



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

Autism and Bipolar Disorder

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Disclosures

Dr. Janet Wozniak receives research support from the Baszucki Brain Research Fund, PCORI and Demarest Lloyd, Jr. Foundation. In the past, Dr. Wozniak has received research support, consultation fees or speaker's fees from Eli Lilly, Janssen, Johnson and Johnson, McNeil, Merck/Schering-Plough, the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH), Pfizer, and Shire. She is the author of the book, *"Is Your Child Bipolar"* published May 2008, Bantam Books.

Her spouse receives royalties from UpToDate; consultation fees from Emalex, Noctrix, Disc Medicine, Avadel, HALEO, OrbiMed, and CVS; and research support from Merck, NeuroMetrix, American Regent, NIH, NIMH, the RLS Foundation, and the Baszucki Brain Research Fund. In the past, he has received honoraria, royalties, research support, consultation fees or speaker's fees from: Otsuka, Cambridge University Press, Advance Medical, Arbor Pharmaceuticals, Axon Labs, Boehringer-Ingelheim, Cantor Colburn, Covance, Cephalon, Eli Lilly, FlexPharma, GlaxoSmithKline, Impax, Jazz Pharmaceuticals, King, Luitpold, Novartis, Neurogen, Novadel Pharma, Pfizer, Sanofi-Aventis, Sepracor, Sunovion, Takeda, UCB (Schwarz) Pharma, Wyeth, Xenopore, Zeo.

Overview:

This presentation is about the comorbidity of bipolar disorder and autism and will discuss an approach to understanding emotional dysregulation in autism



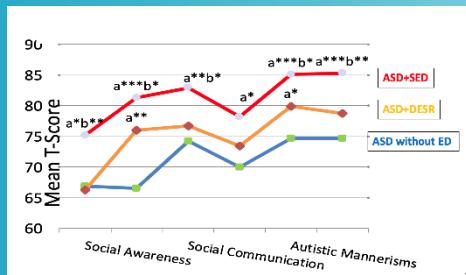
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Youth with autism are often referred due to emotional dysregulation.

The CBCL can delineate different levels of emotional dysregulation in autism



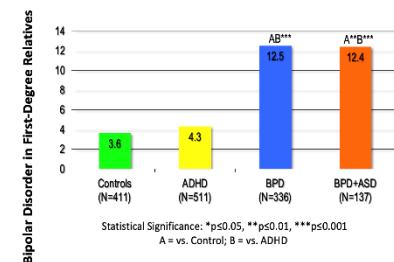
CHILD BEHAVIOR CHECKLIST FOR AGES 6-18

PARENTS' USUAL TYPE OF WORK, even if
Please print. Be sure to answer all items.
ms that describe children and youths. For each item that describes your c
le the 2 if the item is **very true or often true** of your child. Circle the 1 if the it
he item is **not true** of your child, circle the 0. Please answer all items as well
ur child.
as you know) 1 = Somewhat or Sometimes True

There are clinically distinct subtypes of ASD with and without deficient emotional self regulation and severe emotional dysregulation

Comorbidity analysis:

Autism + ADHD is common and associated with more severe emotional dysregulation than ADHD.
BPD comorbid with autism is a bona fide comorbidity and responds to SGA treatment similar to bipolar without autism.

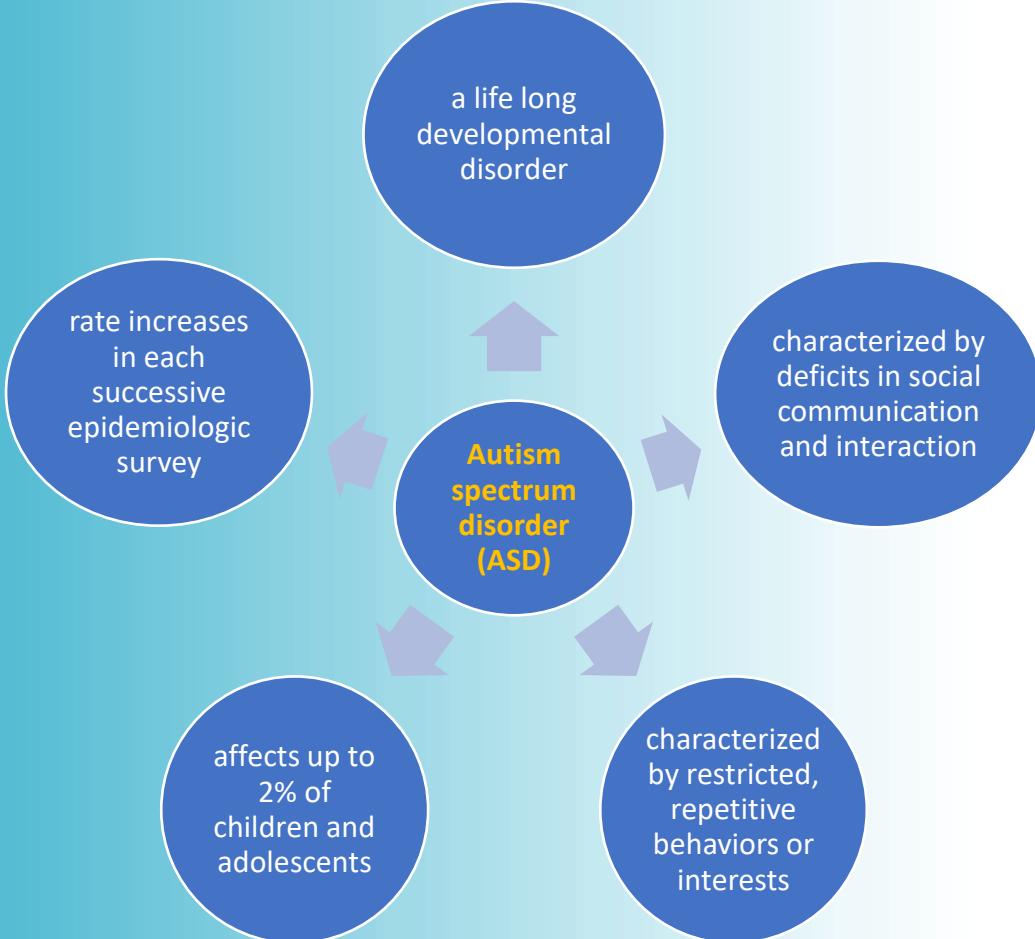


Emotional Dysregulation is not a diagnostic feature of autism



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American Psychiatric Association 2000; Blumberg 2013

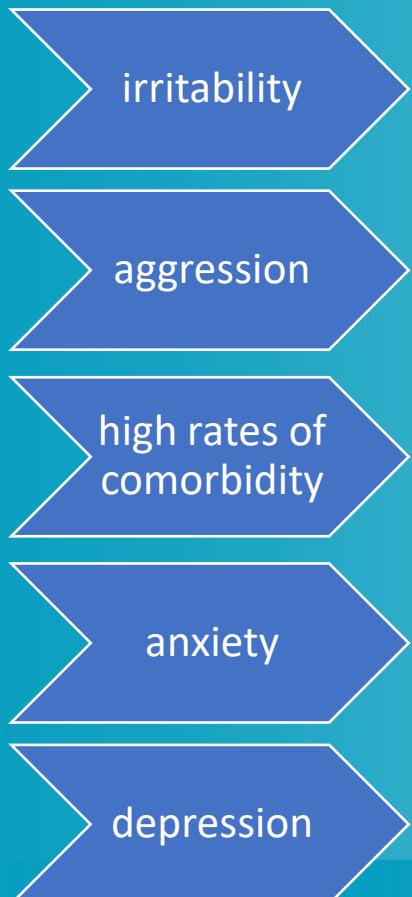
Autism often presents with emotional instability



Joshi 2010, 2014a; Sverd 1995, 2003; Wozniak 1997



Autism accounts for 2-14% of psychiatry outpatient referrals, often due to emotional dysregulation

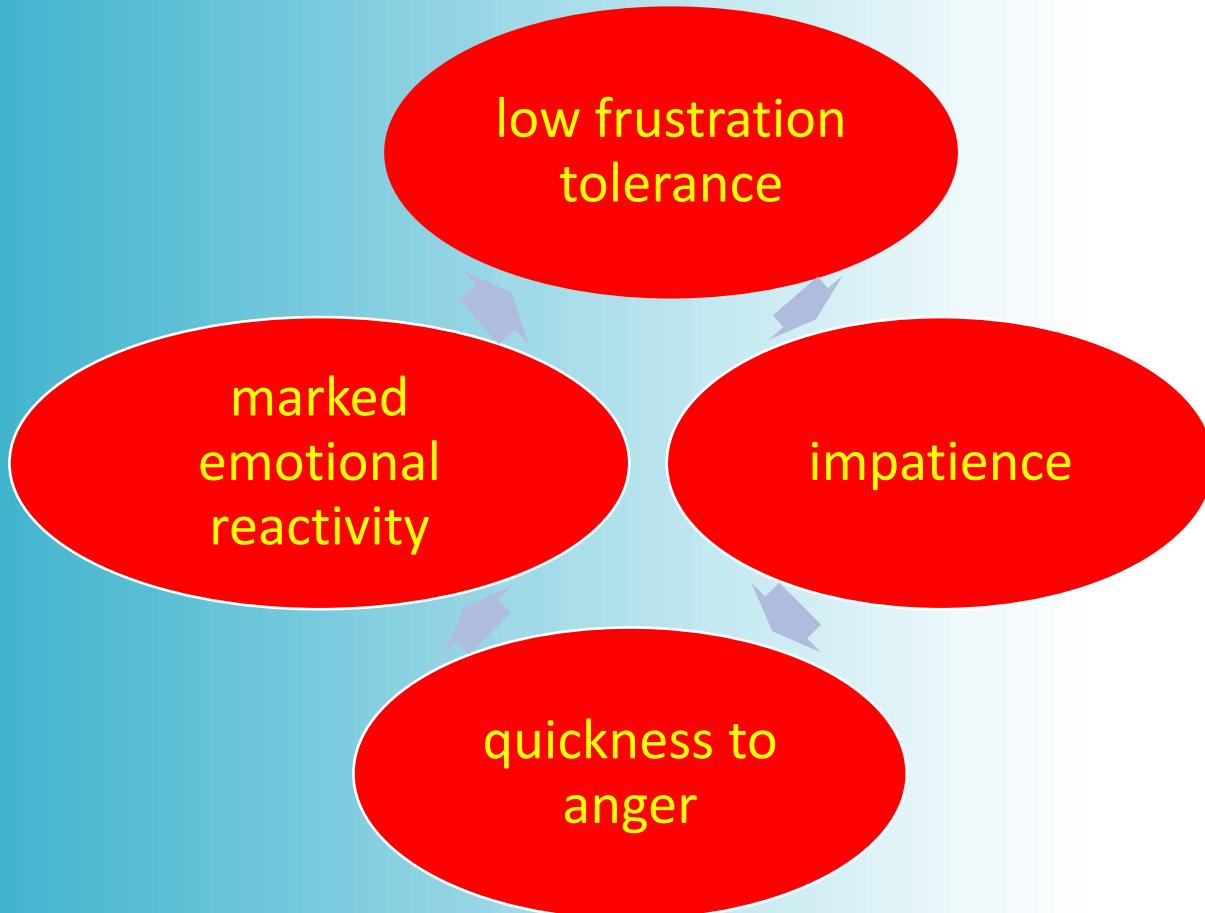


Due to the frequency of emotional problems, questions exist as to whether emotional dysregulation is intrinsic to autism or due to comorbidity with other disorders

Recent reports suggest high prevalence of emotional dysregulation (ED) in individuals with ASD, varying from 50% to more than 60%

McCracken 2002; RUPP 2005;
Gadow 2004; Vickerstaff 2007;
Sterling 2008; Mazefsky 2014;
Samson 2014

Emotional dysregulation is a form of poor self-regulation





Our MGH group has published extensively on the utility of the CBCL in identifying *bipolar disorder* in youth

FOCUS ON CHILDHOOD AND ADOLESCENT MENTAL HEALTH

The Child Behavior Checklist-Pediatric Bipolar Disorder Profile Predicts a Subsequent Diagnosis of Bipolar Disorder and Associated Impairments in ADHD Youth Growing Up: A Longitudinal Analysis

Bipolar Disorders

Original Article

The Child Behavior Checklist in children: a receiver operating characteristic curve analysis

CBCL Clinical Scales Discriminate Prepubertal Children with Structured Interview-Derived Diagnosis of Mania from Those with ADHD

Joseph Biederman, M.D., Janet Wozniak, M.D., Kathleen Kiley, B.A., Stuart Abram, B.A., Stephen Faraone, Ph.D., Eric Mick, B.A., Elizabeth Munley, R.A., and Ilana Kraus, M.D.

ABSTRACT

Objective: To examine the diagnostic utility of the Child Behavior Checklist (CBCL) in identifying children with a positive family history of bipolar disorder (BP) and to determine the receiver operating characteristic (ROC) curve for the CBCL in predicting a subsequent diagnosis of bipolar disorder (BP) in youth. **Method:** We examined the strength of associations between each CBCL scale and the outcome of interest in a sample of 471 probands from two family studies of attention-deficit hyperactivity disorder (ADHD) and their 410 siblings. **Results:** We found that the CBCL Attention Problems, Aggressive Behavior, and Anxious/Depressed subscales were associated with a subsequent diagnosis of BP in probands. **Conclusion:** These findings indicate that the CBCL can be used to identify children at increased risk for BP.

Keywords: Bipolar disorder, Child Behavior Checklist, Diagnostic utility, Family history, Mania, Prepubertal children, Psychopathology, Psychiatric disorders, Psychiatry, Pediatrics, Adolescent, Psychiatry, 1990-2000, Adolescent, Key Words: Child Behavior Checklist, Diagnostic utility, Family history, Mania, Prepubertal children, Psychopathology, Psychiatric disorders, Psychiatry, Pediatrics, Adolescent, Psychiatry, 1990-2000

Stephen V. Faraone, Ph.D., Joseph Biederman, M.D., Michael Monuteaux, Ph.D., and Janet R. Wozniak, M.D.

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Joseph V. Faraone, Ph.D., Robert R. Althoff, Ph.D., James J. Hudzik, Ph.D., Michael Monuteaux, Ph.D., and Joseph Biederman, M.D.

ABSTRACT

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RESEARCH

Suggestive Linkage of the Child Behavior Checklist Juvenile Bipolar Disorder Phenotype to 1p21, 6p21, and 8q21

Mya E. Doyle, Ph.D., Joseph Biederman, M.D., Manuel A.R. Ferreiro, Ph.D., Patricia Wong, B.A., Jordan W. Smoller, M.D., Sc.D., Stephen V. Faraone, Ph.D.

Abstract: Several studies have documented a profile of elevated scores on the Attention Problems, Aggressive Behavior and Anxious/Depressed scales of the Child Behavior Checklist (CBCL) in youth with bipolar disorder. The sum of these scales, referred to as the Child Behavior Checklist Juvenile Bipolar Disorder (CBCL-JBD) phenotype, has modest diagnostic utility, and is included in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Recently, a scan of this measure in ADHD sibling pairs revealed a region of suggestive linkage to chromosome 8q21. The current study aimed to further identify quantitative trait loci (QTLs) associated with the CBCL-JBD phenotype by using a dense and, thus, arguably, more powerful panel of single-nucleotide polymorphism (SNP) markers in a different ADHD sibling pair sample. Subjects were 765 individuals from 154 families with CBCL data enrolled in a large ADHD linkage analysis completed using a multipoint maximum likelihood components approach implemented using the statistical program SOLAR. Results of the linkage analysis of the CBCL-JBD phenotype were as follows: at least one QTL was supported by empirically derived criteria for a significant linkage ($p < .0001$), LOD = .00037, LOD = 2.76, epzl3.3 ($p = .00054$), LOD = 2.60, and Sqz21.13 ($p = .0081$), which surpassed the threshold for suggestive linkage ($p = .002$). These regions have been

published previously by our group using a different set of SNPs and linkage analysis methods.

