Autism Spectrum Disorder

GAGAN JOSHI, MD
Associate Professor of Psychiatry
Director, Autism Spectrum Disorder Program
The Bressler Clinical & Research Program for Autism Spectrum Disorder
Massachusetts General Hospital, Harvard Medical School

Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

PLEASE CONFIRM THAT DISCLOSURES MATCH WITH SUBMITTED DISCLOSURES

Research Support:

PI for Investigator-Initiated Studies:

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-American Academy of Child and Adolescent Psychiatry
-Canadian Academy of Child and Adolescent Psychiatry
-The Israeli Society for ADHD

Features of AUTISM

CORE Features

Impaired Social-Emotional Competence

I. Non-verbal communication (NVC)
- Eye contact (joint-attention)
- Receptive and Expressive emotional NVC (facial expression, verbal tone, touch)

II. Verbal communication
- Level of verbal communication
- Atypical style of speech (pedantic, professorial)

III. Emotional processing
- Emotional awareness, recognition
- Emotional expression (verbal & non-verbal)
- Empathy (Theory of mind)

IV. Social (inter-personal) processing
- Social motivation & awareness
- Sharing (activities, affect, back & forth conversations)
- Contextual understanding (social adaptability)

V. Abstracting ability
- Black & white/concrete/literal thinking
- Tolerance for ambiguity

VI. Introspective/Introceptive ability
(self awareness of cognition, emotions, & physiological state)
- Psychological mindedness

VII. Executive Control
(moderation of emotions, motivations, interests)
- All or none approach (lack moderation)
- Abnormal intensity of interests

Restricted/Repetitive Behaviors (RRBs)

VIII. Cognitive/Behavioral Rigidity
- Routines (routine-bound)
- Rituals (verbal & motor)
- Resistance to change (transitional difficulties)
- Rigid pattern of thinking (rule-bound/highly opinionated)
- Lack spontaneity/tolerance for unstructured time
- Social inflexibility

IX. Repetitive patterns
- Speech (delayed echolalia, scripting, idiosyncratic phrases)
- Motor mannerisms (flapping, clapping, rocking, swaying)
- Interests (non-progressive, non-social)

X. Atypical Salience
- Interests (odd/idiosyncratic)
- Social-emotional stimuli
- Atypical fears

XI. Sensory Dysregulation
- Atypical sensory perceptions/responses

ASSOCIATED Features

- Intellectual disability
- Novelty averse behaviors
- Poor motor co-ordination

DSM Criteria for Autism

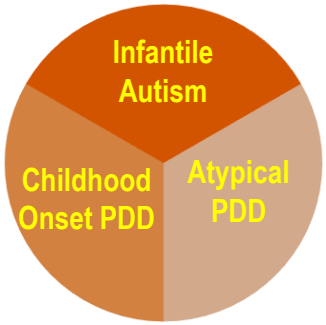
Schizophrenic reaction - Childhood Type

DSM-I
(1952)

Schizophrenia - Childhood Type

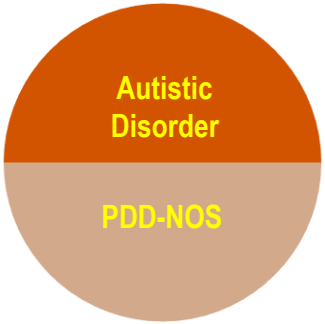
DSM-II
(1968)

Pervasive Developmental Disorders



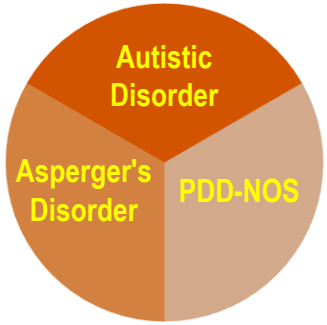
DSM-III
(1980)

Pervasive Developmental Disorders



DSM-III-R
(1987)

Pervasive Developmental Disorders



DSM-IV/R
(1994/2000)

Autism Spectrum Disorder

DSM-5
(2013)

DSM-5 Diagnostic Criteria for Autism

Autism Spectrum Disorder (299.00)

A Persistent deficits in social interaction and communication
as manifested by lifetime history of *all three* of the following:

I Deficits in social-emotional reciprocity
- Inability to initiate or respond to social interactions
- Inability to share affect, emotions, or interests
- Difficulty in initiating or in sustaining a conversation

II Deficits in nonverbal communicative behaviors used for social interaction
- Abnormal to total lack of understanding and use of eye contact, affect, body language, and gestures
- Poorly integrated verbal and nonverbal communication

III Deficits in developing, maintaining, and understanding relationships
- Difficulty in adjusting behavior to social contexts
- Difficulty in making friends
- Lack of interest in peers

B Restricted, repetitive, and stereotyped patterns of behavior, interests, or activities
as manifested by lifetime history of *at least two* of the following:

I Stereotyped or repetitive speech, motor movements, or use of objects
- Motor stereotypies or mannerisms (lining up toys)
- Echolalia, stereotyped, or idiosyncratic speech

II Excessive adherence to sameness, routines, or ritualized patterns of verbal or nonverbal behavior
- Transitional difficulties
- Greeting rituals
- Rigid patterns of thinking

III Highly restricted, fixated interests that are abnormal in intensity or focus
- Preoccupation with excessively circumscribed or perseverative interests

IV Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment
- Sensory integration issues
- Apparent indifference to pain/temperature
- Excessive smelling, touching, or visual fascination with lights or movements

C Symptoms must be present in the early developmental period
Symptoms may not fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life.

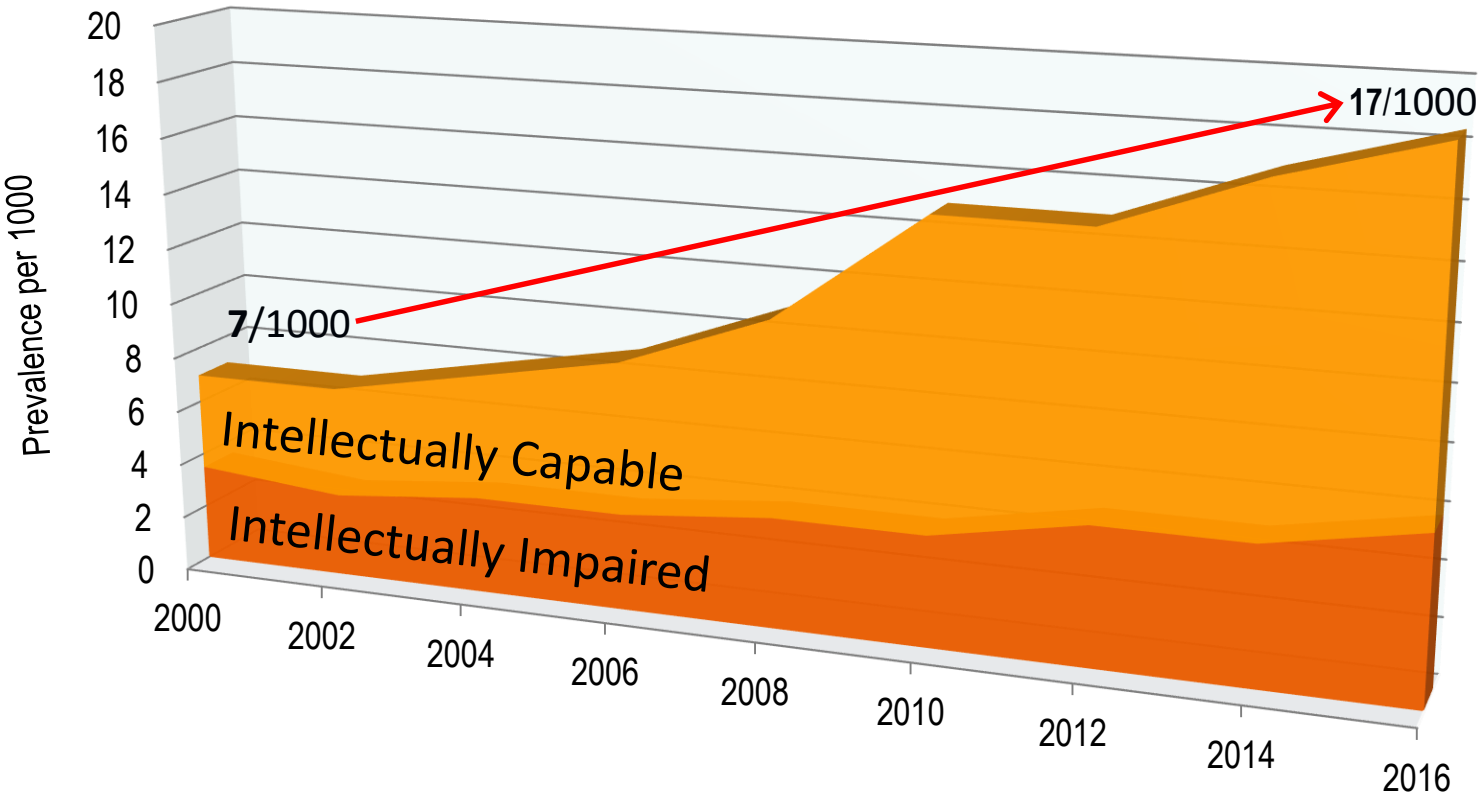
D Symptoms cause clinically significant impairment in functioning

E These disturbances are not better explained by intellectual disability
To make comorbid diagnoses of ASD & ID, social communication should be below that expected for general developmental level.

***Specify* if:**

With or without accompanying intellectual impairment
With or without accompanying language impairment
Associated with a known medical or genetic condition or environmental factor
Associated with another neurodevelopmental, mental, or behavioral disorder
With catatonia

Prevalence of ASD



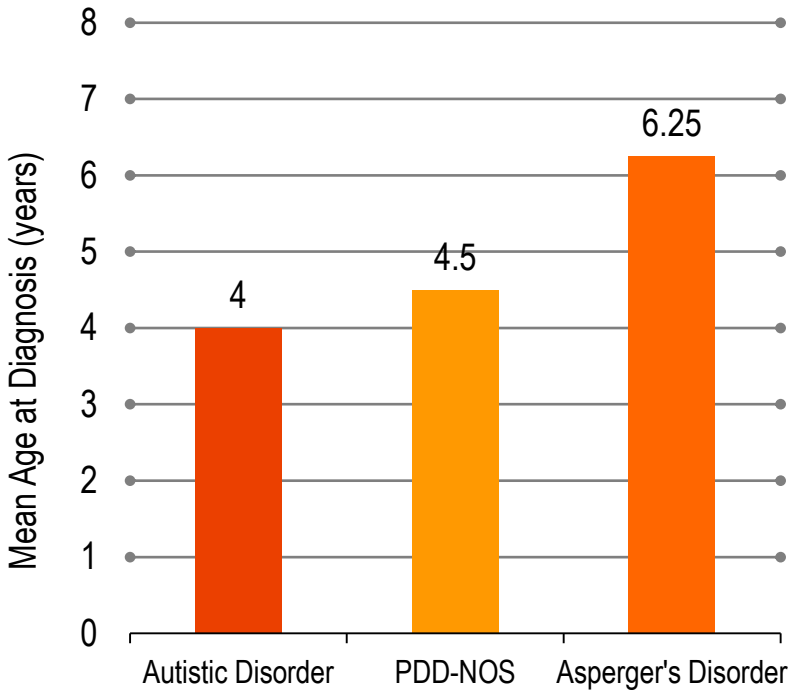
Substantial rise in the prevalence of AUTISM in intellectually capable populations

Centers for Disease Control & Prevention (CDC) Surveys: ADDM Network Surveys
2000, 2002, 2004, 2006, 2008, 2010, 2012, 2014, 2016

Age at Diagnosis of ASD

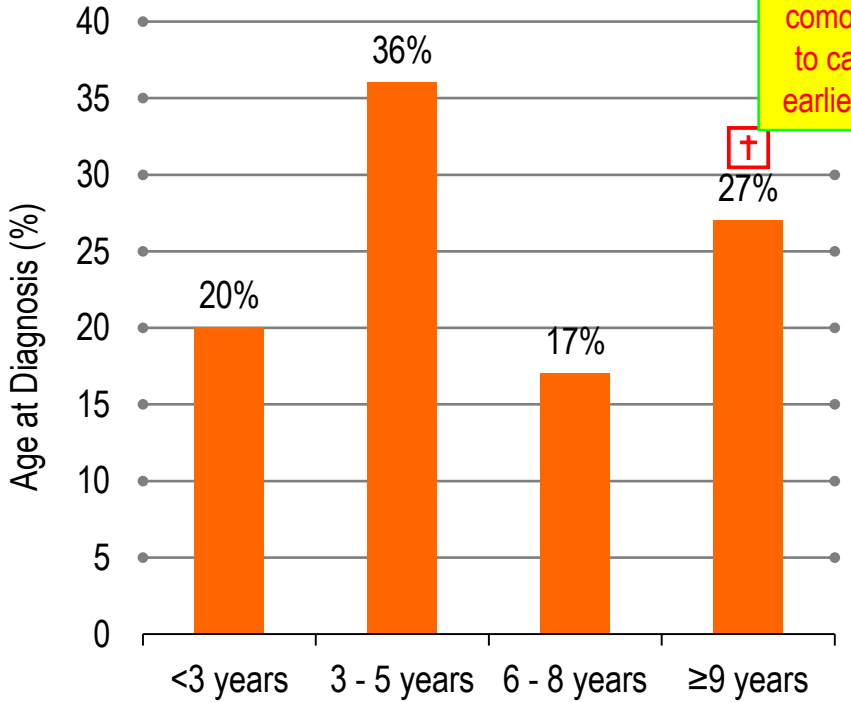
By DSM-IV Diagnosis

(In Children 8 years Old)



By Age Range

†80% more likely to have psychiatric comorbidity compared to cases identified at earlier ages (<9 years)



Delayed Diagnosis of Broader Phenotype of Autism

Autism & Developmental Disabilities Monitoring Network Surveillance Year 2002, 2008, 2010;
Levy et al., 2010

SOCIAL RESPONSIVENESS SCALE©

SOCIAL RESPONSIVENESS SCALE AUTOSCORE™ FORM | John N. Constantino, M.D. | **PARENT REPORT**

DIRECTIONS
For each question, circle the number that best describes the child's behavior *over the past 6 months.*

Child's Name: _____ Chronological Age: _____

Gender (required): ☐ Female ☐ Male Ethnicity: _____

Respondent's Name: _____ Administration Date: _____

Relationship to Child: ☐ Mother ☐ Father ☐ Other _____

PLEASE PRESS HARD WHEN MARKING YOUR RESPONSES.

