

Adult Autism

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Disclosures

My spouse/partners and I have the following relevant financial relationship with a commercial interest to disclose (within the past 12 months):

Commercial Interest	What was received	For what role?
AACAP; American Physician Institute; Optum Health Education; Regional Council of Child and Adolescent Psychiatry of Eastern Pennsylvania and Southern New Jersey; Hackensack Meridian Health	Honorarium	Speaker
Genentech	Research support	Site PI

Learning Objectives

At the conclusion of this presentation, the participant should be able to:

- Appreciate the prevalence of Autism in intellectually capable populations
- Highlight the profile of psychopathology associated with Autism
- Assess Autism in psychiatrically referred populations
- Understand the neurochemical underpinnings of Autism that has potential to guide treatment for core features of Autism
- Review anti-ADHD response in adults with ASD

Core Features of AUTISM

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 (perspective taking)

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/Interoceptive ability

- (self awareness of cognition, emotions, & physiological state)
- Psychological mindedness

Restricted/Repetitive Behaviors (RRBs)

VII. 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

VIII. Repetitive Patterns

- Speech (echolalia, scripting, idiosyncratic phrases)
- Motor mannerisms (flapping, clapping, rocking, swaying)
- Interests (non-progressive, non-social)

IX. Atypical Salience

- Social-emotional stimuli
- Interests (odd/idiosyncratic)

X. Executive DysControl

- (moderation of emotions, motivations, interests, relationship)
- All or none approach (lack moderation)
- Abnormal intensity of interests

XI. Sensory Dysregulation

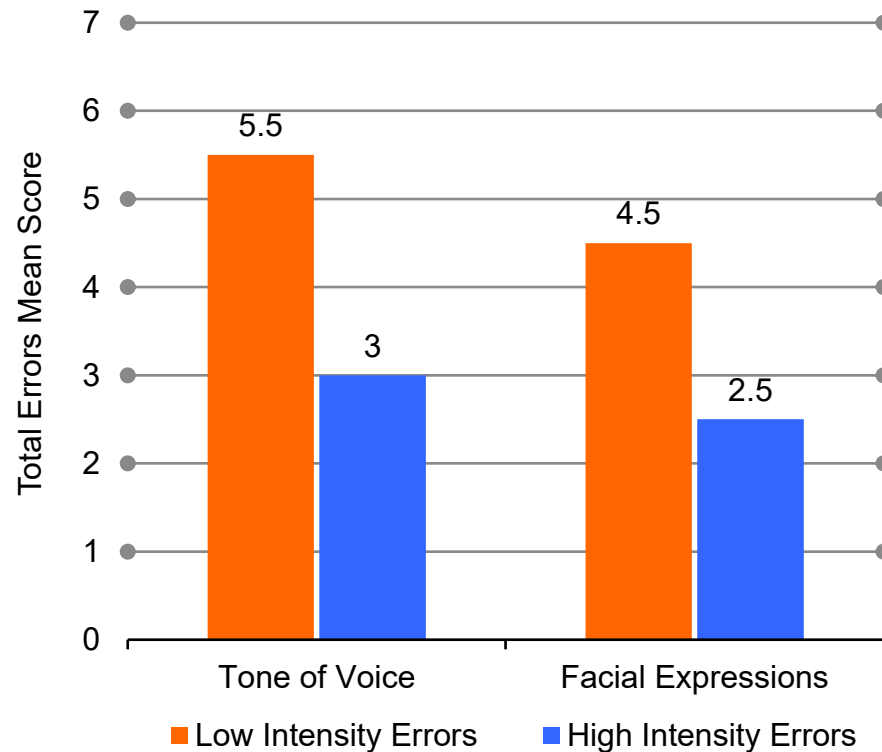
- Atypical sensory perceptions/responses
- Sensory preferences

Non-verbal Communication Performance

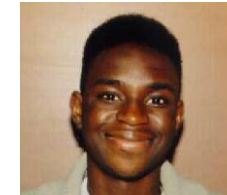
Reading Non-Verbal Emotional Cues: DANVA2 Performance

Errors in Reading Non-verbal Emotions

Low Intensity Cues



High Intensity Cues



DSM-5-TR 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*** 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 problem
- With catatonia

DSM-5-TR Communication Disorders

Social (Pragmatic) Communication Disorder (F80.89/315.39)

A. Persistent deficits in social use of verbal and nonverbal communication

as manifested by all of the following:

I. Deficits in social communication

- Inability to initiate communication
- Inability to share communication

II. Inability to adapt manner of communication with social context/needs

- Manner of speech does not change with social situations (relative age, relationship, or familiarity with the reciprocating individual)
- Use of overly formal language

III. Difficulties in regulating social communication

- Inability to take turns in conversation
- Inability to rephrase
- Poorly integrated verbal and nonverbal communication

IV. Impaired understanding of implicit communication

- Too literal and doesn't get the implied meaning of conversation (puns, sarcasm)
- Difficulty understanding ambiguous meanings of language (idioms, humor, metaphors, meanings that requires context for interpretation)

B. Symptoms cause clinically significant impairment in functioning

C. Symptoms must be present in the early developmental period

- Symptoms may not fully manifest until social communication demands exceed limited capacities.

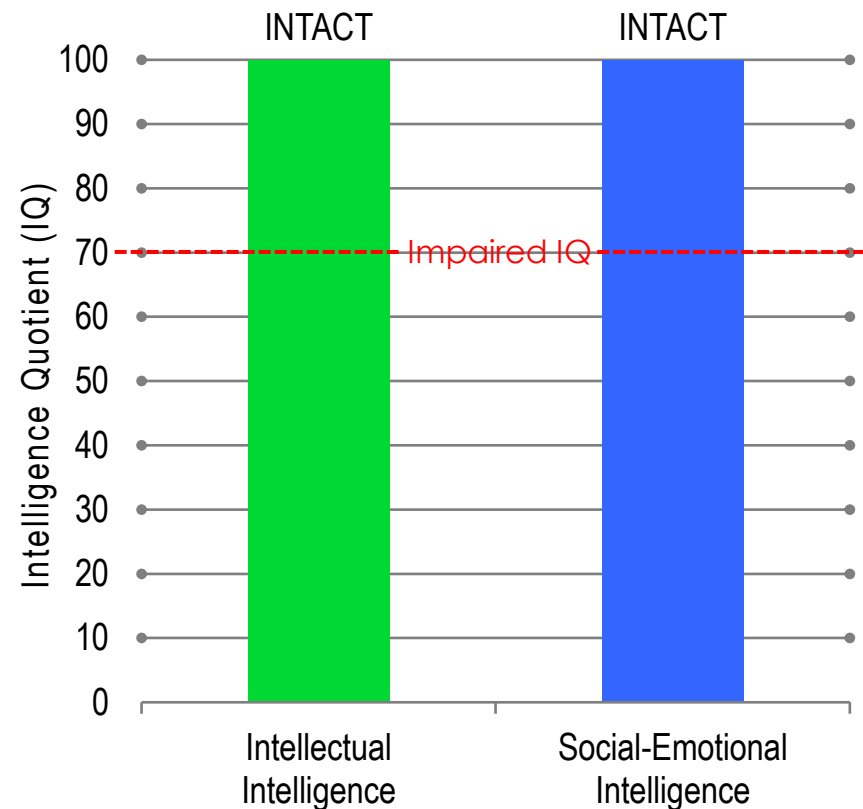
D. These disturbances are not better explained by ASD, ID, or mental disorder