Keywords: Bipolar disorder, Child Behavior Checklist, Diagnostic utility, Family history, Mania, Prepubertal children, Psychopathology, Psychiatric disorders, Psychiatry, Pediatrics, Adolescent, Psychiatry, 1990-2000, Adolescent, Key Words: Child Behavior Checklist, Diagnostic utility, Family history, Mania, Prepubertal children, Psychopathology, Psychiatric disorders, Psychiatry, Pediatrics, Adolescent, Psychiatry, 1990-2000

Joseph Biederman, M.D., James Chan, J., Stephen V. Faraone, Ph.D., K. Yvonne Woodworth, Ph.D., Thomas Spencer, Ph.D., Janet R. Wozniak, M.D.

ABSTRACT

Objective: Children with deficits in emotional regulation operationalized by scores on the Child Behavior Checklist (CBCL) Attention Problems, Aggressive Behavior, and Anxious-Depressed subscales are more likely than others to manifest adverse outcomes. However, the transmission of this profile has not been well studied. The main aim of this study was to investigate the familiality of this profile. **Method:** Participants were youth probands with bipolar I (BP-I) disorder ($N = 14$), ADHD ($N = 83$), and controls ($N = 117$) and their siblings. Based on the CBCL emotional dysregulation profile, we classified children with severe emotional dysregulation (aggregate cut-off score ≥ 210) and emotional dysregulation (aggregate cut-off score ≥ 180 and < 210). **Results:** Emotional dysregulation profile scores correlated positively between probands and siblings. **Conclusion:** Youth with emotional dysregulation are at increased risk to have siblings with similar deficits, suggesting that emotional dysregulation runs in families. *[J of Att Dis. 2010; 22(9):848-854]*

J Affect Disord. 2014 August ; 165: 81–86. doi:10.1016/j.jad.2014.04.021.

Further Evidence that Severe Scores in the Aggression/Anxiety-Depression/Attention Subscales of Child Behavior Checklist (Severe Dysregulation Profile) Can Screen for Bipolar Disorder Symptomatology: A Conditional Probability Analysis

Mai Uchida^{a,b}, Stephen V Faraone^c, MaryKate Martelon^a, Tara Kenworthy^a, K Yvonne Woodworth^a, Thomas Spencer^{a,b}, Janet Wozniak^{a,b}, and Joseph Biederman^{a,b,*}

^aClinical and Research Programs in Pediatric Psychopharmacology and ADHD, Massachusetts General Hospital, Boston, MA, USA

^bDepartment of Psychiatry, Harvard Medical School, Boston, MA, USA

^cDepartments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA

NEW RESEARCH

Study checklist

Eric Mick, Sc.D., James McGough, M.D., Sandra Loo, M.D., Alysa E. Doyle, Ph.D., Janet Wozniak, M.D., Timothy E. Wilens, M.D., Susan Smoller, Ph.D., James McCracken, M.D., Joseph Biederman, M.D., Stephen V. Faraone, Ph.D.

Abstract: Objective: A potentially useful tool for understanding the distribution and determinants of emotional dysregulation in children is a Child Behavior Checklist profile, comprising the Attention Problems, Anxious/Depressed, and Aggressive Behavior clinical subscales (CBCL-DP). The CBCL-DP induces a heritable trait that increases susceptibility for later psychopathology, including severe mood problems and aggressive behavior. We have conducted a genome-wide association study of the CBCL-DP in children with attention-deficit/hyperactivity disorder (ADHD). Method: Families were ascertained at Massachusetts General Hospital and University of California, Los Angeles. Genotyping was conducted with the Illumina HumanCore BeadChip array (Illumina, San Diego, CA) and PLINK (v1.9) was used for extension of PLINK. Results: CBCL-DP scores were significantly associated with ADHD affected trio families from the

Certain CBCL scores- AAA profile- are associated with a diagnosis of pediatric bipolar disorder



The Child Behavior Checklist (CBCL) is a parent completed rating scale that is easy to administer and score

Please print CHILD BEHAVIOR CHECKLIST FOR AGES 6-18

For office use only
ID # _____

CL _____
FL _____
DADENTS' USUAL TYPE OF WORK even if not working now.

Please print. Be sure to answer all items.

N Below is a list of items that describe children and youths. For each item that describes your months, please circle the 2 if the item is **very true or often true** of your child. Circle the 1 if the item is **true** of your child. If the item is **not true** of your child, circle the 0. Please answer all items as well as you can. Some items will seem to apply to your child.

0 = Not True (as far as you know) 1 = Somewhat or Sometimes True

0 1 2	1. Acts too young for his/her age	0 1 2	32. Feels he/she is not good enough
T 0 1 2	2. Drinks alcohol without parents' approval (describe): _____	0 1 2	33. Feels or says he/she is not good enough
M	3. Argues a lot	0 1 2	34. Feels others are not nice to him/her
G 0 1 2	4. Fails to finish things he/she starts	0 1 2	35. Feels worthless
S 0 1 2	5. There is very little he/she enjoys	0 1 2	36. Gets hurt a lot
N 0 1 2	6. Bowel movements outside toilet	0 1 2	37. Gets in many fights
S 0 1 2	7. Bragging, boasting	0 1 2	38. Gets teased a lot
— 0 1 2	8. Can't concentrate, can't pay attention for long	0 1 2	39. Hangs around with others who get in trouble
I. 0 1 2	9. Can't get his/her mind off certain thoughts; obsessions (describe): _____	0 1 2	40. Hears sound or voices that aren't there (describe): _____
to 0 1 2	10. Can't sit still, restless, or hyperactive	0 1 2	41. Impulsive or acts without thinking

0 1 2 20. Destroys his/her own things

0 1 2 21. Wishes he/she were not here

0 1 2 22. Would rather be alone than with others

0 1 2 23. Lying, cheating

0 1 2 24. Fingernails

0 1 2 25. Nervous, highstrung, or tense

0 1 2 26. Nervous movements or twitching (describe): _____

0 1 2 27. Tantrums

0 1 2 28. Bullied by other kids

0 1 2 29. Didn't participate, doesn't move bowels

120 statements about the child's behavior

1. Acts too young for his/her age
2. Drinks alcohol without parents approval
3. Argues a lot
4. Fails to finish things he/she starts
5.

Parents score choosing from Likert scale responses

0=not true

1=somewhat or sometimes true

2=Very true or often true

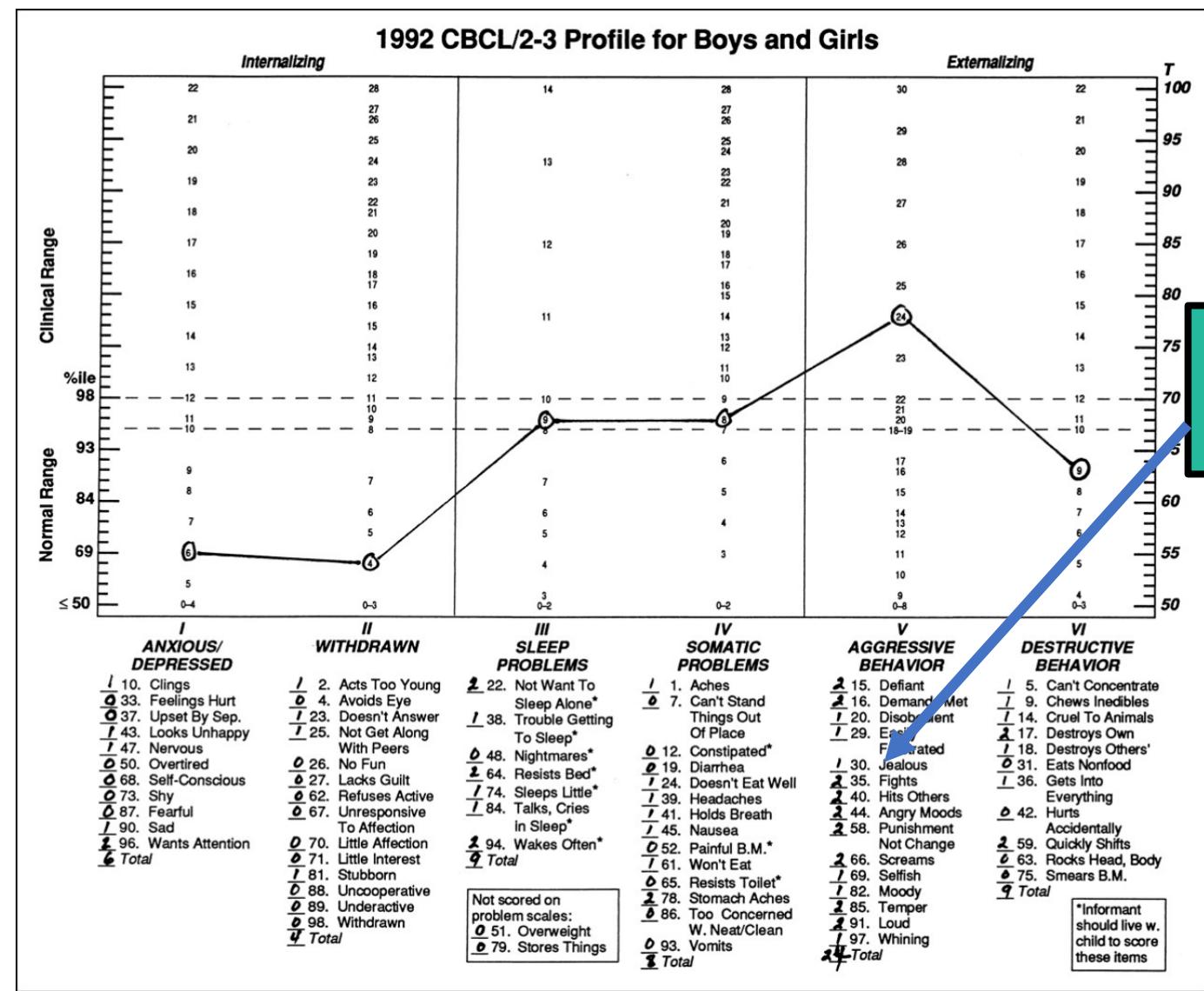
The 120 statements are grouped into 8 subscales or syndrome scales

How to score a CBCL



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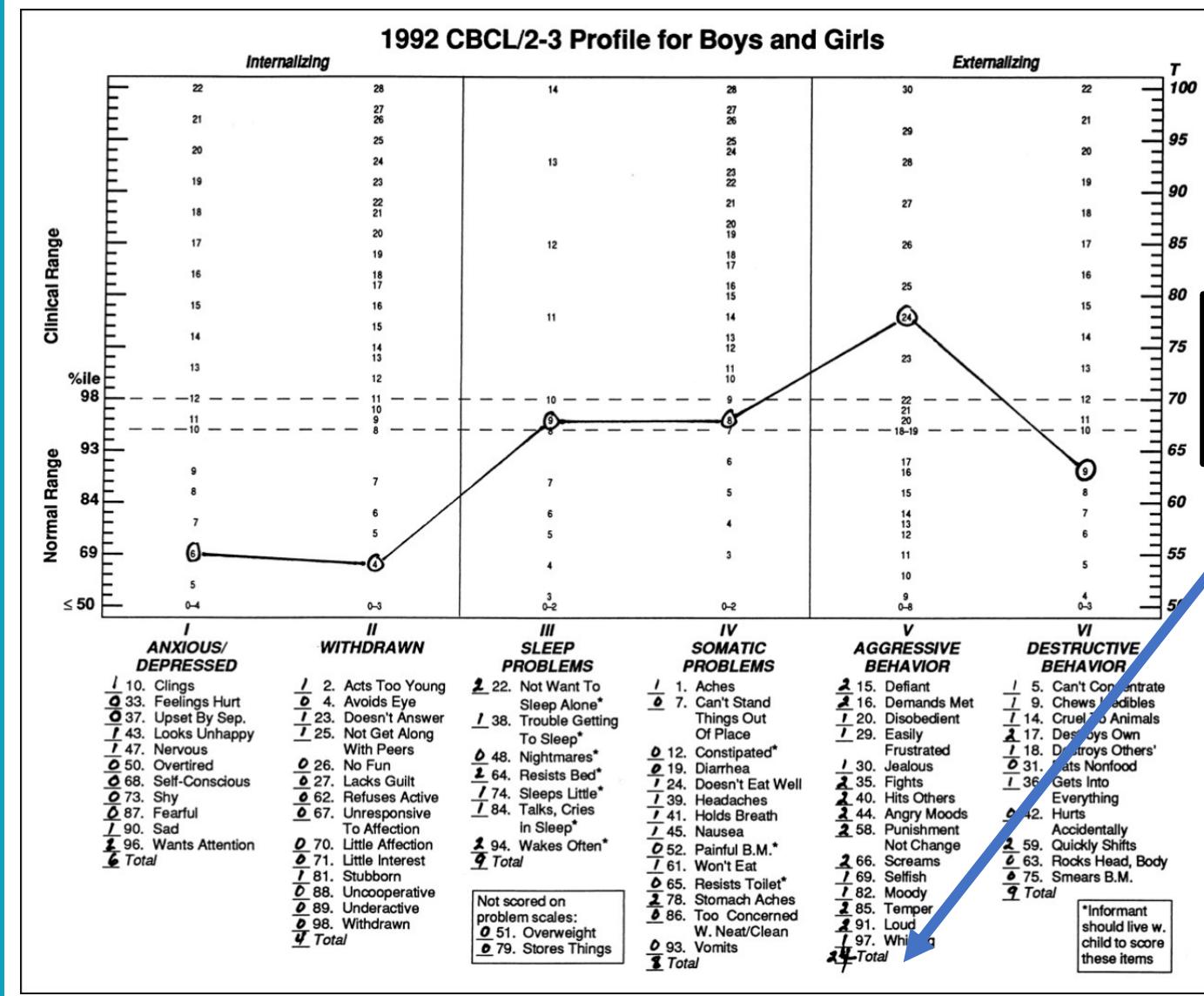


