Autism Spectrum Disorder

Assessment & Management

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DSM-5 Diagnostic Criteria for Autism

Autism Spectrum Disorder (F84.0/299.00)

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, & 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.

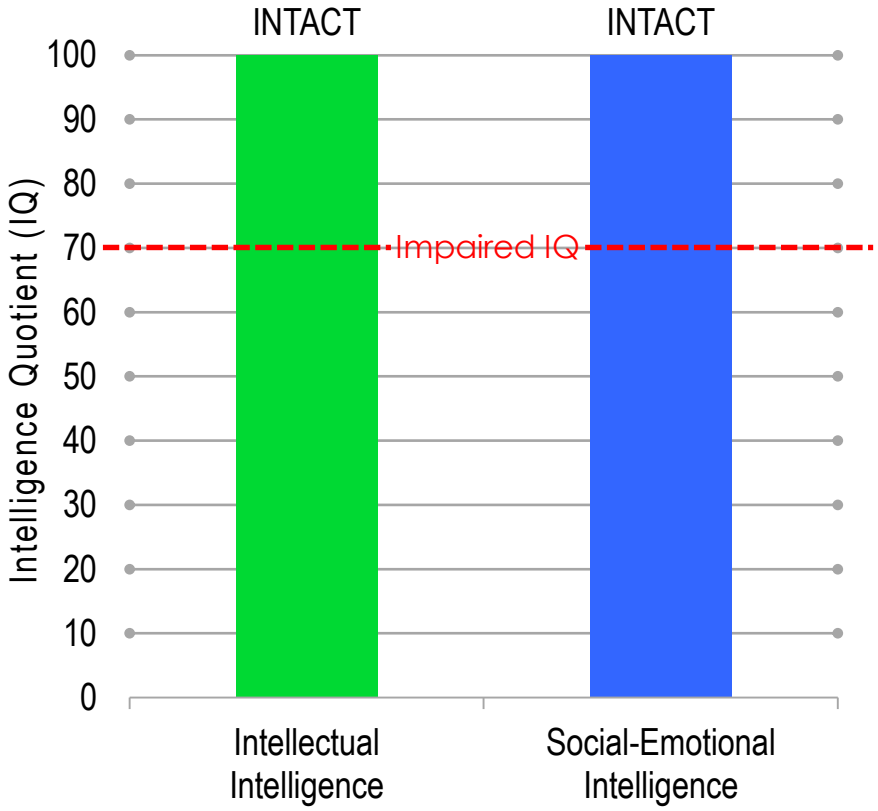
Note: Individuals with well-established DSM-IV ASD diagnosis should be given
the DSM-5 ASD diagnosis.

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

Domains of Intelligence

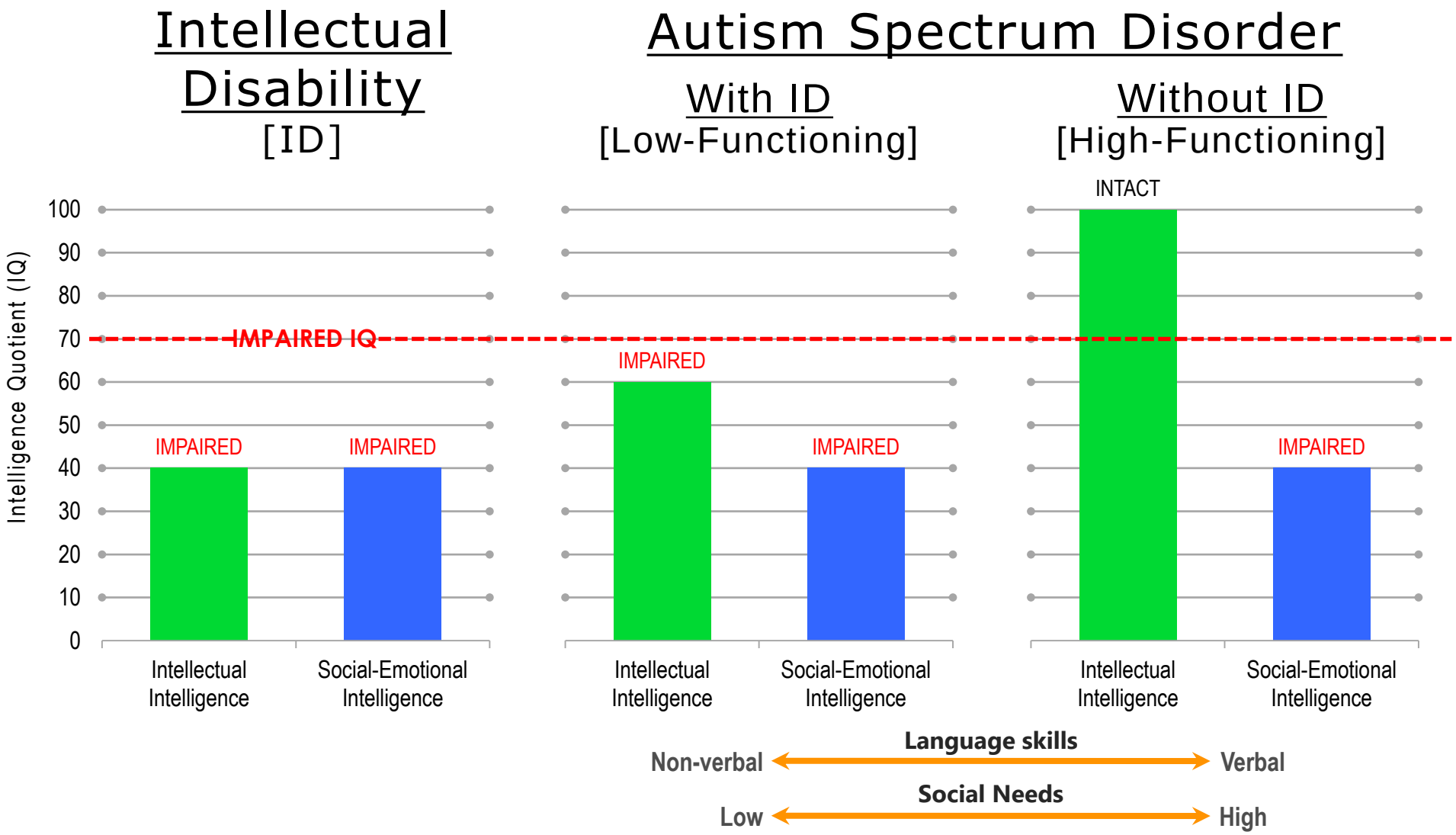
Neurotypicals

Intellectual IQ
- Verbal ability
- Logical reasoning skills
- Problem solving skills
- Mathematical ability

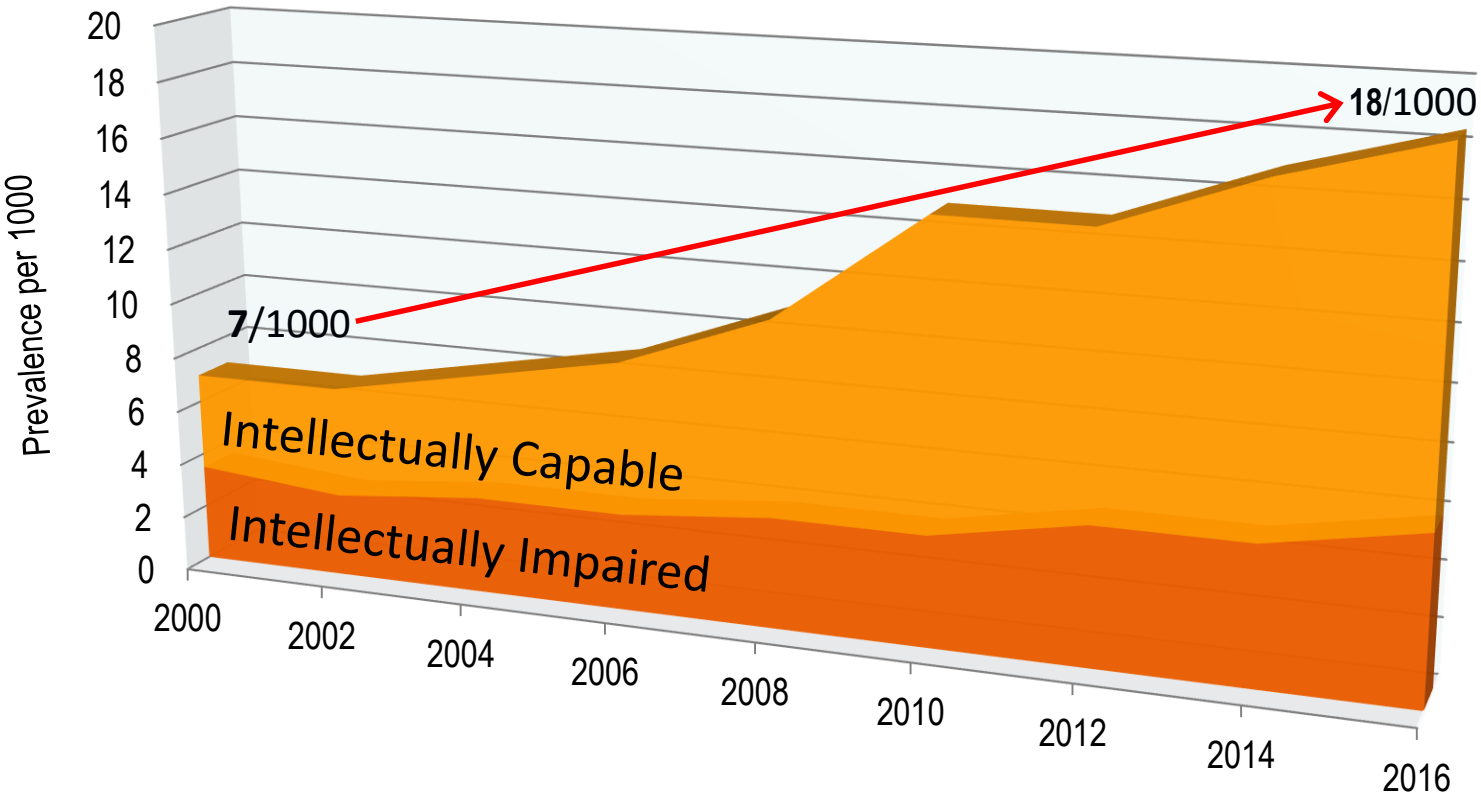


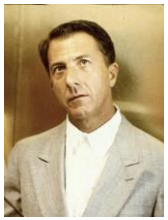
Social-Emotional IQ
- Non-verbal communication
- Salience
- Empathy/ToM
- Cognitive flexibility
- Abstracting ability
- Executive control
- Introspective ability
- Contextual Understanding

Intelligence Profile in AUTISM



Prevalence of ASD



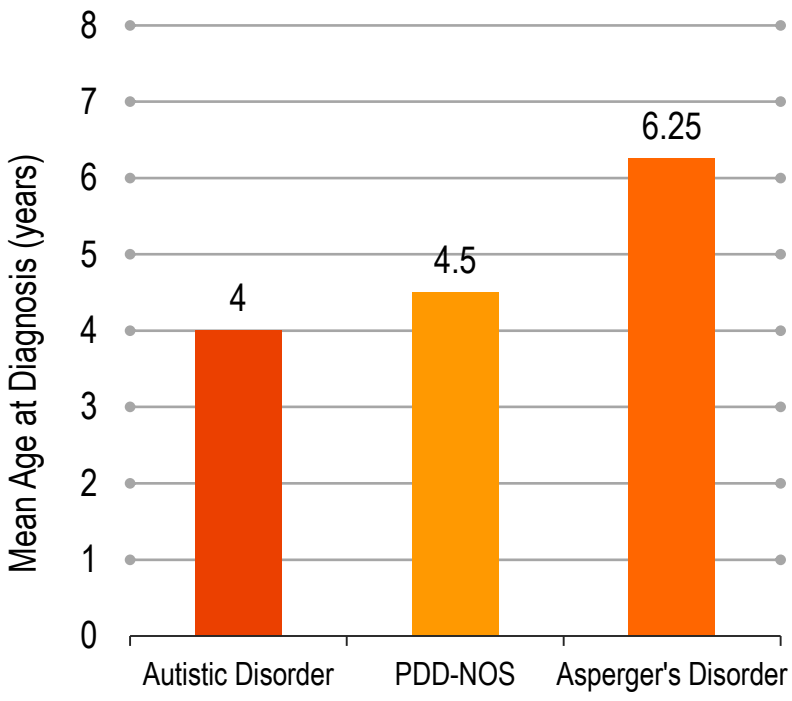


Substantial rise in the prevalence of AUTISM in intellectually capable populations