Domains of Intelligence

Neurotypicals

Intellectual IQ

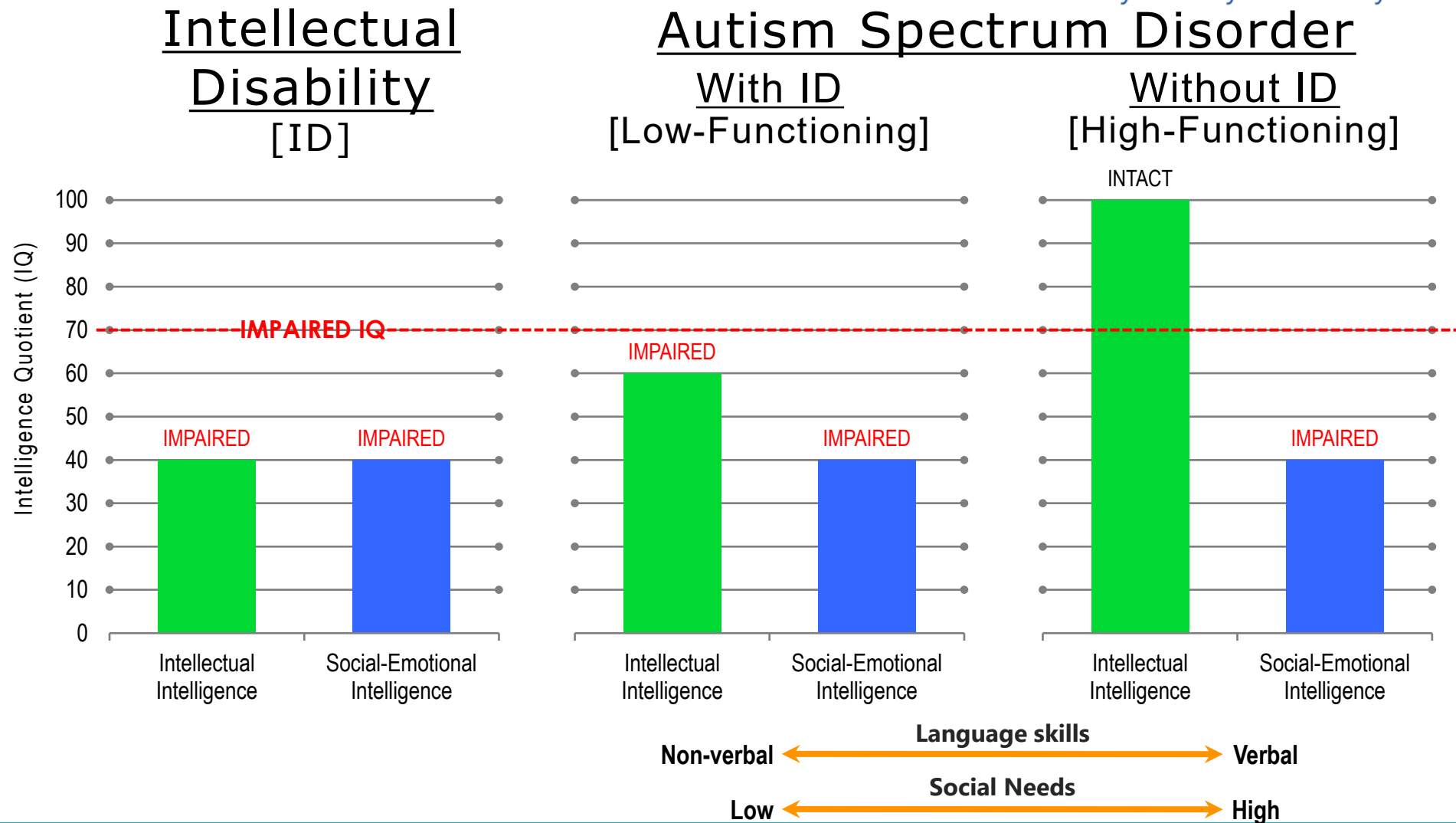
- Verbal ability
- Logical reasoning skills
- Problem solving skills
- Mathematical ability



Social-Emotional IQ

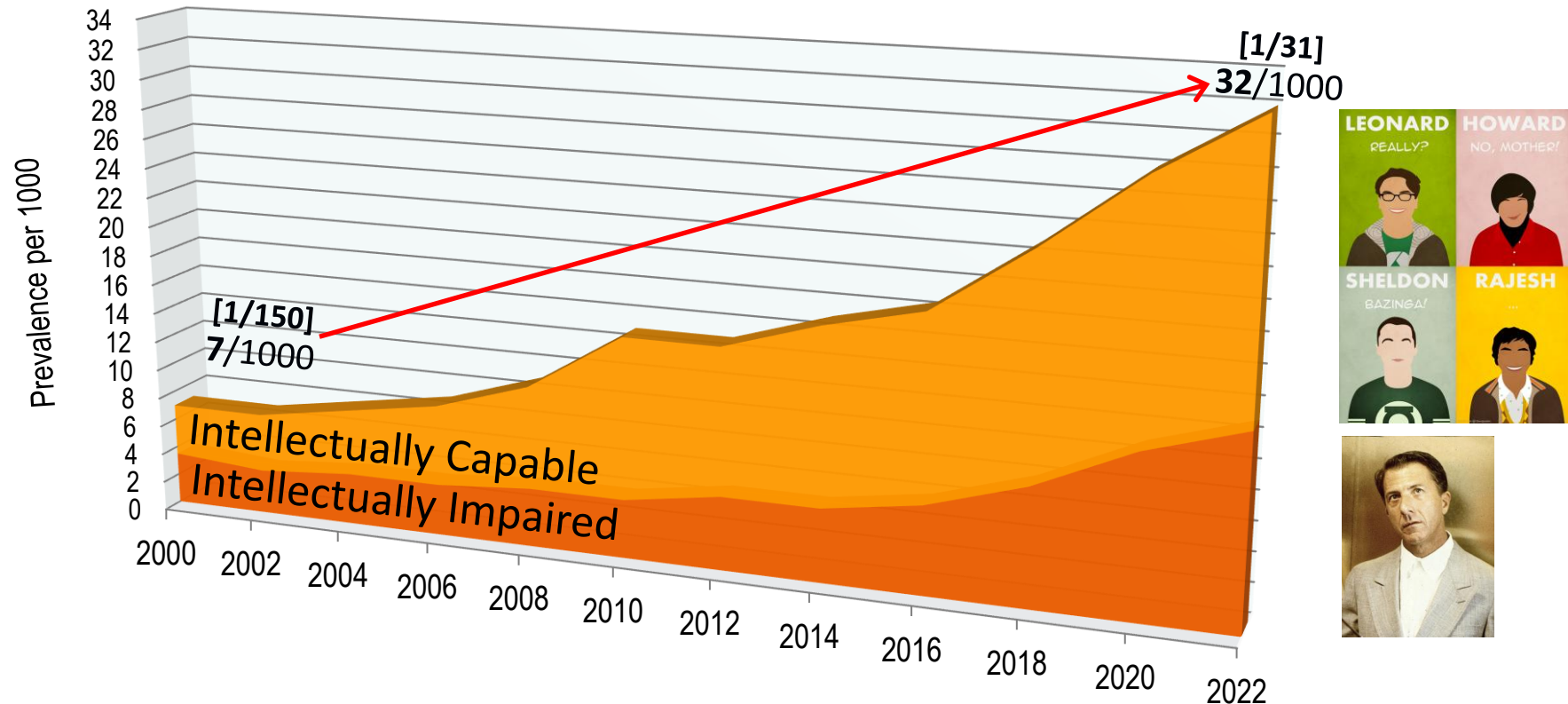
- Non-verbal communication
- Salience
- Empathy/ToM
- Cognitive flexibility
- Abstracting ability
- Executive control
- Introspective ability
- Contextual Understanding

Intelligence Profile in AUTISM



Prevalence of AUTISM

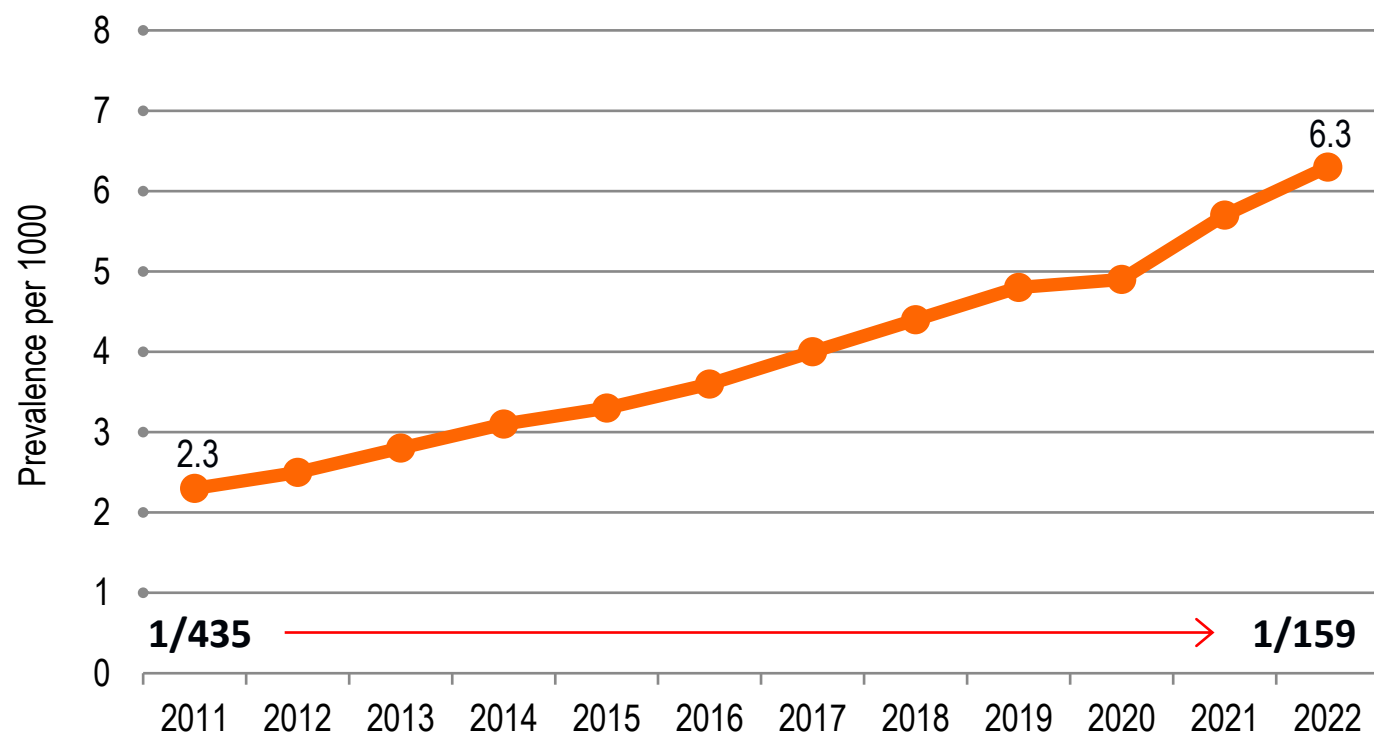
Children (8 years old) with AUTISM (USA)