How to score a CBCL



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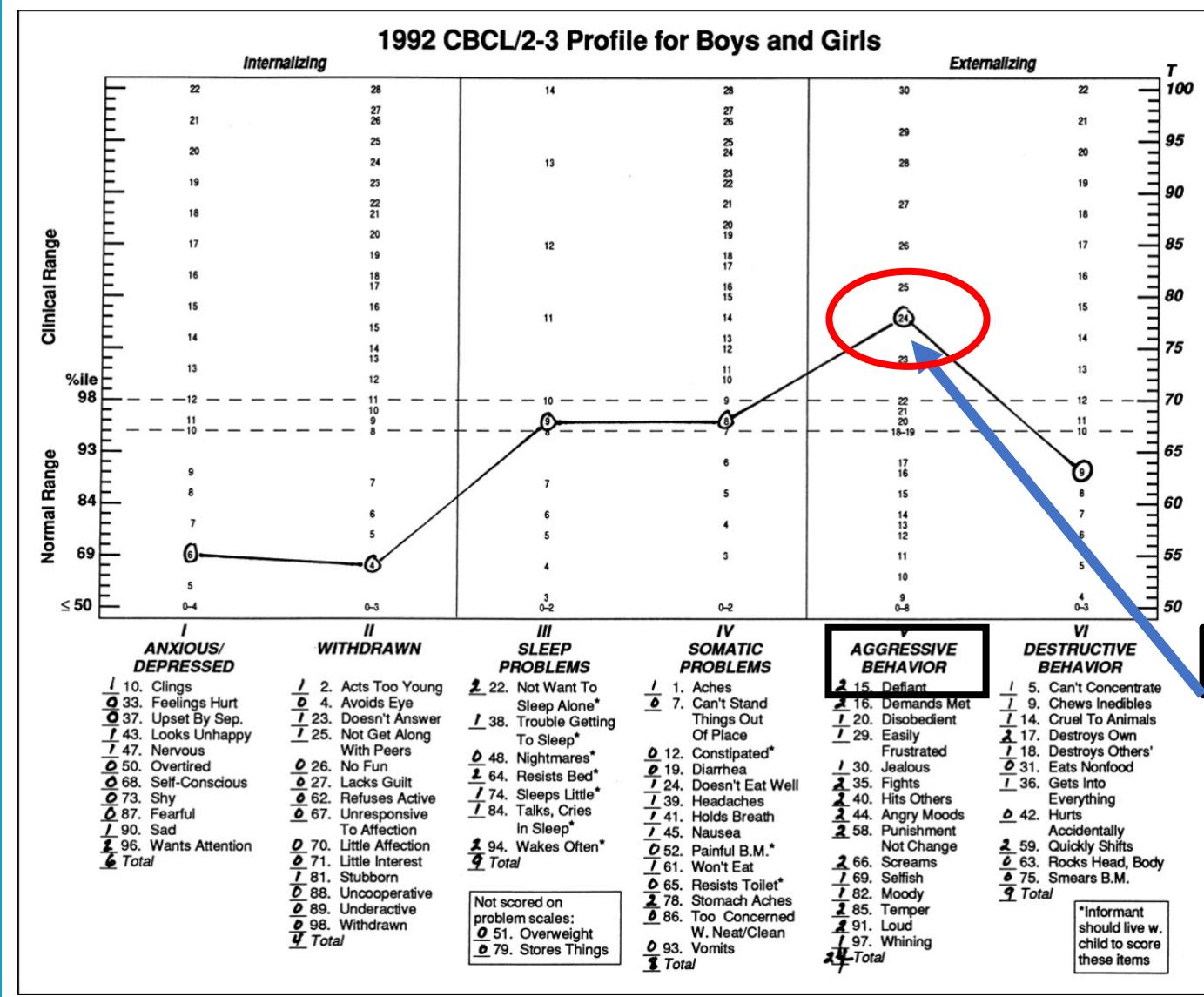


How to score a CBCL



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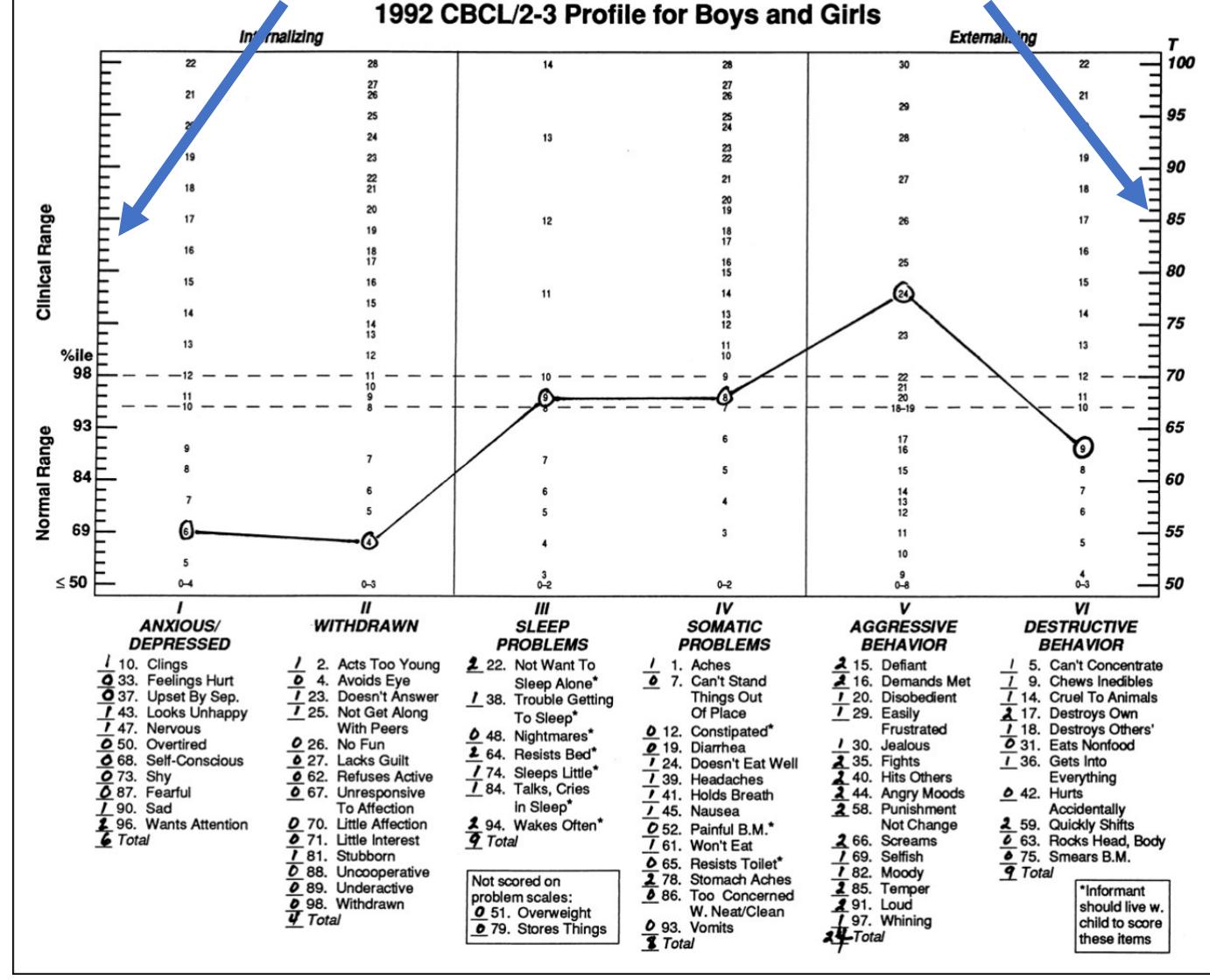
1. Enter all the scores (0, 1, 2) for each of the 120 questions under the different subscale groups

2. Total the score for each subscale

3. Plot the total score on the scale above

Percentile is on the left

T-Score is on the right



1. Enter all the scores (0, 1, 2) for each of the 120 questions under the different subscale groups

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3. Plot the total score on the scale above

Percentile is on the left

T-Score is on the right

2 CBCL/2-3 Profile for Boys and Girls

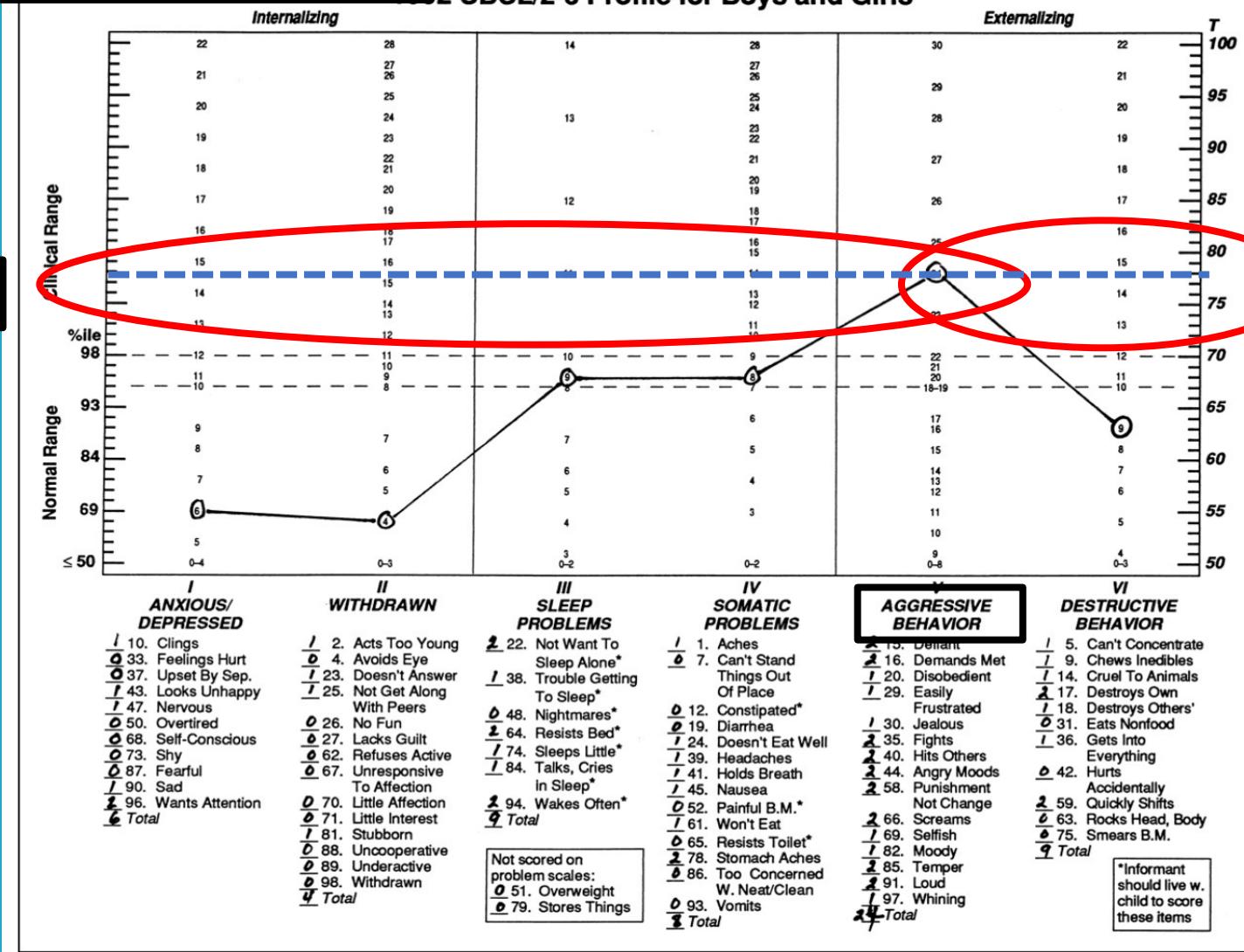


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92nd percentile

T-Score=78

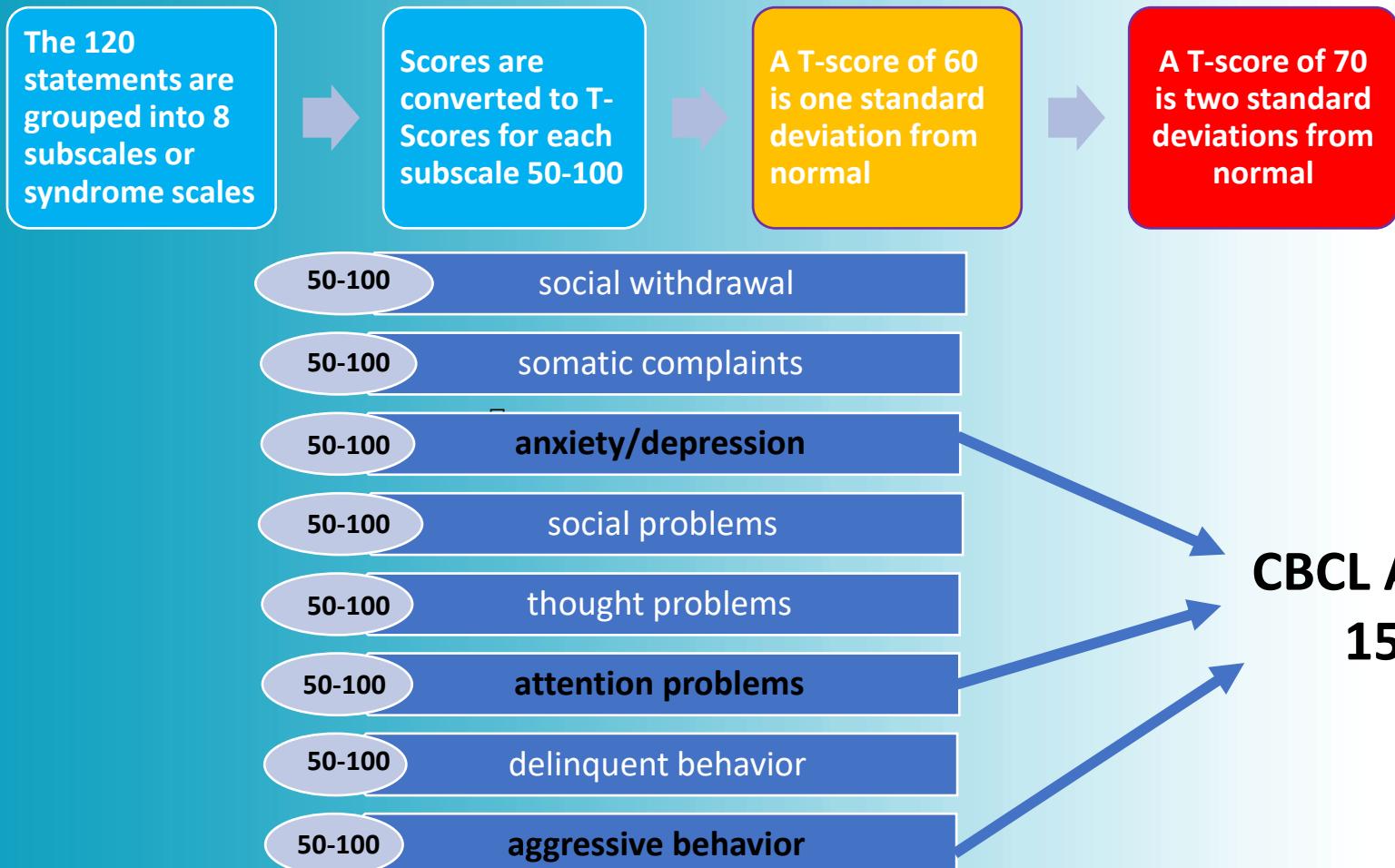


The CBCL uses a normative sample to create standard scores. T

These compare the raw score to what would be typical compared to responses for youths of the same gender and similar age.

The standard scores are scaled so that 50 is average for the youth's age and gender, with a standard deviation of 10 points.