Age at Diagnosis of Autism

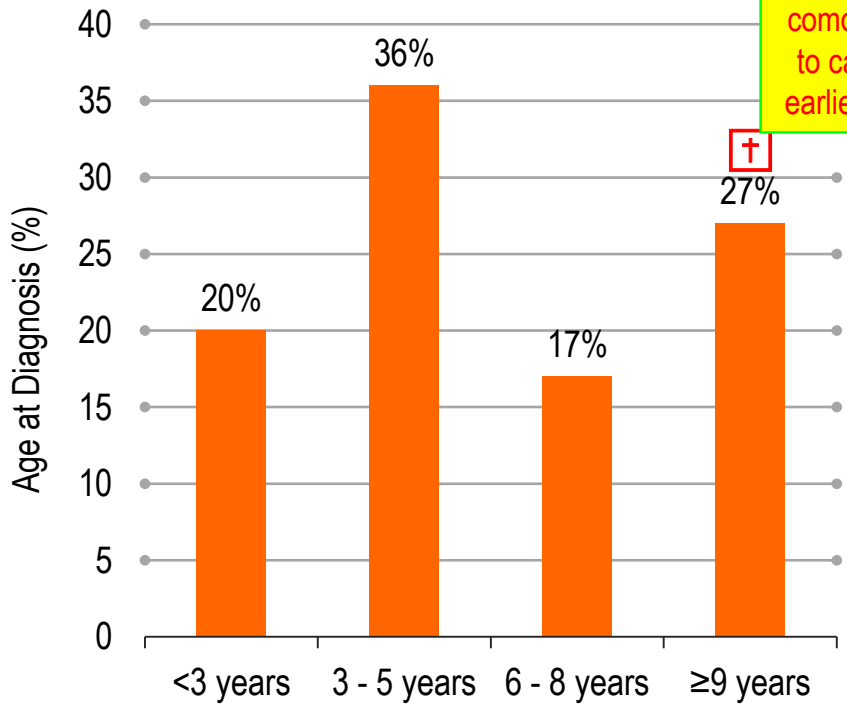
By DSM-IV Diagnosis

(In Children 8 years Old)



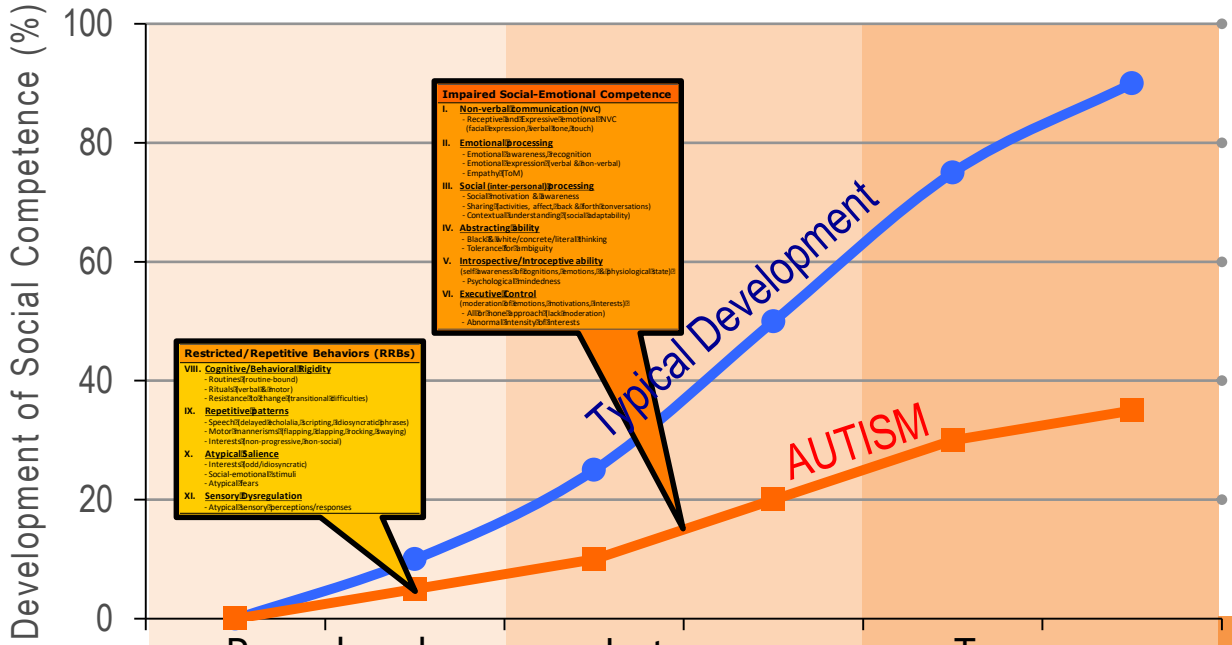
By Age Range

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



Factors associated with delay in diagnosis of AUTISM

Social-emotion Competence Across the Lifespan



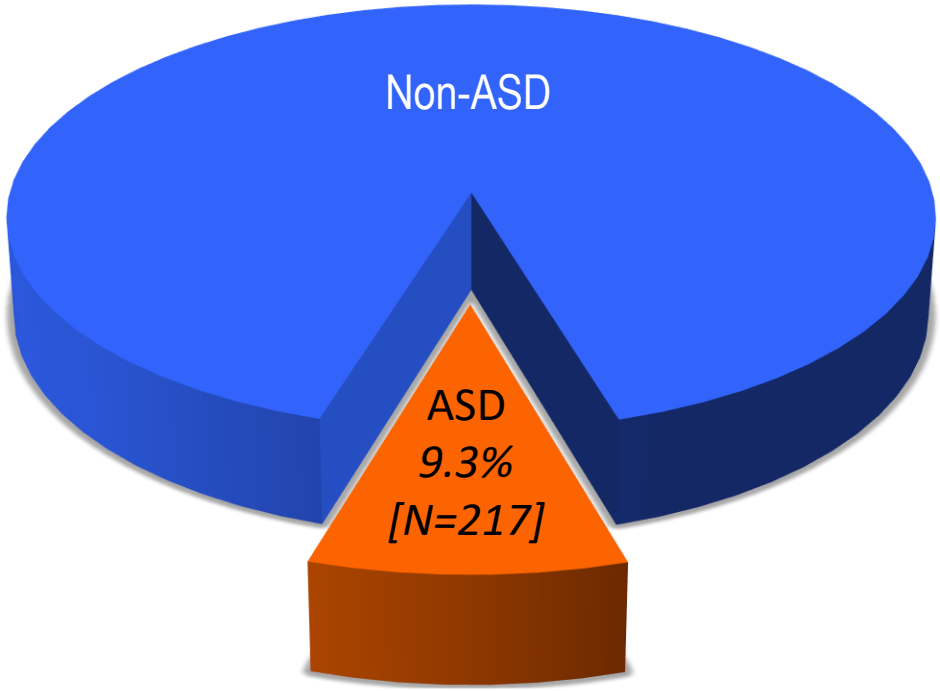
Areas of Social-emotional Development

- Non-verbal communication skills
- Social skills
- Empathy
- Abstracting ability
- Cognitive Flexibility
- Executive Control
- Introspective ability

Preschool (0–5 years)	Latency (6–12 years)	Teenage (13–18 years)	Young Adult (19–35 years)	Adult (≥36 years)
• Minimal social-emotion demands • ± Superior intellectual capacity	• Socially isolated • Bullied • Impaired intellectual functioning	• Social difficulties (friends, prom, dating) • Impaired intellectual performance	• ± Intellectual success • Challenges: -Social & relationship -transition to adulthood	• Delayed social milestones (marriage, children) • Social-emotional isolation
• **Sensory Dysregulation**	• **Present with ADHD**	• **At risk for depression, anxiety, psychosis**	• **At risk for drug abuse**	• **Suffer from anxiety & mood dysregulation**

Social phase *Professional Phase*

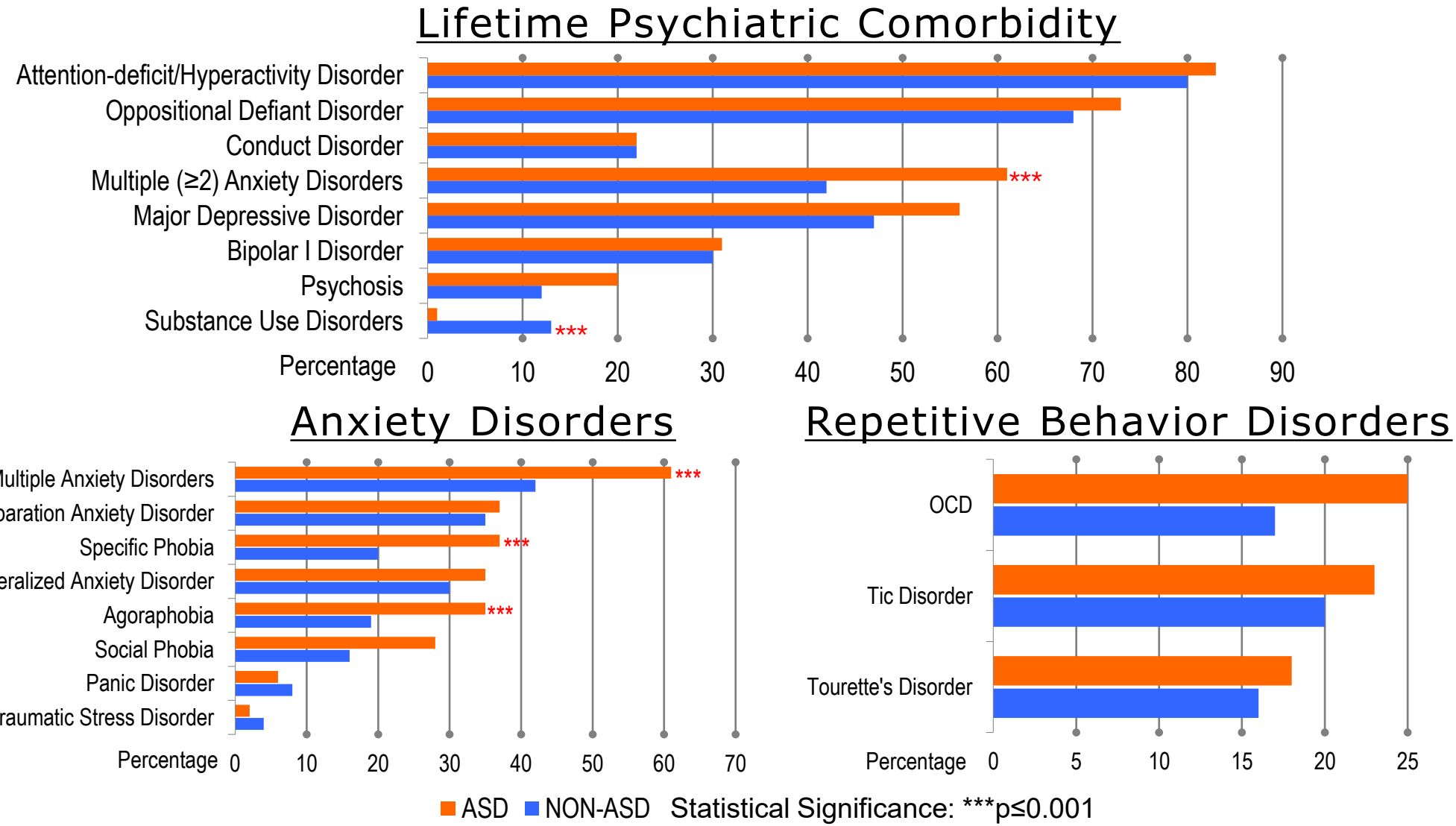
Prevalence of ASD in Psychiatrically Referred Youth