**Substantial rise in the prevalence of AUTISM
in intellectually capable populations**

Prevalence of ASD

AUTISM Across Lifespan (USA)



Mental Health Research Network (MHRN)

- Medical health records review
- 12-sites in 10 states in US (NC, SC, MA, MI, MN, CO, GA, HI, WA, OR)
- Youth (<18 years): 73%
- Females: 26%

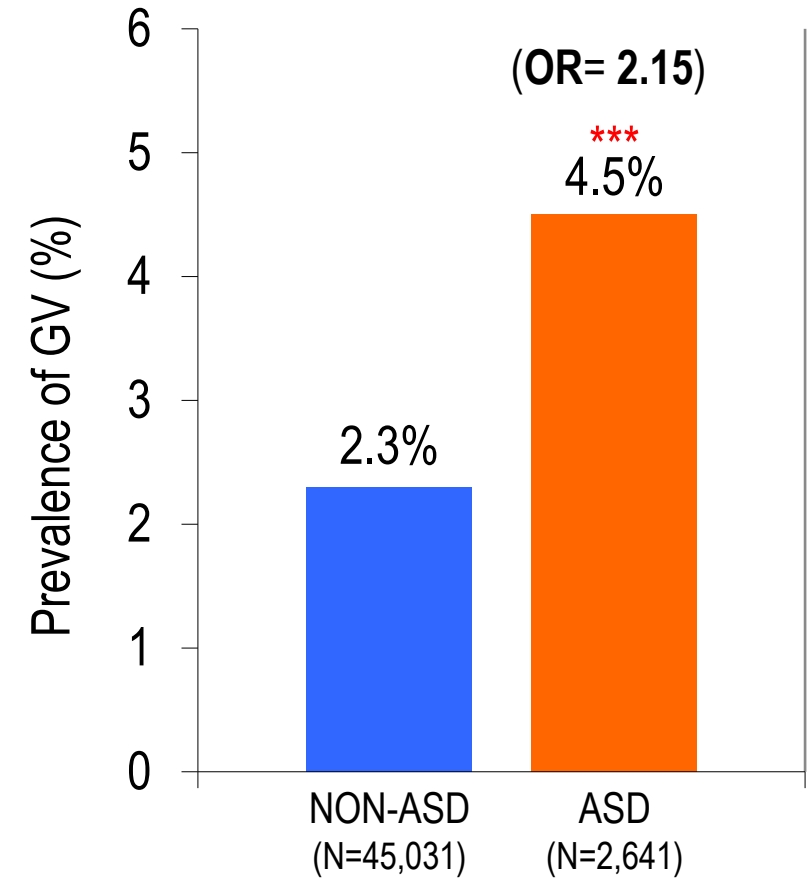
Prevalence of ASD increased by 175% in last decade
Greatest relative increase in prevalence: - adults (26-34 year; 450%)
- Female vs male

Prevalence of Gender Variance in Clinically Referred Populations

Gender Variance (GV)

Gender identity
differs from
sex assigned at birth

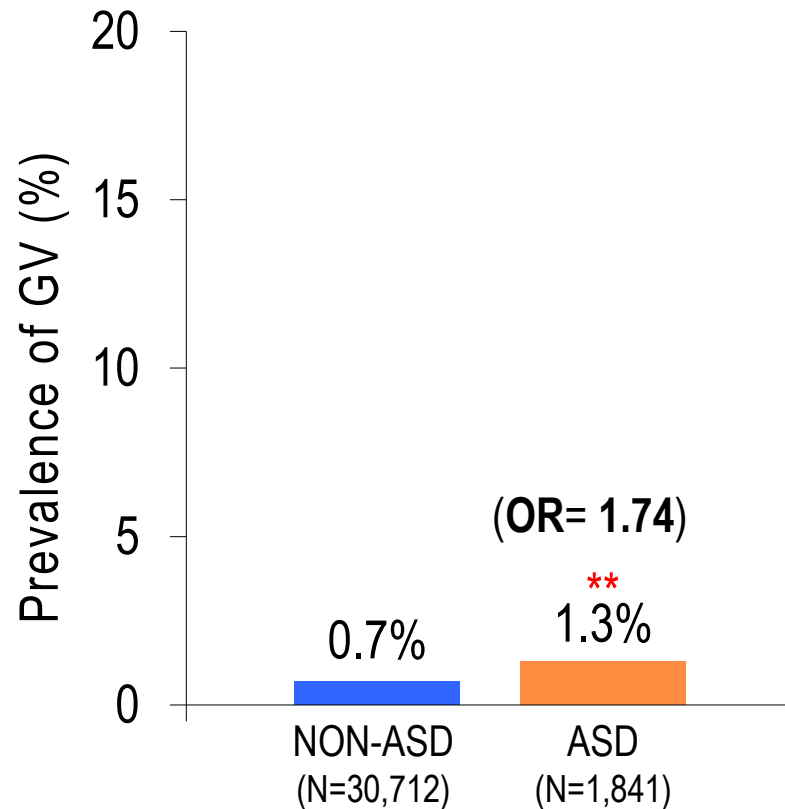
**Higher prevalence of GV in youth with
AUTISM**



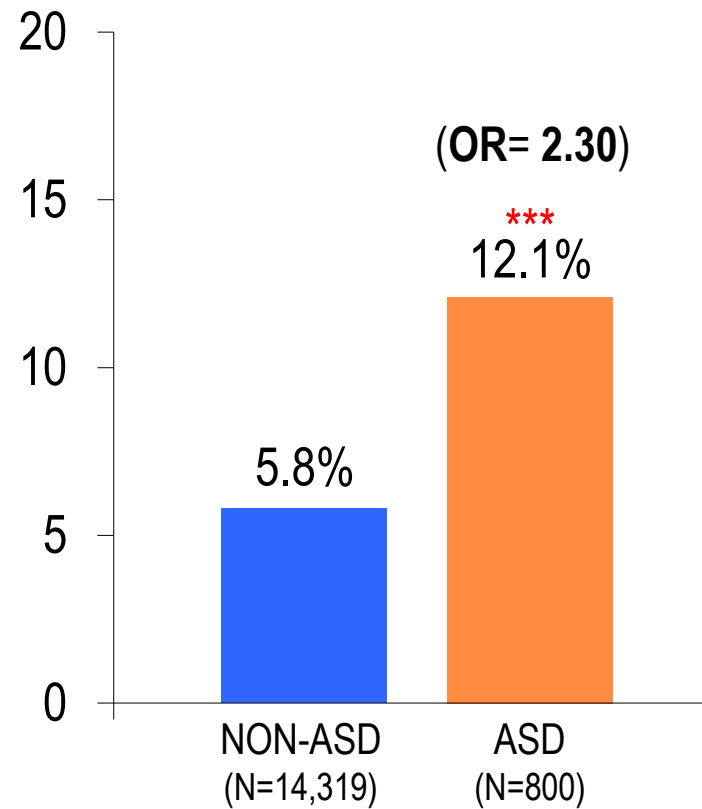
Statistical Significance: * $P \leq .05$, ** $P \leq .01$, *** $P \leq .001$

