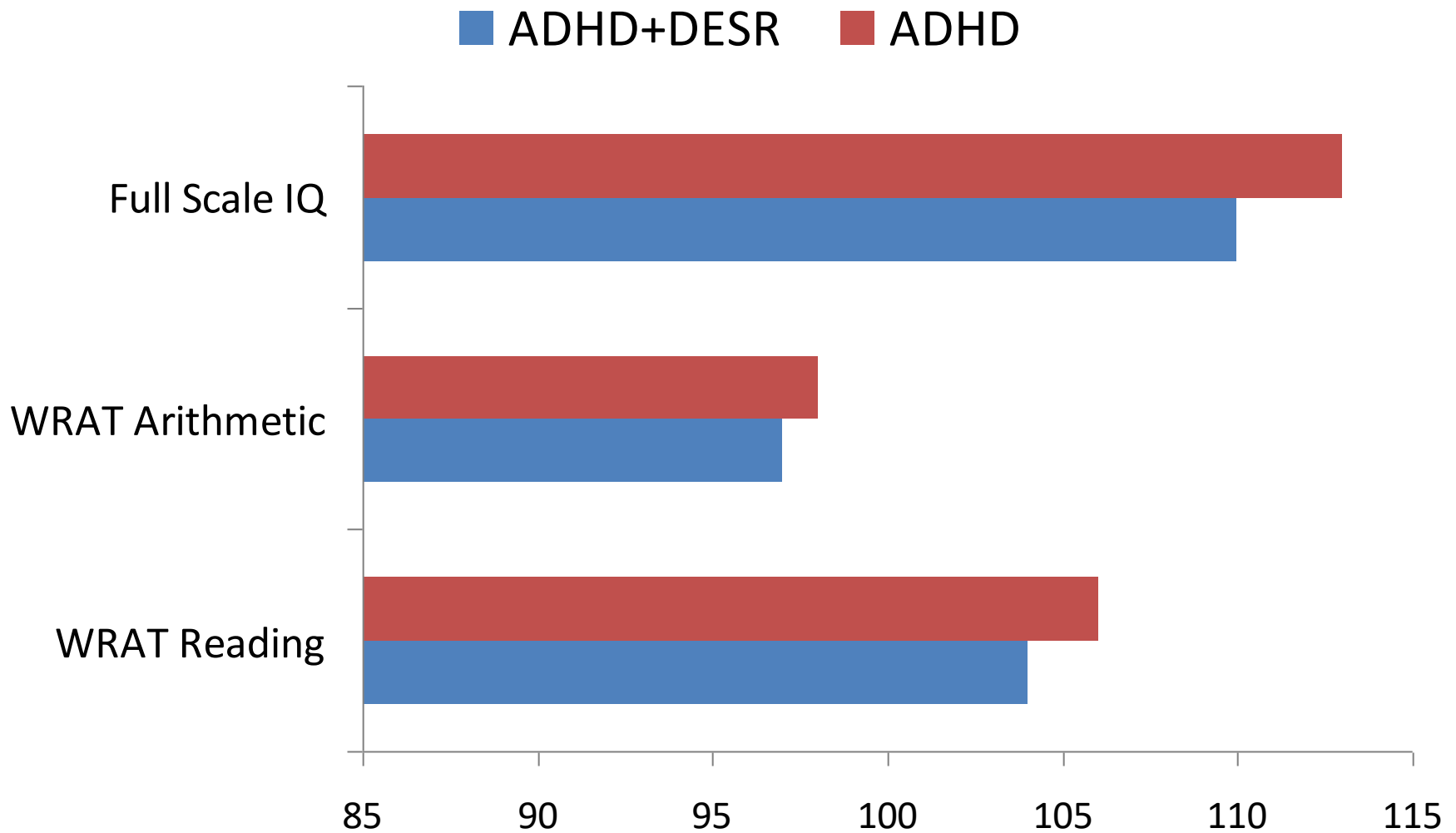


**WHAT DESR WAS NOT ASSOCIATED  
WITH**



# Intellectual Functioning and DESR

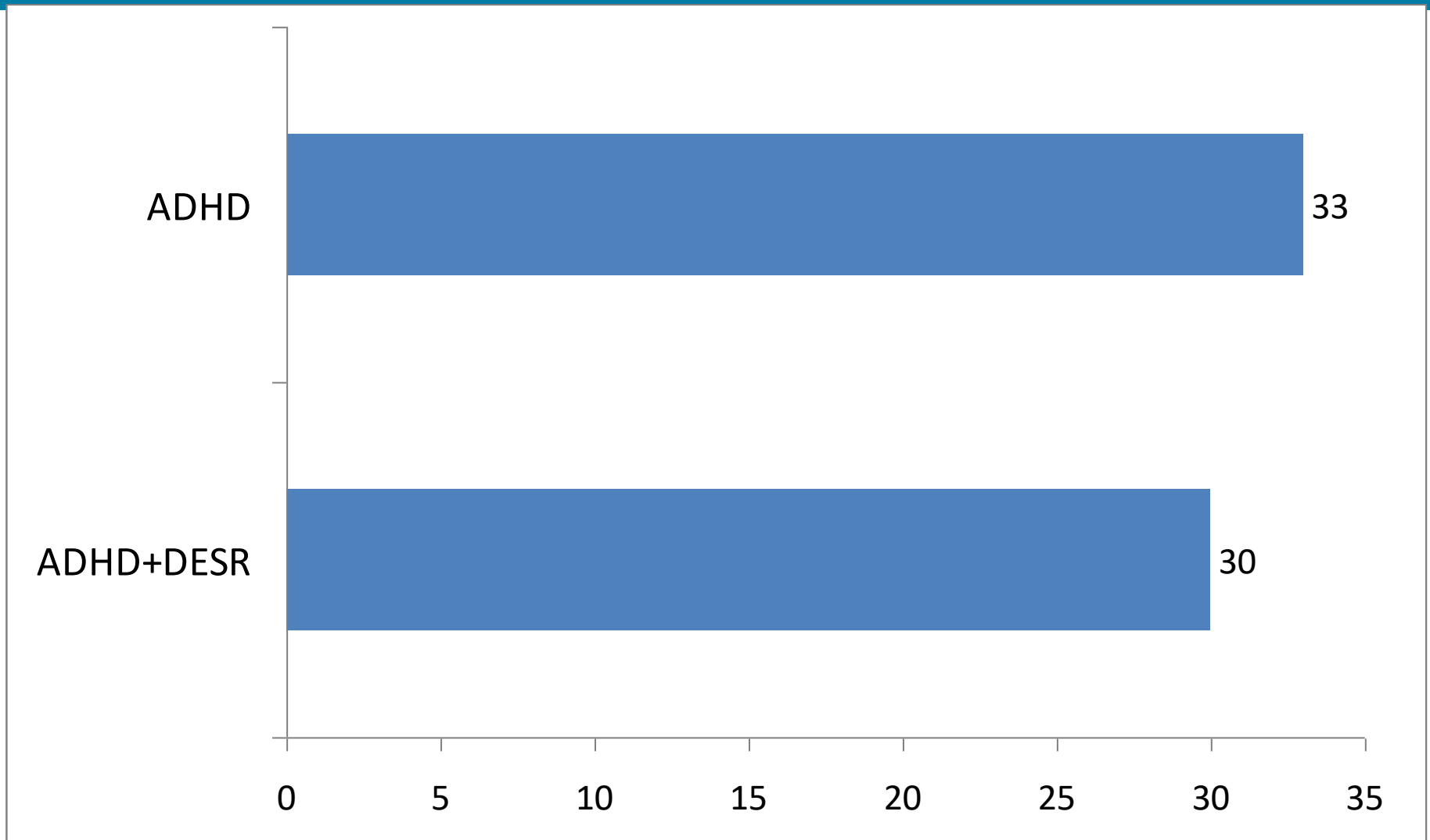
(Surman et al., American J Psychiatry, 2011)





# Rates of Executive Function Disorder in ADHD Adults With and Without DESR

(Surman et al., American J Psychiatry, 2011)





# Summary of DESR Findings in Adults with ADHD

- **A Large Community Sample of Adults with and without ADHD reveals:**
- **DESR questionnaire validity**
  - Acceptable internal consistency
  - Correlated with functional impairment
- **A sizeable majority of ADHD Adults had DESR**
- **Comorbidity did not account for DESR in ADHD adults**



Article

# Deficient Emotional Self-Regulation and Adult Attention Deficit Hyperactivity Disorder: A Family Risk Analysis

Craig B.H. Surman, M.D.

Joseph Biederman, M.D.

Thomas Spencer, M.D.

Dayna Yorks, B.A.

Carolyn A. Miller, B.A.

Carter R. Petty, M.S.

Stephen V. Faraone, Ph.D.

**Objective:** A growing body of research suggests that deficient emotional self-regulation (DESR) is prevalent and morbid among patients with attention deficit hyperactivity disorder (ADHD). Family studies provide a method of clarifying the co-occurrence of clinical features, but no family studies have yet addressed ADHD and DESR.