The Child Behavior Checklist has 8 clinical subscales



We operationalized profiles of Emotional Dysregulation based on the composite T-scores of three CBCL subscales



AAA CBCL T-Score range is 150-300

Anxiety/ Depression 50-100

Aggression 50-100

Attention 50-100

A score of 150-180 is considered in the normal to subclinical range

if all 3 scores of the AAA were one SD from normal (60), the total would be 180

if all 3 scores of the AAA were two SD from normal (70), the total would be 210

Emotional Dysregulation (ED) can be characterized by **DESR** (CBCL Score 180-210) which is less severe than **SED** (CBCL Score >210)



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DESR Deficient Emotional Self Regulation

composite T-score AAA between 1 and 2 SD from normal

>180

<210



SED Severe Emotional Dysregulation

composite T-score AAA greater than 2 SDs from normal

greater than 210

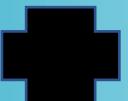
Hypotheses and objectives



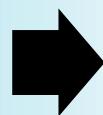
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**CBCL can identify
different levels of
emotional
dysregulation**



**Youth with autism are
often referred due to
emotional issues**



**We studied ASD youth
with different levels of
emotional dysregulation**

We hypothesized:
The two CBCL-ED
profiles (DESR and
SED) in youth with
ASD would identify
associated patterns
of clinical correlates

Our first main objective:
To assess prevalence and
severity of Emotional
Dysregulation (ED) in
psychiatrically referred
youth with ASD

Our second main objective:
To investigate whether the two
severity levels of CBCL profiles for
ED can help distinguish clinically
distinct levels of deficits in ASD



High Risk for Severe Emotional Dysregulation in Psychiatrically Referred Youth with Autism Spectrum Disorder: A Controlled Study

Gagan Joshi^{1,2,3} · Janet Wozniak^{1,2,3} · Maura Fitzgerald^{1,2} · Stephen Faraone^{4,5} · Ronna Fried^{1,2,3} · Maribel Galdo^{1,2} ·
Stephanie L. Furtak^{1,2} · Kristina Conroy^{1,2} · J. Ryan Kilcullen^{1,2} · Abigail Belser^{1,2} · Joseph Biederman^{1,2,3}

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Abstract

To assess prevalence and severity of emotional dysregulation (ED) in psychiatrically referred youth with autism spectrum disorder (ASD). ASD youth (N=123) were compared to youth with attention-deficit/hyperactivity disorder (ADHD) and controls. The majority of psychiatrically referred youth with ASD had positive Child Behavior Checklist-ED (CBCL-ED) profile that was significantly higher than in youth with ADHD (82 vs. 53%; $p < 0.001$). The severe emotional dysregulation (SED) profile was significantly greater in ASD youth than ADHD (44 vs. 15%; $p < 0.001$). In the presence of SED profile ASD youth suffered from greater severity of autism, associated psychopathology, and psychosocial dysfunction. Greater than expected prevalence of SED in psychiatrically referred youth with ASD that identifies distinct clinical correlates associated with severe morbidity and dysfunction.

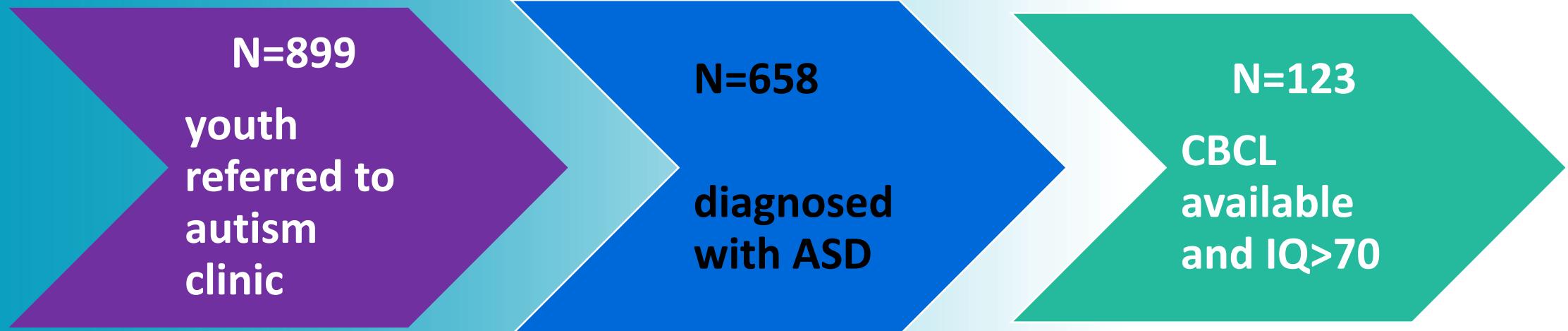
Keywords Autism spectrum disorder · Emotional dysregulation · CBCL · Youth



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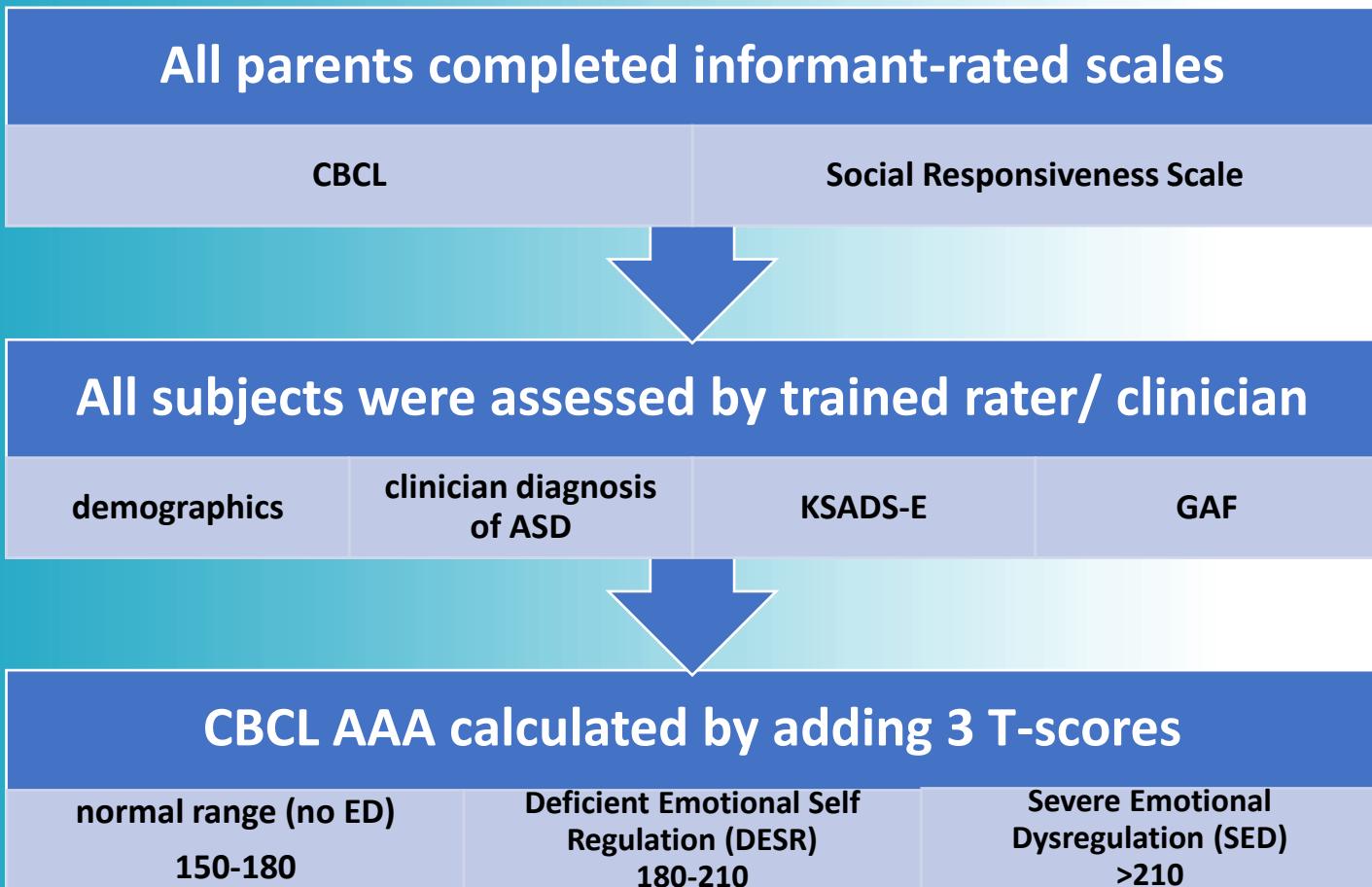
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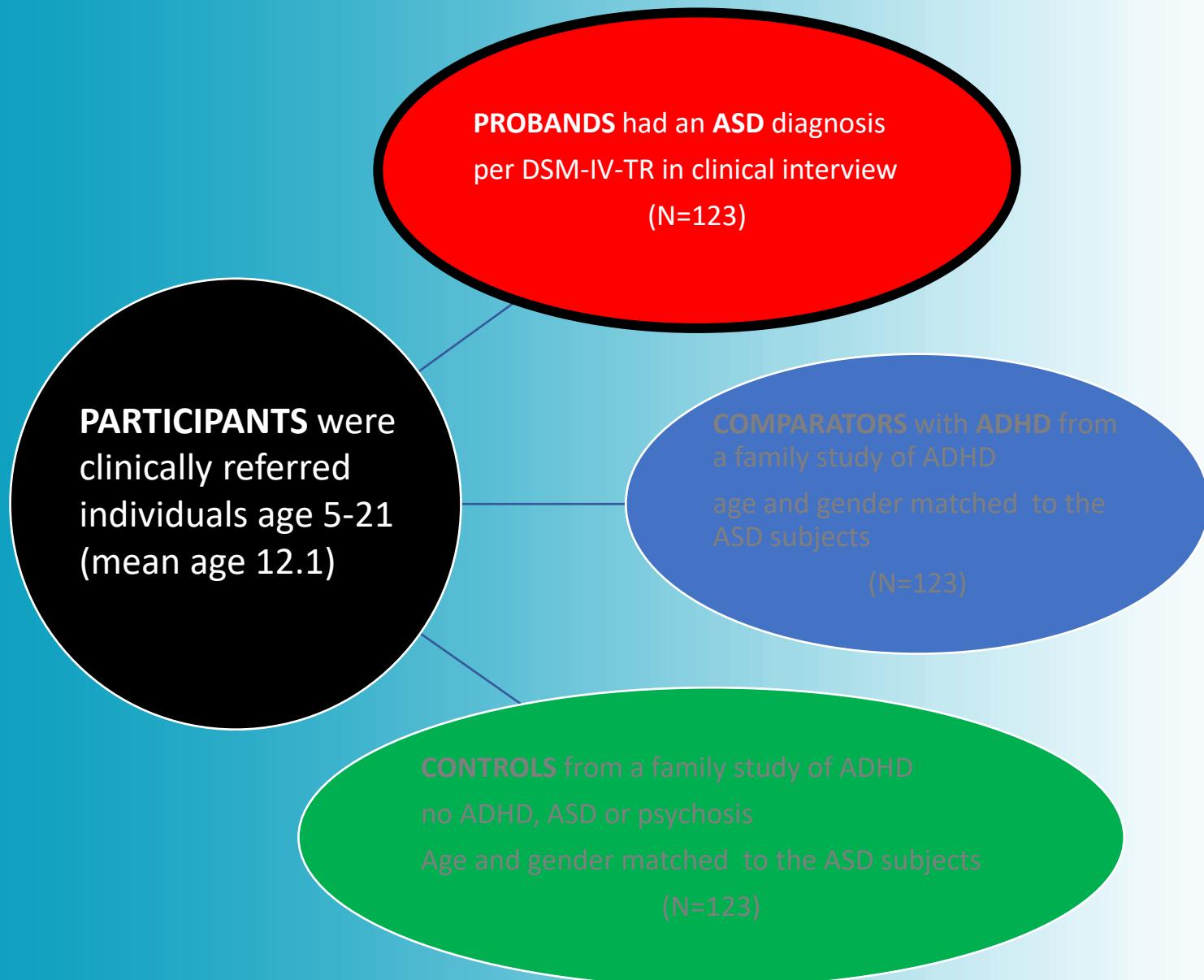
ASD participants came from an autism outpatient clinic



The Alan and Lorraine Bressler Clinical and Research Program for Autism Spectrum Disorder
Massachusetts General Hospital, Harvard Medical School

We used both parent- and clinician completed rating scales

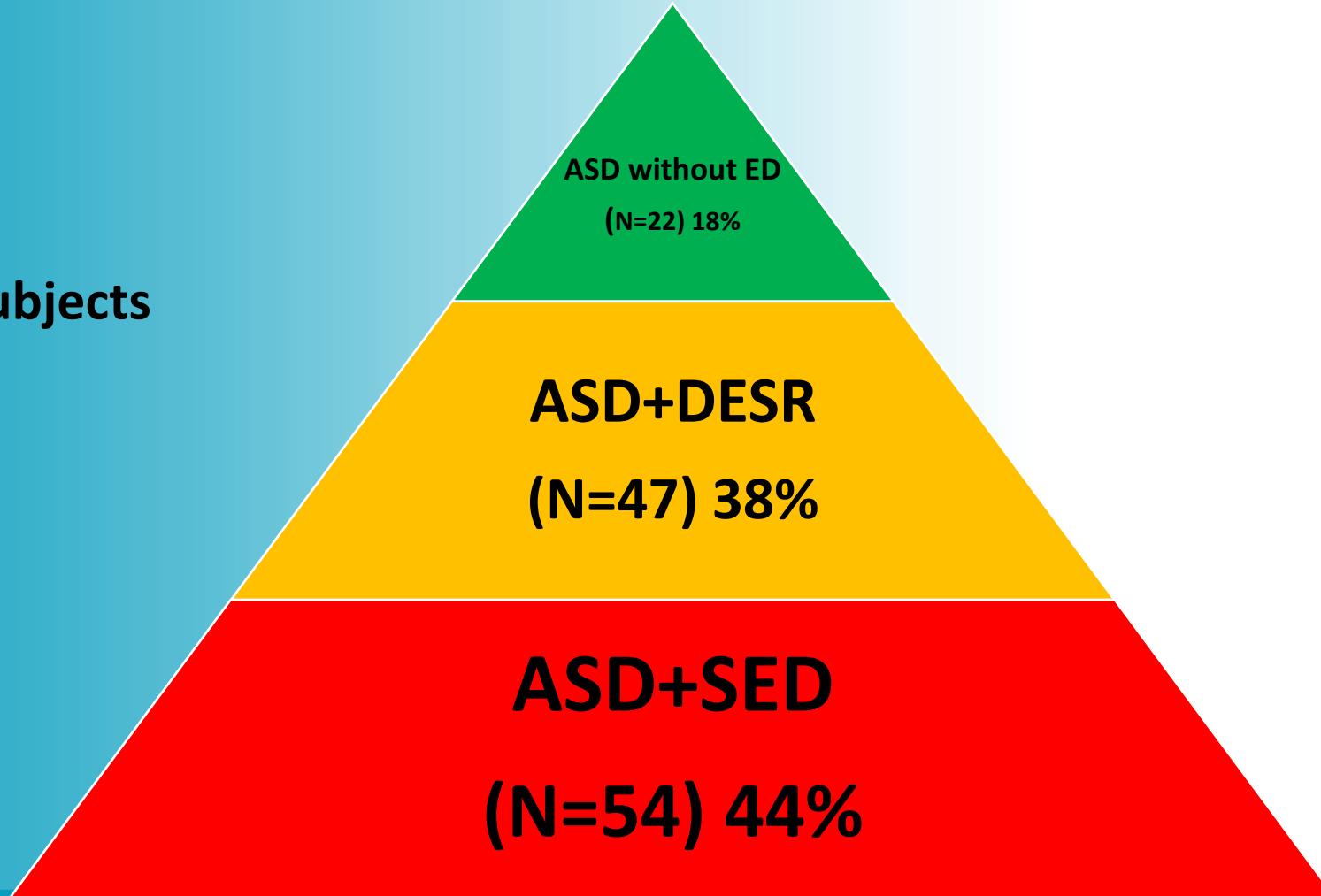




ASD + Severe Emotional Dysregulation was more common than ASD+ DESR which was more common than ASD without ED

Total Autism Subjects

N=123





ASD without ED
versus
ASD+DESR
versus
ASD+SED

No difference in repeating a grade 16%, tutoring 72% or special class 55%*

*except special class placement lower for ASD without ED, 29%

No difference in treatment**

Same percent with “severely impairing” ASD
45-65%

Same mean duration of disorder
(7-8 years)