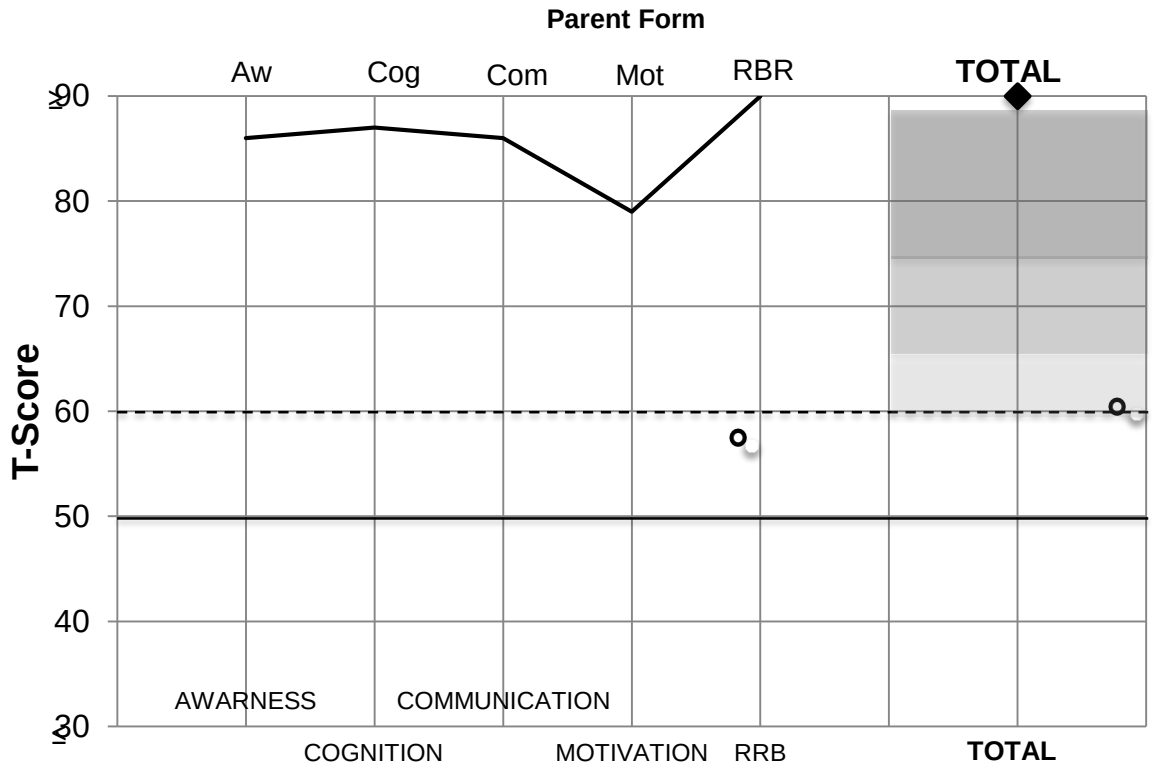
1 = NOT TRUE 2 = SOMETIMES TRUE 3 = OFTEN TRUE 4 = ALMOST ALWAYS TRUE

1. Seems much more fidgety in social situations than when alone.	1	2	3	4
2. Expressions on his or her face don't match what he or she is saying.	1	2	3	4
3. Seems self-confident when interacting with others.	1	2	3	4
4. When under stress, he or she shows rigid or inflexible patterns of behavior that seem odd.	1	2	3	4
5. Doesn't recognize when others are trying to take advantage of him or her.	1	2	3	4
6. Would rather be alone than with others.	1	2	3	4
7. Is aware of what others are thinking or feeling.	1	2	3	4
8. Behaves in ways that seem strange or bizarre.	1	2	3	4
9. Clings to adults, seems too dependent on them.	1	2	3	4
10. Takes things too literally and doesn't get the real meaning of a conversation.	1	2	3	4
11. Has good self-confidence.	1	2	3	4
12. Is able to communicate his or her feelings to others.	1	2	3	4
13. Is awkward in turn-taking interactions with peers (e.g., doesn't seem to understand the give-and-take of conversations).	1	2	3	4
14. Is not well coordinated.	1	2	3	4
15. Is able to understand the meaning of other people's tone of voice and facial expressions.	1	2	3	4
16. Avoids eye contact or has unusual eye contact.	1	2	3	4
17. Recognizes when something is unfair.	1	2	3	4
18. Has difficulty making friends, even when trying his or her best.	1	2	3	4
19. Gets frustrated trying to get ideas across in conversations.	1	2	3	4
20. Shows unusual sensory interests (e.g., mouthing or spinning objects) or strange ways of playing with toys.	1	2	3	4
21. Is able to imitate others' actions.	1	2	3	4
22. Plays appropriately with children his or her age.	1	2	3	4
23. Does not join group activities unless told to do so.	1	2	3	4
24. Has more difficulty than other children with changes in his or her routine.	1	2	3	4
25. Doesn't seem to mind being out of step with or "not on the same wavelength" as others.	1	2	3	4
26. Offers comfort to others when they are sad.	1	2	3	4
27. Avoids starting social interactions with peers or adults.	1	2	3	4
28. Thinks or talks about the same thing over and over.	1	2	3	4
29. Is regarded by other children as odd or weird.	1	2	3	4
30. Becomes upset in a situation with lots of things going on.	1	2	3	4
31. Can't get his or her mind off something once he or she starts thinking about it.	1	2	3	4
32. Has good personal hygiene.	1	2	3	4

Continue on back page...

33. Is socially awkward, even when he or she is trying to be polite.	1	2	3	4
34. Avoids people who want to be emotionally close to him or her.	1	2	3	4
35. Has trouble keeping up with the flow of a normal conversation.	1	2	3	4
36. Has difficulty relating to adults.	1	2	3	4
37. Has difficulty relating to peers.	1	2	3	4
38. Responds appropriately to mood changes in others (e.g., when a friend's or playmate's mood changes from happy to sad).	1	2	3	4
39. Has an unusually narrow range of interests.	1	2	3	4
40. Is imaginative, good at pretending (without losing touch with reality).	1	2	3	4
41. Wanders aimlessly from one activity to another.	1	2	3	4
42. Seems overly sensitive to sounds, textures, or smells.	1	2	3	4
43. Separates easily from caregivers.	1	2	3	4
44. Doesn't understand how events relate to one another (cause and effect) the way other children his or her age do.	1	2	3	4
45. Focuses his or her attention to where others are looking or listening.	1	2	3	4
46. Has overly serious facial expressions.	1	2	3	4
47. Is too silly or laughs inappropriately.	1	2	3	4
48. Has a sense of humor, understands jokes.	1	2	3	4
49. Does extremely well at a few tasks, but does not do as well at most other tasks.	1	2	3	4
50. Has repetitive, odd behaviors such as hand flapping or rocking.	1	2	3	4
51. Has difficulty answering questions directly and ends up talking around the subject.	1	2	3	4
52. Knows when he or she is talking too loud or making too much noise.	1	2	3	4
53. Talks to people with an unusual tone of voice (e.g., talks like a robot or like he or she is giving a lecture).	1	2	3	4
54. Seems to react to people as if they are objects.	1	2	3	4
55. Knows when he or she is too close to someone or is invading someone's space.	1	2	3	4
56. Walks in between two people who are talking.	1	2	3	4
57. Gets teased a lot.	1	2	3	4
58. Concentrates too much on parts of things rather than seeing the whole picture. For example, if asked to describe what happened in a story, he or she may talk only about the kind of clothes the characters were wearing.	1	2	3	4
59. Is overly suspicious.	1	2	3	4
60. Is emotionally distant, doesn't show his or her feelings.	1	2	3	4
61. Is inflexible, has a hard time changing his or her mind.	1	2	3	4
62. Gives unusual or illogical reasons for doing things.	1	2	3	4
63. Touches others in an unusual way (e.g., he or she may touch someone just to make contact and then walk away without saying anything).	1	2	3	4
64. Is too tense in social settings.	1	2	3	4
65. Stares or gazes off into space.	1	2	3	4

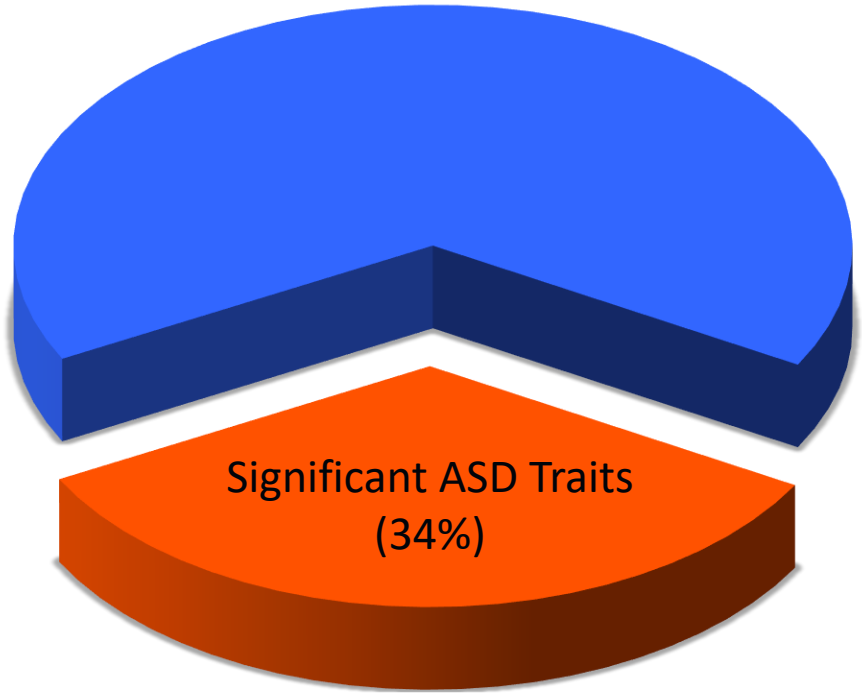
SRS-2: Results



Raw Score	17	26	44	20	40	147
T-score	86	87	86	79	90	90

Autistic Traits in Psychiatrically Referred Youth

Attending Psychiatry Outpatient Clinic



Total N: 303

Age Range: 4-18 years

IQ: Predominantly Intact

SRS Screen^{+} for ASD: 34% (N=110)
(Raw score: ♂>70; ♀>65)