**Method:** Participants were 83 probands with and without ADHD and 128 siblings. All were assessed for axis I DSM-IV conditions with structured diagnostic interviews. The authors defined DESR in adult probands and siblings using items from the Barkley Current Behavior Scale. Analyses tested hypotheses about the familial relationship between ADHD and DESR.

**Results:** Siblings of ADHD probands were at elevated risk of having ADHD, irrespective of the presence or absence of DESR in the proband. The risk for DESR was

elevated in siblings of ADHD plus DESR probands but not in siblings of ADHD probands. ADHD and DESR cosegregated in siblings. The risk for other psychiatric disorders was similar in siblings of the ADHD proband groups.

**Conclusions:** The pattern of inheritance of ADHD with DESR preliminarily suggests that DESR may be a familial subtype of ADHD. Our data suggest that DESR is not an expression of other axis I DSM-IV disorders or of nonfamilial environmental factors. The authors cannot exclude contribution of non-axis-I DSM-IV disorders to risk for DESR and cannot determine whether the cosegregation of ADHD in DESR within families is a result of genes or familial environmental risk factors. Further investigation of DESR and its correlates and treatment both in and outside the context of ADHD is warranted.

(*Am J Psychiatry* Surman et al.; *AiA*:1–7)



# Summary

- Deficits in emotional regulation are frequently associated with ADHD in both children and adults
- Deficits in emotional regulation are independent of psychiatric comorbidity
- Deficits in emotional regulation are associated with functional impairment in both pediatric and adult patients with ADHD
- Deficits in emotional regulation have neurobiological underpinnings





# What DESR is Not



# Disruptive Mood Dysregulation Disorder (DMDD)

- Severe recurrent temper outbursts manifested verbally and/or behaviorally that are grossly out of proportion in intensity or duration to the situation or provocation
- The temper outbursts occur >3 times per week
- **The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day**
- **Does not meet criteria for BP disorder**



# Reactive Attachment Disorder

- A. A consistent pattern of inhibited, emotionally withdrawn behavior toward adult caregivers, manifested by both :**
  - 1. The child rarely or minimally seeks comfort when distressed**
  - 2. The child rarely or minimally responds to comfort when distressed**
- B. A persistent social and emotional disturbance characterized by at >2 of:**
  - 1. Minimal social and emotional responsiveness to others**
  - 2. Limited positive affect**
  - 3. Episodes of unexplained irritability, sadness, or fearfulness that are evident even during nonthreatening interactions with adult caregivers**