***except worse GAF scores for ASD+SED

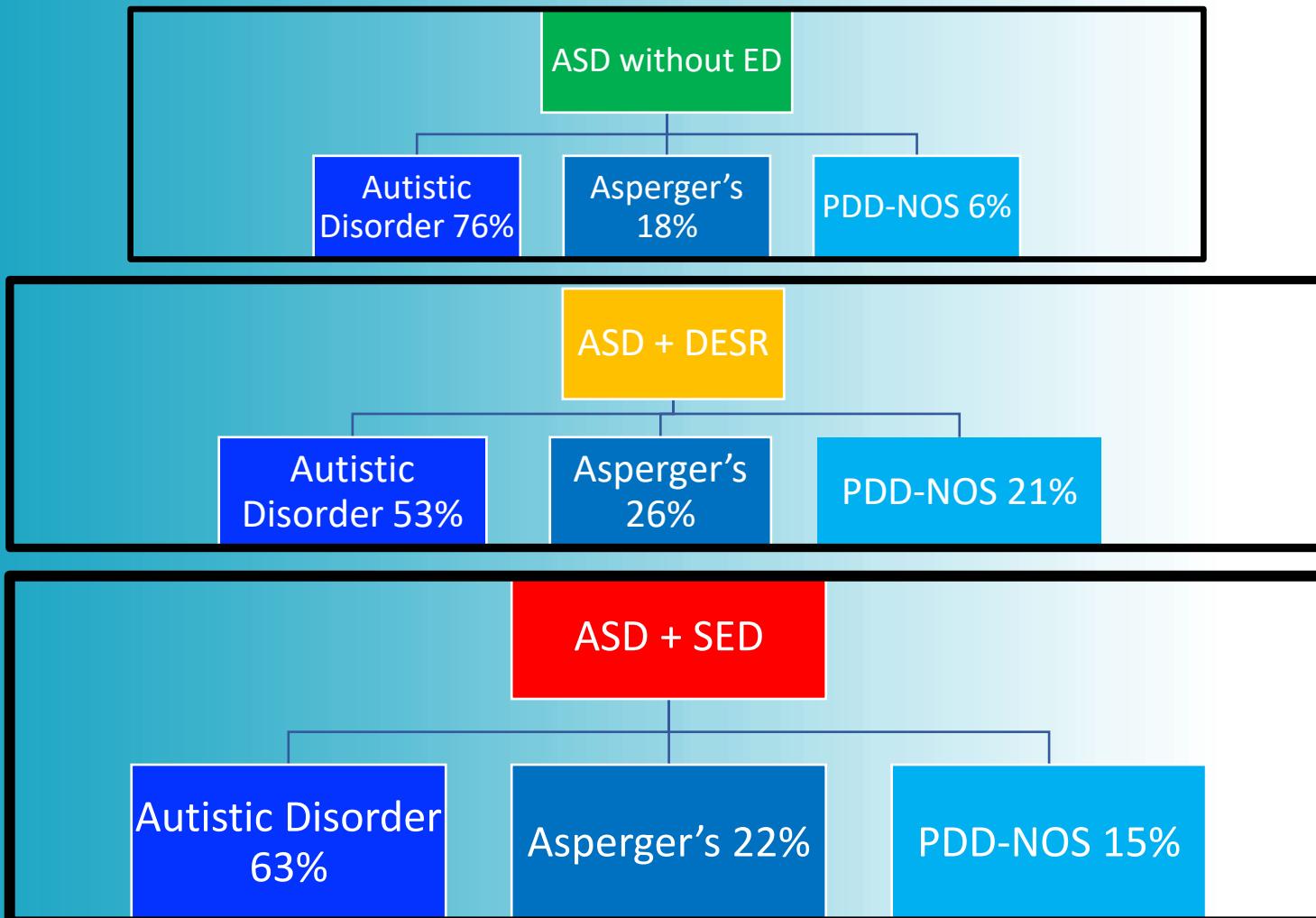
Same mean age of onset
(age 3-4 years)

No differences in IQ, SES, Race, Sex

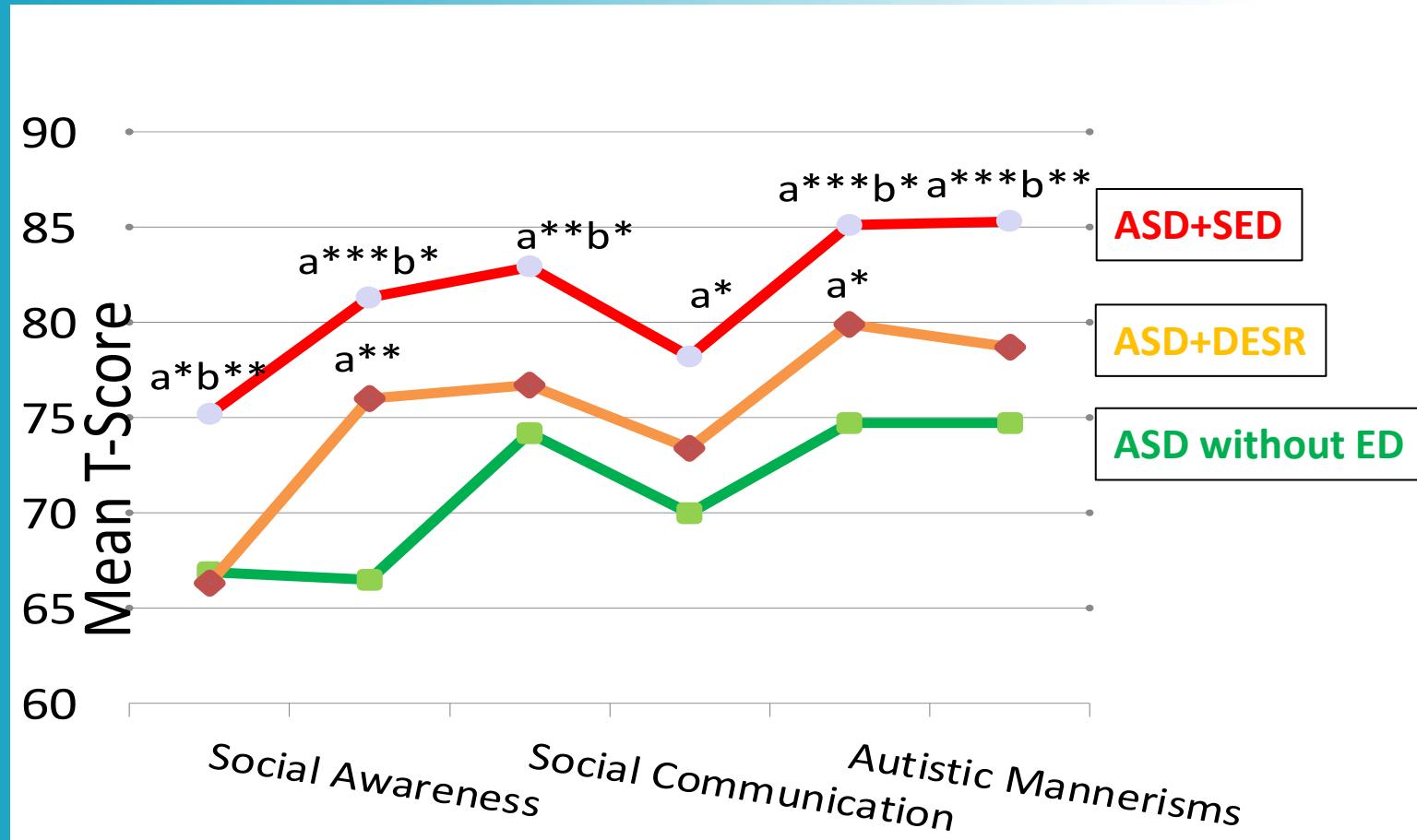
**except Medications (+/- Therapy) and Hospitalization rates for *Comorbid Conditions* are higher in ASD+SED

There were many similarities across the 3 types of autism with varying levels of emotional dysregulation

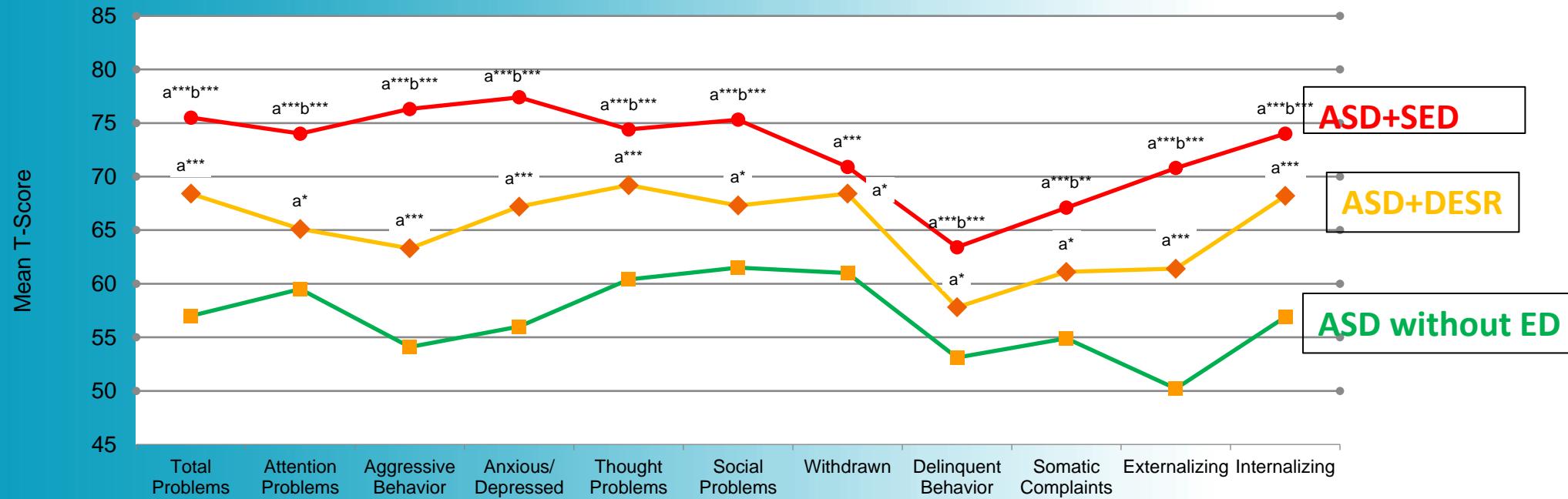
The distribution of ASD subtypes did not significantly differ across the three groups



Scores on the *Social Responsiveness Scale* were the worst in ASD youth with **SED** (CBCL >210)

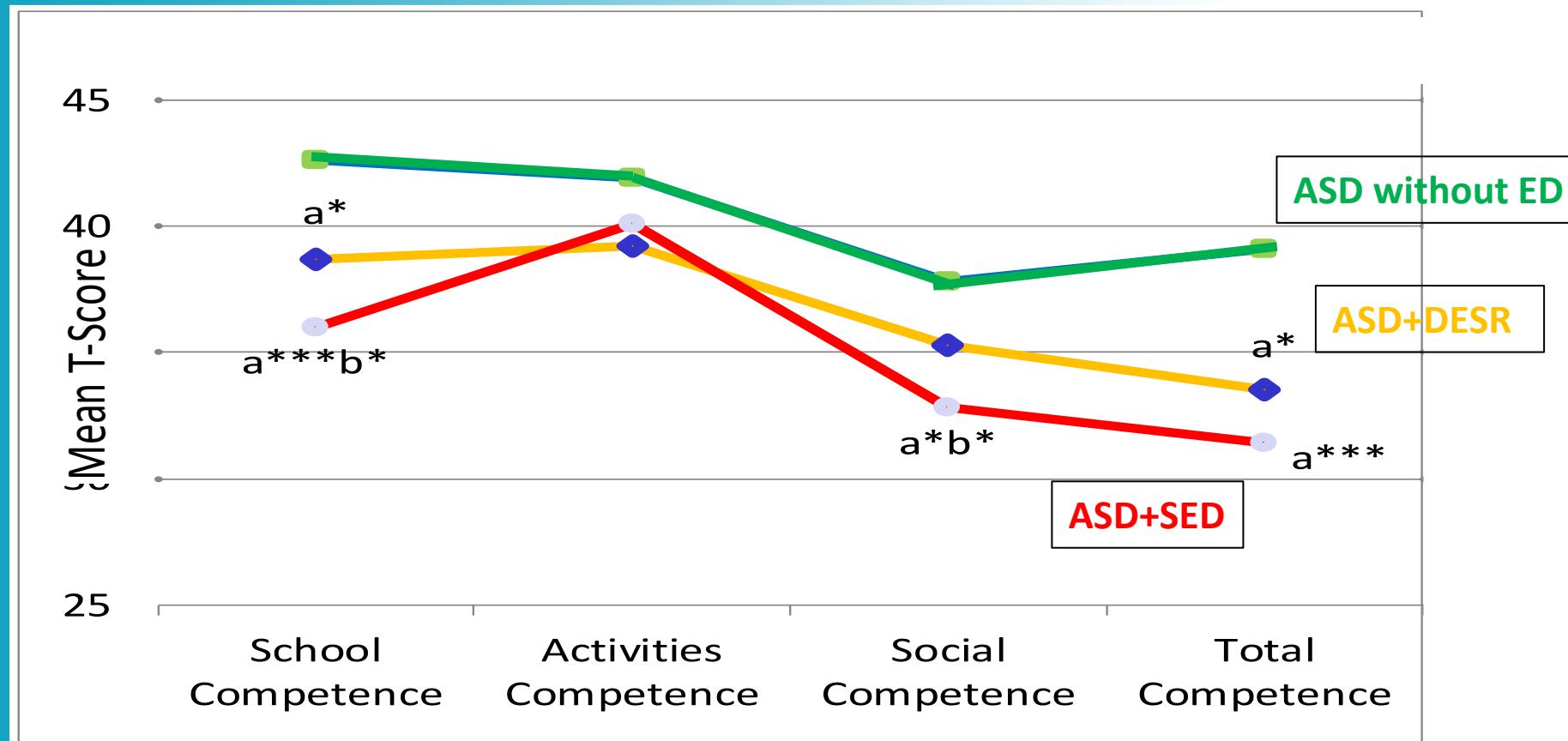


Scores on the clinical *CBCL subscales* were the worst in ASD youth with **SED** (*CBCL >210*)



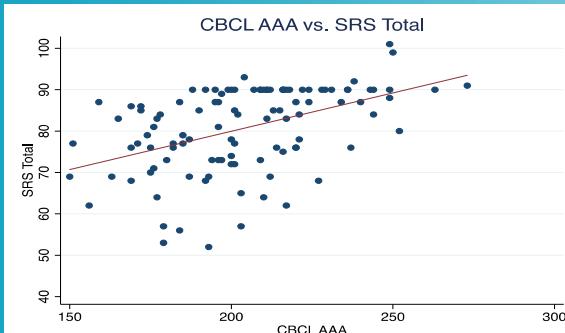
^aversus ASD-ED; ^bversus ASD+DESR; *p<0.05; **p<0.005; ***p<0.001; [†]N: ASD-ED=16-22; ASD+DESR=39-47; ASD+SED=47-53

Scores on the clinical *CBCL Social Competence subscales* were the worst in ASD youth with DESR and SED



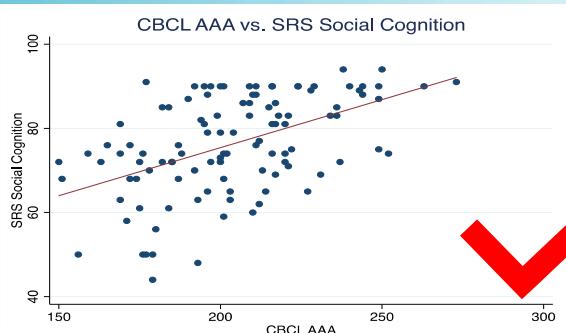
^a versus ASD-ED; ^b versus ASD+DESR; *p<0.05; **p<0.005; ***p<0.001; [†]N: ASD-ED=16-22; ASD+DESR=39-47; ASD+SED=47-53