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

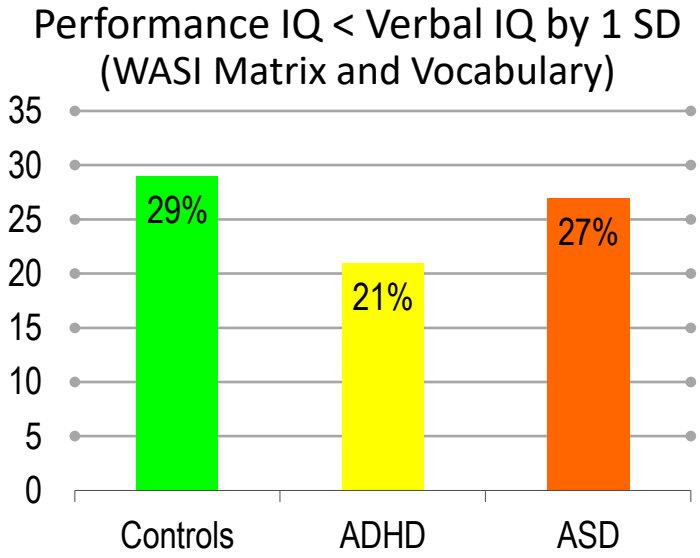
Psychiatric Comorbidity in ASD



Autism Diagnostic Challenges: Institutional Factors & Myths

- Psychiatric disorders are uncommon with AUTISM
- AUTISM Training related Issues

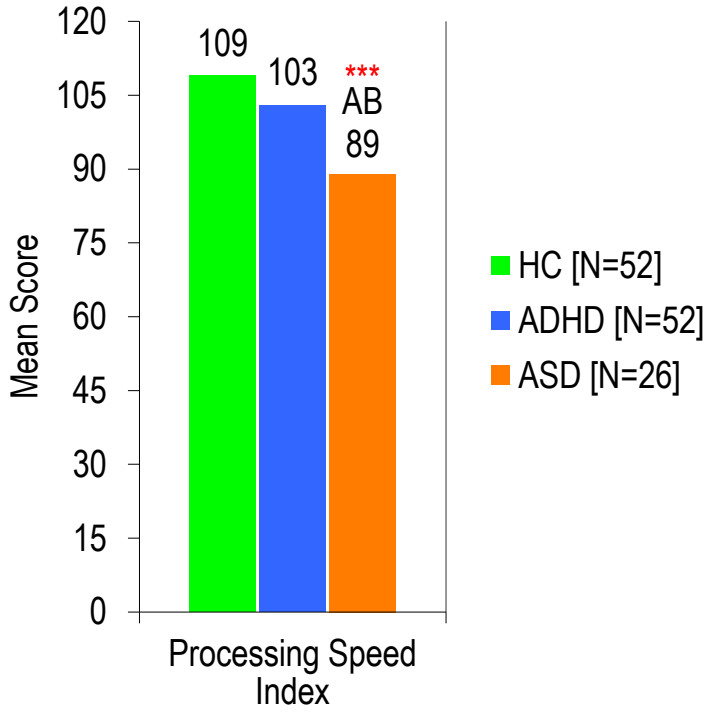
- Autism is diagnosed early in life
- Diagnosis of ASD requires:
  - Diagnostic tools: ADIR/ADOS
  - Genetic work-up
  - Neuropsychological assessment



Neuropsychological Correlates of HF-ASD

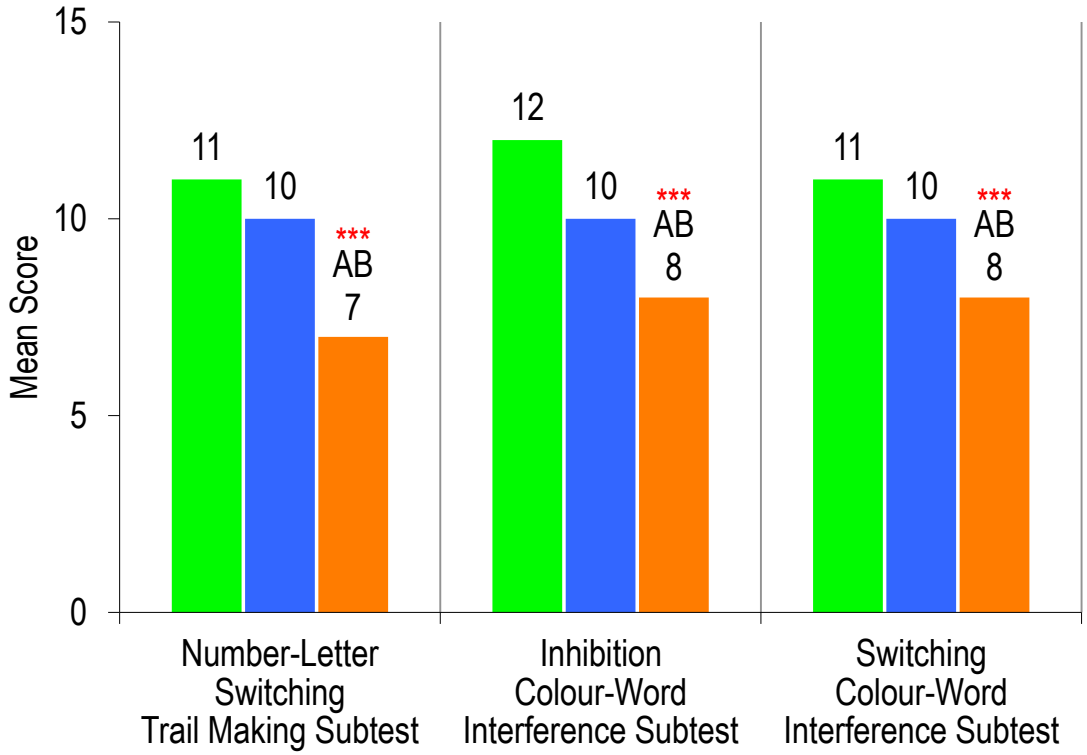
Processing Speed

Wechsler Adult Intelligence Scale (WAIS-III)



Cognitive Flexibility

Delis Kaplan Executive Function System (D-KEFS)



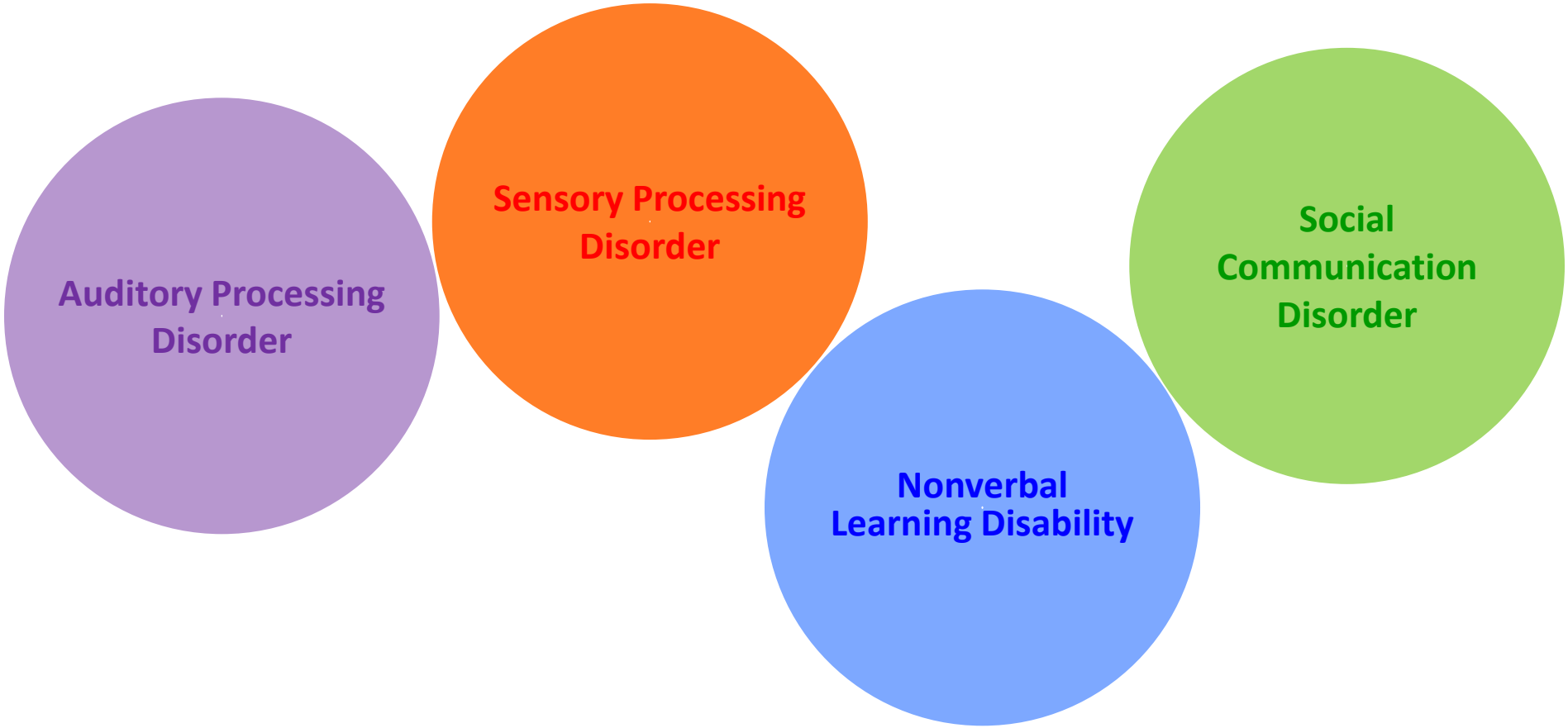
HC=Healthy Controls; A=Versus HC, B=Versus ADHD; Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Red Flags for Assessing ASD

Features

- Sensory dysregulation
- Cognitive rigidity
- In-coordination
- Social immaturity
- Odd/quirky behaviors
- High IQ
- Sibling with ASD

Conditions Suggestive of ASD



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...