One-third of youth screened positive for ASD

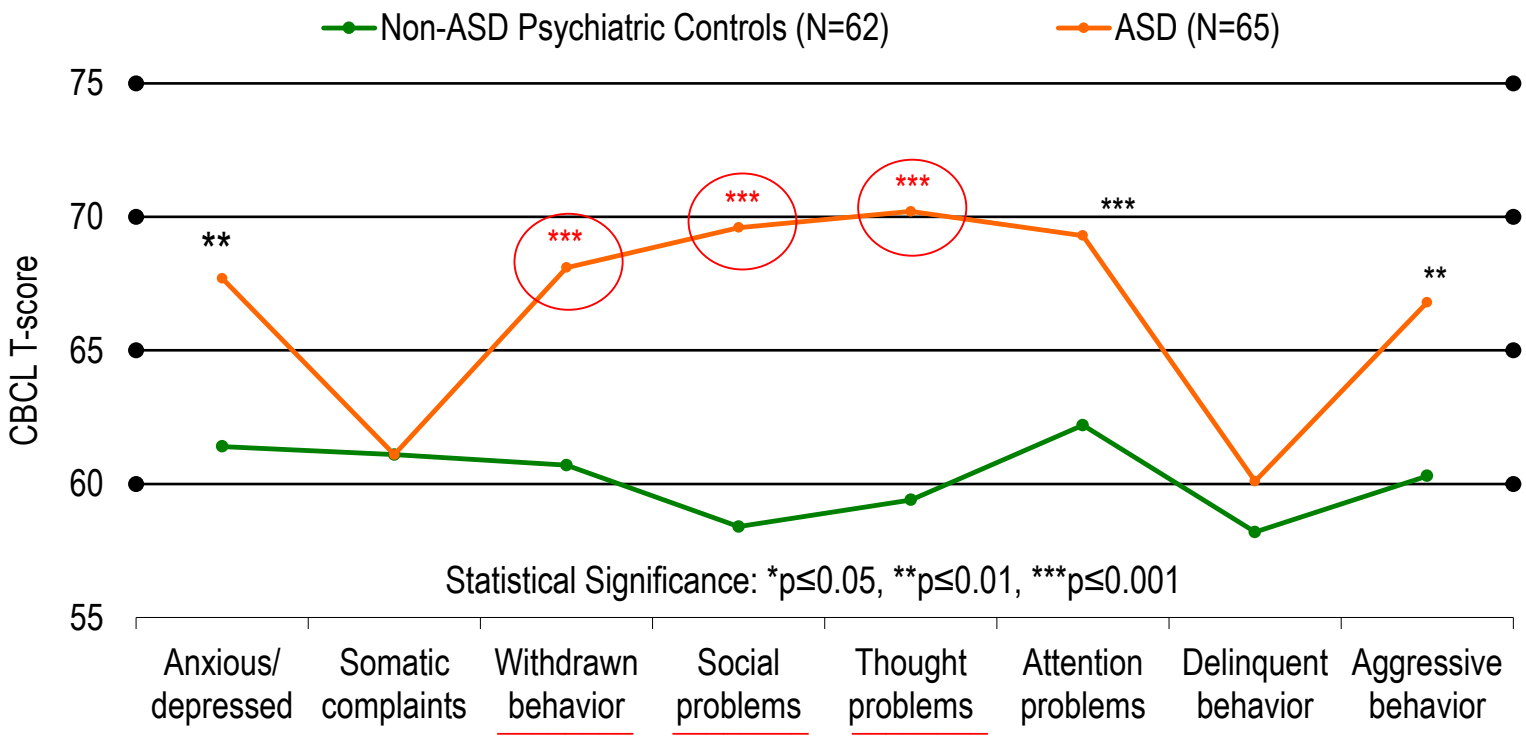
Recognition of Autism in Psychiatrically Referred Youth

Axis I:	Anxiety Disorder NOS
	R/O Specific Phobia (of doctors and the medical setting)
	R/O Obsessive-Compulsive Disorder
	R/O Generalized Anxiety Disorder
	R/O ADHD
	R/O Bipolar Disorder
	R/O Pervasive Developmental Disorder NOS
Axis II:	Deferred
Axis III:	Cystic Fibrosis
Axis IV:	Primary support group; educational
Axis V:	50

ASD Under-recognized in Psychiatric Populations

CBCL – ASD Profile

Level of Dysfunction on Child Behavior Checklist in Psychiatrically Referred Youth



ASD Youth
Age range: 6-18 years

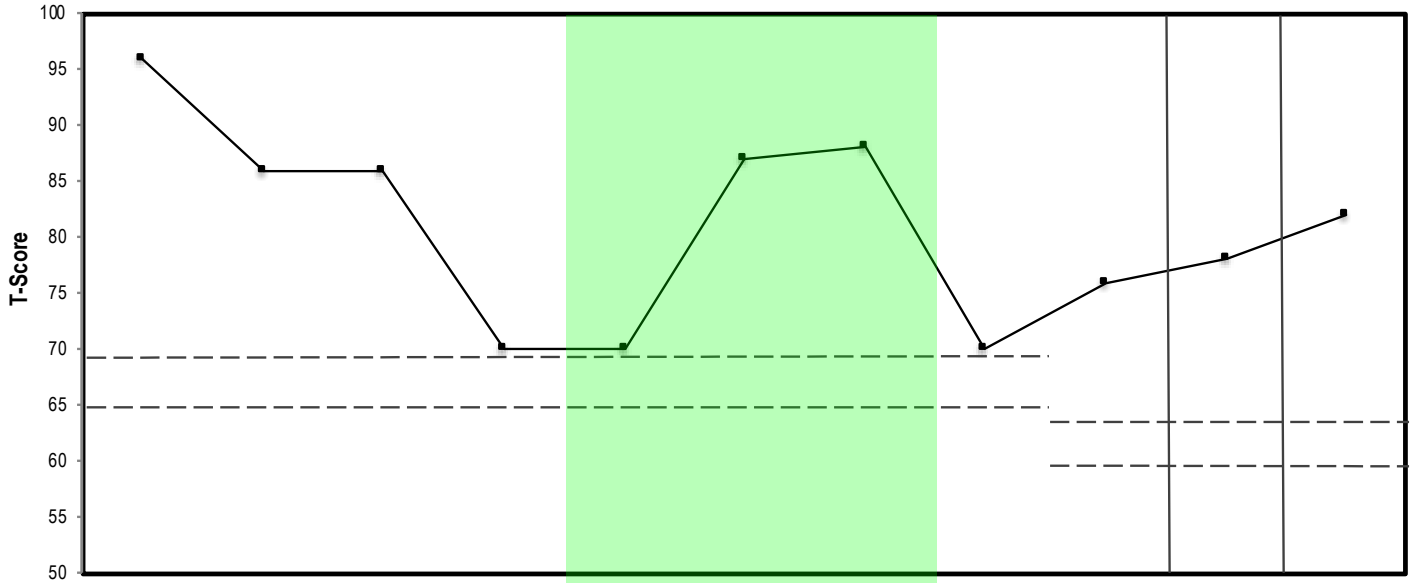
IQ
Mean IQ: 99 ±14
IQ>70: 100%

ASD Subtypes
Autistic Disorder = 52%
Asperger's Disorder = 25%
PDD-NOS = 23%

CBCL-ASD Subscales (Withdrawn behavior, Social, & Thought Problems) aggregate cutoff T-score of ≥195 is suggestive of ASD

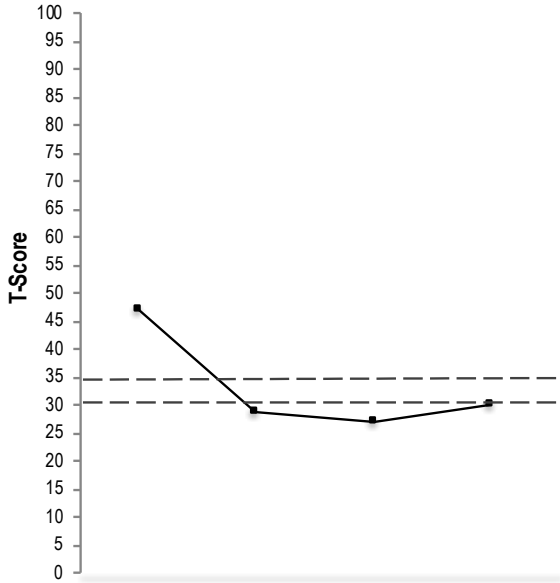
CBCL: Results

Syndrome Scale, Externalizing, Internalizing & Total Problems Scores



	Attention Problems	Anxious/ Depressed	Aggressive Behavior	Somatic Complaints	Withdrawn/ Depressed	Thought Problems	Social Problems	Rule-Breaking Behavior	External	Internal	Total Problem
R-Score	19	19	27	7	6	20	17	7	34	32	133
T-Score	96	86	86	70	70	87	88	70	76	78	82
Threshold	*Borderline: 65-69 Clinical: ≥ 70*								*Borderline: 60-63 Clinical: ≥ 63*		

Competence Scale Scores



	Activities	Social	School	Total
R-Score	11	3.5	2	16.5
T-Score	47	29	27	30
Threshold	*Borderline: 31-35 Clinical: ≥ 36*			

MGH Autism Spectrum Disorder DSM-5 Diagnostic Symptom Checklist©

Name_____ Age_____years Gender: Male / Female

Assessment Guidelines: 1. Incorporate information from clinical observation and all available sources
2. Offer suggested prompts to elicit features of concern

Diagnostic Features

A Deficits in Social Communication and Interaction (as manifested by lifetime history of **all three** of the following)

Absent (No=1) Unsure (Subthr=2) Present (Full=3)

1. **Deficits in social-emotional reciprocity** – ± +
   - Does not share or respond appropriately to others' feelings
   - Seems unaware of others' feelings or is unable to express his/her feelings
   - Does not offer or seek comfort or seeks comfort in an odd way
   - Socially inappropriate responses
   - Inability to spontaneously share their own or others' enjoyment, achievements, or interests
   - Inability to engage in a cooperative (give and take) activity with others
   - Difficulty with initiating or in sustaining a conversation
   - Limited ability to engage in back and forth reciprocal conversation (especially on other person's topic of interest)
   - Does not talk to be friendly or social (lacks ability to make small talk)
2. **Deficits in nonverbal communicative behaviors used for social interaction** – ± +
   - Poor eye contact (impaired joint attention: does not use or respond to eye gaze or pointing to share attention)
   - Does not show or understand gestures (facial expression [social smile] or body language)
   - Does not use or understand tone of voice (e.g., sarcasm)
3. **Deficits in developing, maintaining, and understanding relationships** – ± +
   - Limited interest in peers
   - Difficulty making or maintaining friendship with peers
   - Rigid or atypical social interests and behaviors
   - Difficulty adopting behavior to different social contexts (contextually inappropriate behavior)
   - Does/did not engage in pretend play
   - Inability to imitate others' personal behaviors
   - Too literal: doesn't get the implied meaning in conversations (puns, jokes)

B Restricted, Repetitive Patterns of Behavior, Interests, or Activities (as manifested by lifetime history of **at least two** of the following)

1. **Stereotyped or repetitive motor movements, speech, or use of objects** (Stimming) – ± +

   Stereotyped and repetitive motor mannerisms
   - Flapping, clapping, finger flicking
   - Whole body movement (e.g., rocking, swaying)
   - Repetitive use of objects (e.g., lining-up, flipping, or spinning objects)

   Stereotyped, repetitive, or idiosyncratic speech
   - Often uses odd phrases or words (including neologisms)
   - Repeats words, sentences, or scripts (scripting) in the exact same way (including delayed echolalia)
   - Refers to self in third person (pronominal reversal)
   - Has unusual tone (monotonous, high-pitched, robotic) or style of speech (pedantic, professorial)
2. **Inflexible adherence to routines or ritualized patterns of verbal or nonverbal behavior** – ± +
   - Strong need for sameness from day-to-day (routine bound)
   - Gets unusually upset if routine or environment changes (transitional difficulties)
   - Verbal or nonverbal rituals (fixed sequence of utterances or nonverbal behaviors)
   - Has a hard time changing his/her mind (cognitive rigidity: rule bound/highly opinionated)
3. **Highly restricted, fixated interests that are abnormal in intensity or focus** – ± +
   - Very narrow range of interests (circumscribed, non-progressive, non-social)
   - Unusual intensity of interest(s) that are odd or peculiar in quality (e.g., preoccupation with names of train stations, war battles)
   - Extreme preoccupation with usual interest(s)
   - Engages in certain activities repetitively (e.g., watching the same movie over and over again)
4. **Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment** – ± +
   - Unusual attachment to object(s)
   - Does not use objects for their intended purpose (e.g., plays with the wheels of a toy car)
   - Tendency to hyper-focus on minor details without ability to grasp the broader concept

   Sensory Dysregulation (touch, sound, smell, taste, visual, pain, kinetic, temperature, pressure, proprioceptive)
   - Hypersensitive to neutral stimuli (Sensory Integration Issues)
   - Hyposensitive to certain stimuli
   - Extreme response to certain neutral or pleasant stimuli
   - Unusual sensory interests (unusual fascination to certain neutral or unpleasant stimuli) (e.g., excessive smelling or touching objects, visual fascination with light or movement)

Absent (No=1) Unsure (Subthr=2) Present (Full=3)

C Symptoms Present in the Early Developmental Period – ± +

D Clinically Significant Impairment in Social, Occupational, or other Important Areas of Functioning