AAA score correlates moderately with SRS total score for Social Cognition and Autistic Mannerisms



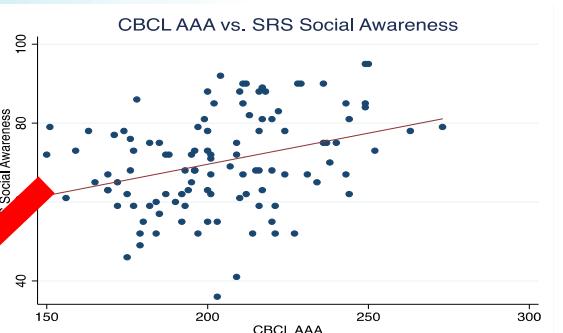
$r_s=0.50, df=106, p<0.001$

Moderate correlation



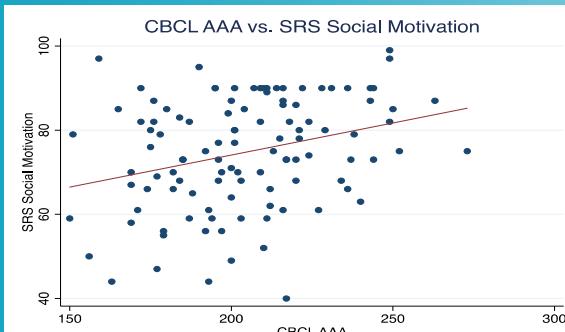
$r_s=0.48, df=106, p<0.001$

Moderate correlation



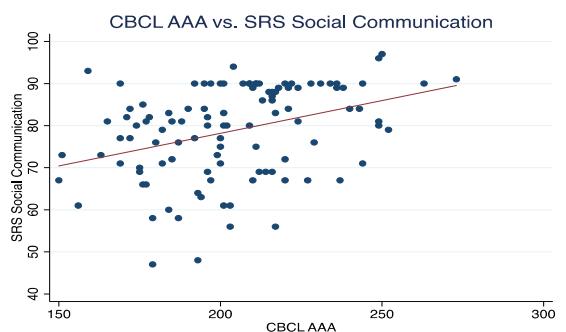
$r=0.33, df=108, p<0.001$

Weak correlation



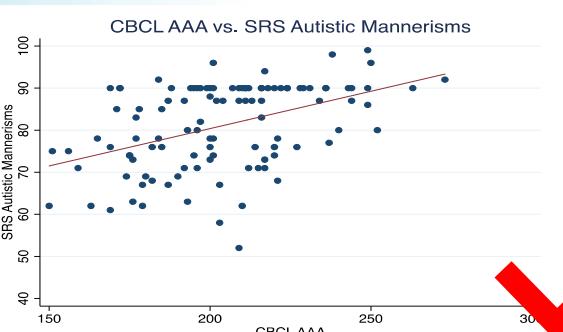
$r_s=0.29, df=107, p=0.002$

Weak correlation



$r_s=0.37, df=106, p<0.001$

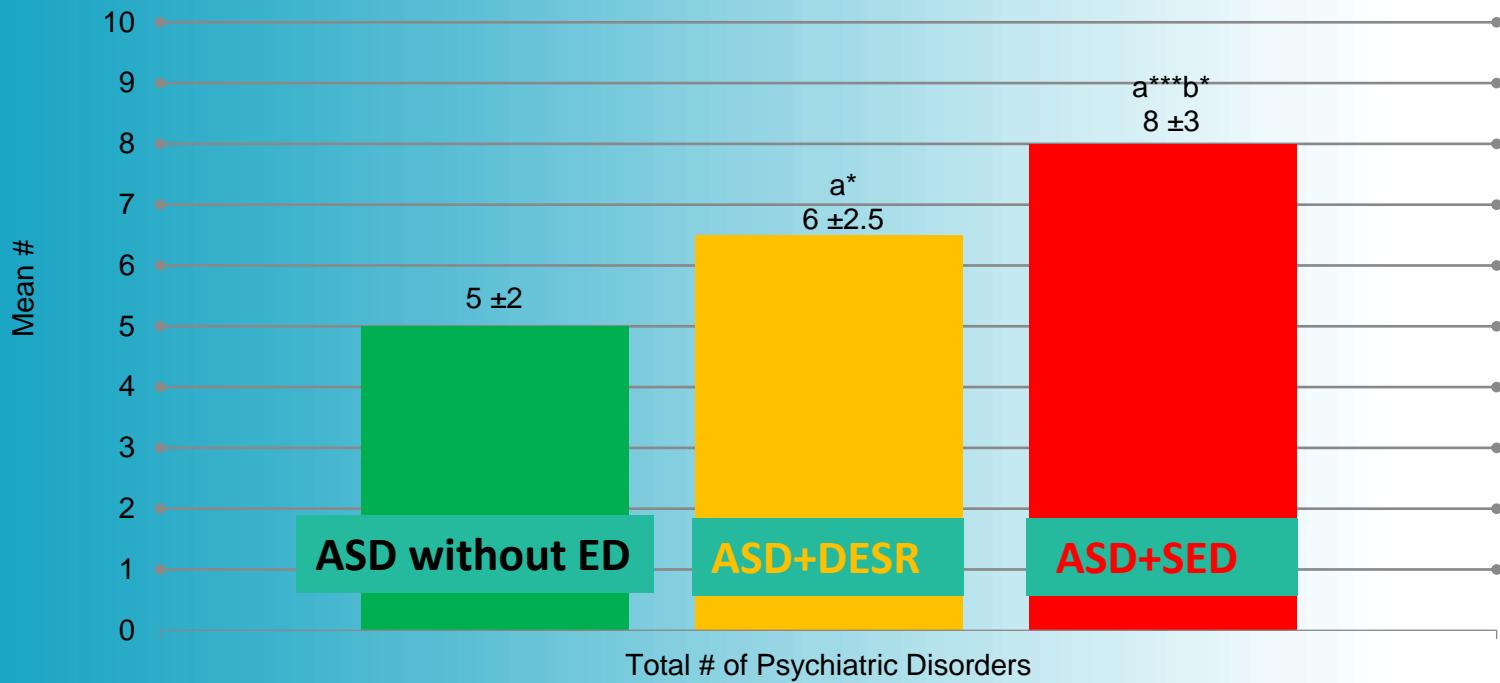
Weak correlation



$r_s=0.44, df=107, p<0.001$

Moderate correlation

ASD youth with SED (CBCL >210) have a greater total number of psychiatric disorders



^a versus ASD-ED; ^b versus ASD+DESR; *p<0.05; **p<0.005; ***p<0.001;

[†]N: ASD-ED=20-22; ASD+DESR=38-39; ASD+SED=42-44

ASD youth have high rates of comorbid conditions, like bipolar (especially ASD+SED)



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	ASD-ED N = 22 [†]	ASD + DESR N = 47 [†]	ASD + SED N = 54 [†]	Test Statistic	P-Value
	N (%)	N (%)	N (%)		
ADHD	12 (60)	31 (79)	34 (79)	$\chi^2_2=3.23$	0.20
Disruptive Behavior Disorders	11 (52)	25 (64)	35 (82) ^{a*b*}	$\chi^2_2=7.24$	0.03
Major Depressive Disorder	7 (33)	14 (36)	30 (68) ^{a*b**}	$\chi^2_2=11.22$	0.004
Bipolar Disorder	2 (10)	7 (18)	20 (45) ^{a***b*}	$\chi^2_2=12.19$	0.002
Multiple (≥ 2) Anxiety Disorders	11 (52)	25 (64)	31 (72)	$\chi^2_2=2.43$	0.30
Substance Use Disorders ^{††}	0 (0)	0 (0)	2 (10)	Exact	0.33

[†] Sample sizes vary. ASD-ED: N=20-22, ASD + DESR: N=38-39, ASD + SED: N=42-44

^{††} Age restricted to >12 . ASD-ED: N=13, ASD + DESR: N=18, ASD + SED: N=20

^a Compared to ASD. ^b Compared to ASD + DESR. *P<0.05, **P<0.005, ***P<0.001



Comorbidity in ASD is common

J Autism Dev Disord (2010) 40:1361–1370
DOI 10.1007/s10803-010-0996-9

ORIGINAL PAPER

The Heavy Burden of Psychiatric Comorbidity in Youth with Autism Spectrum Disorders: A Large Comparative Study of a Psychiatrically Referred Population

Gagan Joshi · Carter Petty · Janet Wozniak ·
Aude Henin · Ronna Fried · Maribel Galdo ·
Meghan Kotarski · Sarah Walls · Joseph Biederman

Published online: 23 March 2010
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Abstract The objective of the study was to systematically examine patterns of psychiatric comorbidity in referred youth with autism spectrum disorders (ASD) including autistic disorder and pervasive developmental disorder not otherwise specified. Consecutively referred children and adolescents to a pediatric psychopharmacology program were assessed with structured diagnostic interview and measures of psychosocial functioning. Comparisons were made between those youth satisfying diagnostic criteria for ASD and age and sex matched youth without ASD referred to the same clinical program. 9.3% (217/2323) of the referred youth (age range: 3–17 years) met DSM-III-R criteria for ASD. ASD youth suffered from significantly higher number of comorbid disorders than comparisons (6.4 ± 2.7 vs. 5.2 ± 2.9 ; $p < 0.001$). Ninety-five percent of the youth with ASD had three or more

high levels of psychiatric comorbidity comparable to the referred population with ASD. These findings emphasize the importance of psychiatric comorbidity afflicting youth with ASD as important targets for intervention.

Keywords Autism spectrum disorders · Psychiatric comorbidity · Children

Introduction

Autism spectrum disorders (ASD) are developmental disorders distinguished by difficulties with social and behavioral characteristics that are estimated to

J Autism Dev Disord
DOI 10.1007/s10803-012-1679-5

ORIGINAL PAPER

Psychiatric Comorbidity and Functioning in a Clinically Referred Population of Adults with Autism Spectrum Disorders: A Comparative Study

Gagan Joshi · Janet Wozniak · Carter Petty · Mary Kate Martelon ·
Ronna Fried · Anela Bolfek · Amelia Kotte · Jonathan Stevens · Stephannie L. Furtak ·
Michelle Bourgeois · Janet Caruso · Ashley Caron · Joseph Biederman

© Springer Science+Business Media New York 2012

Abstract To systematically examine the patterns of psychiatric comorbidity and functioning in clinically referred adults with autism spectrum disorders (ASD). Psychiatrically referred adults with and without ASD were compared on measures assessing for psychiatric comorbidity and psychosocial functioning. Sixty-three adults with ASD participated in the study (mean age: 29 ± 11 years). Adults with ASD in their lifetime suffered from a higher burden of psychiatric disorders (6 ± 3.4 vs. 3.5 ± 2.7 ; $p < 0.001$) including major depressive disorder and multiple anxiety disorders, and were functionally more impaired with a significant proportion having received both counseling and pharmacotherapy. Adults with ASD have high levels of psychiatric comorbidity and dysfunction comparable to a clinically referred population of adults without ASD.

Keywords Autism spectrum disorders · Psychiatric comorbidity · Adults

Introduction

Autism spectrum disorders (ASD) are characterized by a variable presentation of problems with socialization, communication, and behavior, and are estimated to affect more than 1% of children and adolescents in the general population (*Diagnostic and Statistical Manual of Mental Disorders* 1994; Kogan et al. 2009). Although ASD is well characterized in pediatric populations (Joshi et al. 2010; de Bruin et al. 2007; Wozniak et al. 1997; Simonoff et al. 2008), the prevalence and clinical characteristics of this lifelong disorder remain understudied in adult populations. Moreover, despite the fact that youth with ASD suffer from high rates of various psychiatric disorders (Joshi et al. 2010; de



ASD youth with all levels of emotional dysregulation have high rates of comorbid ADHD

	ASD-ED N = 22 [†]	ASD + DESR N = 47 [†]	ASD + SED N = 54 [†]	Test Statistic	P-Value
	N (%)	N (%)	N (%)		
ADHD	12 (60)	31 (79)	34 (79)	$\chi^2_2=3.23$	0.20
Disruptive Behavior Disorders	11 (52)	25 (64)	35 (83) ^{a*b*}	$\chi^2_2=7.24$	0.03
Major Depressive Disorder	7 (33)	14 (36)	30 (68) ^{a*b**}	$\chi^2_2=11.22$	0.004
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Multiple (≥ 2) Anxiety Disorders	11 (52)	25 (64)	31 (72)	$\chi^2_2=2.43$	0.30
Substance Use Disorders ^{††}	0 (0)	0 (0)	2 (10)	Exact	0.33

[†] Sample sizes vary. ASD-ED: N=20-22, ASD + DESR: N=38-39, ASD + SED: N=42-44

^{††} Age restricted to >12 . ASD-ED: N=13, ASD + DESR: N=18, ASD + SED: N=20

^a Compared to ASD. ^b Compared to ASD + DESR. *P<0.05, **P<0.005, ***P<0.001



PROBANDS had an **ASD** diagnosis
per DSM-IV-TR in clinical interview
(N=123)

PARTICIPANTS were
clinically referred
individuals age 5-21
(mean age 12.1)

COMPARATORS with **ADHD** from
a family study of **ADHD**
age and gender matched to the
ASD subjects
(N=123)

CONTROLS from a family study of **ADHD**
no **ADHD**, **ASD** or **psychosis**
Age and gender matched to the **ASD** subjects
(N=123)

**We expanded our investigation of
emotional dysregulation in **ASD** by
comparing **ASD** youth (high rates of **ADHD**)
to matched **ADHD** youth without **ASD**
(and controls)**



All analyses between the ASD, ADHD and Control Groups were controlled for race, IQ and SES