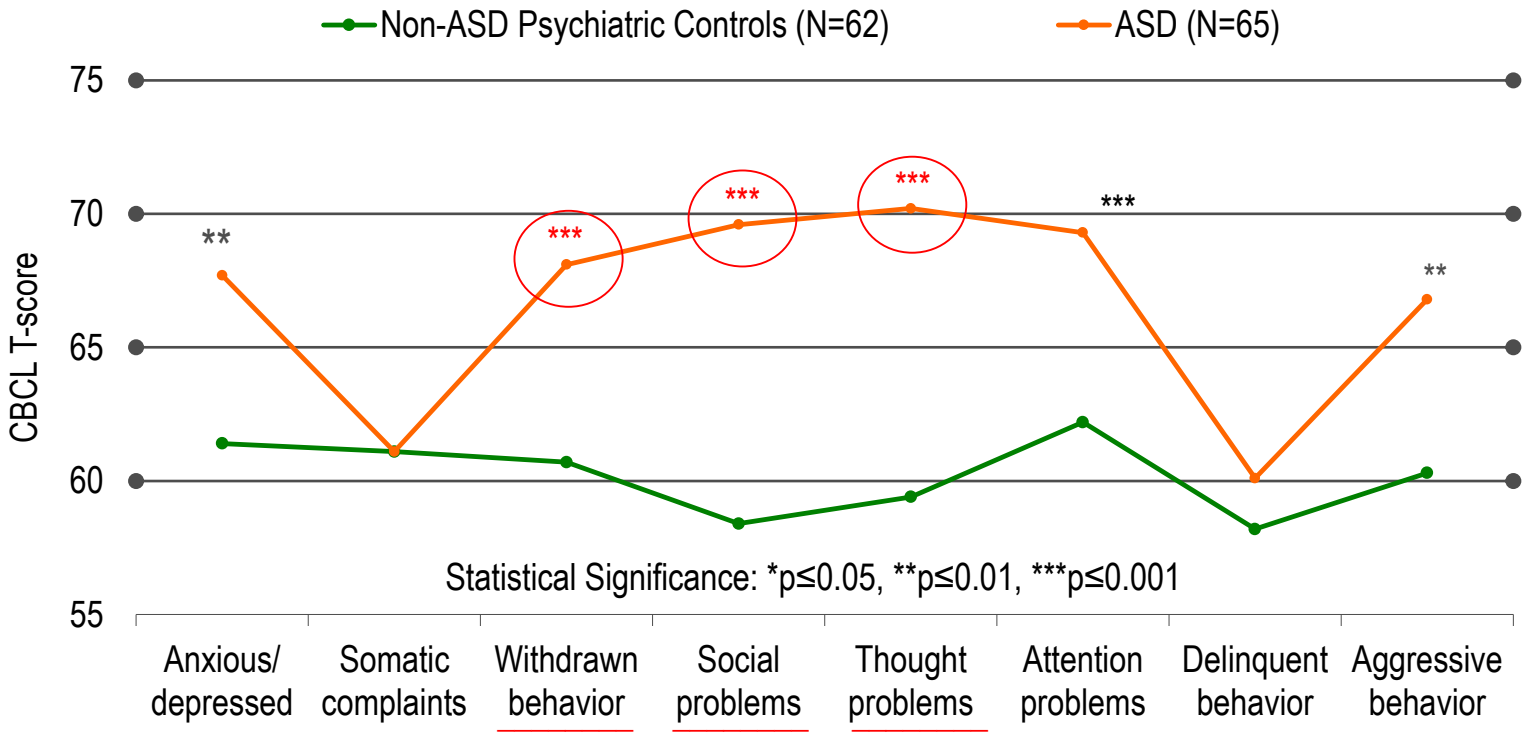
33. Is socially awkward, even when he or she is trying to be polite.	1	2	3	4
34. Avoids people who want to be emotionally close to him or her.	1	2	3	4
35. Has trouble keeping up with the flow of a normal conversation.	1	2	3	4
36. Has difficulty relating to adults.	1	2	3	4
37. Has difficulty relating 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

Social Responsiveness Scale - Subscale Items

SOCIAL AWARENESS	SOCIAL COGNITION	SOCIAL MOTIVATION	SOCIAL COMMUNICATION	AUTISTIC MANNERISMS
Expressions on his or her face don't match what he or she is saying	Concentrates too much on parts of things rather than seeing the whole picture	Avoids starting social interactions with peers or adults	Is awkward in turn-taking interactions with others	Rigid or inflexible patterns of odd behavior under stress
Seems to reach to people as if they are objects	Becomes upset in a situation with lots of things going on	Avoids people who want to be emotionally close to him or her	Is inflexible, has a hard time changing his or her mind	Unusual sensory interests or strange ways of playing with toys
Doesn't mind being out of step with or "not on the same wavelength" as others	Is able to understand the meaning of other people's tone of voice & facial expressions	Would rather be alone than with others	Has trouble keeping up with the flow of a normal conversation	Can't get mind off thinking about something
Is aware of what others are thinking or feeling	Seems overly sensitive to sounds, textures, or smells	Does not join group activities unless told to do so	Is socially awkward, even when trying to be polite	Has repetitive, odd behaviors such as hand flapping or rocking
Has good personal hygiene	Is imaginative, good at pretending	Has good self-confidence	Is able to communicate feelings to others	Difficulty with changes in routine
Focuses his or her attention to where others are looking and listening	Doesn't recognize when others are trying to take advantage of him or her	Seems self-confident when interacting with others	Has difficulty making friends, even when trying his or her best	Thinks or talks about the same thing over and over
Walks in between people who are talking	Recognizes when something is unfair	Stares or gazes off into space	Is too silly or laughs inappropriately	Has an unusually narrow range of interests
Knows when he or she is talking too loud or making too much noise	Doesn't understand how events relate to one another (cause and effect)	Seems much more fidgety in social situations than when alone	Avoids eye contact or has unusual eye contact	Does extremely well at a few tasks, but does not do as well at most other tasks
	Has a sense of humor, understands jokes	Is too tense in social settings	Has overly serious facial expressions	Touches others in an unusual way
	Takes things too literally and doesn't get the real meaning of a conversation	Clings to adults, seems too dependent on them	Talks to people with an unusual tone of voice	Is regarded by other children as odd or weird
	Is overly suspicious	Separates easily from caregivers	Has difficulty relating to peers	Is not well coordinated
	Gives unusual or illogical reasons for doing things		Responds appropriately to mood changes in others	Behaves in ways that seem strange or bizarre
			Is emotionally distant, doesn't show feelings	
			Offers comfort to others when they are sad	
			Has difficulty relating to adults	
			Plays appropriately with peers	
			Is able to imitate others' actions	
			Knows when he or she is too close to someone or is invading someone's space	
			Gets teased a lot	
			Gets frustrated trying to get ideas across in conversations	
			Wanders aimlessly from one activity to another	
			Has difficulty answering questions directly and ends up talking around the subject	

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

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_____

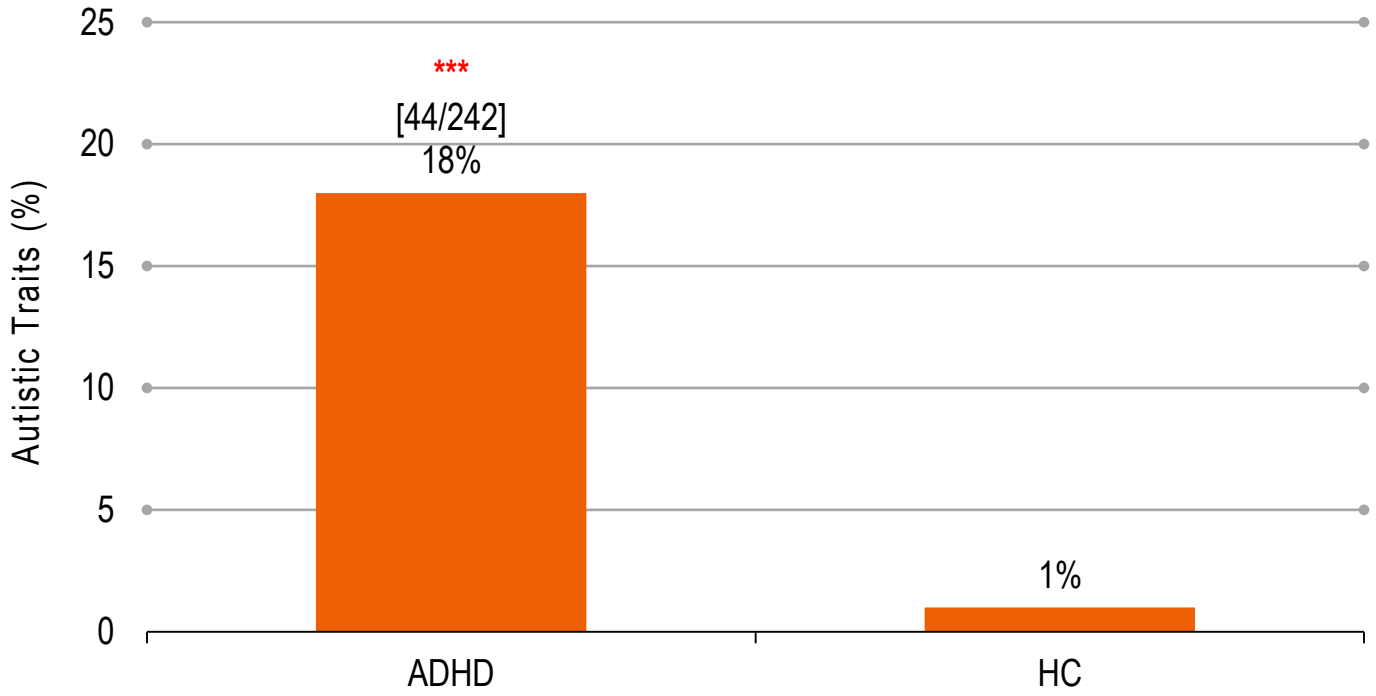
Concurrent Validity

Diagnostic Correspondence with:

- SRS: 95%
- ADOS: 86%

Prevalence of Significant Autistic Traits in ADHD

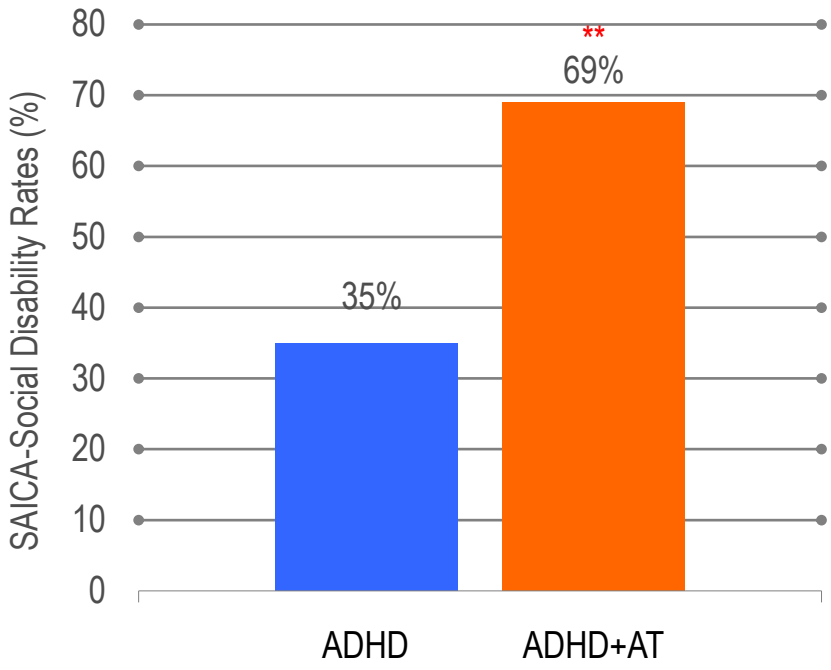
CBCL-AT Profile



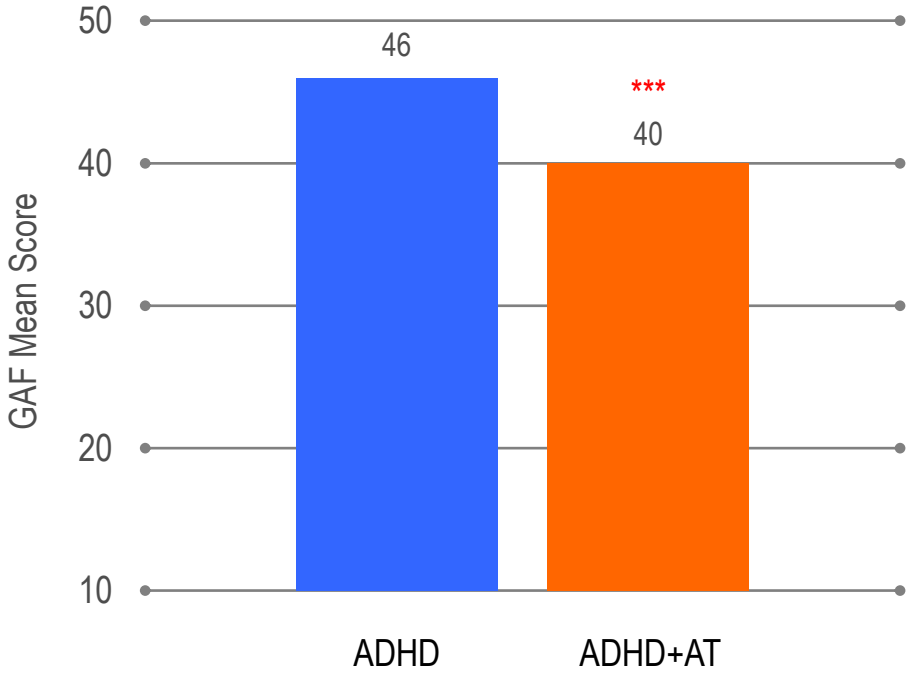
Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Disability Associated with Autistic Traits