1. Severity of deficits in social communication and interaction (Domain-A) <1 1 2 3
   Level 1: Without support, some significant deficits in social communication
   Level 2: Marked deficits with limited initiations and reduced/atypical responses
   Level 3: Minimal social communication
2. Severity of restricted, repetitive, and stereotyped patterns of behaviors (Domain-B) <1 1 2 3
   Level 1: Significant interference in at least one context
   Level 2: Obvious to the casual observer and occurs across contexts
   Level 3: Marked interference in daily life

Diagnosis (ASD if Domain A and B criteria are met; SCD if only Domain A criteria are met) – SCD ASD

Specifiers

1. Associated with Intellectual Disability (ID; IQ < 70) – ± +
2. Associated with a structural language impairment: Lack language Single words Phrase – ± +
3. Associated with known factors: Medical condition Genetic condition Environmental factors – ± +

   _____
4. Associated with another neurodevelopmental, mental, or behavioral disorder – ± +

   _____
5. Associated with Catatonia – ± +

Associated Features

1. Fine or gross motor coordination impairment – ± +
2. Novelty averse behaviors (limited diet) – ± +
3. Self-injurious behaviors – ± +
4. History of developmental regression (loss of acquired social or language skills) – ± +

Clinician_____ Date_____

Concurrent Validity

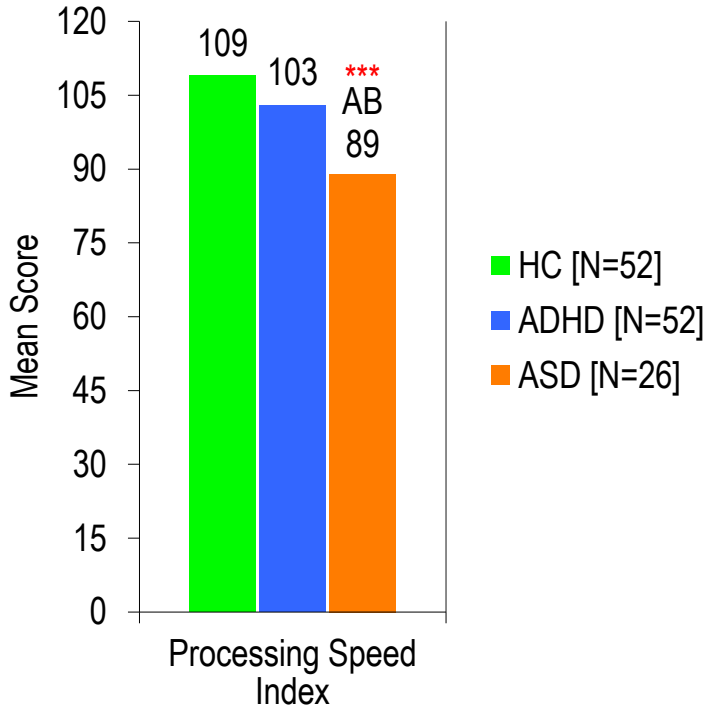
Diagnostic Correspondence with:

- SRS: 95%
- ADOS: 86%

Neuropsychological Correlates of HF-ASD

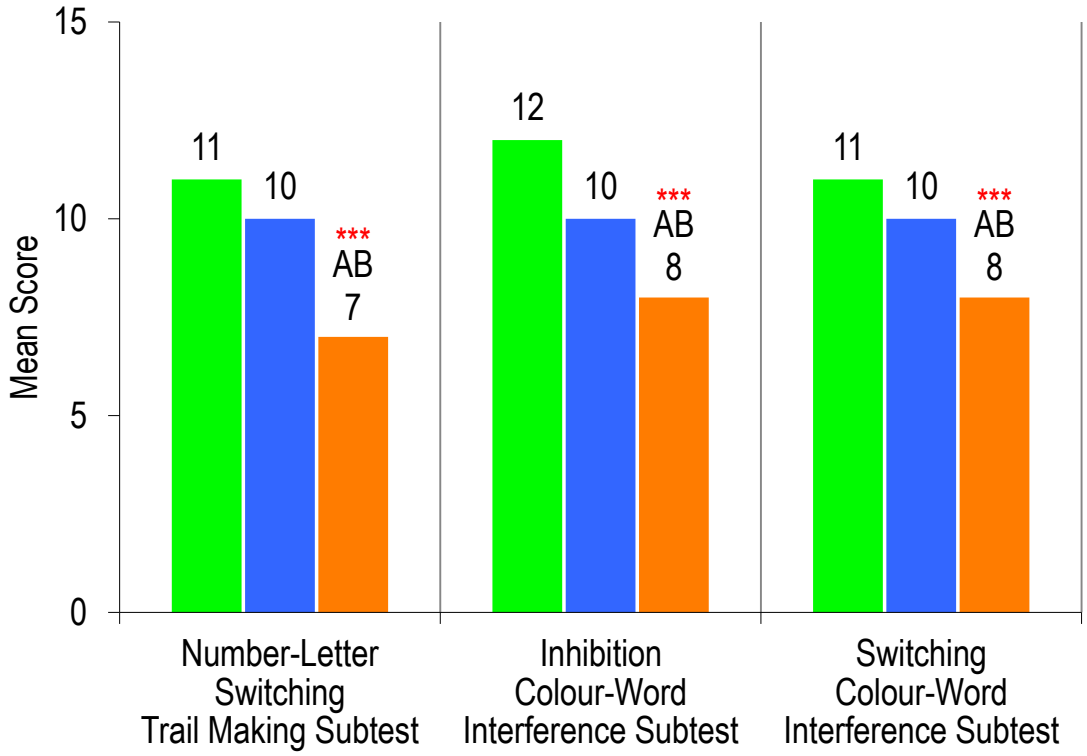
Processing Speed

Wechsler Adult Intelligence Scale (WAIS-III)



Cognitive Flexibility

Delis Kaplan Executive Function System (D-KEFS)

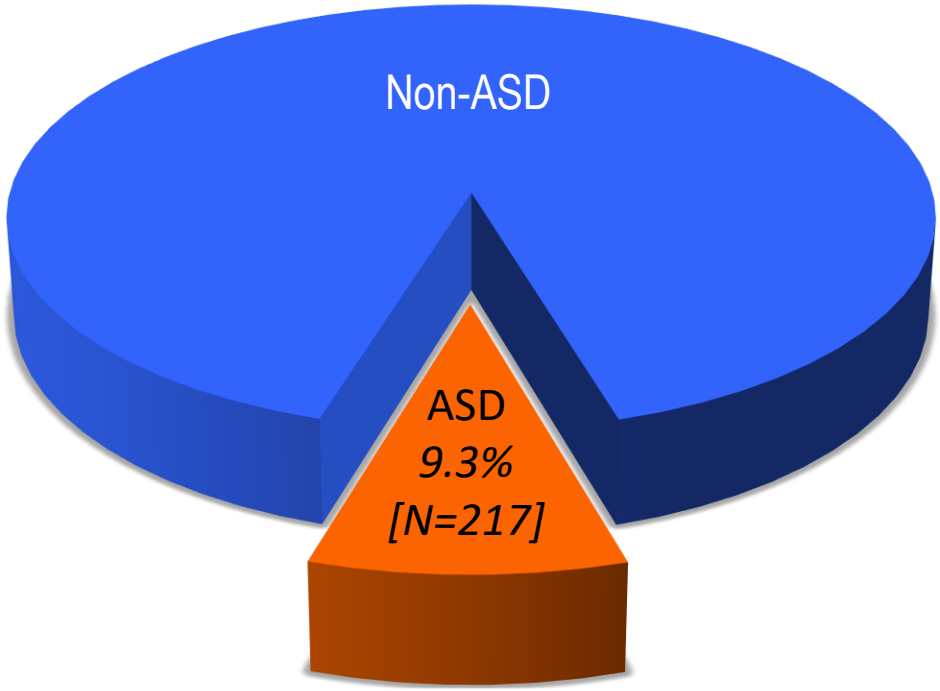


HC=Healthy Controls; A=Versus HC, B=Versus ADHD; Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Autism Diagnostic Interview-Revised (ADI-R)
Autism Diagnostic Observation Schedule (ADOS)

- Semi-structured assessment
- Requires trained raters
  (training is expensive, time consuming, and not readily available)
- Assessment is expensive, time-consuming, with limited accessibility
- ? sensitivity to detect ASD in high-functioning and in adult populations
- ? validity in populations with emotional and behavioral difficulties

Prevalence of ASD in Psychiatrically Referred Youth



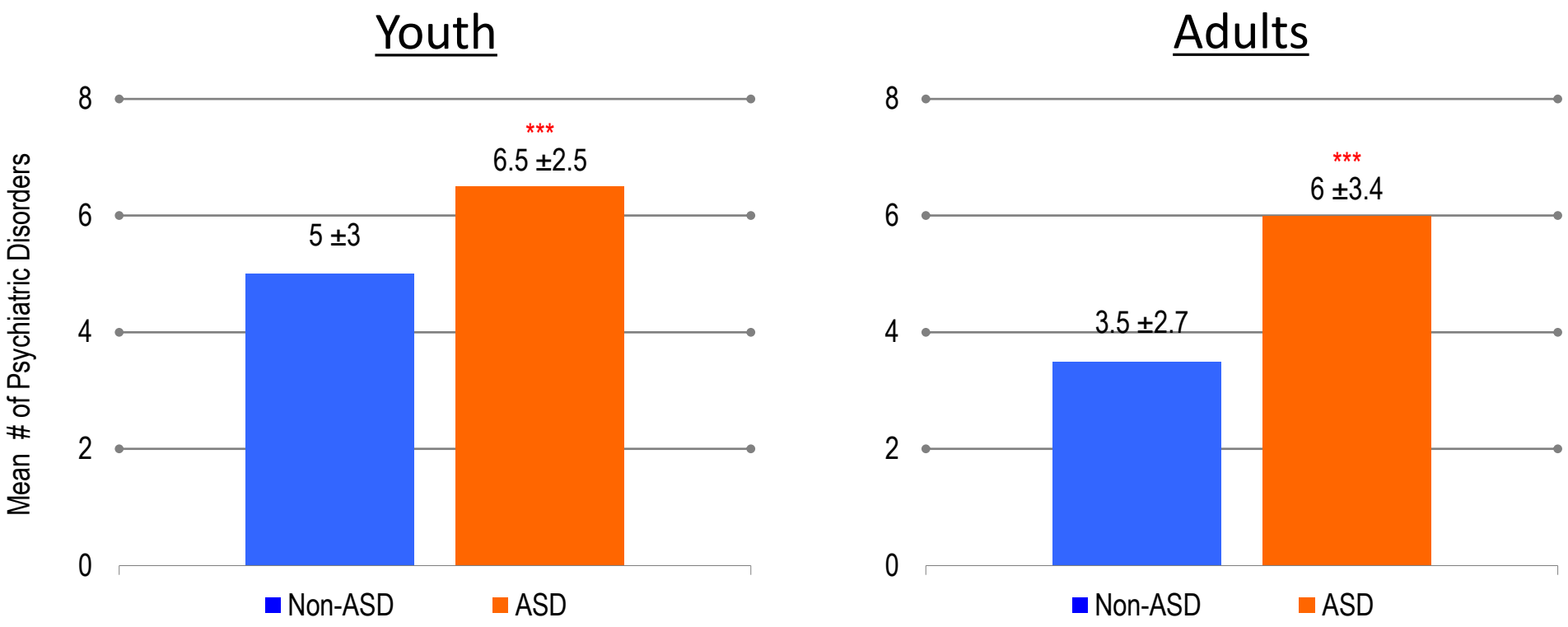
Total N:	2323
Total Duration:	15 years (1991-2006)
Male:	87%
Age *(yrs)*:	9.7 ±3.6 (3-17)
Intellectual Ability & Language Skills:	Clinically not impaired in majority of the referred youth