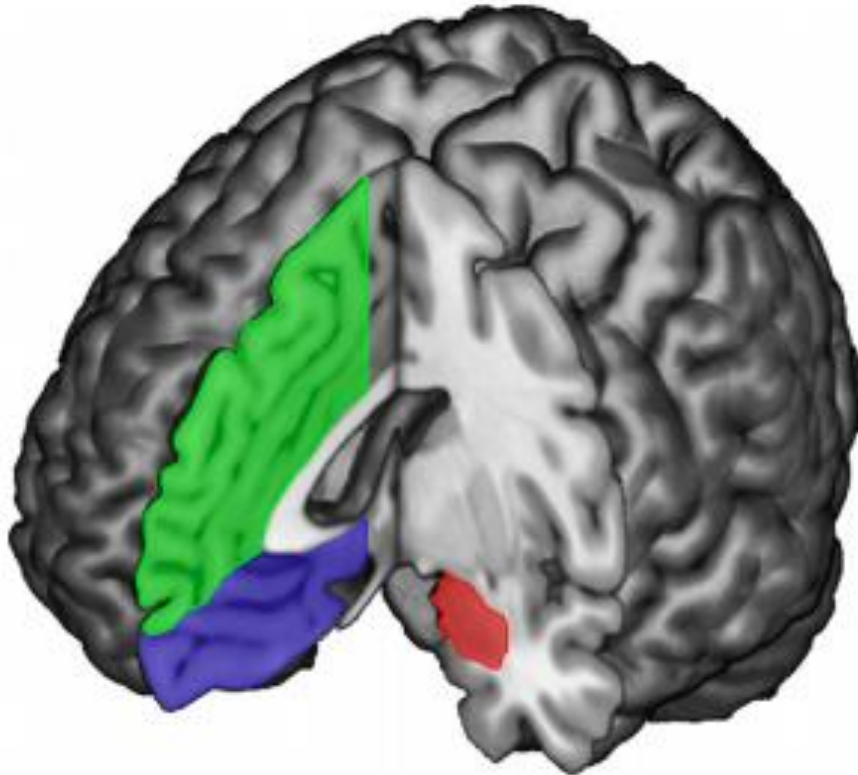




# **DOES EMOTIONAL DYSREGULATION HAVE NEURAL UNDERPINNINGS? NEUROIMAGING FINDINGS**



# Amygdala-Prefrontal Circuitry



Amygdala: Red

Ventromedial prefrontal cortex: Blue

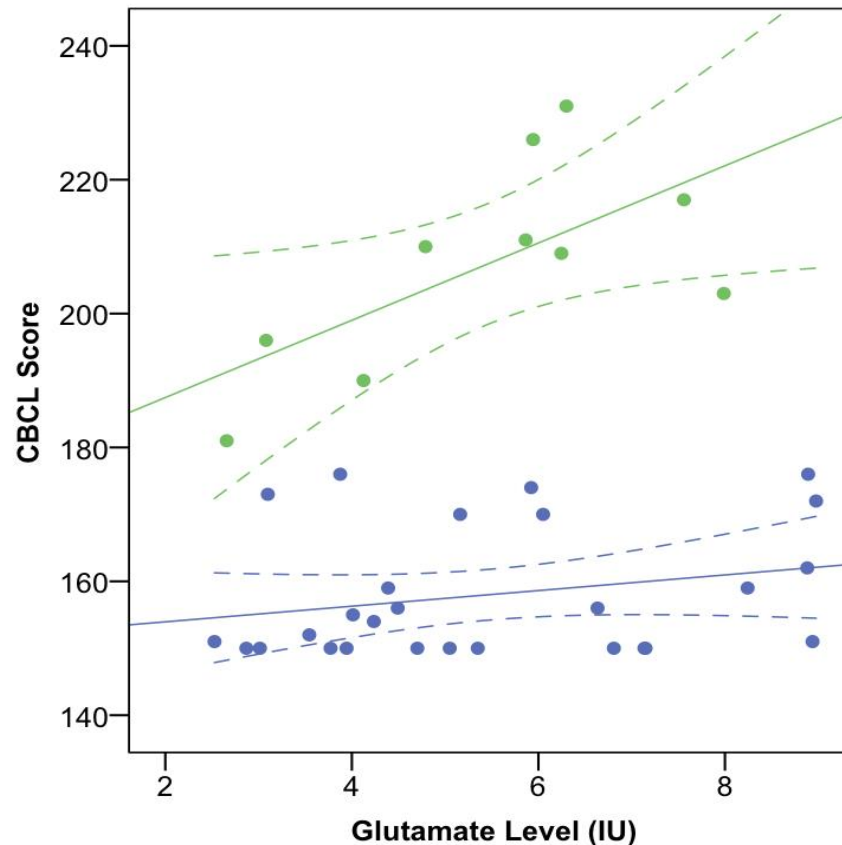
Dorsomedial prefrontal cortex: Green

**Fig. 1.** Structural magnetic resonance image of the human brain highlighting the major components of the amygdala-prefrontal circuitry: amygdala (red), ventromedial prefrontal cortex (blue), and dorsomedial prefrontal cortex (green) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

(Kim 2011 Behavioral Brain Research)