Social Disability

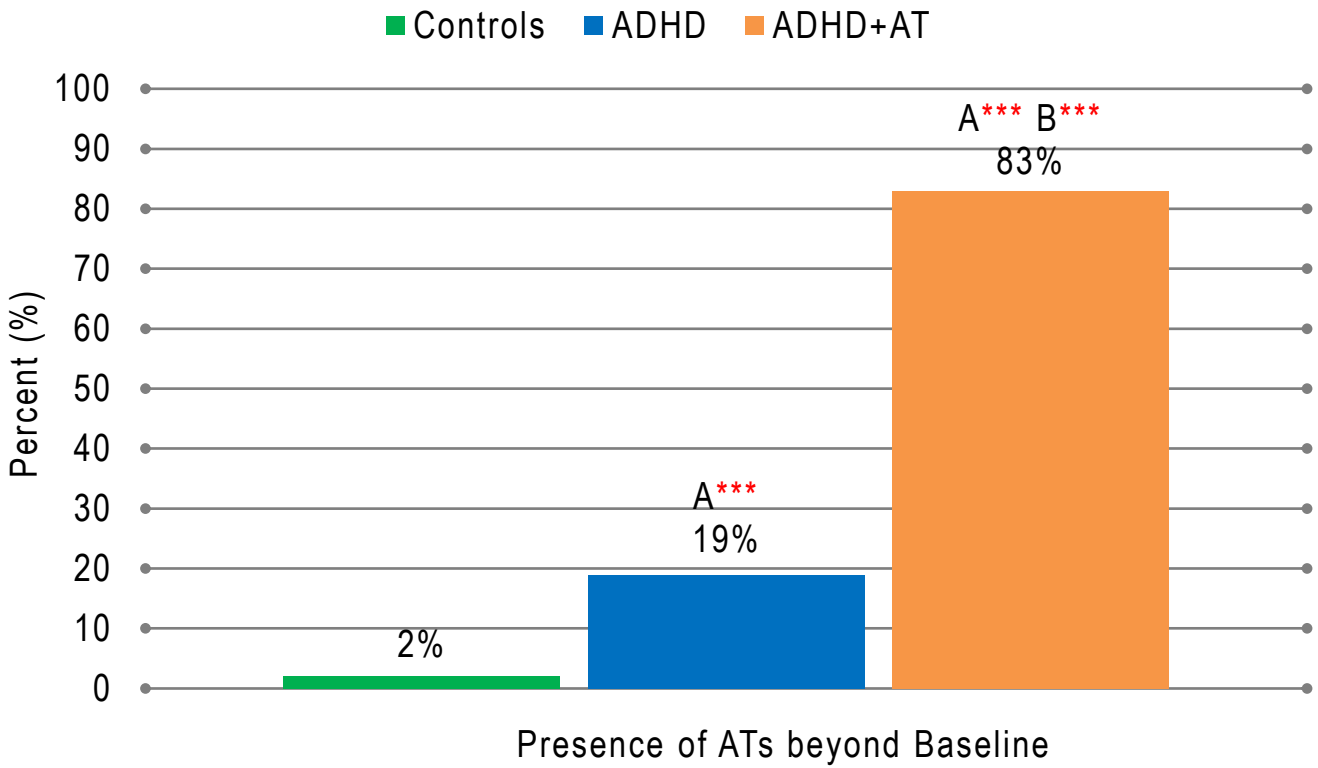


Global Functioning



Statistical Significance: **p<.01; ***p<.001

Stability of Autistic Traits in ADHD

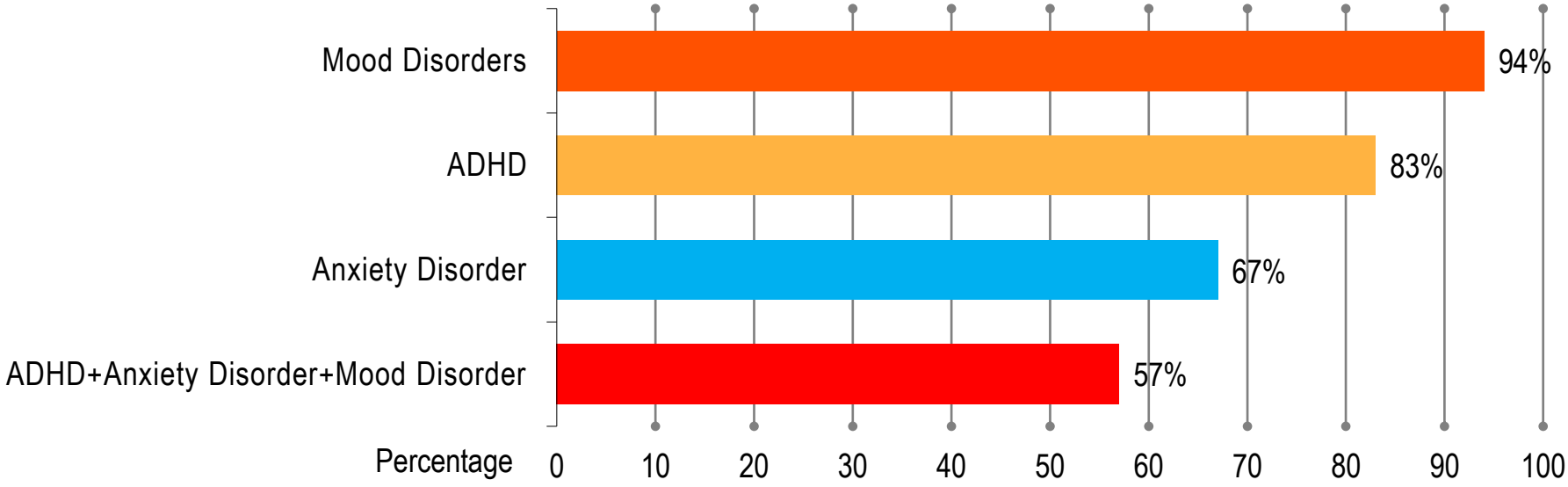


Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001
A= versus HC; B=versus ADHD