Autism Prevalence >5-fold Higher than General Population

Joshi et al., 2010

Burden of Psychopathology in ASD

Lifetime Psychiatric Comorbidities

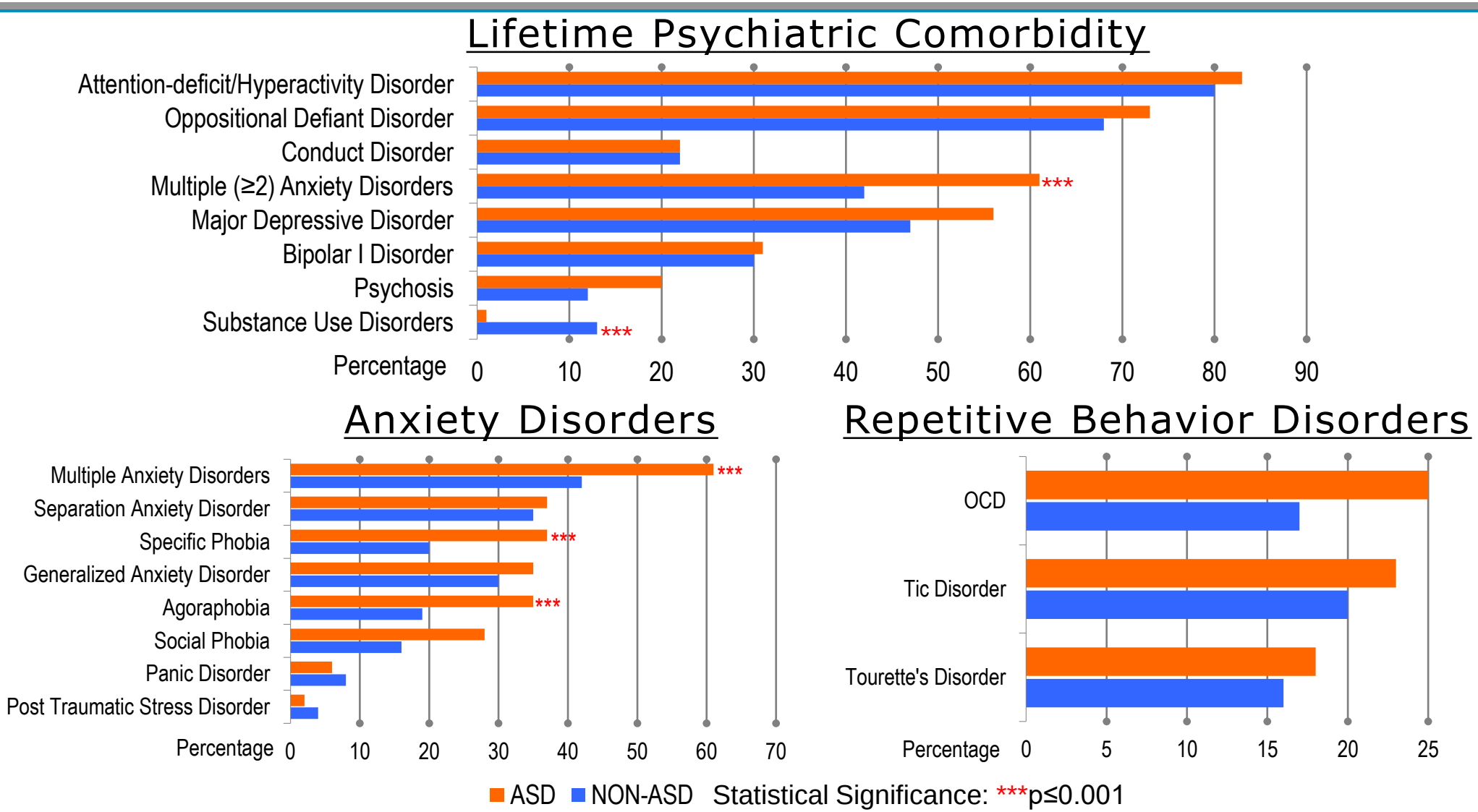


Statistical Significance: ***p≤0.001

Greater Burden of Psychopathology

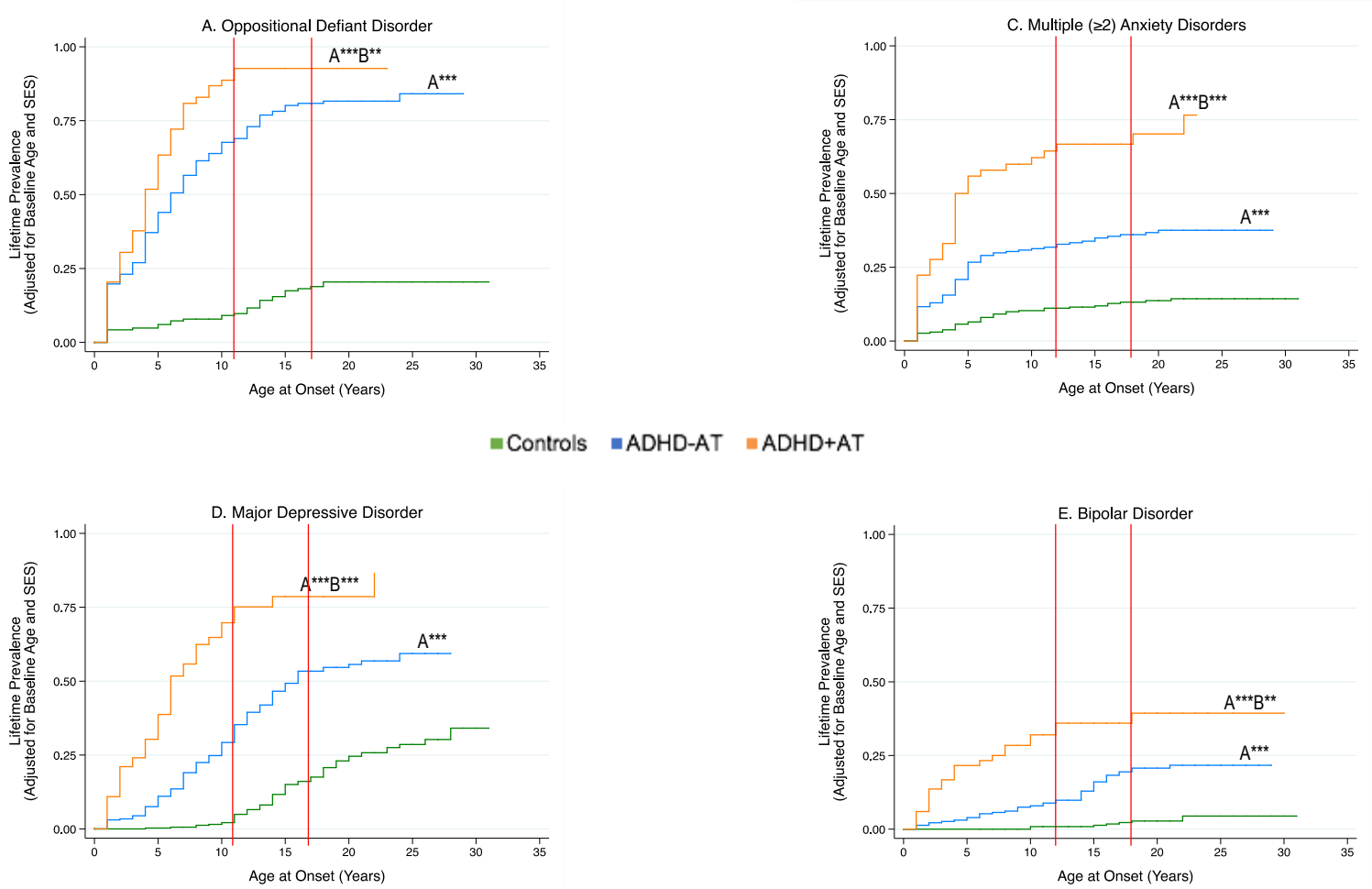
Joshi et al., 2010, 2013

Psychopathology Associated with ASD



Joshi et al., 2010

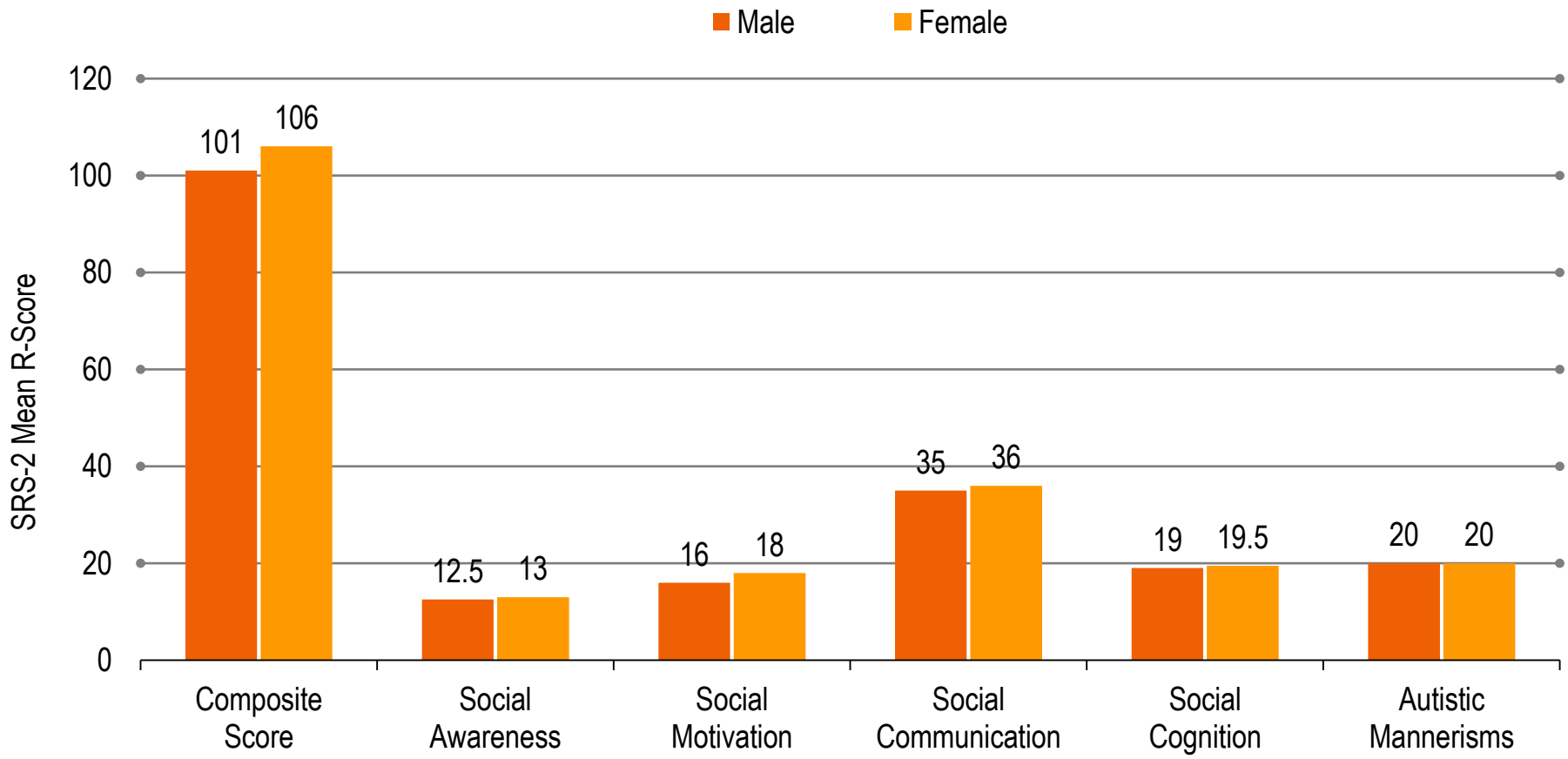
Risk for Psychiatric Disorders in ASD



*p<0.05, **p<0.005, ***p<0.001; [A] Versus Controls. [B] Versus ADHD-AT

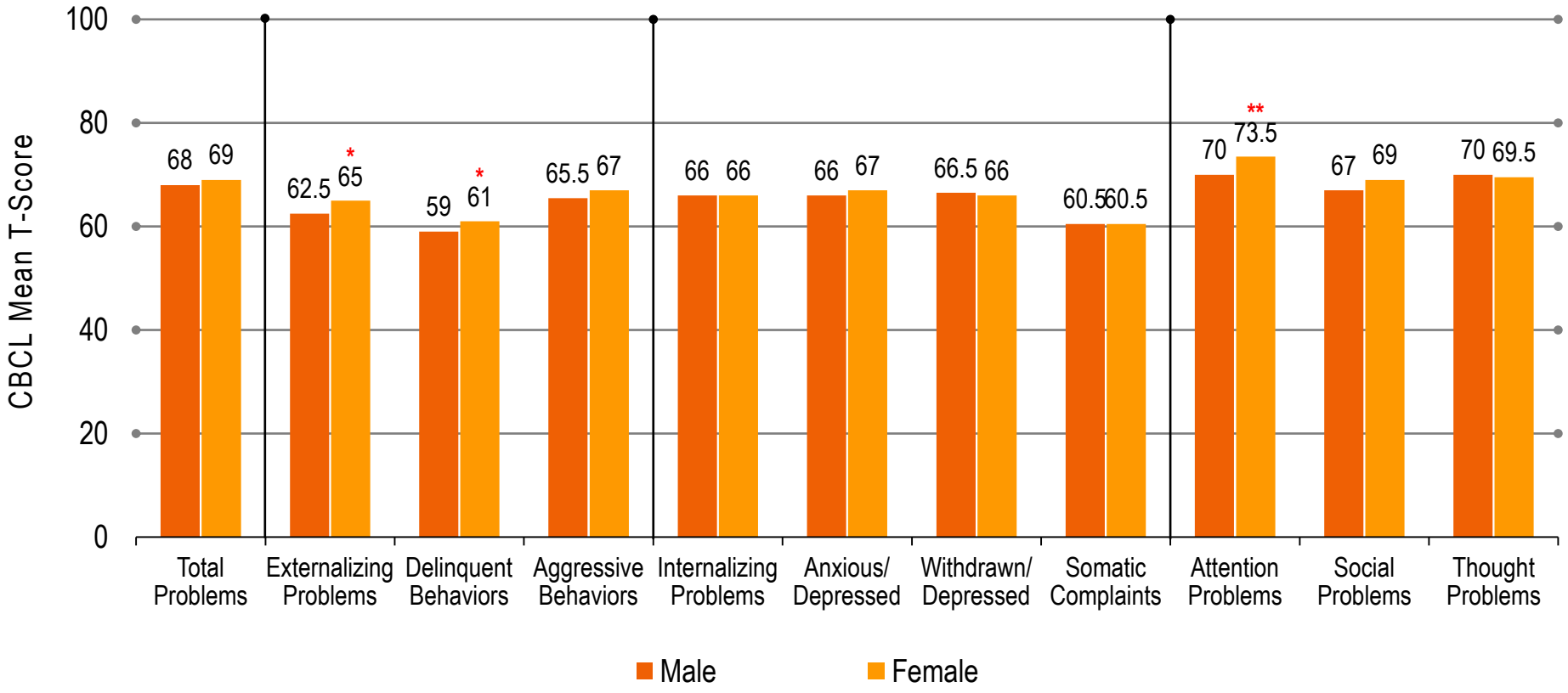
Gender Profile of Autistic Traits

Social Responsiveness Scale (SRS-2)