# Spectroscopic Findings of CBCL Scores vs Glutamate levels in the Anterior Cingulate

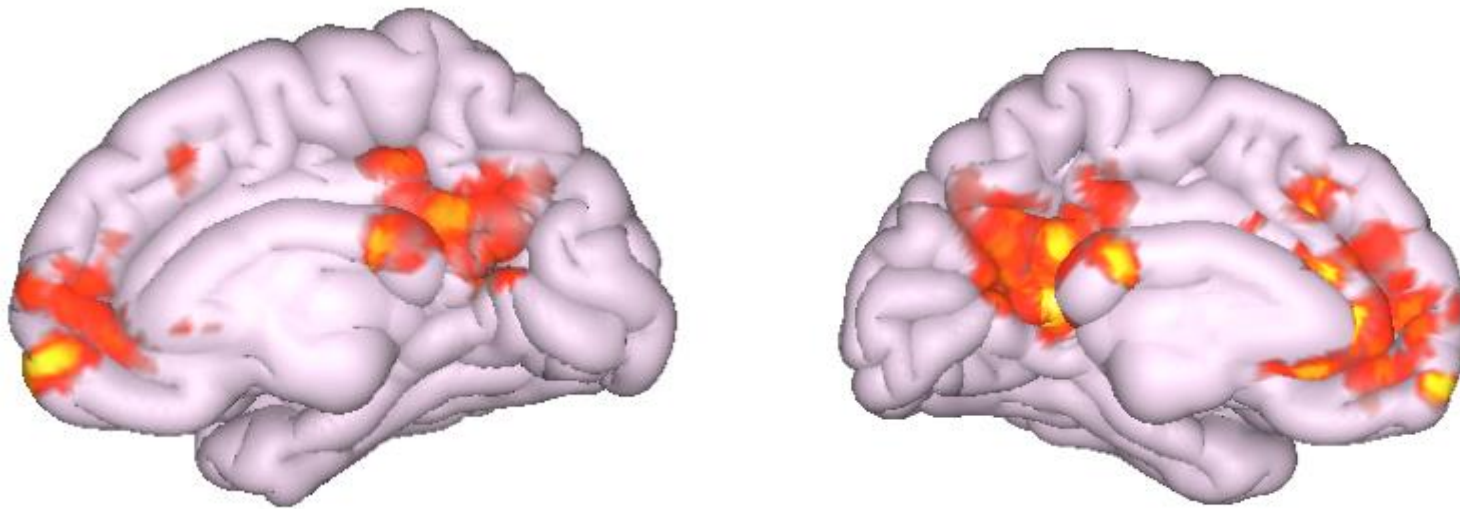


Wozniak et al 2012

Solid lines represent the linear fits to the low score group data (blue) and high score group data (green). Dashed lines represent 95% confidence intervals.