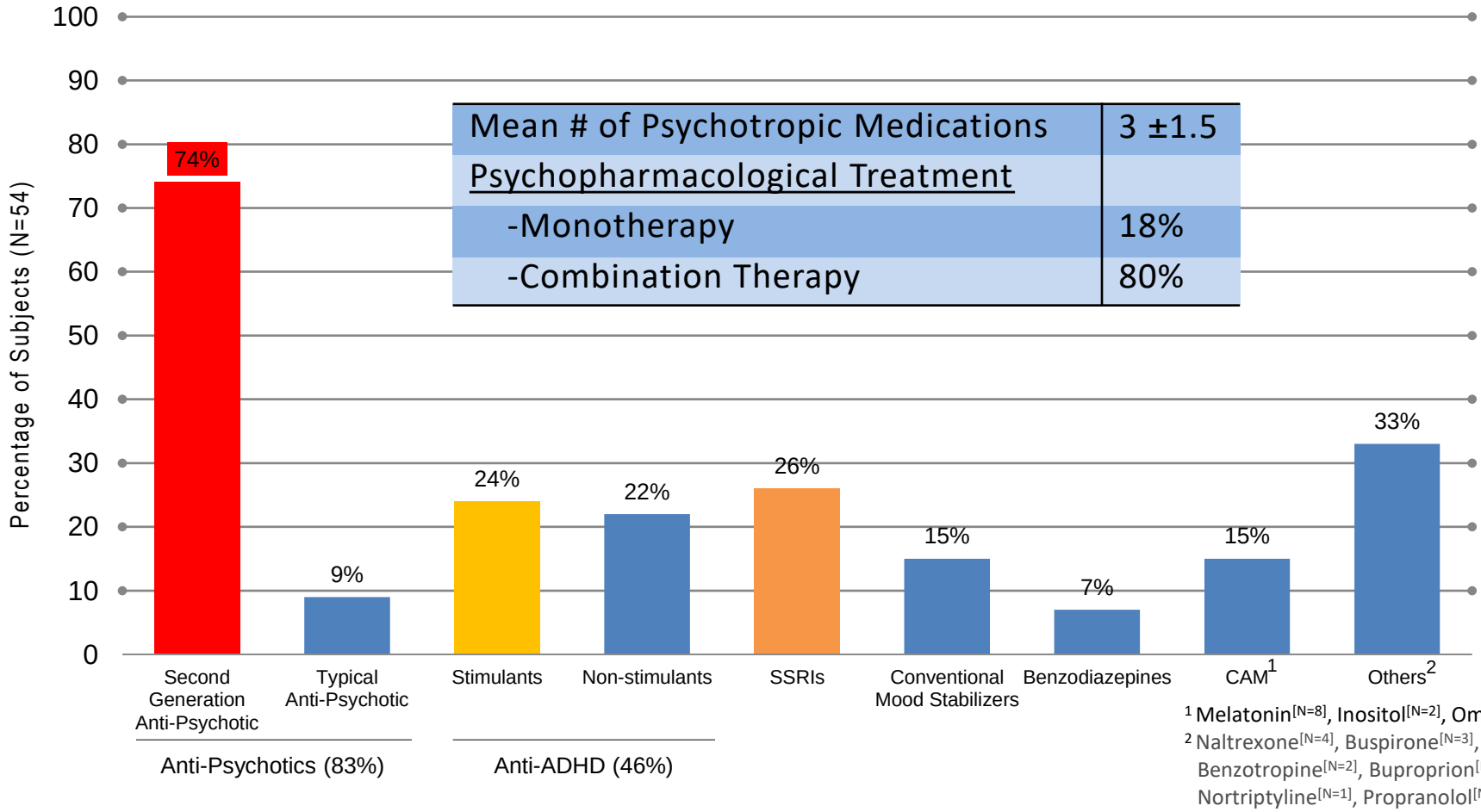
Prescribing Patterns: Clinical Profile

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

Associated Psychopathology



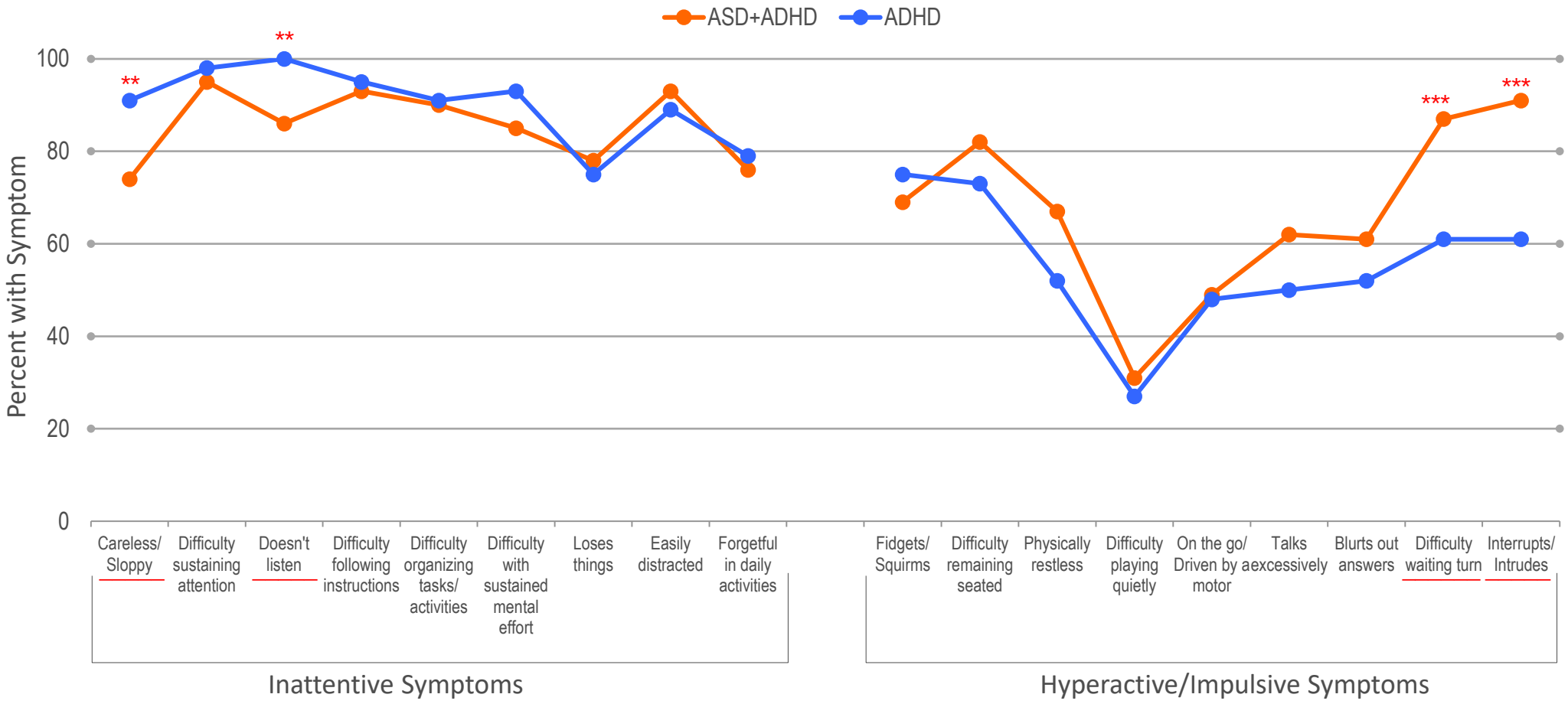
Prescribing Patterns: Treatment Profile



[1] Melatonin[N=8], Inositol[N=2], Omega-3 FA[N=1]
[2] Naltrexone[N=4], Buspirone[N=3], Metformin[N=3], Benzotropine[N=2], Buproprion[N=2], Duloxetine[N=2], Nortriptyline[N=1], Propranolol[N=1]

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

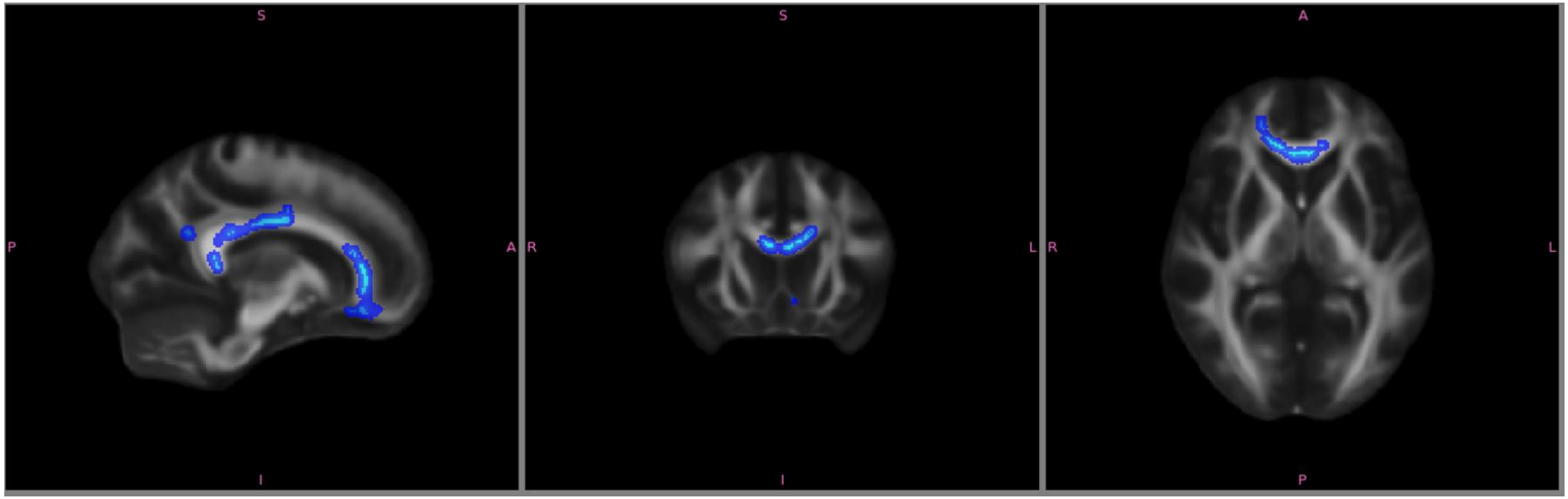
ADHD Symptom Profile in ASD



Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Diffusion Tensor Imaging Findings in ADHD±ASD

Similar ADHD Profile of DTI Underconnectivity in ASD with ADHD



Corpus Collosum DTI underconnectivity

Treatment of ADHD in ASD

- ADHD is the most common psychopathology associated with HF-ASD
- Anti-ADHD medication is the most widely prescribed treatment in individuals with ASD
- Stimulants are the most widely prescribed psychotropic agent in youth with ASD (12% of the ASD population)
- Methylphenidate is the most commonly prescribed stimulant in youth with ASD

Review

Pharmacotherapy of attention deficit/hyperactivity disorder in individuals with autism spectrum disorder: A systematic review of the literature

Psychopharm

Journal of Psychopharmacology
1–8

DOI: 10.1177/0269881120972336
journals.sagepub.com/home/jop
SAGE

Gagan Joshi[1,2,3], Timothy Wilens[1,2,3], Elizabeth S Firmin[1,2], Barbora Hoskova[1,2] and Joseph Biederman[1,2,3]

Abstract

Aim: To assess the empirical evidence for the treatment of attention deficit/hyperactivity disorder (ADHD) in populations with autism spectrum disorder (ASD).

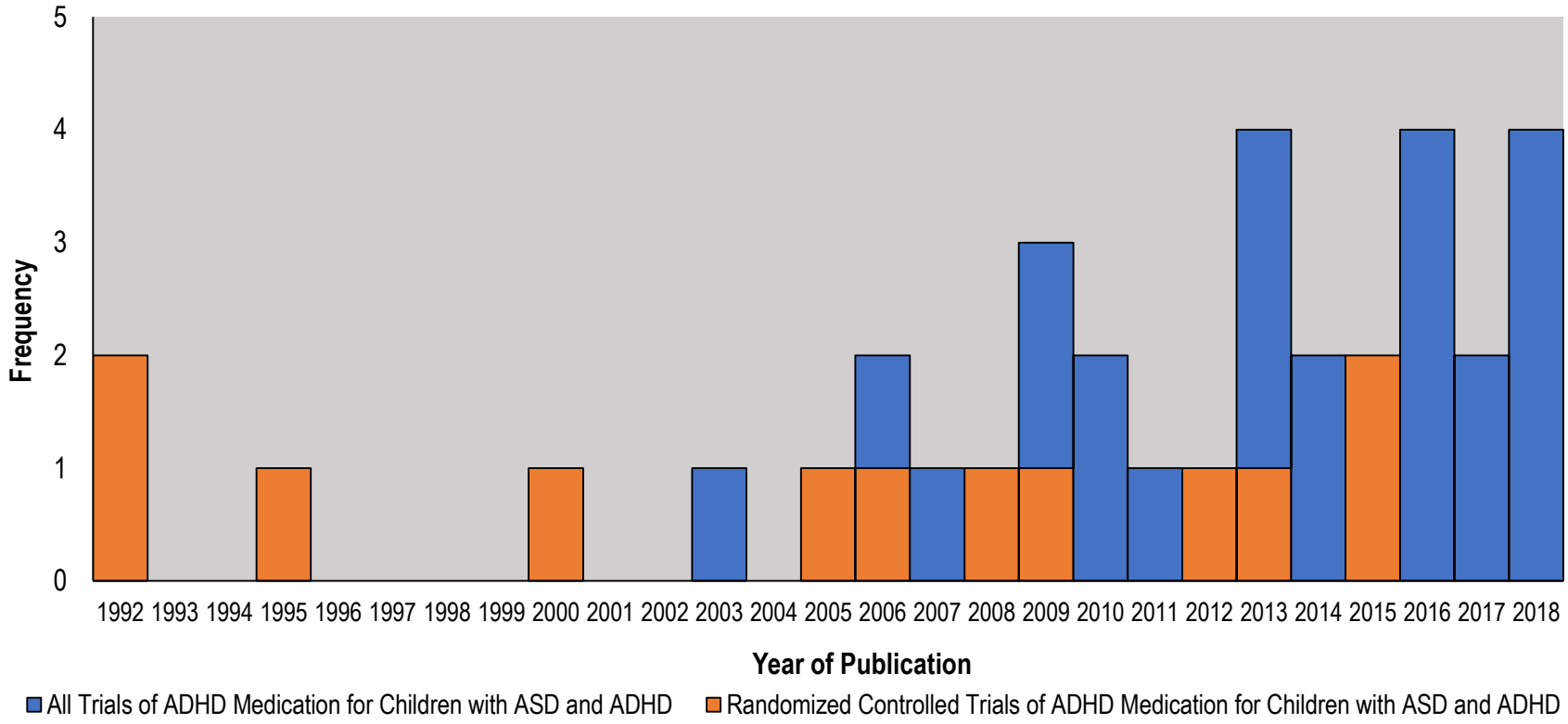
Methods: A systemic PubMed, PsychINFO, Embase, and Medline database search of peer-reviewed literature was conducted. Included in the review were controlled trials published in English with sample sizes ⩾10 participants examining the safety and efficacy of anti-ADHD medication in ASD populations. Data was extracted on relevant variables of study design, demographics, associated psychopathology, medication dose, efficacy, and tolerability.

Results: Nine controlled trials met the inclusion and exclusion criteria: five with methylphenidate, three with atomoxetine, and one with guanfacine. Sample sizes ranged from 10 to 128 with 430 children participating across all the trials. In all the trials, treatment response was significantly superior to placebo. However, almost all trials assessed only hyperactivity, and most included only participants with intellectual disability with high levels of irritability. None of the trials distinguished agitation from hyperactivity. The response on hyperactivity for methylphenidate and atomoxetine was less than that observed in the neurotypical population; however, the response for guanfacine surpassed results observed in neurotypical populations. Treatment-emergent mood lability (i.e. mood dysregulation and mood-related adverse events) was frequently associated with methylphenidate and guanfacine treatments. Worse treatment outcomes were associated with individuals with lower intellectual capability compared with those with higher IQs.

Conclusions: here is a scarcity of controlled trials examining ADHD treatments in ASD populations, particularly in intellectually capable individuals with ASD and in adults. Response to ADHD medications in ASD were adversely moderated by the presence of intellectual disability and mood lability.