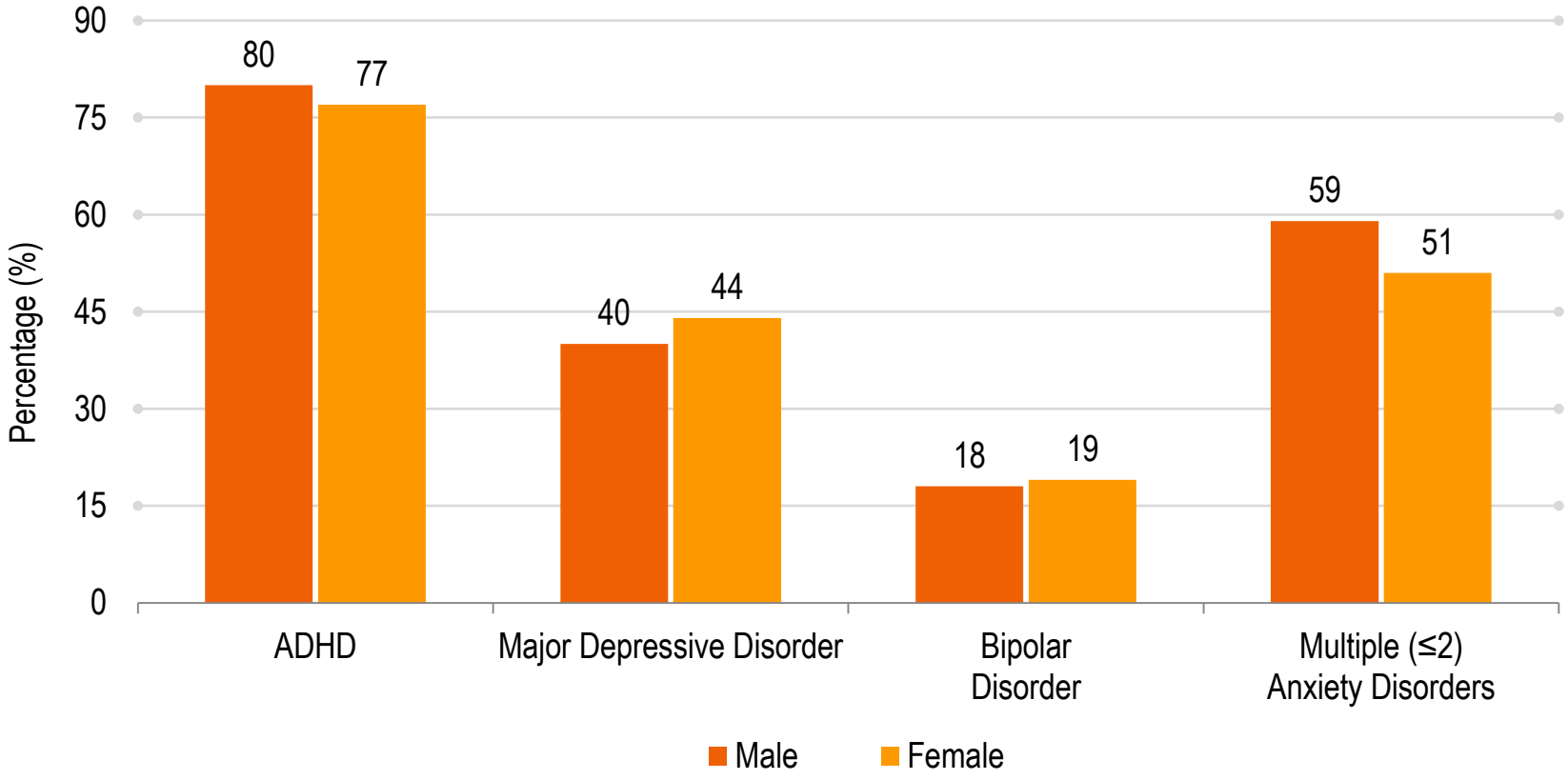
Gender Profile of Psychopathology

Child Behavior Checklist (CBCL)



Statistical Significance: *p≤0.05, **p≤0.01

Gender Profile of Psychiatric Disorders



Emotional Dysregulation in ASD

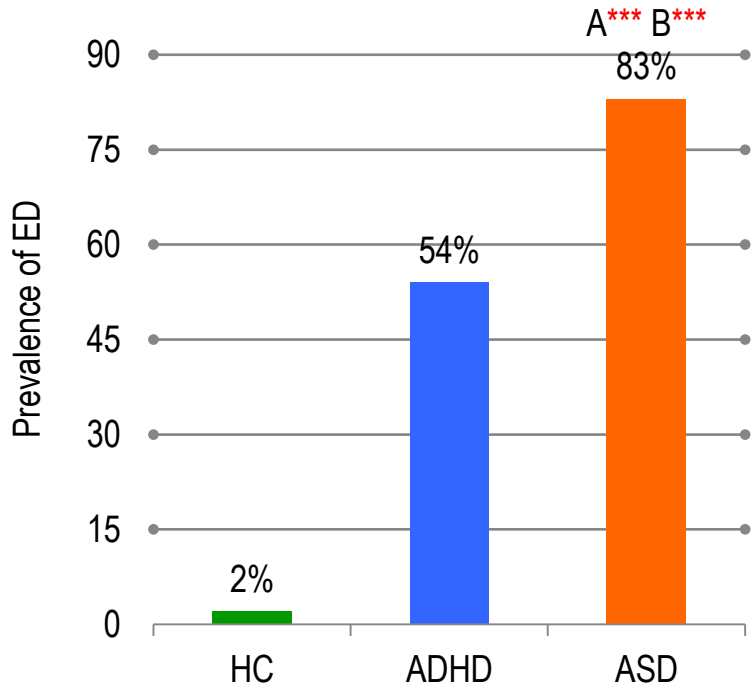
Child Behavior Checklist -Emotional Dysregulation Profile (CBCL-ED)

CBCL-ED profile based on the composite T-scores of CBCL subscales:

- Attention
- Aggression
- Anxious/Depressed

CBCL-AAA Subscales Composite T-Score	Level of Emotional Dysregulation (ED)
<180	Low/No ED
≥180	Presence of ED

Prevalence of ED in Psychiatrically Referred ASD Youth

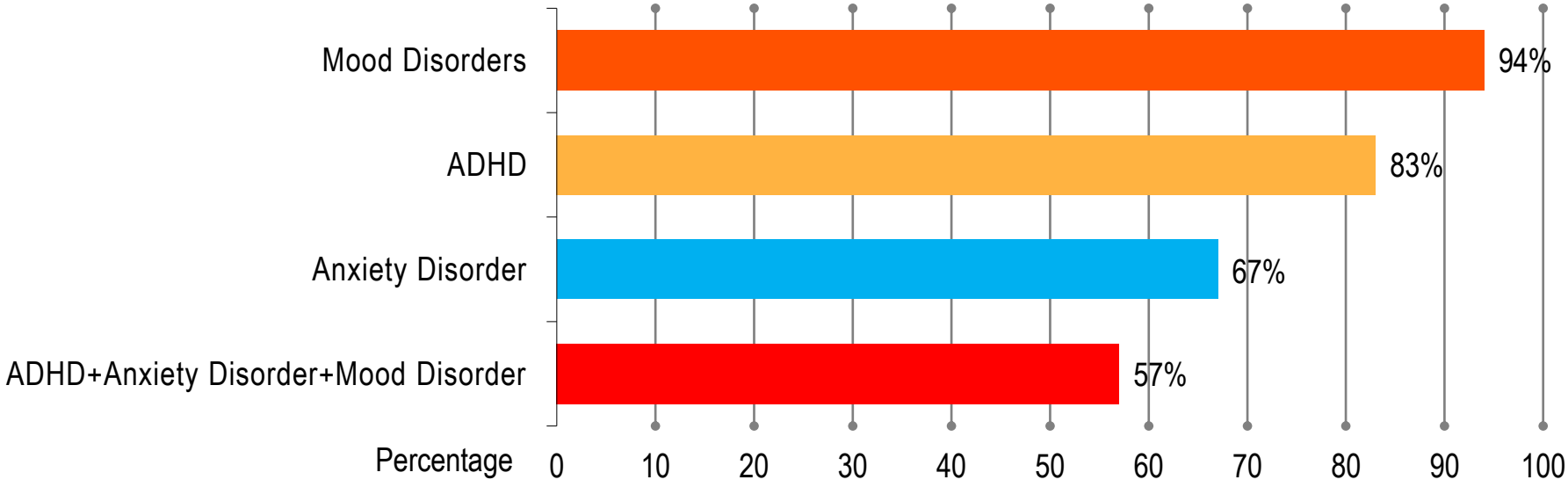


Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001
A = vs. HC; B = vs. ADHD

Prescribing Patterns: Clinical Profile

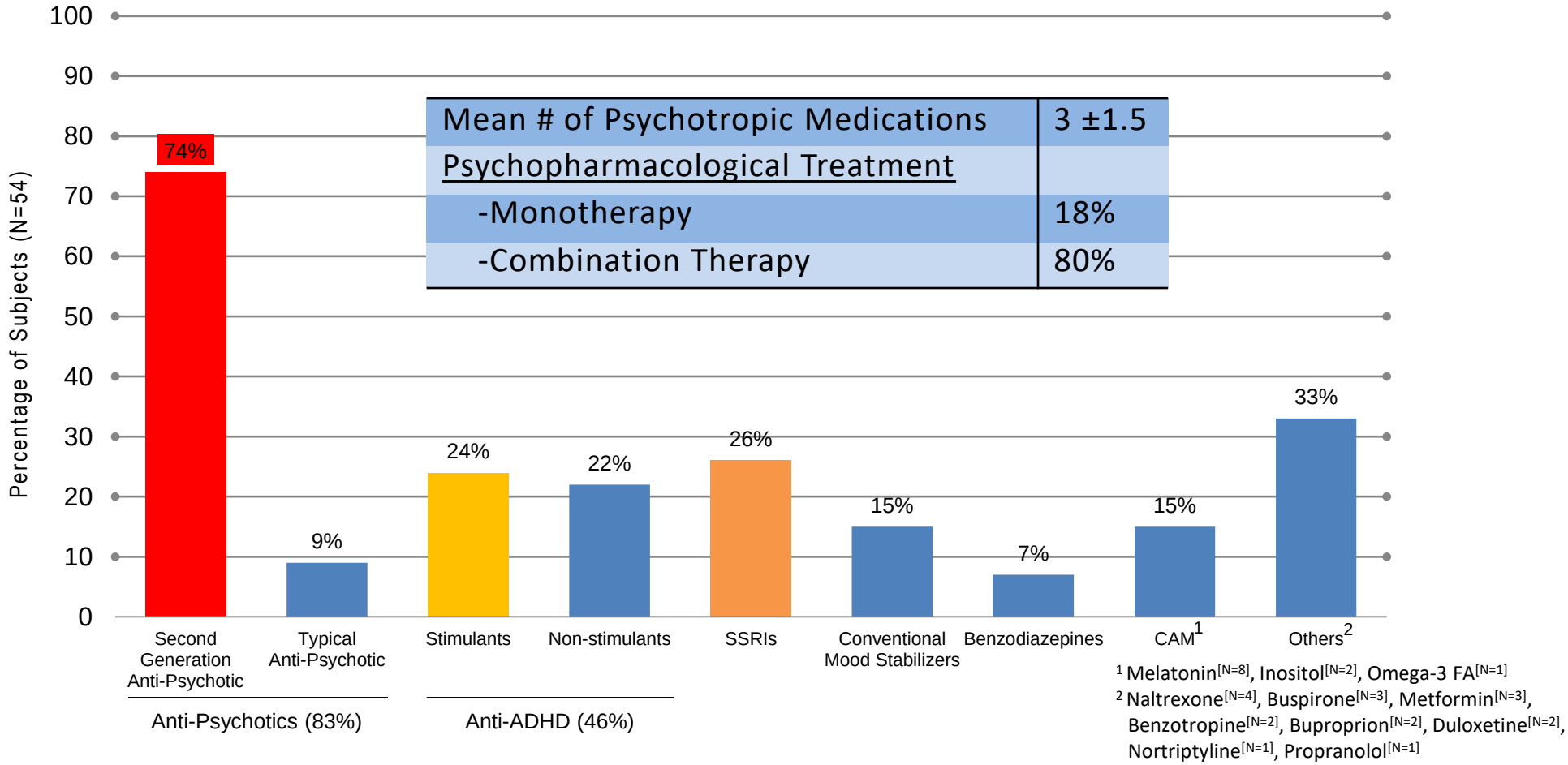
Total N	54
Age *(yrs)*	13 ±3 (7-19)
Male	76%
Autistic Disorder	61%
Asperger's Disorder/PDD-NOS	39%