Prevalence of Gender Variance in AUTISM Across Lifespan

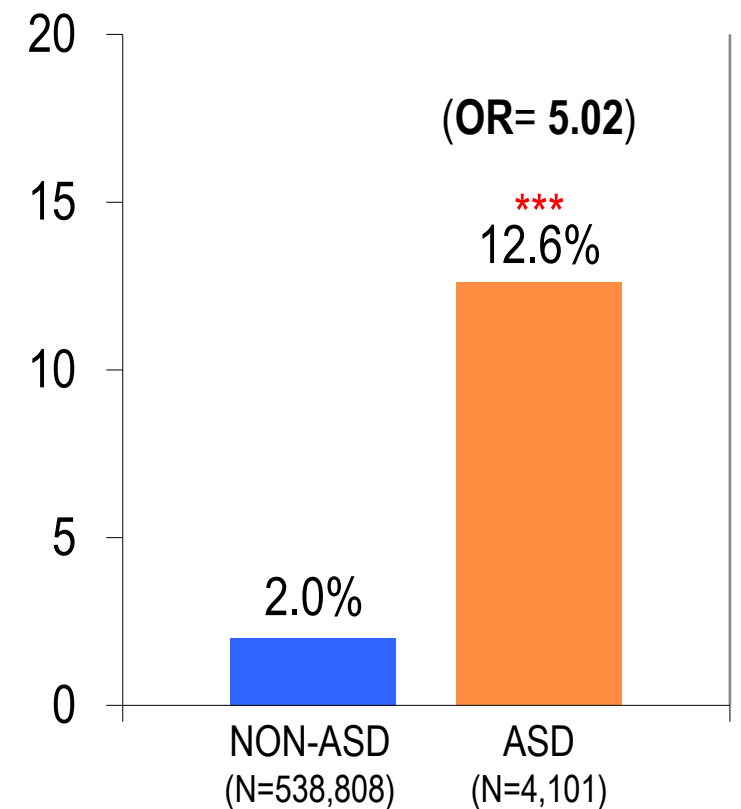
Children with ASD



Adolescents with ASD



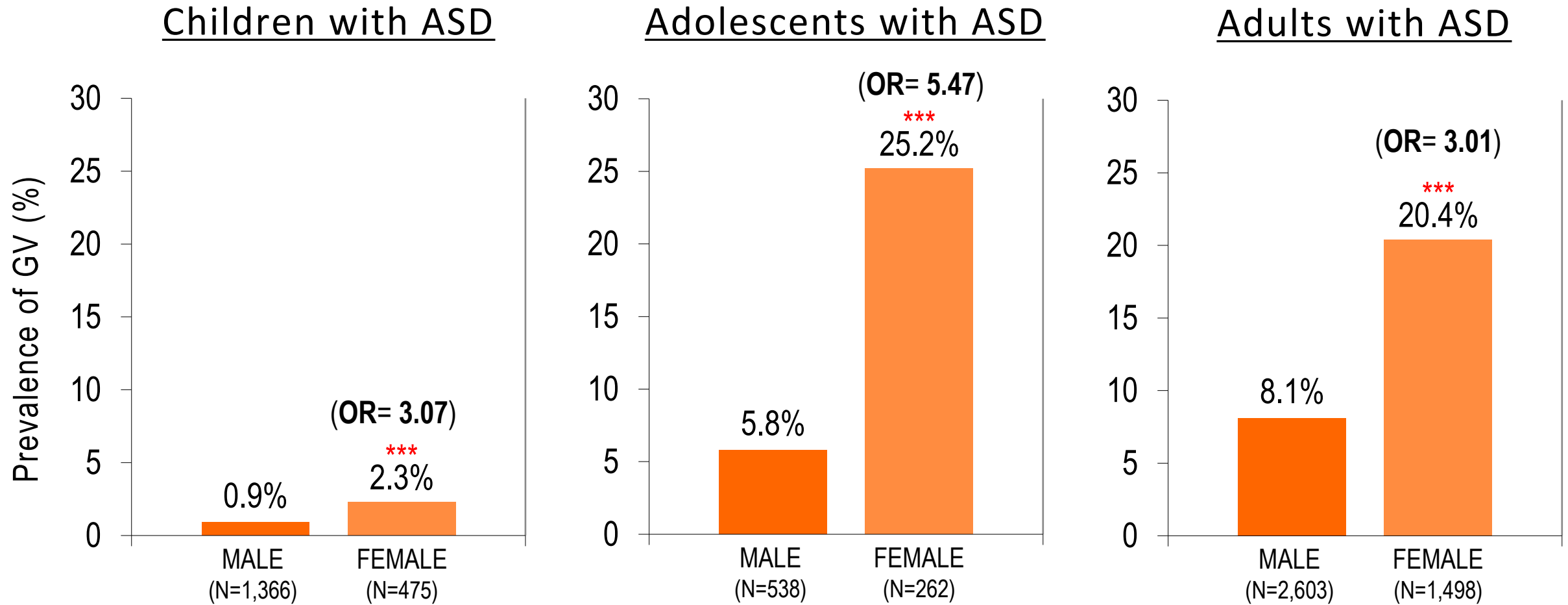
Adults with ASD



Statistical Significance: ** $P \leq .01$, *** $P \leq .001$

Higher rates of GV in AUTISM individuals assigned female at birth

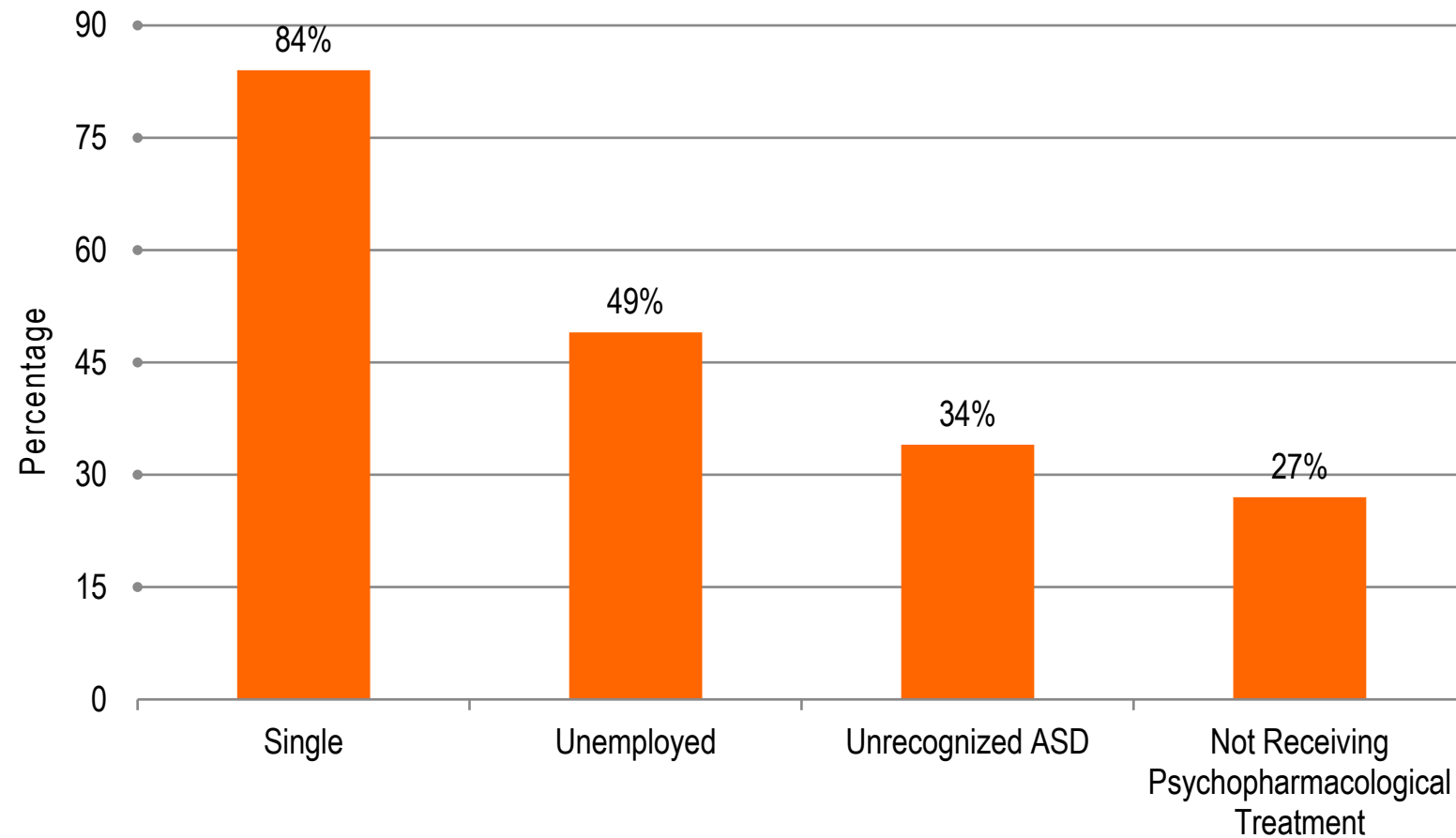
Prevalence of Gender Variance in AUTISM Based on Sex Assigned at Birth



Statistical Significance: *** $P \leq .001$

Higher rates of GV in AUTISM youth assigned female at birth

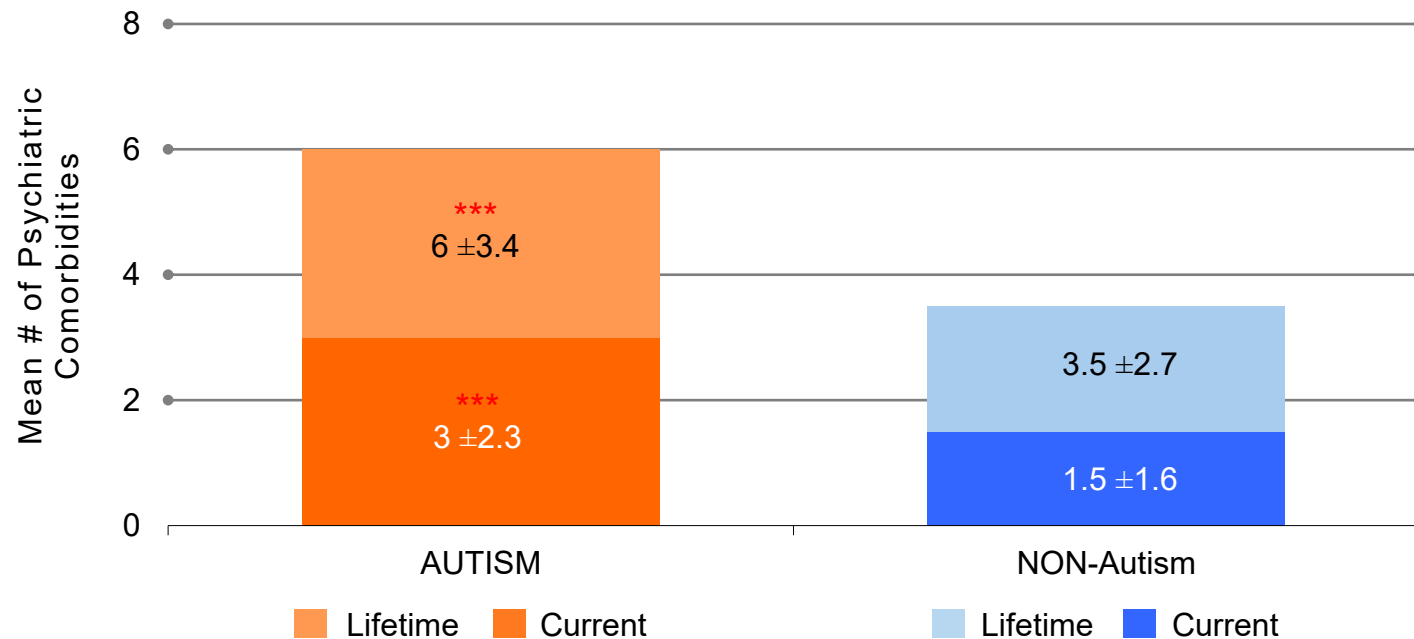
Characteristics of Adults Attending Specialized Clinic for AUTISM