Anti-ADHD Controlled Trials in ASD

Frequency of Published Anti-ADHD Treatment Trials in ASD



Total Controlled Trials: N=12

Limitations of Previous Controlled Trials of ADHD in ASD

- No trials on Mixed Amphetamine Salts in ASD
- No trials in Adults with ASD
- Trials predominantly conducted in *Intellectually Impaired* populations with ASD
- Recruited ASD participants with significantly elevated levels of *Irritability*
- Majority of trials assessed for *Hyperactivity* response

Six-week Open-label Trial of Methylphenidate Extended-release Liquid Formulation (Quillivant XR) for the Treatment of ADHD in Adults with HF-ASD

Clinical Trials Registration @ ClinicalTrials.gov
Registration Number: NCT02096952
URL: https://clinicaltrials.gov/ct2/show/NCT02096952?term=NCT02096952

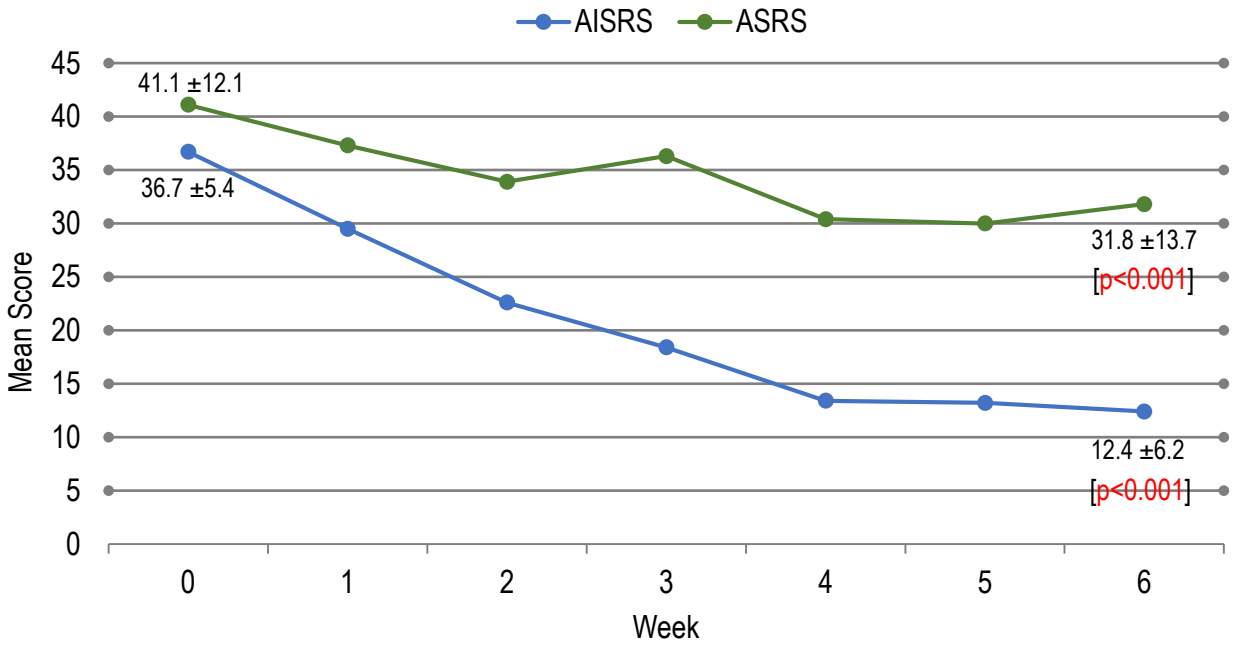
Study Approved by: Partners Human Research Committee Institutional Review Board

Study Funded by: Pfizer, Inc.

Treatment Response: ADHD Symptoms

Clinician-Rated: Adult Investigator Symptom Report Scale (AISRS)

Patient-Rated: Adult Self-Report Scale (ASRS)



Participants

Total participants	15
Gender *(male)*	12 (80%)
Ethnicity *(Caucasian)*	14 (93%)

Age *(years)*

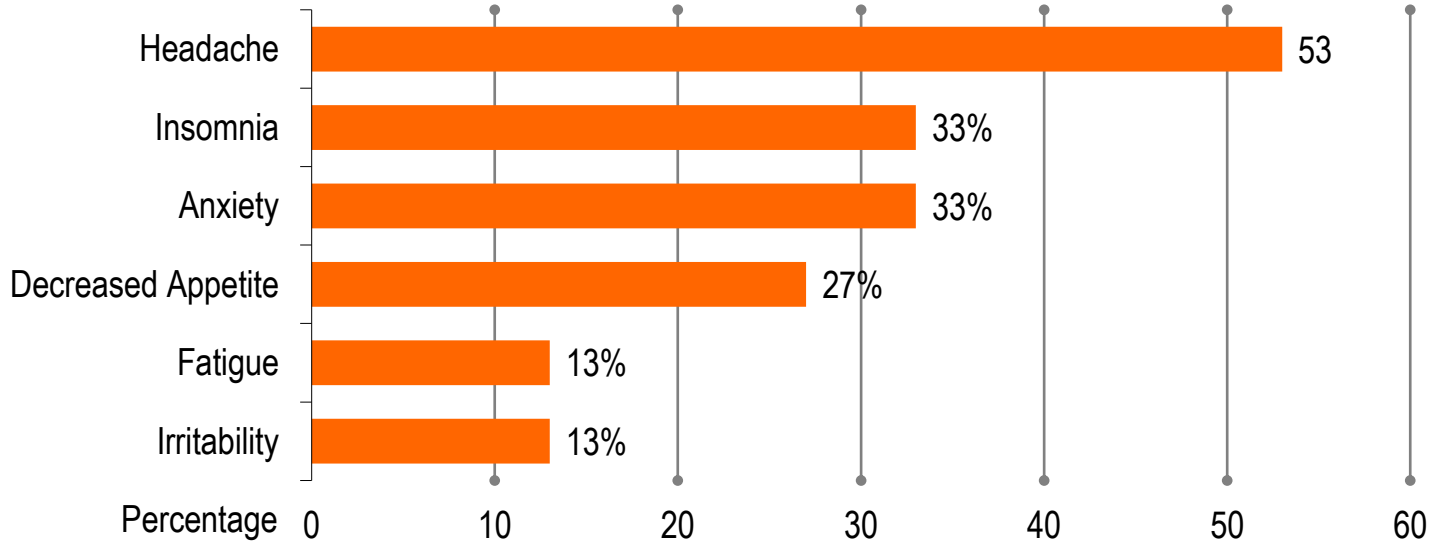
Mean	25 ±4.5
Range	19-34

Study Medication (MPH-ER)

Mean dose	50 ±15 mg/day
Dose range	20-60 mg/day

Adverse Events

Adverse Events (Mild-Moderate Severity)



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

Risperidone & Aripiprazole (FDA approved)

- 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

Divalproex Sodium: Promising as an anti-irritability agent [N=27]

N-Acetylcysteine: Holds promise as an anti-irritability agent [N=29]

Risperidone + Parent Training*

(*Weekly ABA based therapy sessions for ASD & noncompliance)

24-week RCT in Youth with ASD

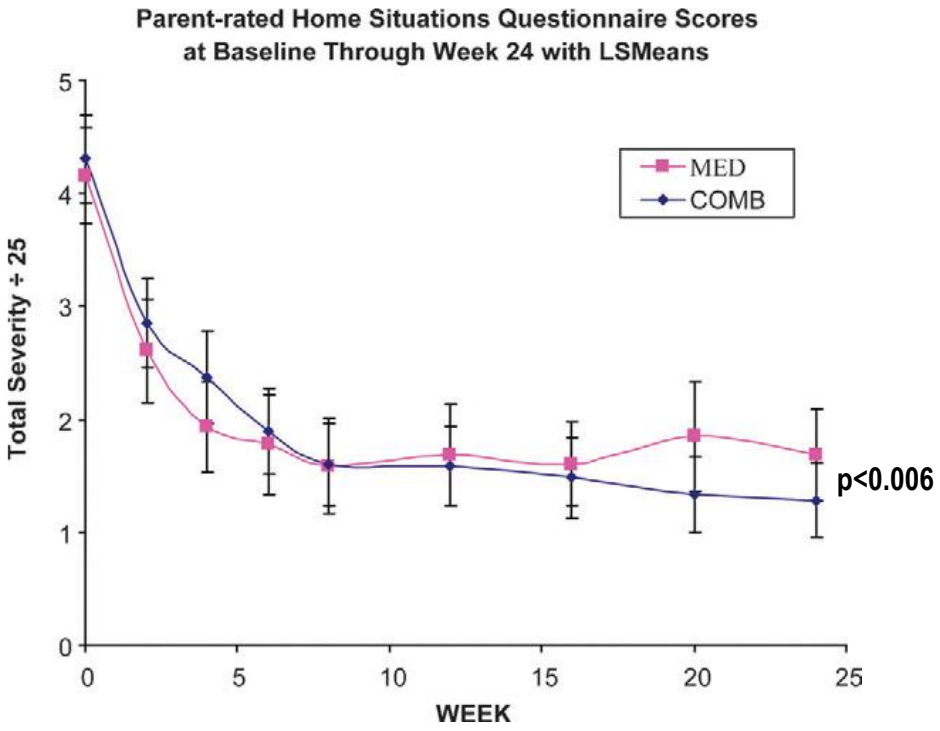
ASD + Sign. Irritability: N=124 [RISP+PT=75]

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

Male: 85%

Mean Age [Range]: 7.5 [4–13] years

IQ>70 : 66%

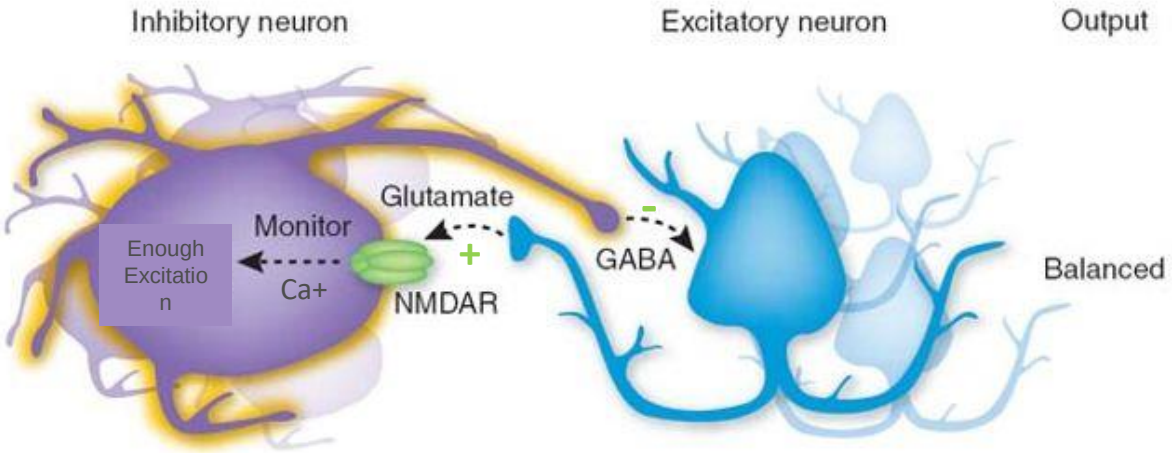


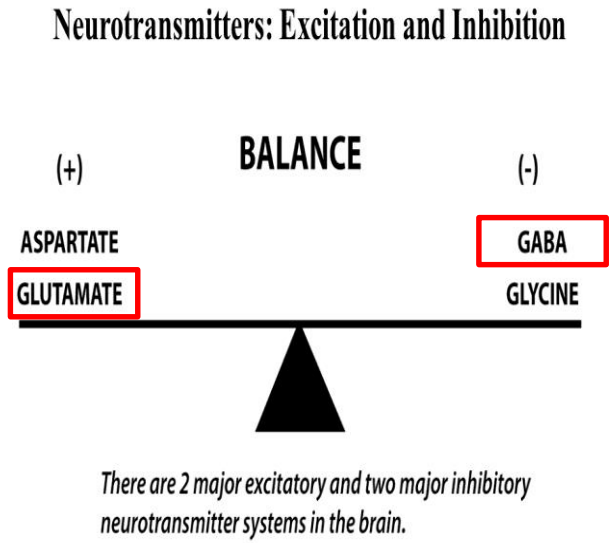
PT+RISP superior to RISP

- Mean Dose [mg/day]:
  PT+RISP$^{[2mg/day]}$ < RISP$^{[2.25mg/day]}$ [p=0.04]
- Maladaptive Behavioral Improvement (% ⇊ HSQ):
  PT+RISP > RISP [p=0.006; ES=0.34]