Associated Psychopathology



Shekunov, Wozniak, Joshi et al., 2017

Prescribing Patterns: Treatment Profile



93% of ASD youth were prescribed NON-FDA approved medication

Shekunov, Wozniak, Joshi et al., 2017

U.S. Food and Drug Administration (FDA)

Risperidone* and **Aripiprazole****

FDA approved for the treatment of

irritability including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods

in children and adolescents with

autistic disorder

(ages: 6-17* / 5-16** years)

Agents for Treatment of Irritability/Aggression in Youth with Autistic Disorder

Risperidone & Aripiprazole

- Typically expected short- & long- term treatment response
- Rapid (< 1 week) and robust anti-irritability/aggression response
- Additionally effective in managing hyperactivity & repetitive behaviors
- Short-term treatment associated with weight gain as expected (risperidone > Aripiprazole)

Lurasidone: Efficacy NOT superior to placebo

RUPP Autism Network, 2002; Owen et al., 2009

Risperidone + Parent Training*

(*ABA based therapy for ASD & noncompliance)

24-week RCT in Youth with ASD

ASD + Sign. Irritability: N=124 [RISP+PT=75]

[ABC-Irritability score ≥18 + CGI-S ≥4]

Male: 85%

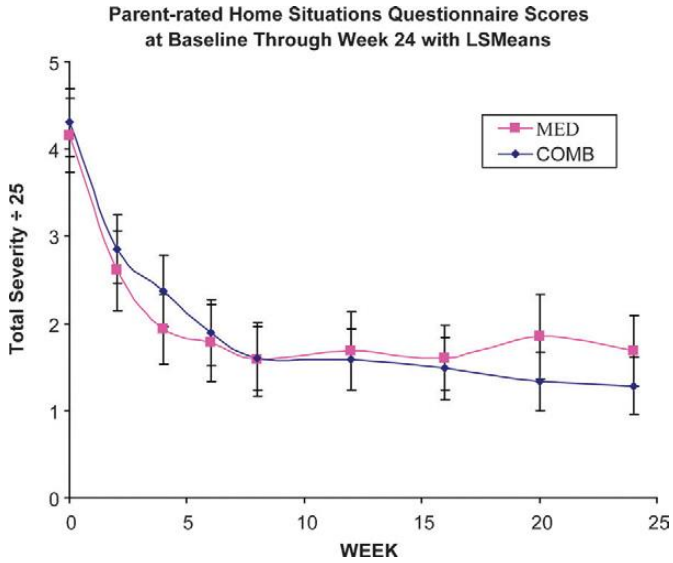
Mean Age [Range]: 7.5 [4–13] years

IQ>70 : 66%

Efficacy

PT+RISP superior to RISP

- Mean Dose [mg/day]:
  PT+RISP[2mg/day] < RISP[2.25mg/day] [p=0.04]
- Noncompliance Improvement (% ⇓⇓ HSQ):
  PT+RISP[71%] > RISP[60%] [p=0.006; ES=0.34]
- Behavioral Improvement (⇓⇓ ABC-subscales):
  - ABC-Irritability[p=0.01; ES=0.48]
  - ABC-Hyperactivity[p=0.04; ES=0.55]
  - ABC-Stereotypy[p=0.04; ES=0.23]



Tolerability

Common AEs

Rhinitis	80%
Inc. appetite	75%
Weight gain	75%
Fatigue	75%
Sialorrhoea	42%
Enuresis	39%

Scahill et al., 2012

CNS Neurosciences & Therapeutics

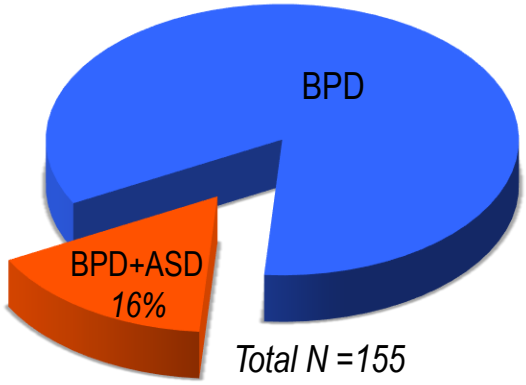
ORIGINAL ARTICLE

CNS Neuroscience & Therapeutics

Response to Second Generation Antipsychotics in Youth with Comorbid Bipolar Disorder and Autism Spectrum Disorder

Gagan Joshi,[1,2] Joseph Biederman,[1,2] Janet Wozniak,[1,2] Robert Doyle,[1,2] Paul Hammerness,[1,2] Maribel Galdo,[1] Nora Sullivan,[1] Courtney Williams,[1] Kristin Brethel,[1] K. Yvonne Woodworth[1] & Eric Mick[1,2]

1 Pediatric Psychopharmacology Research Department, Massachusetts General Hospital, MA, USA
2 Harvard Medical School, Boston, MA, USA

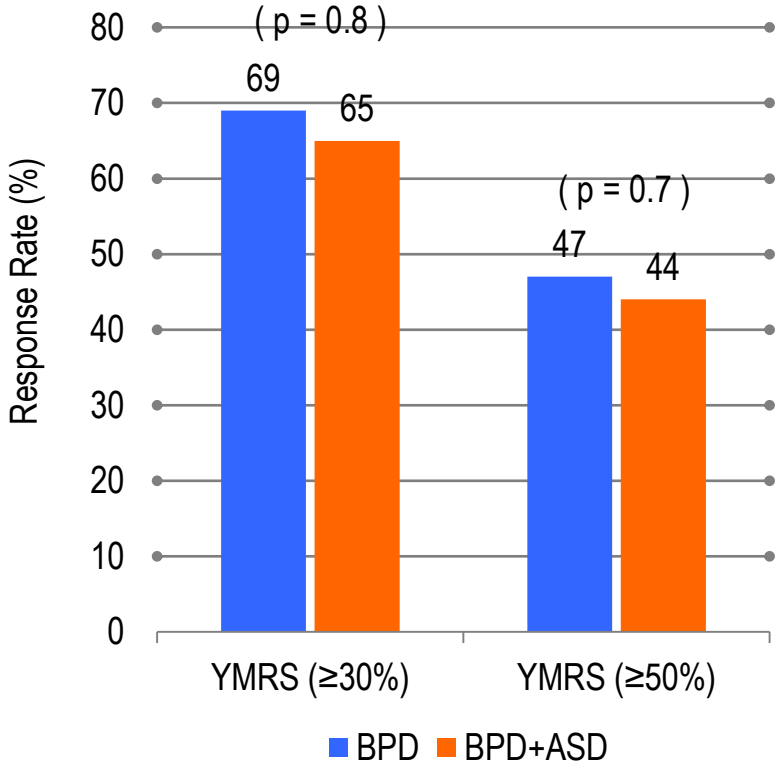


SUMMARY

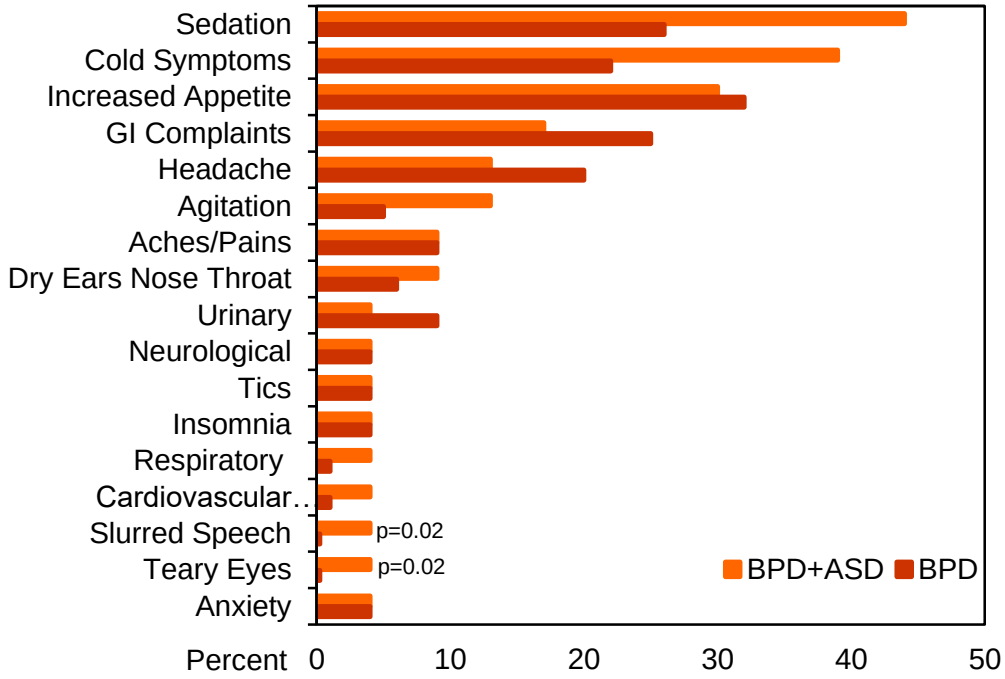
Objective: To assess the impact of comorbid autism spectrum disorders (ASD) on the response to second-generation antipsychotics (SGA) in pediatric bipolar disorder (BPD). **Methods:** Secondary analysis of identically designed 8-week open-label trials of SGA monotherapy (risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole) in youth with BPD. **Results:** Of the 151 BPD subjects 15% ($n = 23$) met criteria for comorbid ASD. There were no differences in the rate of antimanic response (YMRS change ≥30% or CGI-Improvement ≤2: 65% vs. 69%; $P = 0.7$) in the presence of comorbid ASD. **Conclusion:** No difference observed in the rate of antimanic response or tolerability to SGA monotherapy in the presence of ASD comorbidity.