Joshi et al., 2013

Burden of Psychopathology in Psychiatrically Referred Adults with AUTISM

Number of Psychiatric Comorbidities



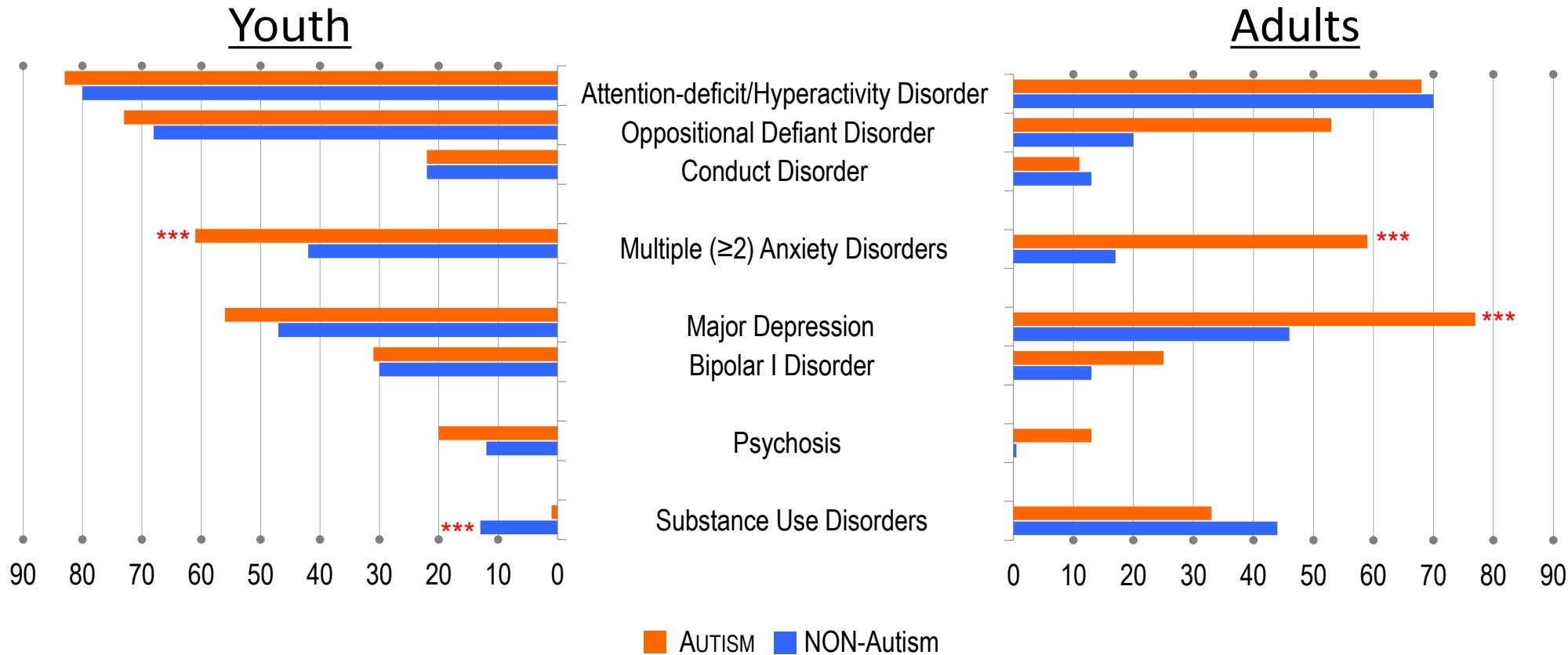
Statistical Significance: *** $p \leq 0.001$

Greater burden of psychiatric conditions in adults with AUTISM

Joshi et al., 2013

Psychopathology Associated with AUTISM in Psychiatrically Referred Populations

Lifetime Psychiatric Comorbidity



Statistical Significance: *** $p \leq 0.001$

Joshi et al., 2010, 2013

Red Flags for Assessing AUTISM

Features

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

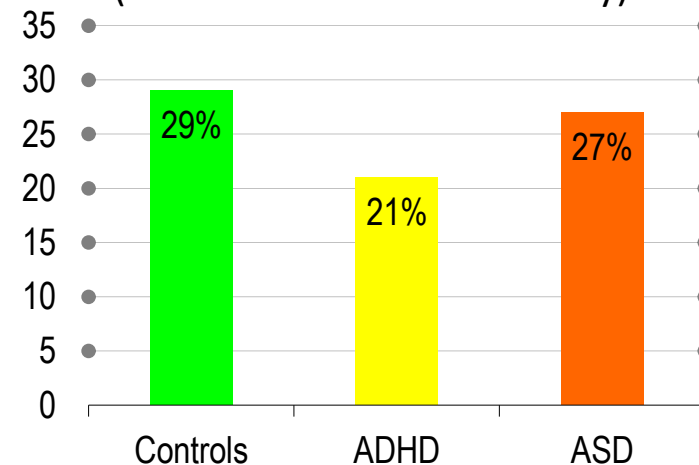
Psychiatric Disorders

- Reactive Attachment Disorder
- Social Communication Disorder
- Avoidant/restrictive food intake disorder (ARFID)
- Negative features of Schizophrenia
- Social Anxiety Disorder
- Pediatric onset OCD
- Cluster A Personality Disorder (Schizoid, Schizotypal)
- Cluster C Personality Disorder (Avoidant, Obsessive-Compulsive)

AUTISM Diagnostic Challenges: Institutional Factors & Myths

- AUTISM is diagnosed early in life
- Diagnosis of AUTISM requires:
 - Diagnostic tools: ADIR/ADOS
 - Genetic work-up (*Familial work-up*)
 - Neuropsychological assessment

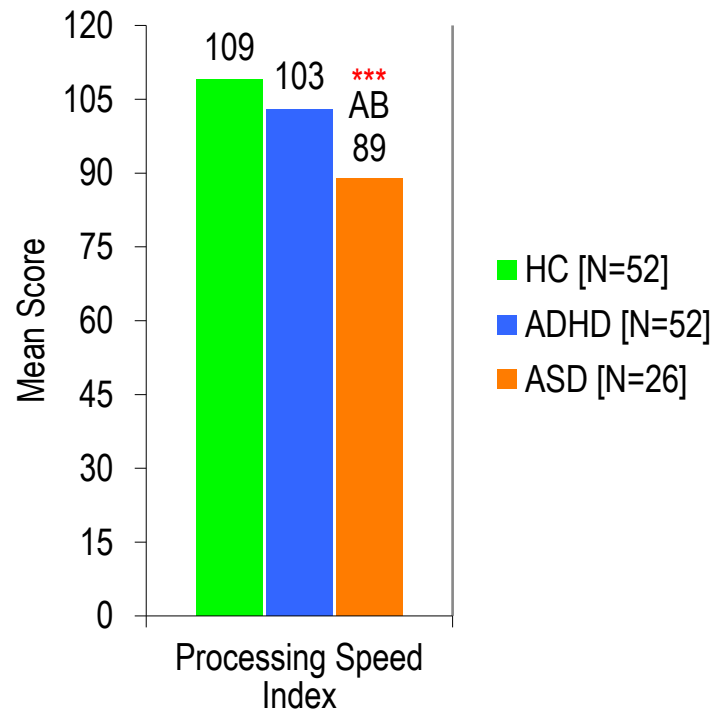
Performance IQ < Verbal IQ by 1 SD
(WASI Matrix and Vocabulary)