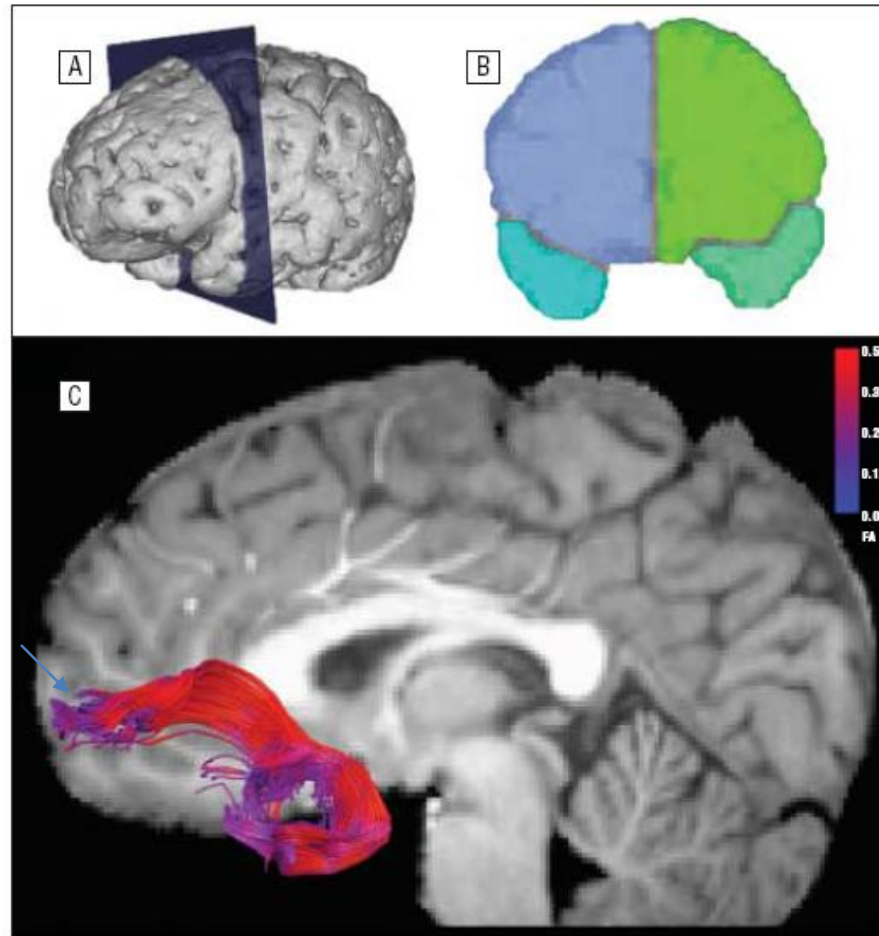


# Resting state functional connectivity between amygdala and MPFC with reappraisal failure (or success)



***Reappraisal score: Self Report Ratings on Negative - Reappraisal***



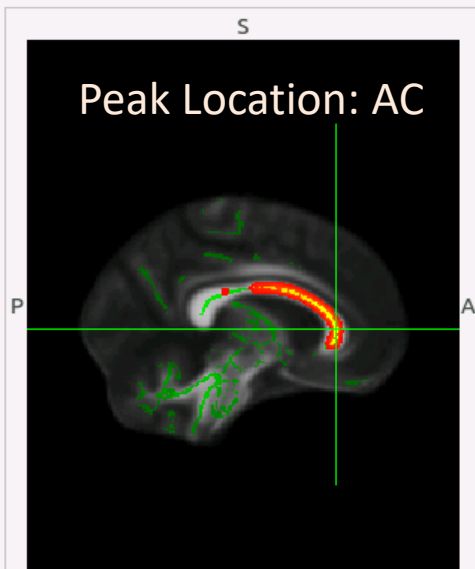
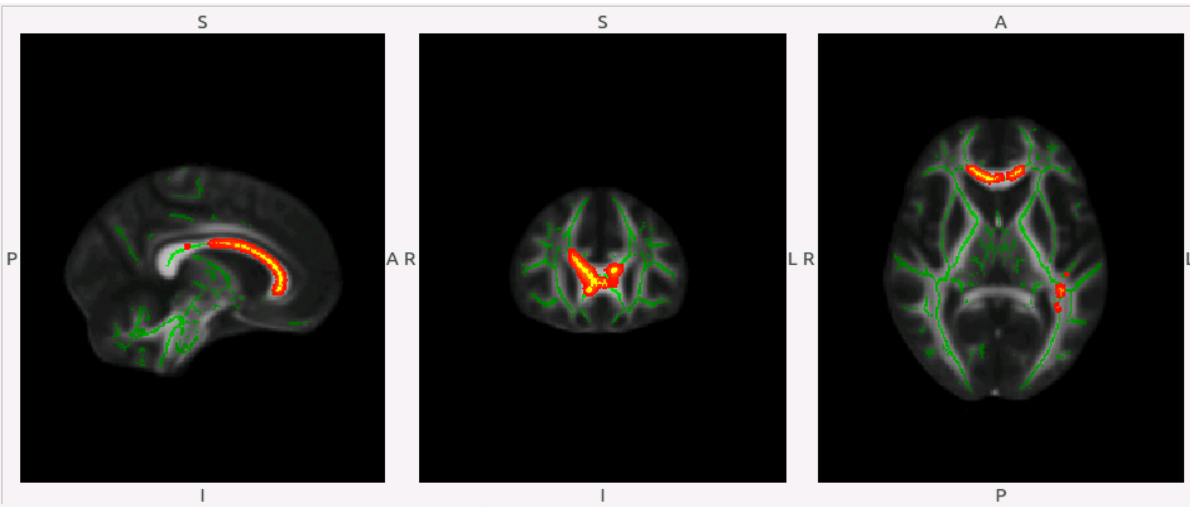


**Figure 1.** Region-of-interest placement for delineation of the bilateral uncinate fasciculus. A, The most posterior coronal section that showed clear separation of the frontal and temporal lobes bilaterally was identified in each individual. B, Bilateral frontal and temporal lobe seed regions of interest were then manually drawn on this section. The Boolean *AND* term was used to select only fibers that crossed through both the temporal and frontal seed regions of interest for tract-based analysis. C, Uncinate fasciculus tracts overlaid on an anatomical T1-weighted image for a single individual. FA indicates fractional anisotropy. For a 3-dimensional rendering, see the video.

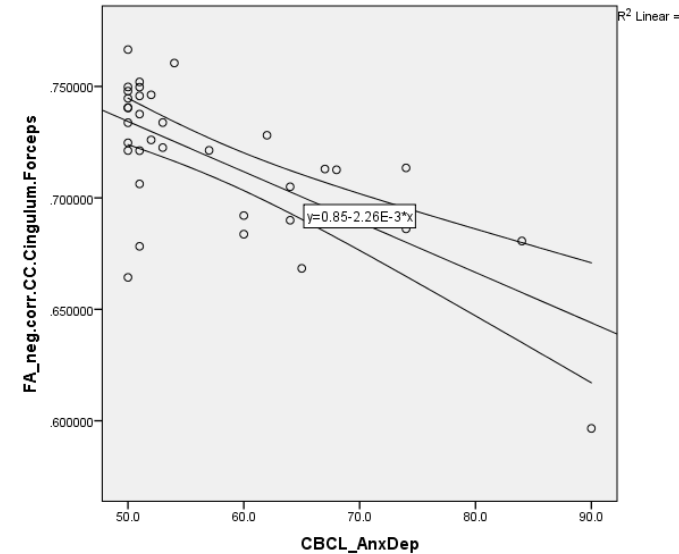
UNCINATE FASCICULUS



# Significant DTI Findings In Prepubertal Children with Emotional Dysregulation



- **Peak location**  
(10, 29, 10 mm (MNI)):  
**Anterior Cingulum (AC)**  
& genu of corpus callosum