SGN Monotherapy Response of ASD Youth with BPD

Rate of Anti-manic Response



Adverse Effects



Joshi et al., 2012

12-Week Controlled Pharmaco-Imaging Trial of Memantine Hydrochloride (Namenda) in Youth with High-Functioning Autism Spectrum Disorder

Clinical Trials Registration @ ClinicalTrials.gov
Registration Number: NCT01972074
URL: https://clinicaltrials.gov/ct2/show/NCT01972074?term=namenda+and+autism&rank=6

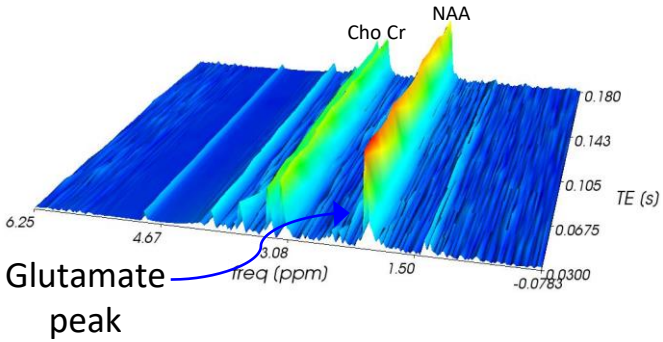
Study Approved by: Partners Human Research Committee Institutional Review Board

Study Funded by: National Institute of Mental Health Award #MH100450

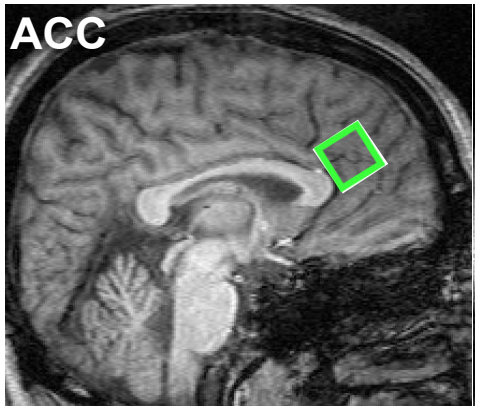
MRS Glutamate Activity in *Pregenual* Anterior Cingulate Cortex

Proton Spectroscopy in Youth with HF-ASD

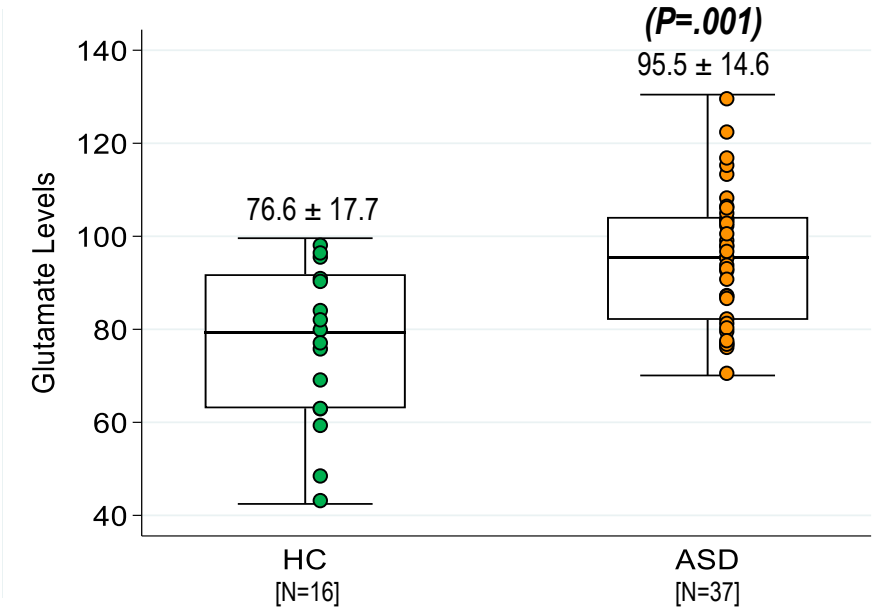
TE - Stepped (J-PRESS) Spectrum



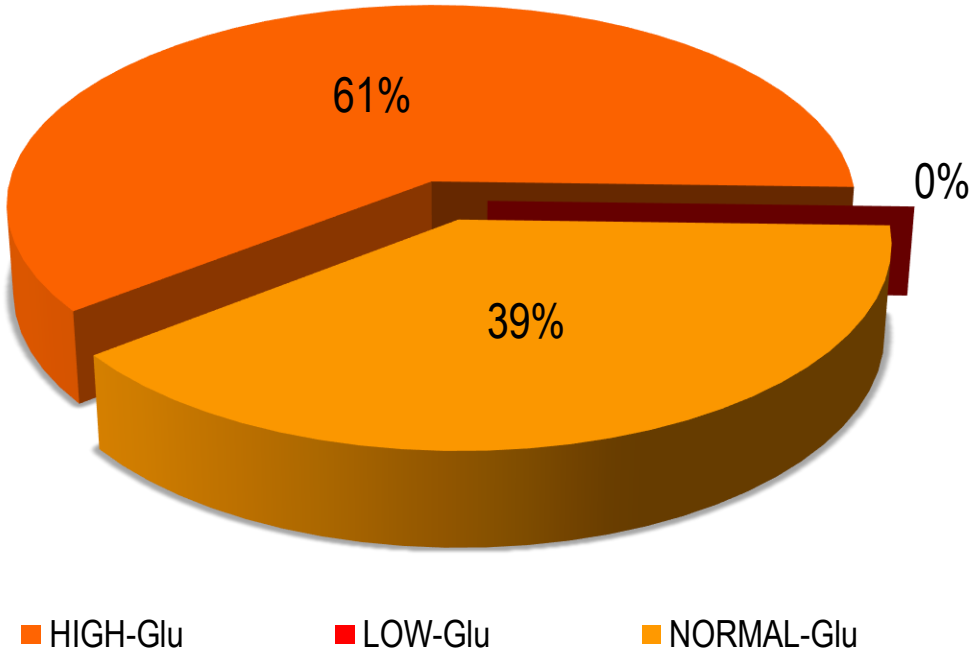
Voxel Placement at *Pregenual* ACC



Baseline Glutamate Levels in *PgACC*



Prevalence of HIGH-Glu Activity in HF-ASD



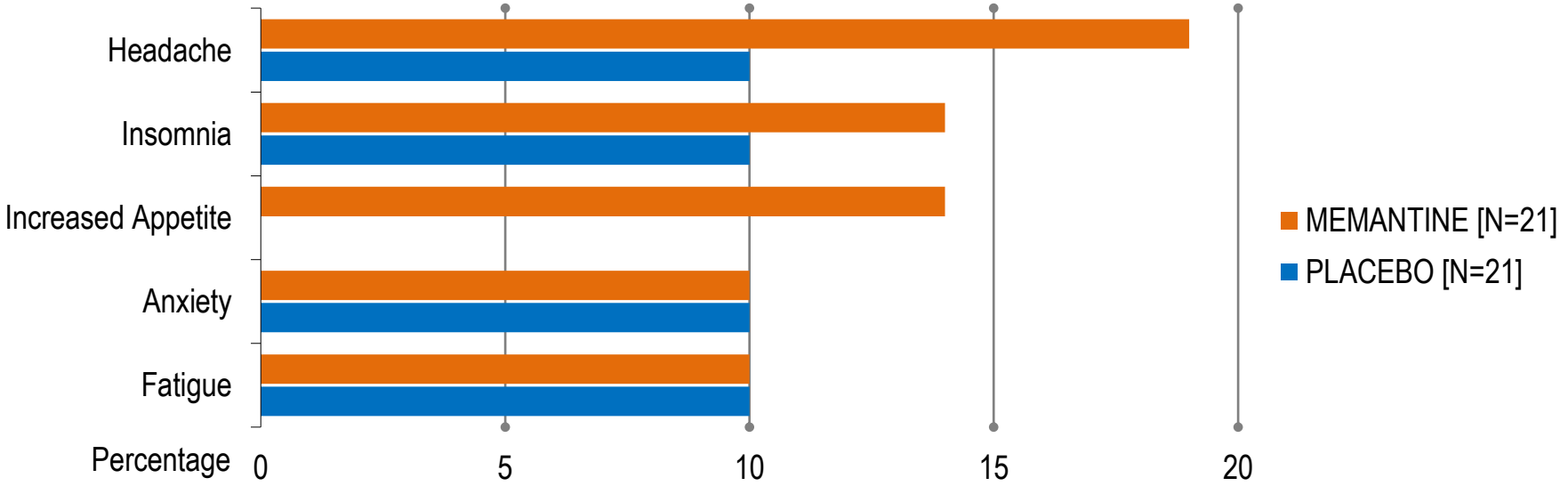
Anti-Glutamate Agent: Memantine Hydrochloride

- Memantine hydrochloride is a:
  - moderate-affinity
  - non-competitive
  - NMDA receptor antagonist
- Memantine is approved by the U.S. Food and Drug Administration for the treatment of moderate to severe Alzheimer's disease.
- Memantine improves or delays the decline in cognition (attention, language, visuo-spatial ability), as well as functioning in adults with dementia

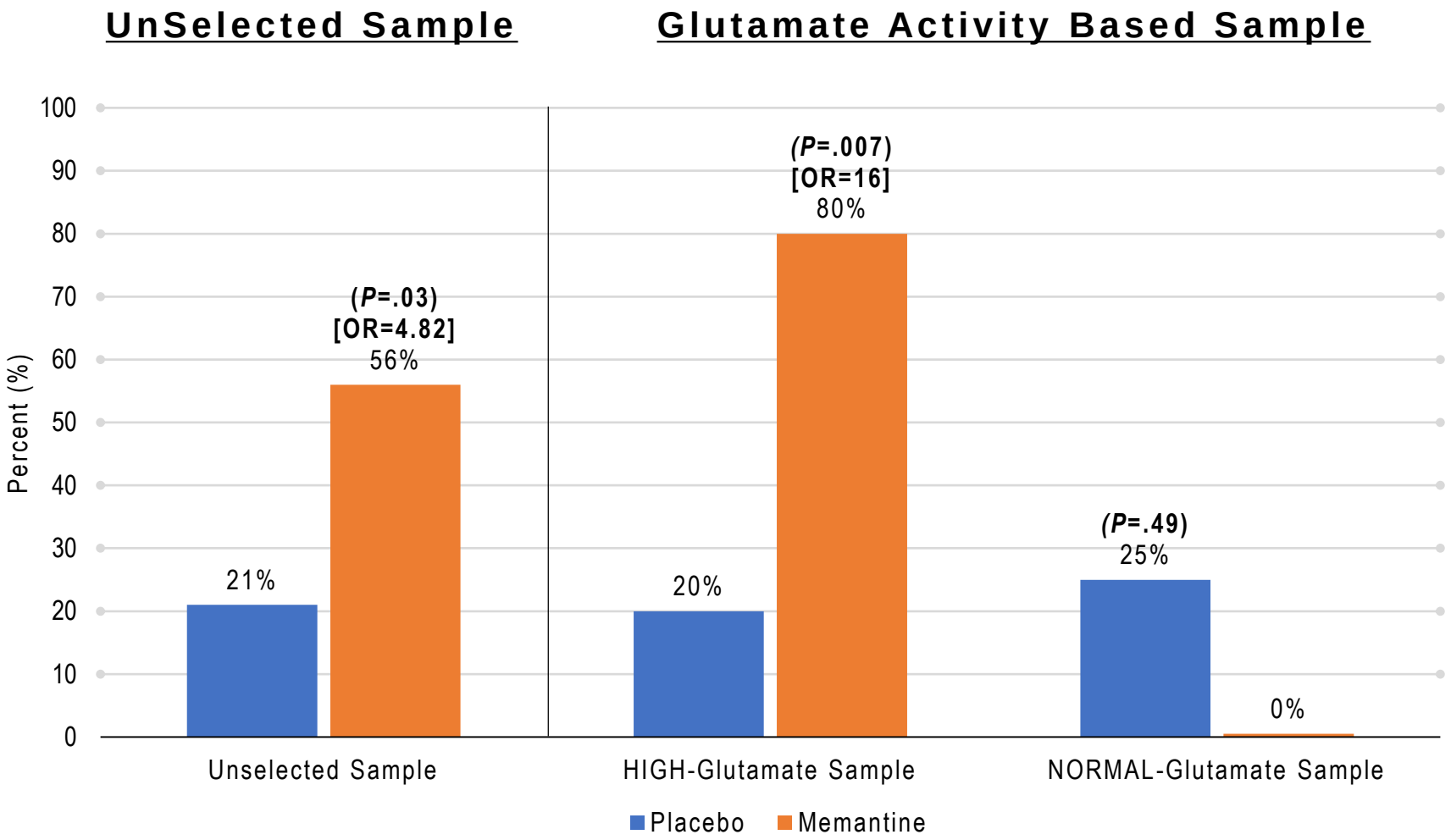
Tolerability

STUDY MEDICATION	MEM[N=21]	PBO[N=21]	p-value [t-statistic]
Dose[Range] *(mg/day)*	19.7 ±1 [15-20]	19 ±3 [10-20]	0.35 [t_{38}=0.94]
@ Maximum Study Dose (20mg/day)	18 (86)	19 (95)	

Adverse Events (Mild-Moderate Severity)



Memantine Response Based on Baseline *Pg*ACC Glu Activity



Treatment Responders (Response criteria: ≥25%⇊SRS+ASD-CGI-I≤2)

In Summary

- Higher than expected prevalence of ASD in psychiatrically referred youth
- Under-recognition of ASD in psychiatrically referred populations
- Youth with ASD suffer from greater burden of psychopathologies
- Symptom profile of psychopathologies in ASD is typical of the disorder
- Paucity of controlled trials for the treatment of psychopathology in ASD
- Subtype of ASD identified based on glutamate dysregulation in *Pg*ACC
- Promising role of glutamate modulators for the treatment of ASD
- Emerging role neuro-imaging guided pharmacotherapy in ASD

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Maribel Galdo, LCSW

Yvonne Woodworth, BA
Daniel Kaufman, BS
Nina Dallenbach, BS
Allison Green, BA
Philia Henderson, BA
Ellesse Cooper
Melissa De Leon

Phone: 617-726-7899
Email: MGH*ASD*program@Partners.org
Facebook: Facebook.com/BresslerMGH