Neuropsychological Correlates of Intellectually Capable AUTISM

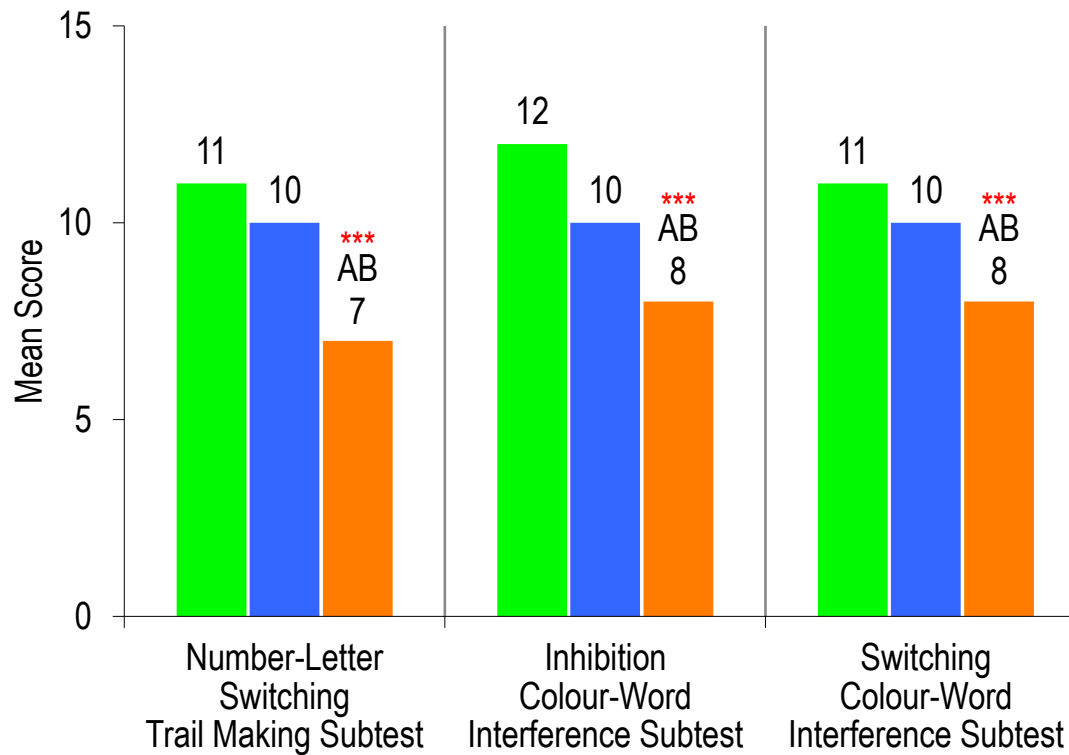
Processing Speed

Wechsler Adult Intelligence Scale
(WAIS-III)



Cognitive Flexibility

Delis Kaplan Executive Function System
(D-KEFS)

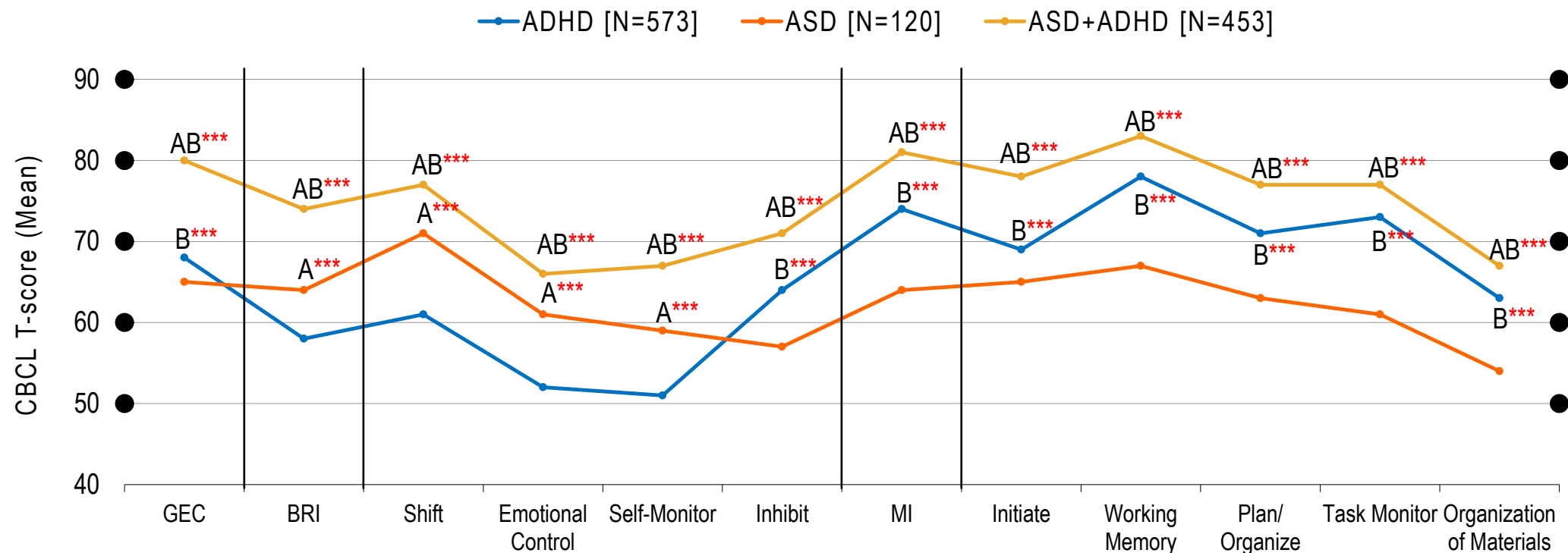


HC=Healthy Controls; A=Versus HC, B=Versus ADHD; Statistical Significance: ***p<0.001

Executive Dysfunction Profile

Levels of Executive function Impairments

(Behavior Rating Inventory of Executive Function – Adult Version [BRIEF-A])

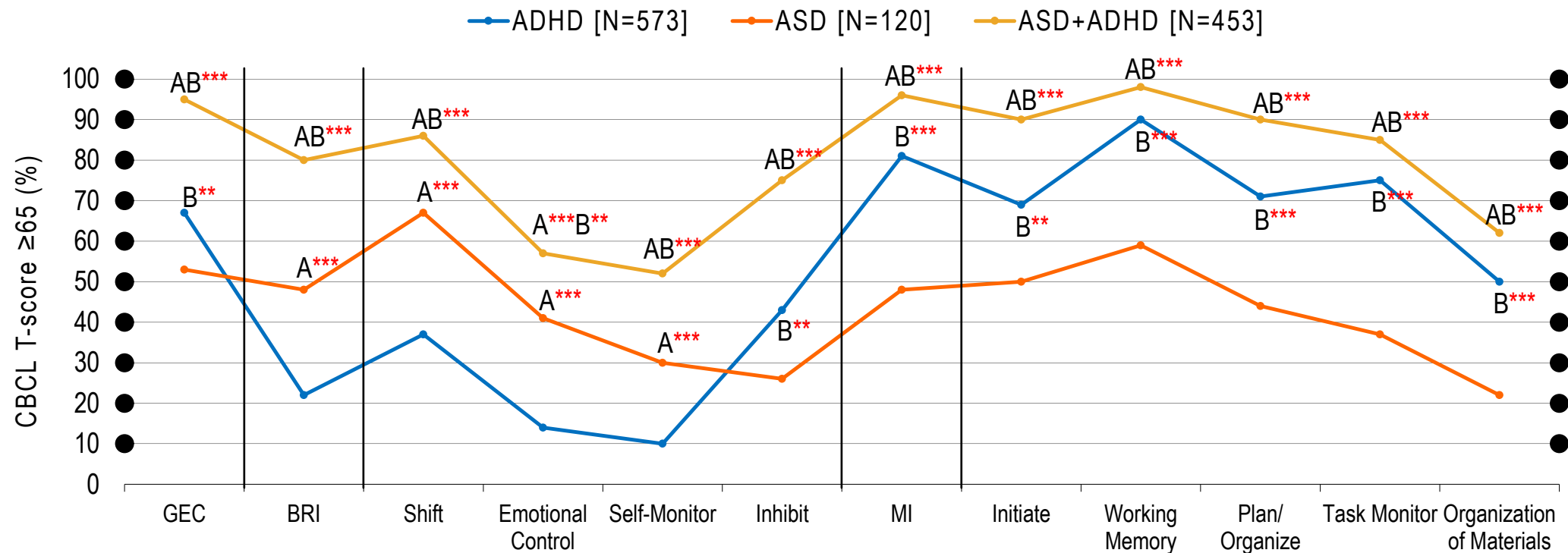


Statistical Significance: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Executive Dysfunction Profile