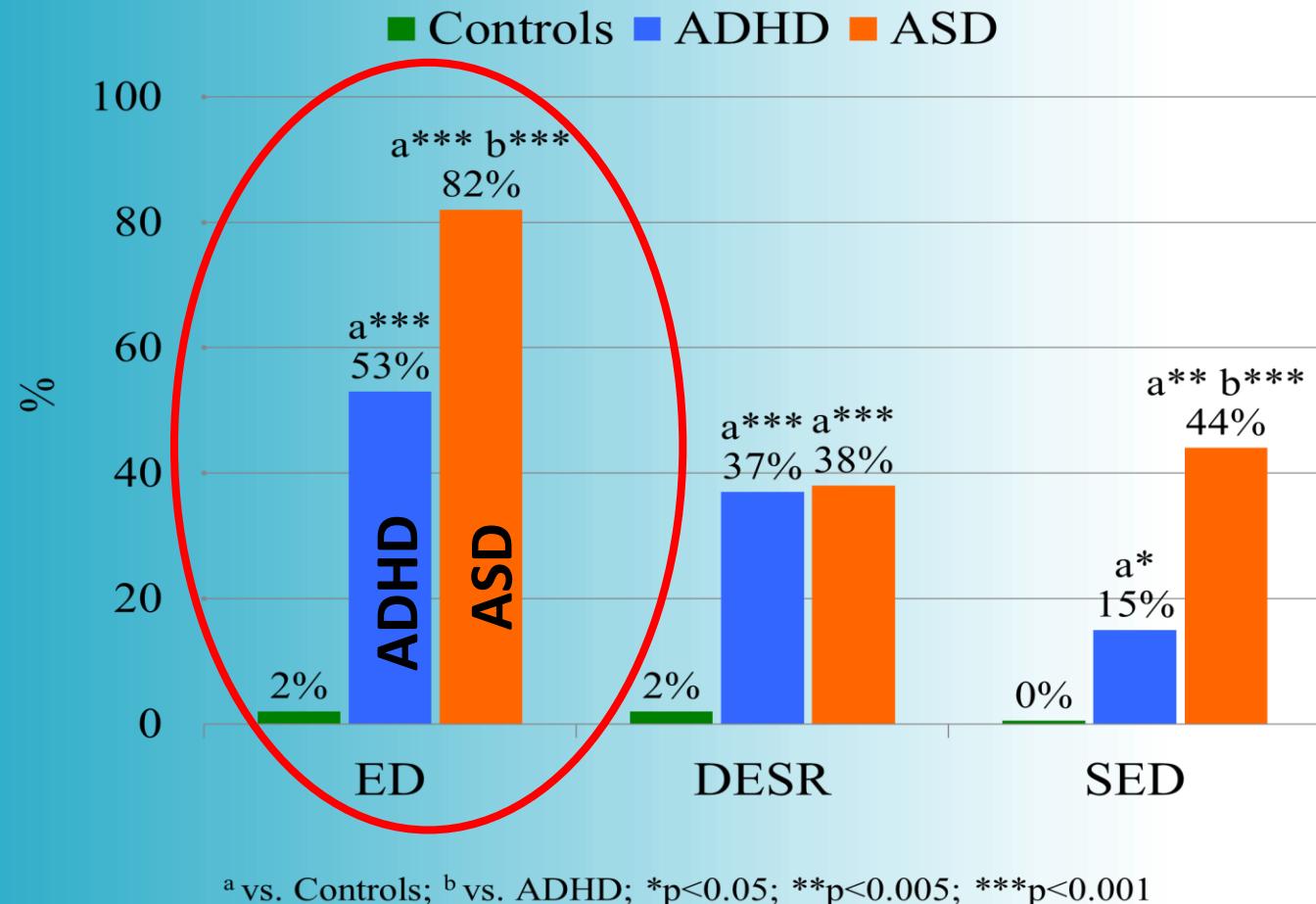
N=123 ASD (with age/gender matched ADHD and control subjects)

	Controls	ADHD	ASD	t-statistic	p-value
	(N=123)	(N=123)	(N=123)		
Age: -Mean	12.2 \pm 3.4	11.4 \pm 2.9	12.1 \pm 3.4	$F_{(2, 366)}=2.06$	0.13
-Range	6-18	6-18	5-21		
Gender: Male	106 (86)	106 (86)	106 (86)	NA	NA
Race: Caucasian	117 (98) ^[N=120]	119 (100) ^[N=119]	108 (88) ^{a***b***}	Exact	<0.001
IQ: -Mean	117 \pm 11	108.8 \pm 13.4 ^{a***}	101.2 \pm 14.8 ^{a***b***}	$F_{(2, 366)}=43.78$	<0.001
-Range	87.5-133	73.5-133	70-141		
SES	1.5 \pm 0.7	1.8 \pm 1 ^{a**}	2.0 \pm 1 ^{[N=107] a***}	$\chi^2_{(2)}=17.75$	<0.001
	ASD	ASD+DESR	ASD+SED		
	(N=22)	(N=22)	(N=22)		
Age: -Mean	13.4 \pm 3.6	12.1 \pm 3.6	12.1 \pm 3.6		
-Range	7-18	6-18	6-18		
Gender: Male	21 (95)	41 (91)	41 (91)		
Race: Caucasian	22 (100)	41 (91)	41 (91)		
	106.1 \pm 16.7	99.1 \pm 16.7	99.1 \pm 16.7		
IQ: -Mean	77-136	70-136	70-136		
-Range	1.8 \pm 0.8 ^[N=22]	2.0 \pm 0.8 ^[N=22]	2.0 \pm 0.8 ^[N=22]		
SES					

- The ASD group had significantly *fewer Caucasians* and *lower IQ* compared to the ADHD and Control groups.
- Both the ASD and ADHD groups had significantly *lower IQ* and *SES* compared to the Control group.

All subsequent analyses between the ASD, ADHD, and Control groups **controlled for race, IQ, and SES**.

Emotional Dysregulation (CBCL AAA > 180) is more common in ASD youth compared to ADHD youth



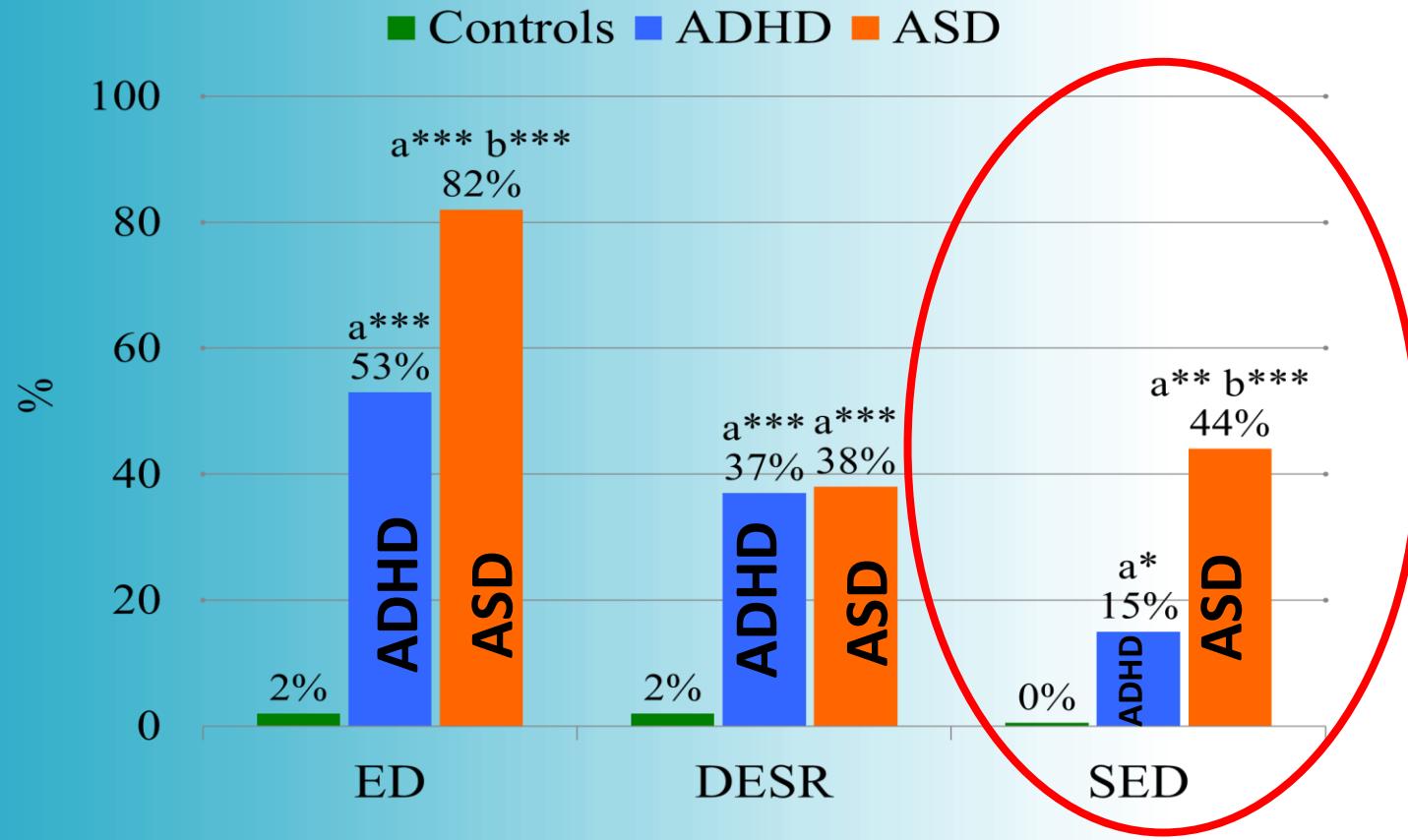
Controlled for differences in SES, race, IQ

And **SED (CBCL >210)**,
but not **DESR (CBCL 180-210)**,
is more common in ASD youth compared to ADHD



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Controlled for differences in SES, race, IQ

WWW.MGHCMEO.ORG

High rates of mood disorders are reported in ASD



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PSYCHIATRY ACADEMY

J Autism Dev Disord (2010) 40:1361–1370					1365
	ASD (N = 217) N (%)	Non-ASD (N = 217) N (%)	χ^2	p-value	Holm's adjusted alpha
Language disorder	105 (48)	59 (27)	18.93	<0.001	0.002
Tic disorder					
Tic disorder (motor or vocal)	50 (23)	43 (20)	0.69	0.41	0.01
Tourette's disorder	40 (18)	34 (16)	0.49	0.48	0.012
Disruptive behavior disorder					
Attention-deficit/hyperactivity disorder	181 (83)	173 (80)	0.75	0.39	0.008
Oppositional defiant disorder	158 (73)	146 (68)	1.49	0.22	0.005
Conduct disorder	47 (22)	48 (22)	0.01	0.90	0.05
Mood disorder					
Major depressive disorder	121 (56)	102 (47)	3.44	0.06	0.004
Bipolar I disorder	68 (31)	65 (30)	0.11	0.74	0.017
Psychosis	42 (20)	27 (12)	4.09	0.04	0.003
Anxiety disorder					
Multiple anxiety disorders (≥ 2)	133 (61)	92 (42)	15.14	<0.001	0.002
Specific phobia	79 (37)	43 (20)	14.09	<0.001	0.003
Separation anxiety disorder	79 (37)	77 (35)	0.04	0.84	0.025
Agoraphobia	77 (35)	41 (19)	14.73	<0.001	0.003
Generalized anxiety disorder					0.006
Social phobia					0.031
Obsessive-compulsive disorder					0.004
Panic disorder					0.007
Posttraumatic stress disorder					0.006
Substance abuse					0.003
Substance dependence					0.004
Cigarette smoking					0.005
Elimination disorder					0.002
Enuresis					
Encopresis					

^a Limited

Assessed with KSADS

Mood Disorders in ASD youth:

- MDD 56%**
- BPD 31%**

Mood Disorders in ASD adults:

- MDD 77%**
- BPD 25%**

J Autism Dev Disord					
Table 2 Psychiatric comorbidities in psychiatrically referred adults with and without ASD					
	ASD (N = 63) N (%)	Non-ASD (N = 63) N (%)	Test statistic	p value	Holm's adjusted alpha
Tic disorder					
Tic disorder (motor or vocal)					
Lifetime	7 (11)	7 (11)	$\chi^2_{(1)} = 0.00$	1.00	0.05
Current	4 (6)	3 (5)	$\chi^2_{(1)} = 0.14$	0.71	0.006
Tourrette's disorder					
Lifetime	3 (5)	0 (0)	$\chi^2_{(1)} = 3.00$	0.08	0.0016
Current	3 (5)	0 (0)	$\chi^2_{(1)} = 3.00$	0.08	0.00156
Disruptive behavior disorder					
Attention-deficit/hyperactivity disorder					
Lifetime	42 (68)	44 (70)	$\chi^2_{(1)} = 0.03$	0.86	0.008
Current	26 (42)	36 (57)	$\chi^2_{(1)} = 2.19$	0.14	0.0017
Oppositional defiant disorder					
Lifetime	33 (53)	9 (2.0)	$\chi^2_{(1)} = 0.89$	0.03	0.0016
Current	17 (27)	5 (1.1)	$\chi^2_{(1)} = 3.27$	0.07	0.0015
Conduct disorder					
Lifetime	7 (11)	8 (1.3)	$\chi^2_{(1)} = 0.09$	0.76	0.007
Current	1 (2)	1 (2)	$\chi^2_{(1)} = 0.00$	1.00	0.025
Antisocial personality disorder					
Lifetime	6 (10)	5 (8)	$\chi^2_{(1)} = 0.00$	1.00	0.017
Current	3 (5)	1 (2)	$\chi^2_{(1)} = 1.00$	0.32	0.0029
Major mood disorder					
Major depressive disorder					
Lifetime	48 (77)	29 (46)	$\chi^2_{(1)} = 11.1$	0.0009	0.00104
Current	19 (31)	14 (2.3)	$\chi^2_{(1)} = 1.00$	0.32	0.00278
Bipolar I disorder					
Lifetime	16 (25)	8 (1.3)	$\chi^2_{(1)} = 3.2$	0.07	0.00147
Current	4 (6)	3 (5)	$\chi^2_{(1)} = 0.14$	0.71	0.0056
Psychosis					
Lifetime	8 (13)	0 (0)	$\chi^2_{(1)} = 8.0$	0.005	0.00119
Current	5 (8)	0 (0)	$\chi^2_{(1)} = 5.0$	0.03	0.00135
Anxiety disorder					
Multiple anxiety disorders (≥ 2)					
Lifetime	37 (59)	11 (1.7)	$\chi^2_{(1)} = 18.8$	<0.0001	0.00096
Current	24 (38)	7 (1.1)	$\chi^2_{(1)} = 10.7$	0.011	0.00106
Specific phobia					
Lifetime	20 (32)	7 (1.1)	$\chi^2_{(1)} = 6.8$	0.01	0.00125
Current	11 (18)	6 (1.0)	$\chi^2_{(1)} = 1.5$	0.23	0.0021
Separation anxiety disorder					
Lifetime	13 (21)	3 (7)	$\chi^2_{(1)} = 5.3$	0.02	0.00131
Current	2 (3)	0 (0)	$\chi^2_{(1)} = 2.00$	0.50	0.0033
Agoraphobia					
Lifetime	22 (35)	4 (6)	$\chi^2_{(1)} = 14.7$	0.0001	0.00102
Current	15 (24)	2 (3)	$\chi^2_{(1)} = 9.9$	0.02	0.00111
Generalized anxiety disorder					
Lifetime	22 (35)	11 (1.7)	$\chi^2_{(1)} = 2.3$	0.13	0.00167
Current	18 (29)	9 (1.6)	$\chi^2_{(1)} = 2.00$	0.16	0.00185
Social phobia					

Joshi 2010, 2012

Is the bipolar disorder in autism *bona fide* bipolar disorder?