Excitatory-Inhibitory Imbalance in ASD

Brain Glutamate – GABA Activity

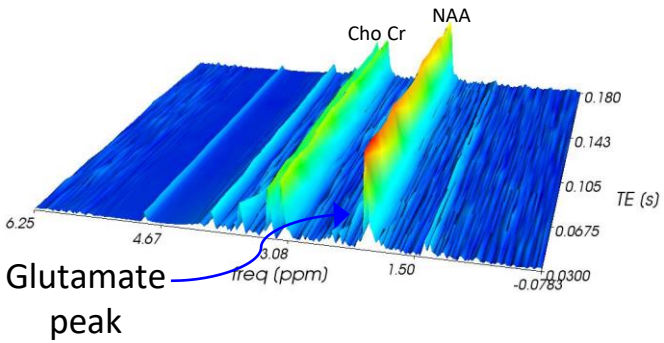


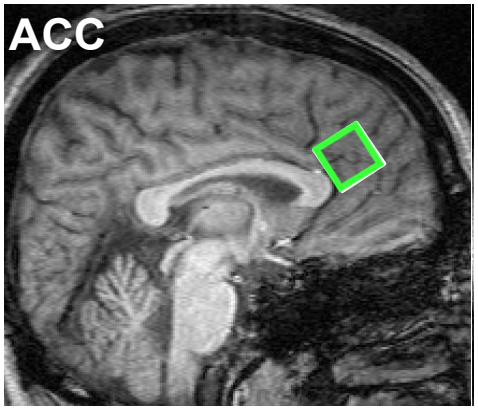


MRS Glutamate Activity in Pregenual Anterior Cingulate Cortex

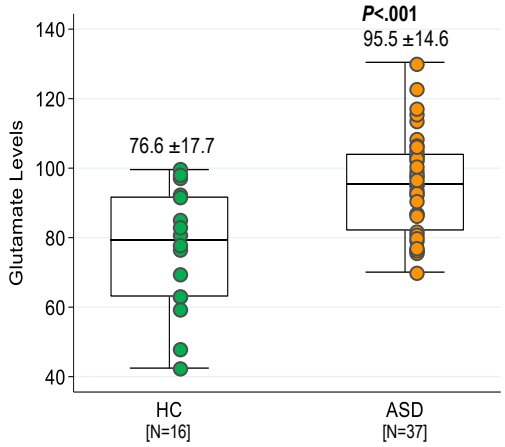
Proton Spectroscopy in Youth with HF-ASD

TE - Stepped (J-PRESS) Spectrum

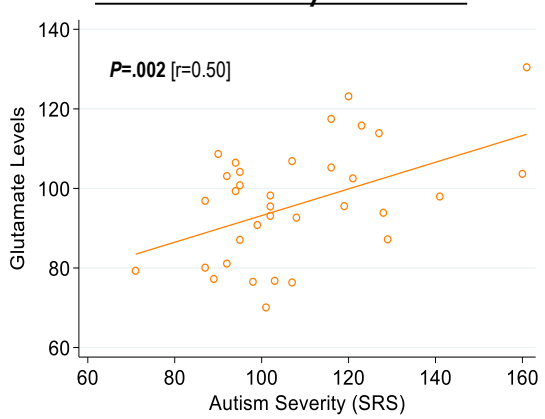




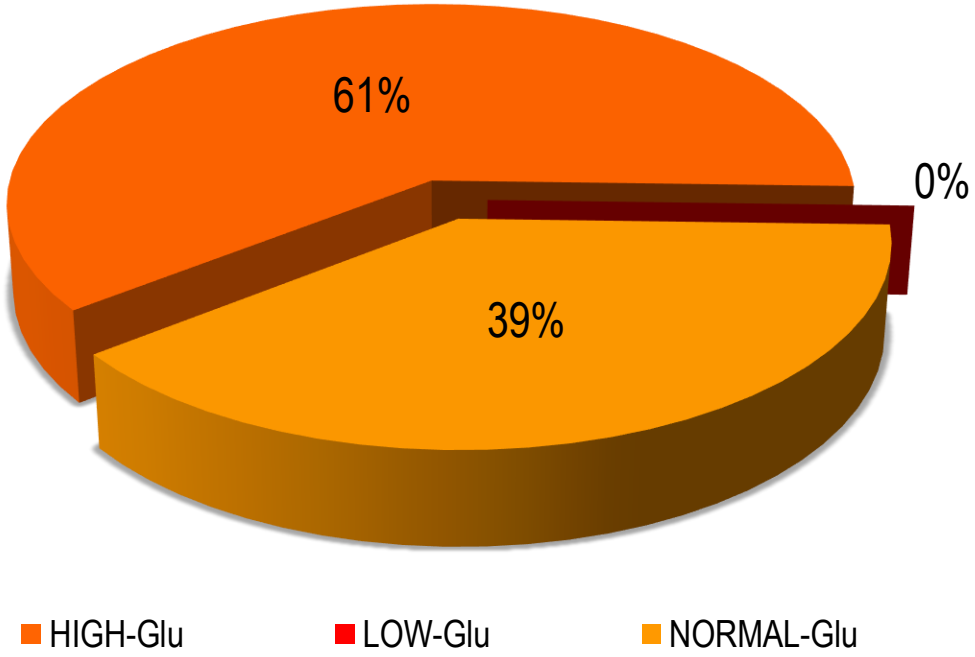
Glutamate Levels in *Pg*ACC



Correlation of *Pg*ACC Glu activity and severity of ASD



Prevalence of HIGH-Glu Activity in HF-ASD



More than a Half of the Youth with ASD suffer from abnormally High Brain Glutamate Activity

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

12-Week Randomized-Controlled Trial of Memantine Hydrochloride (Namenda) in Adolescents 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

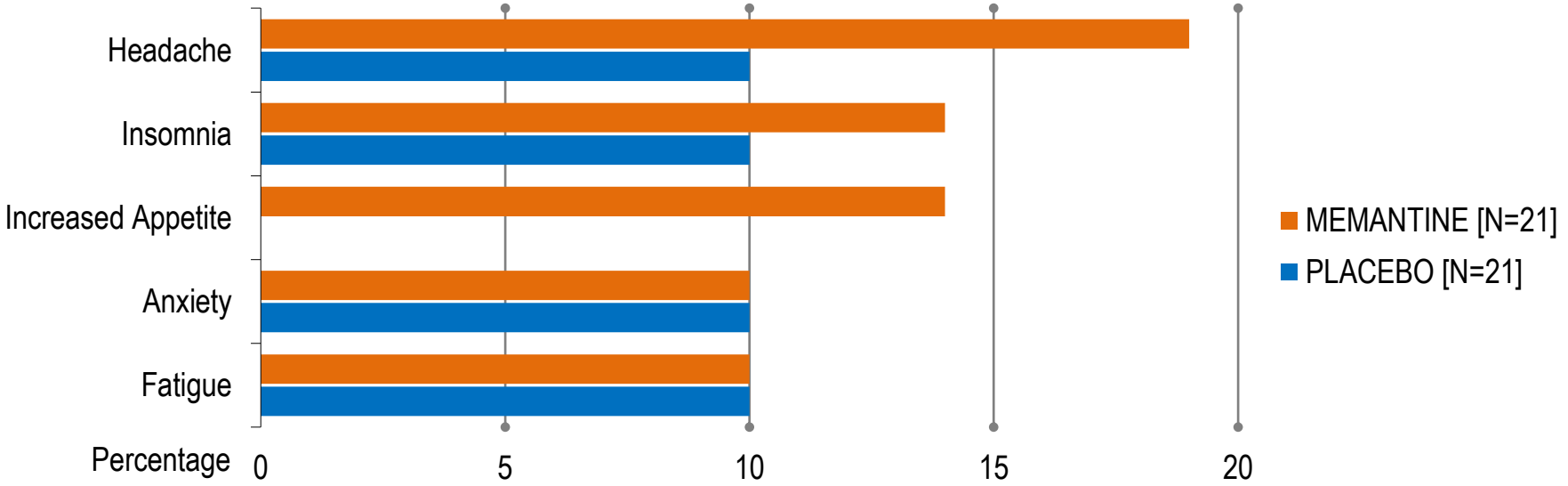
Study Approved by: Partners Human Research Committee Institutional Review Board

Study Funded by: National Institute of Mental Health Career Development Award #K23MH100450

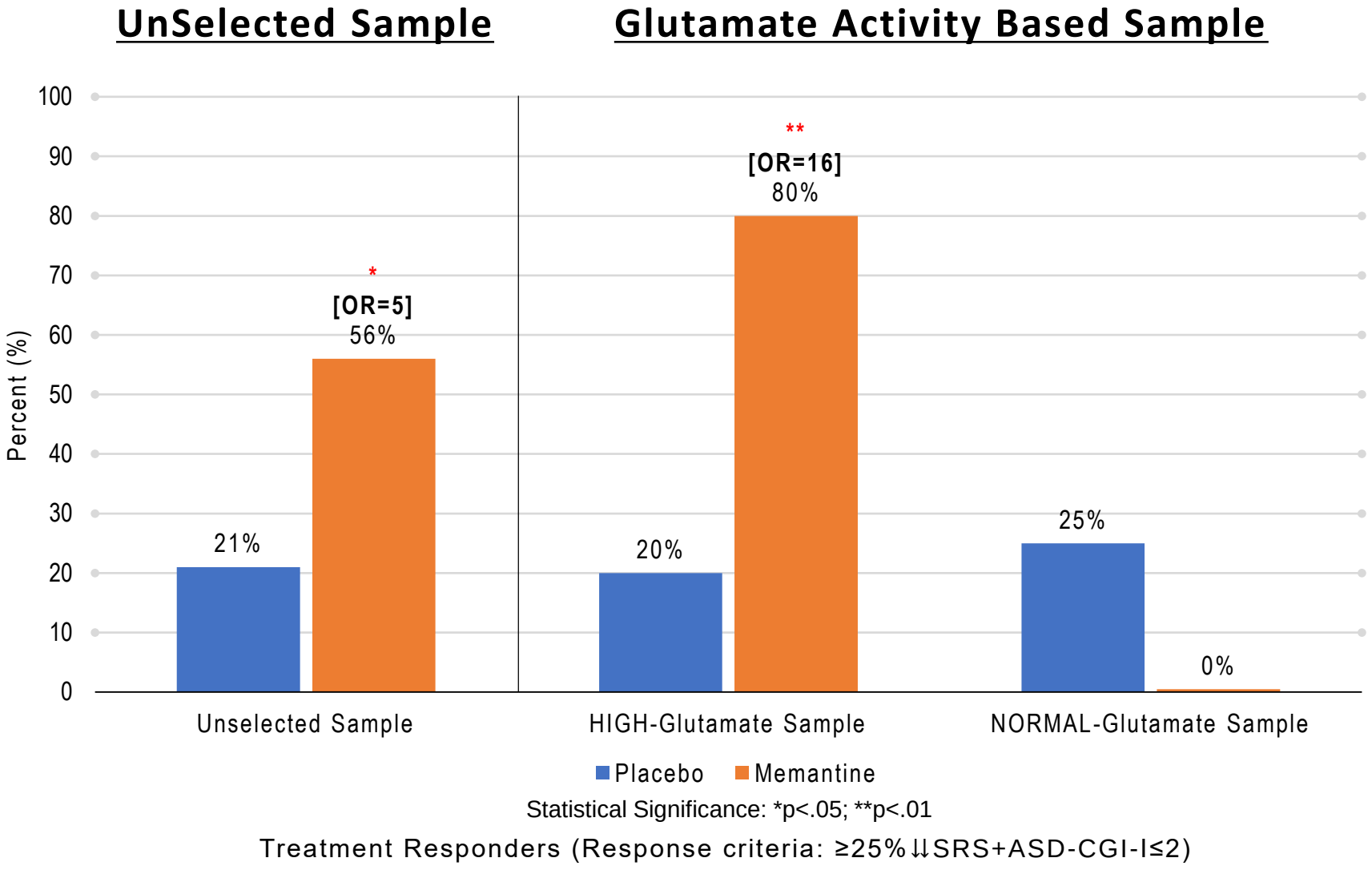
Tolerability

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 Treatment Responders



Statistical Significance: *p<.05; **p<.01

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

Acknowledgments

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