CBCL Emotional Dysregulation scores significantly and negatively correlated with FA in the cingulum & corpus callosum tracts, peaking at the anterior cingulum (AC)



# Anterior Cingulum (AC)

- The anterior cingulum connects the prefrontal cortex with the limbic system
- AC is crucial for processing and regulating emotion
- AC has been associated with regulatory cognitive and emotional control processes
- It is highly implicated in the mood disorder literature



## Original Investigation

# White Matter Structure in Youth With Behavioral and Emotional Dysregulation Disorders


## A Probabilistic Tractographic Study

Amelia Versace, MD; Heather Acuff, BS; Michele A. Bertocci, PhD; Genna Bebek, PhD; Jorge R. C. Almeida, MD, PhD; Susan B. Perlman, PhD; Alexander Leemans, PhD; Claudiu Schirda, PhD; Haris Aslam, BA; Amanda Dwojak, BA; Lisa Bonar, BS; Michael Travis, MD; Mary Kay Gill, RN, MSN; Christine Demeter, MA; Vaibhav A. Diwadkar, PhD; Jeffrey L. Sunshine, MD, PhD; Scott K. Holland, PhD; Robert A. Kowatch, MD, PhD; Boris Birmaher, MD; David Axelson, MD; Sarah M. Horwitz, PhD; Thomas W. Frazier, PhD; L. Eugene Arnold, MD, MEd; Mary A. Fristad, PhD, ABPP; Eric A. Youngstrom, PhD; Robert L. Findling, MD, MBA; Mary L. Phillips, MD, MD(Cantab)

**IMPORTANCE** Psychiatric disorders in youth characterized by behavioral and emotional dysregulation are often comorbid and difficult to distinguish. An alternative approach to conceptualizing these disorders is to move toward a diagnostic system based on underlying pathophysiologic processes that may cut across conventionally defined diagnoses. Neuroimaging techniques have potentials for the identification of these processes.

**OBJECTIVE** To determine whether diffusion imaging, a neuroimaging technique examining white matter (WM) structure, can identify neural correlates of emotional dysregulation in a sample of youth with different psychiatric disorders characterized by behavioral and emotional dysregulation.

**DESIGN, SETTING, AND PARTICIPANTS** Using global probabilistic tractography, we examined relationships between WM structure in key tracts in emotional regulation circuitry (ie,

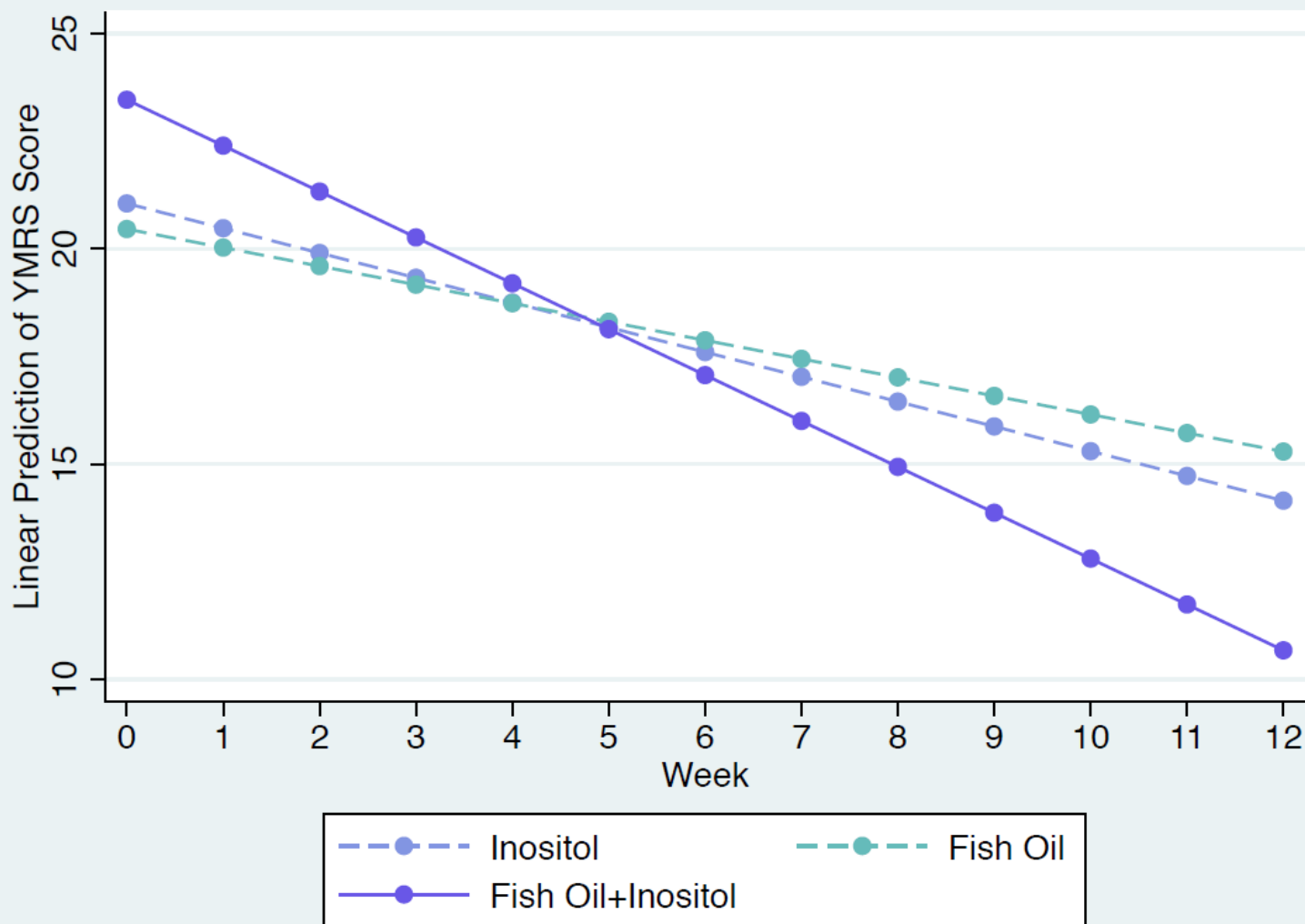
 Supplemental content at  
[jamapsychiatry.com](http://jamapsychiatry.com)