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Assessed with KSADS
Mood Disorders in ASD youth:

- MDD 56%
- BPD 31%

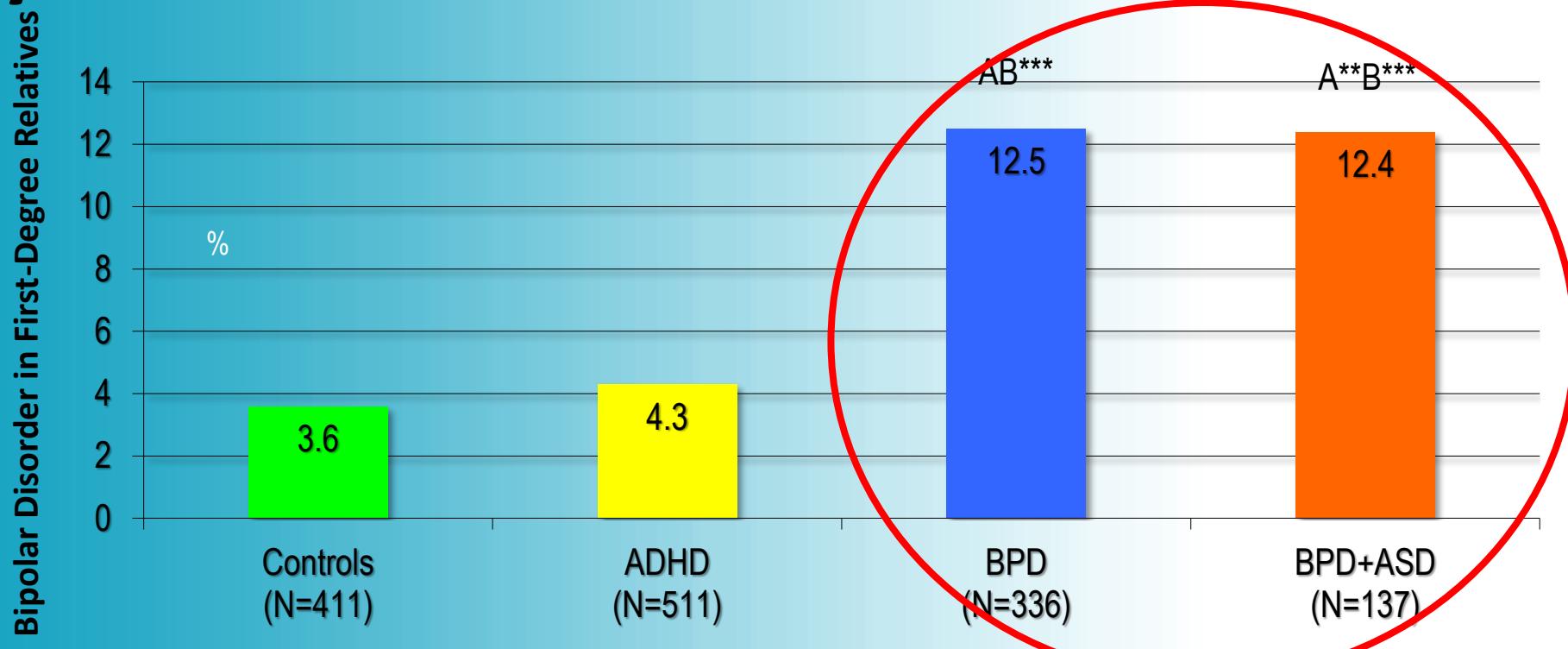
Mood Disorders in ASD adults:

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Table 2 Psychiatric comorbidities in psychiatrically referred adults with and without ASD					
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Conduct disorder					
Lifetime	7 (11)	8 (1.3)	$\chi^2_{(1)} = 0.09$	0.76	0.007
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Antisocial personality disorder					
Lifetime	6 (10)	5 (8)	$\chi^2_{(1)} = 0.00$	1.00	0.017
Current	3 (5)	1 (2)	$\chi^2_{(1)} = 1.00$	0.32	0.0029
Major mood disorder					
Major depressive disorder					
Lifetime	48 (77)	29 (46)	$\chi^2_{(1)} = 11.1$	0.0009	0.00164
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Lifetime	22 (35)	11 (1.7)	$\chi^2_{(1)} = 2.3$	0.13	0.00167
Current	18 (29)	9 (1.6)	$\chi^2_{(1)} = 2.00$	0.16	0.00185
Social phobia					

Joshi 2010, 2012

A family history of bipolar disorder is present in bipolar youth both with and without autism



BPD probands = 108 (relatives N=336)

BPD+ASD probands=47 (relatives N=137)

Statistical Significance: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

A = vs. Control; B = vs. ADHD

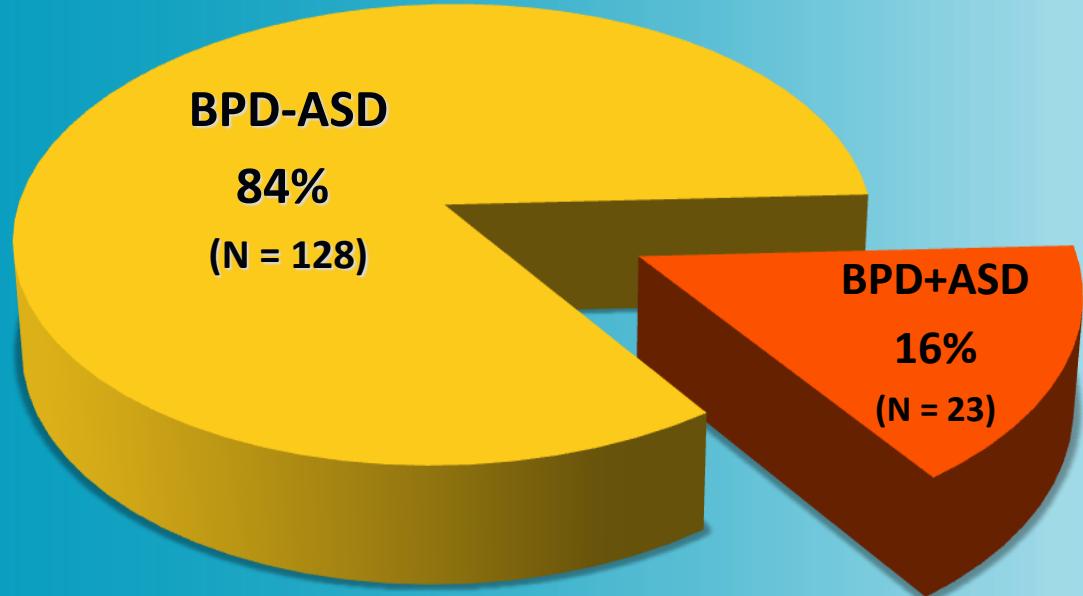
Joshi J Clin Psychiatry. 2013.

Autism is often excluded from clinical trials, but was *included* in our clinical trials of SGAs for bipolar youth (N=151)



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Male and female 4–17 years
Met criteria for bipolar I, II or NOS
8-week, open-label flexible dosing

N=19 aripiprazole (9.4 ± 4.2 mg/day)
N=20 quetiapine (240.4 ± 165.4 mg/day)
N=21 ziprasidone (56.2 ± 34.4 mg/day)
N=52 risperidone (1.3 ± 0.7 mg/day)
N=53 olanzapine (8.5 ± 4.2 mg/day)
with and without topiramate

We conducted a secondary analysis of 6 identically designed open-label trials of SGA therapy for pediatric BPD (N=165) 1999 – 2012, all but one monotherapy

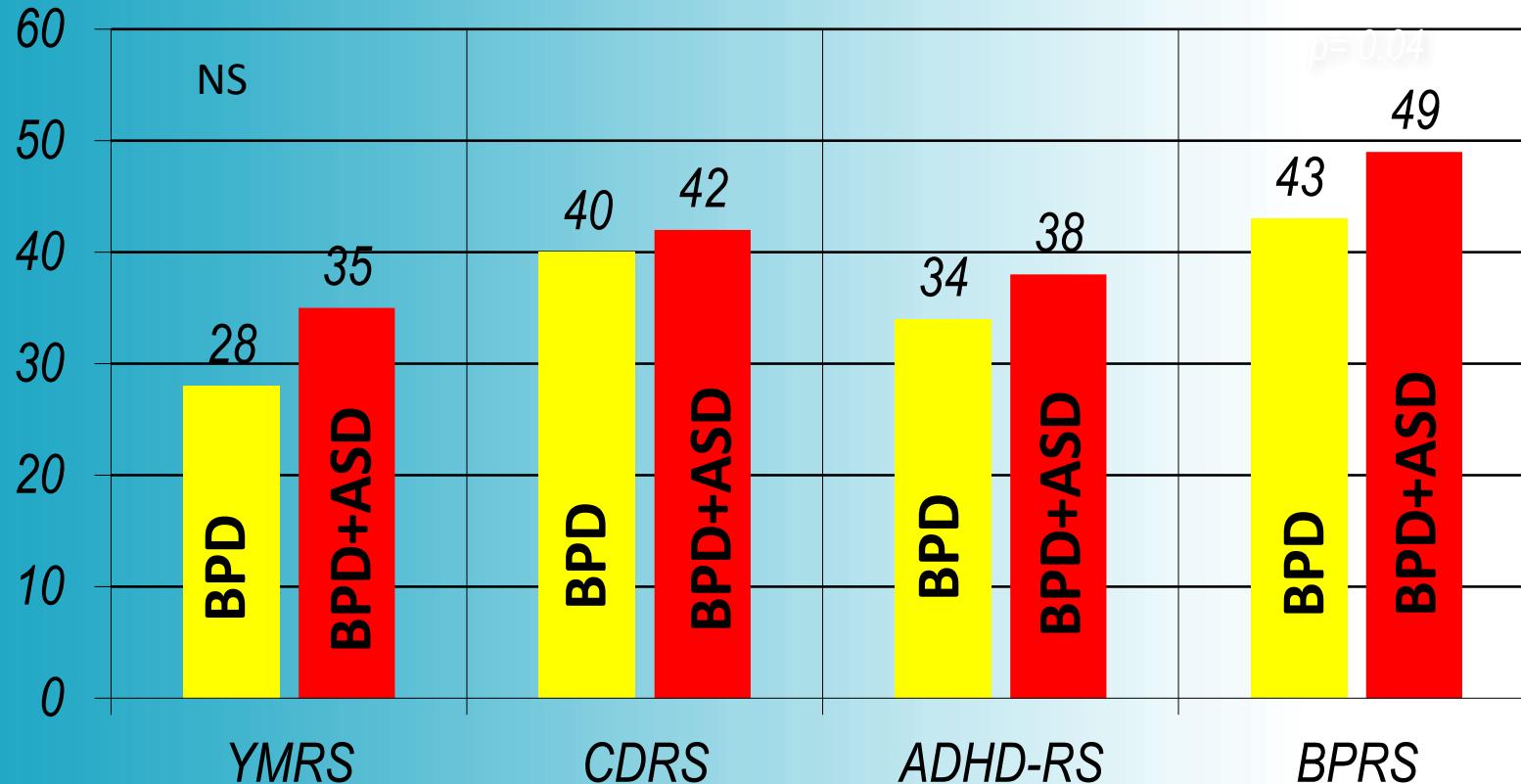
CNS Neurosci Ther. Jan. 2012;18(1):28-33 Biederman (risperidone) 2005; Biederman (olanzapine) 2005; Biederman (aripiprazole) 2007; Biederman (ziprasidone) 2007; Wozniak (olanzapine+topiramate) 2009; Joshi (quetiapine) 2012

Rating scale scores are similar in BPD youth **with** and **without** autism



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PSYCHIATRY ACADEMY



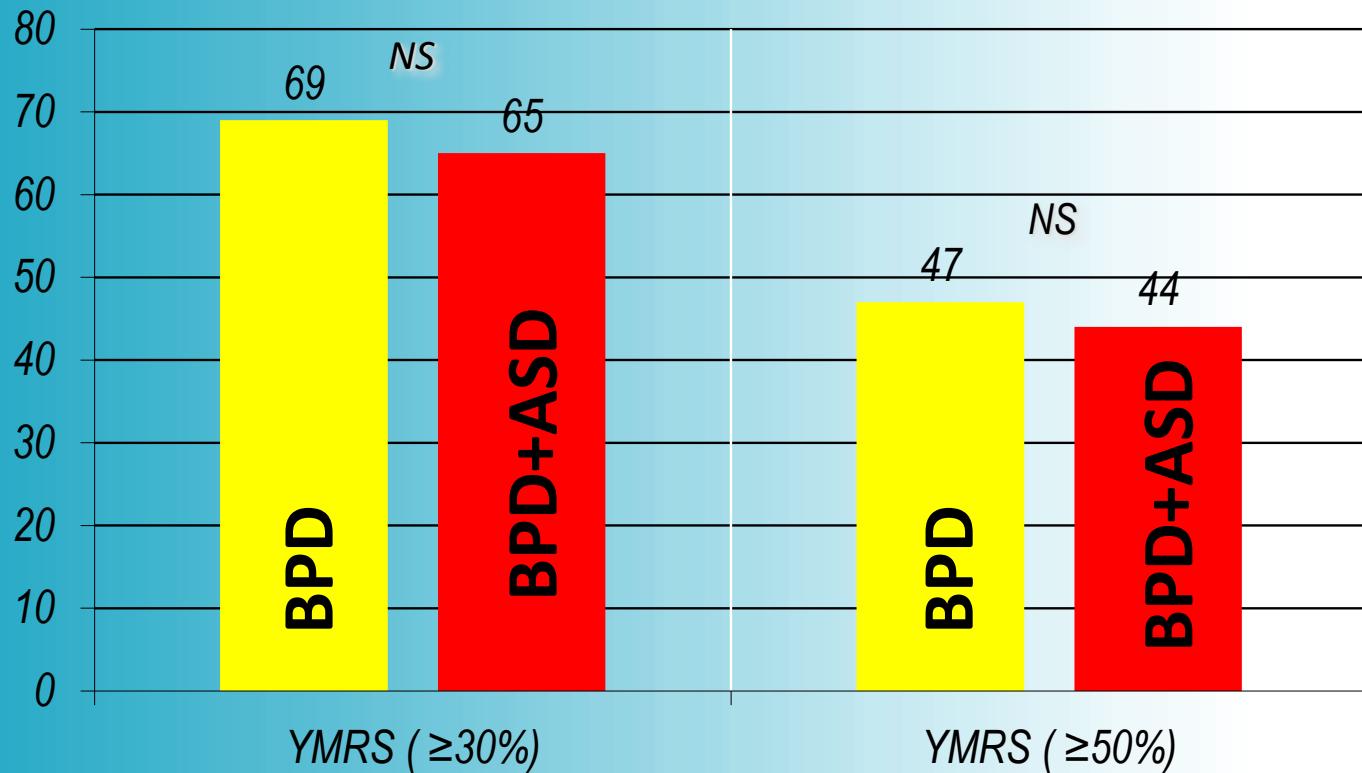
CNS Neurosci Ther. 2012

We found no difference in the anti-manic response of SGAs in bipolar youth **with** and **without** ASD



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GENERAL HOSPITAL

PSYCHIATRY ACADEMY



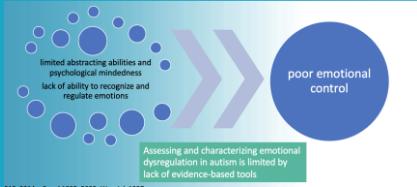
CNS Neurosci Ther 2012

Better methods of assessing and treating ED in autism are needed in the hopes of improving course and outcome of a disorder that is already highly compromising



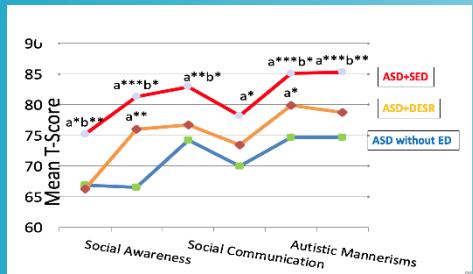
MASSACHUSETTS
GENERAL HOSPITAL

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Youth with autism are often referred due to emotional dysregulation.

The CBCL can delineate different levels of emotional dysregulation in autism



CHILD BEHAVIOR CHECKLIST FOR AGES 6-18

PARENTS' USUAL TYPE OF WORK, even if
Please print. Be sure to answer all items.
ms that describe children and youths. For each item that describes your c
le the 2 if the item is **very true or often true** of your child. Circle the 1 if the it
he item is **not true** of your child, circle the 0. Please answer all items as well
ur child.
as you know) 1 = Somewhat or Sometimes True

There are clinically distinct subtypes of ASD with and without deficient emotional self regulation and severe emotional dysregulation

Comorbidity analysis:

Autism + ADHD is common and associated with more severe emotional dysregulation than ADHD.

BPD comorbid with autism is a bona fide comorbidity and responds to SGA treatment similar to bipolar without autism.