**CONCLUSIONS AND RELEVANCE** These findings suggest that abnormal uncinate fasciculus and cingulum WM structure may underlie emotional, but not behavioral, dysregulation in pediatric psychiatric disorders and that a different neural mechanism may exist for comorbid emotional and behavioral DDs.

February 26, 2014.



# A Randomized Clinical Trial of High EPA Omega-3 Fatty Acids, Inositol, and Their Combination in Children with Bipolar Disorder



Wozniak et al, JCP, in press



# Deficient emotional self-regulation and pediatric attention deficit hyperactivity disorder: a family risk analysis

J. Biederman<sup>1,2\*</sup>, T. Spencer<sup>1,2</sup>, A. Lomedico<sup>1</sup>, H. Day<sup>1</sup>, C. R. Petty<sup>1</sup> and S. V. Faraone<sup>3</sup>

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<sup>2</sup> Psychiatry Department, Harvard Medical School, Cambridge, MA, USA

<sup>3</sup> Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA

**Background.** Although deficient emotional self-regulation (DESR) is associated with attention deficit hyperactivity disorder (ADHD), little research investigates this association and little is known about its etiology. Family studies provide a method of clarifying the co-occurrence of clinical features, but no family studies have yet addressed ADHD and DESR in children.

**Method.** Subjects were 242 children with ADHD and 224 children without ADHD. DESR was operationalized using an aggregate score  $\geq 180$  and  $< 210$  in the anxious/depressed, attention and aggression scales (AAA profile) of the Child Behavior Checklist (CBCL), termed the CBCL-DESR profile. The CBCL-bipolar (CBCL-BP) profile was defined as  $\geq 210$  on the CBCL-AAA scale. We examined the familial transmission of ADHD and the CBCL-AAA scale in families selected through probands with and without these conditions.

**Results.** We found a linear increase in the prevalence of CBCL-DESR in siblings as indexed by the Control, ADHD, ADHD+CBCL-DESR and ADHD+CBCL-BP proband groups. While the ADHD siblings were at elevated risk for both the CBCL-DESR and CBCL-BP compared with non-ADHD siblings, a significantly higher rate of CBCL-BP in the siblings of ADHD+CBCL-BP probands was found compared with siblings of the Control probands.

**Conclusions.** ADHD shows the same degree of familial transmission in the presence or absence of DESR. CBCL-DESR and CBCL-BP are familial, but further work is needed to determine if these definitions are distinctly familial or represent a continuum of the same psychopathology.

Received 17 March 2011; Revised 19 July 2011; Accepted 25 July 2011; First published online 24 August 2011

**Key words:** ADHD, deficient emotional self-regulation, pediatric.

Biederman et al. *Psychol Med* 2012 Mar;42(3):639–46





*"He's just doing that to get attention."*