Frequency of Executive function Impairments

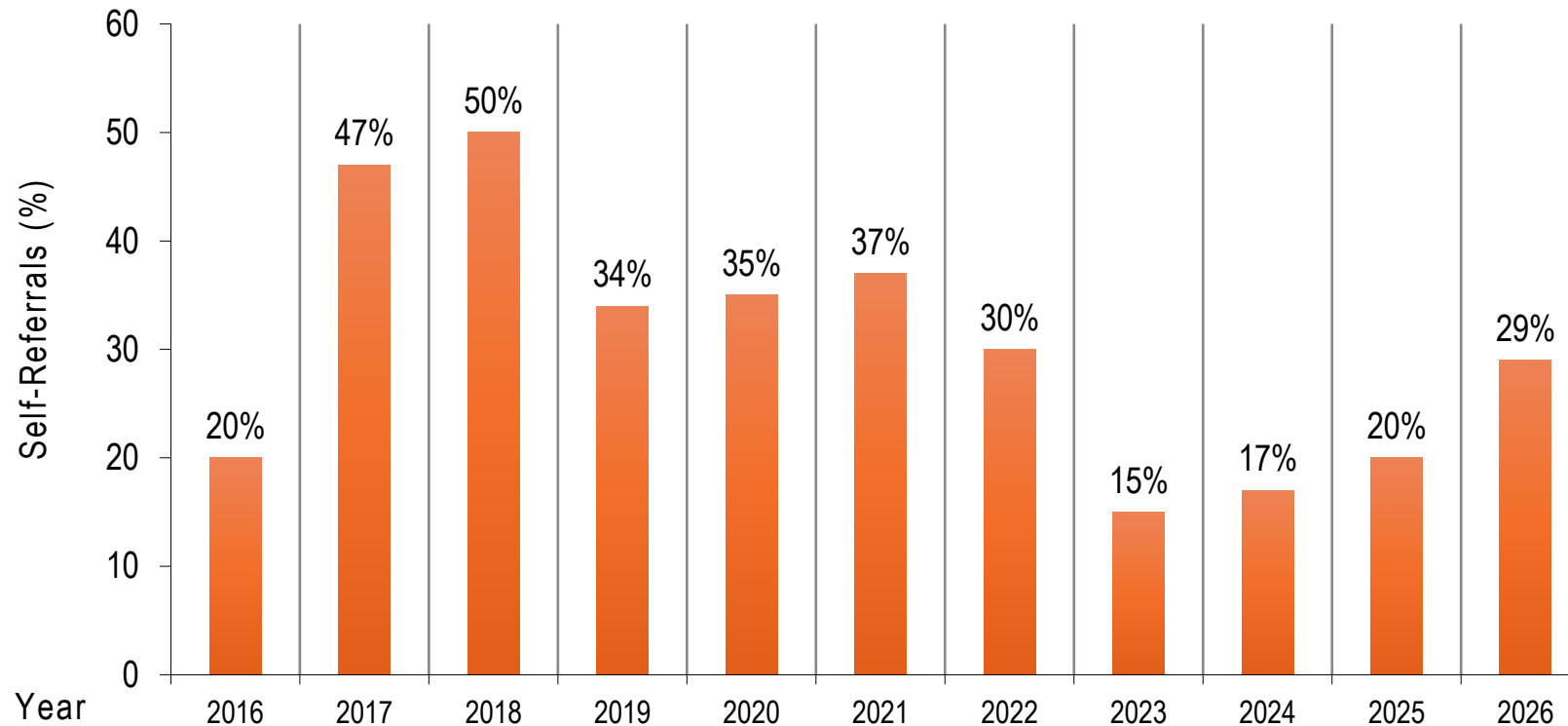
(Behavior Rating Inventory of Executive Function – Adult Version [BRIEF-A])



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

Self-Referrals for Autism Evaluation

Self-Referrals for Autism Evaluation to Bressler Program



**A significant proportion of Referrals for Evaluation of Autism
are Self-Referred**

Social Responsiveness Scale, Second Edition

- Informant- and self- rated screening instrument
- Quantitative measure of autism related social impairments
- Preschool (2.5-4.5 yrs.), School-age (4-18 yrs.), and Adult forms
- 65 item rating scale
- Each item on the scale is rated on a Likert scale from “1” (never true) to “4” (almost always true)
- Requires 15-20 minutes
- The psychometric properties of the SRS are well established (Excellent correspondence between SRS & ADI-R)

School-Age Form

Response Sheet

SRS™-2

Social Responsiveness Scale, Second Edition

John N. Constantino, MD



Child and Rater Information			
Child's name	Gender ☐ Male ☐ Female	Date of rating	Assessment ID
School or clinic		Child's age in years	Grade
Rater's name	Relationship to rated individual ☐ Mother ☐ Father ☐ Other custodial adult ☐ Teacher ☐ Other specialist		

Instructions: For each question, please circle the number that best describes this child's behavior over the past 6 months.

	Not True	Sometimes True	Often True	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 (for example, 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

Continued on next page

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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	Gets frustrated trying to get ideas across in conversations	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	Has repetitive, odd behaviors such as hand flapping or rocking
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	Can't get mind off thinking about something
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	Knows when he or she is too close to someone or is invading someone's space	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	Has difficulty answering questions directly and ends up talking around the subject	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	
			Avoids eye contact or has unusual eye contact	
			Gets teased a lot	
			Is awkward in turn-taking interactions with others	
			Wanders aimlessly from one activity to another	
			Talks to people with an unusual tone of voice	

Social Responsiveness Scale

Scoring Algorithm

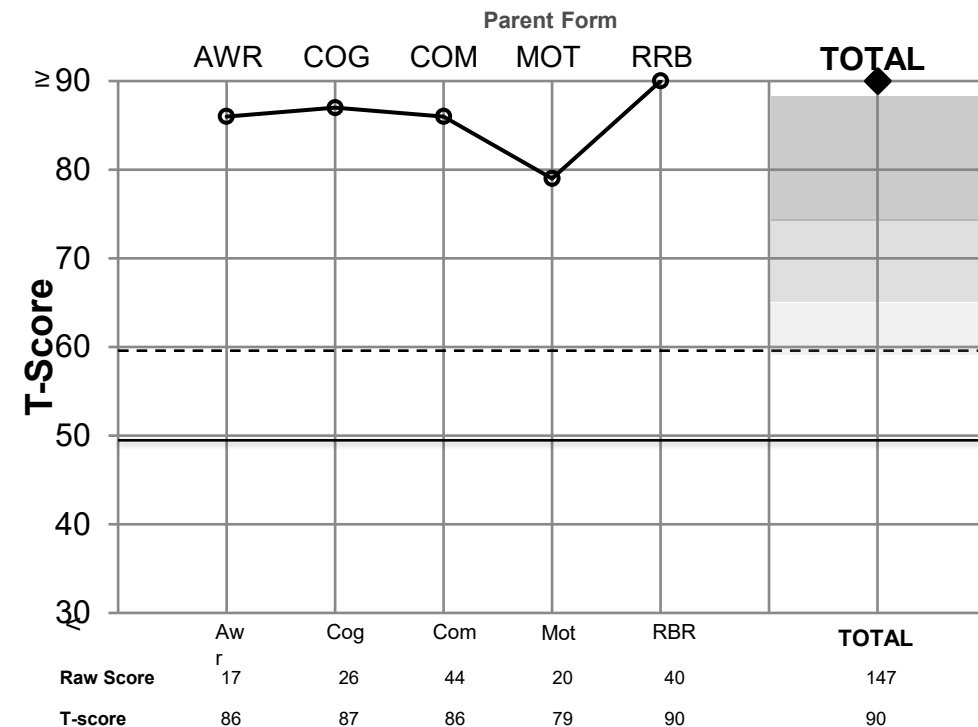
	Total Raw Score			T-Score
	School-Age*		Adult**	
	Male	Female		
<u>Severity Levels</u>				
Normal	≤ 57	≤ 51	≤ 67	≤59
Mild	58 - 72	52 - 65	68 - 84	60 - 65
Moderate	73 - 97	66 - 89	85 - 112	66 - 75
Severe	≥98	≥90	≥113	≥76
<u>Screening Threshold</u>				
Non-referred	≥70	≥70	≥70	
Referred	≥85	≥85	≥85	

*Informant-rated;

**Self & Observer-rated

*Informant-rated; **Self & Observer-rated

Scoring Results



Constantino & Gruber, 2002, 2012

MGH AUTISM SPECTRUM DISORDER DSM-5-TR 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)			

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%

Characterizing Driving Behavior in Young Adults with IC-AUTISM

The MIT AgeLab Driving Simulator



Difficulties attending to the roadway:

- Higher vertical gaze position
- Wider dispersion of horizontal gaze scanning
- Focus more on the median



Drive at higher level of arousal:

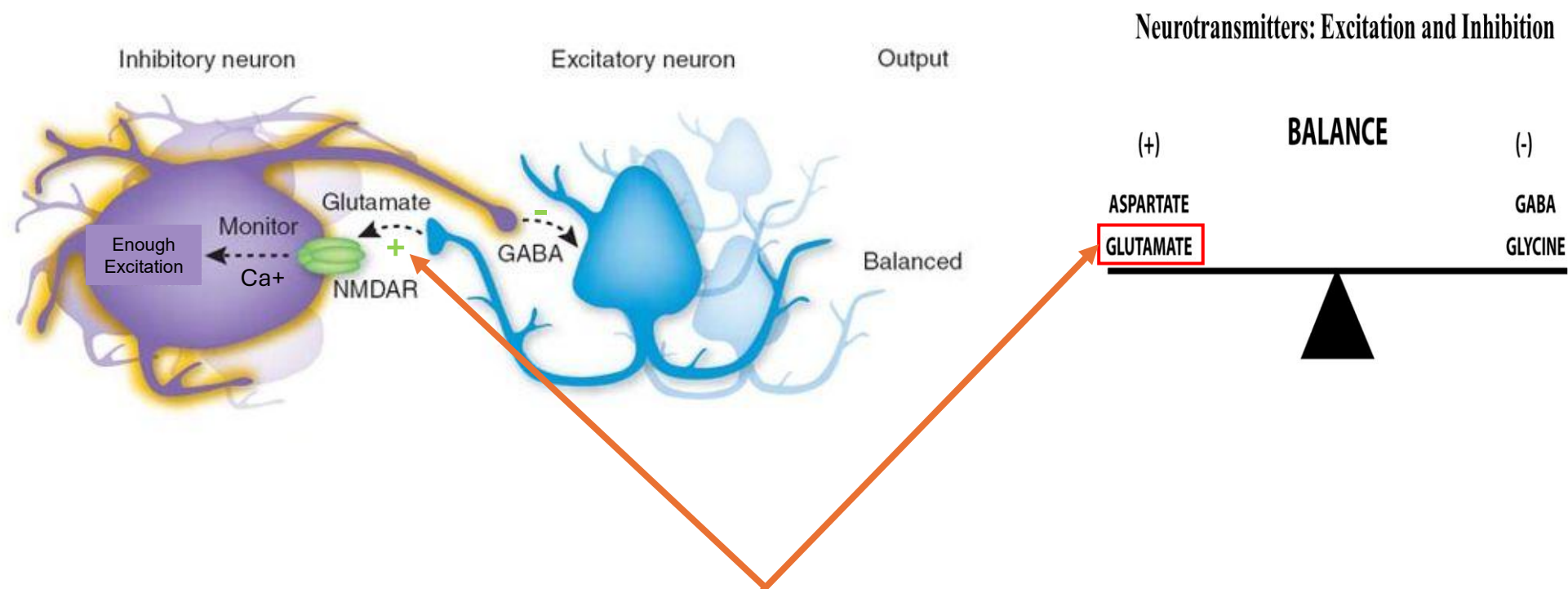
- Increased level of anxiety

Impaired driving ability associated with AUTISM

Reimer, Fried, Biederman et al., 2013

Excitatory-Inhibitory Imbalance in AUTISM

Glutamate – GABA Dysregulation in ASD

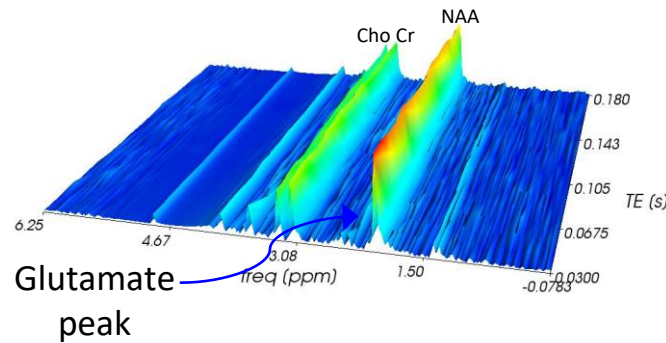


Excessive glutamate activity in AUTISM leads to excitotoxic synaptic damage

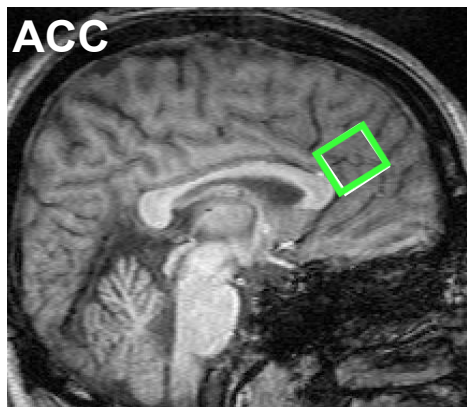
MRS Glutamate Levels in *pregenual* Anterior Cingulate Cortex

Proton Spectroscopy in Youth with HF-ASD

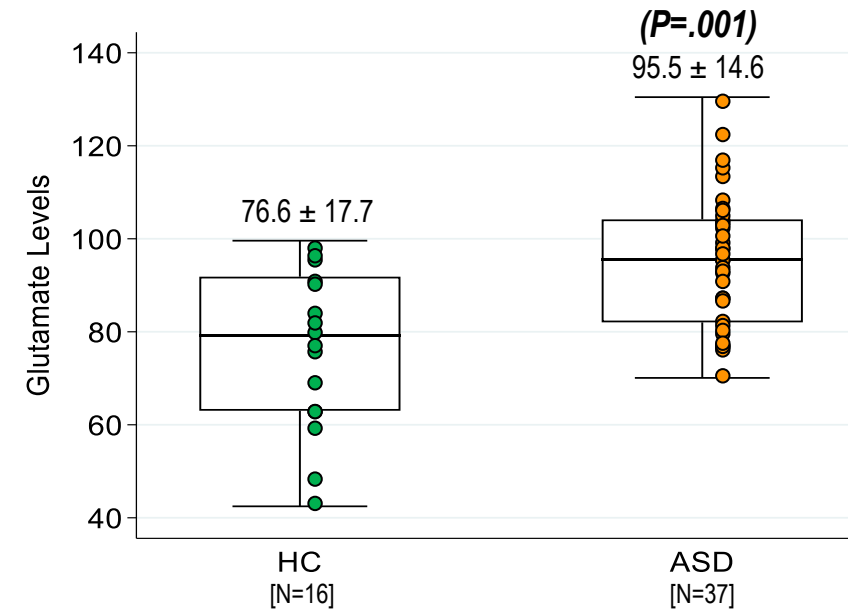
TE - Stepped (J-PRESS) Spectrum



Voxel Placement at *pregenual* ACC

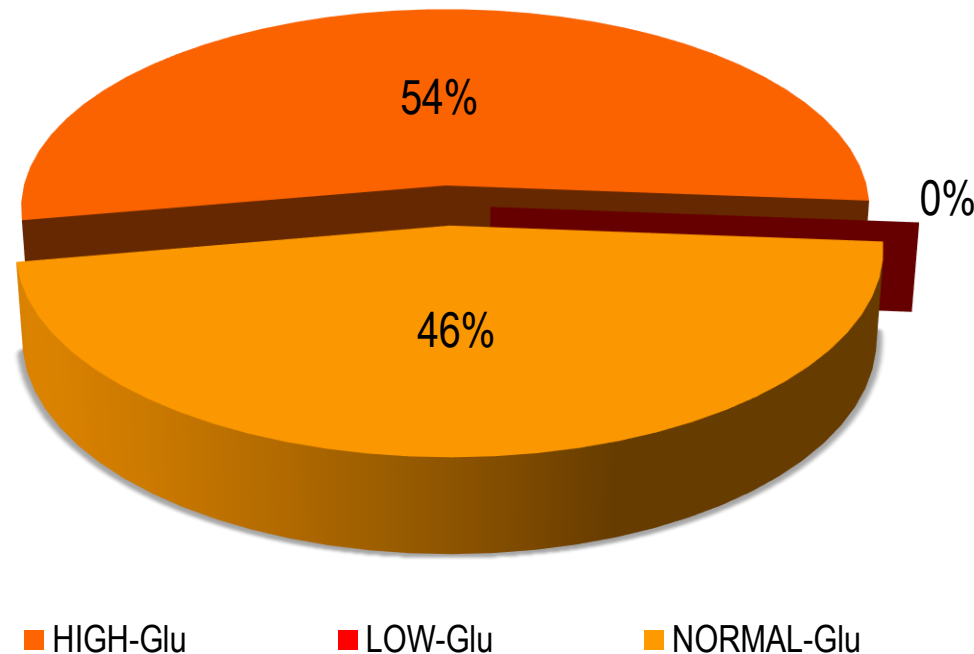


Baseline Glutamate Levels in PgACC



**Abnormally High *pg*ACC Glutamate levels in
AUTISM**

Prevalence of HIGH-Glutamate Levels in AUTISM



More than half of the intellectually intact youth with AUTISM present with abnormally high *pg*ACC glutamate levels in the brain



Original Investigation | Psychiatry

Memantine to Treat Social Impairment in Youths With Autism Spectrum Disorder A Randomized Clinical Trial

Gagan Joshi, MD; Atilla Gönenc, PhD; Maura DiSalvo, MPH; Stephen V. Faraone, PhD; Tolga Atilla Ceranoglu, MD; Amy M. Yule, MD; Mai Uchida, MD; Christopher J. McDougle, MD; Janet Wozniak, MD

Abstract

IMPORTANCE Pharmacologic interventions for addressing social impairments in autism spectrum disorder (ASD) are lacking. Proton magnetic resonance spectroscopy (1H-MRS) studies in individuals with ASD have documented altered glutamate levels in the pregenual anterior cingulate cortex (pgACC).

OBJECTIVES To evaluate the safety and efficacy of memantine for treating social impairments in youths with ASD and to explore pgACC glutamate levels as a potential biomarker for treatment response.

DESIGN, SETTING, AND PARTICIPANTS This 12-week, placebo-controlled, double-blind, parallel-design randomized clinical trial was conducted between January 20, 2015, and July 11, 2018. The study population comprised youths aged 8 to 17 years with ASD without intellectual disability ($IQ \geq 85$) recruited from ambulatory psychiatry clinics at an academic institution. Age- and sex-matched healthy control participants provided reference data for pgACC glutamate levels. Data analysis was conducted between January 7, 2020, and December 19, 2024.

INTERVENTIONS Participants with ASD were randomized to memantine or placebo, with dose titration up to 20 mg/d. 1H-MRS scans were acquired to assess pgACC glutamate levels.

Key Points

Question Does treatment with memantine improve social functioning in youths with autism spectrum disorder (ASD) without intellectual disability?

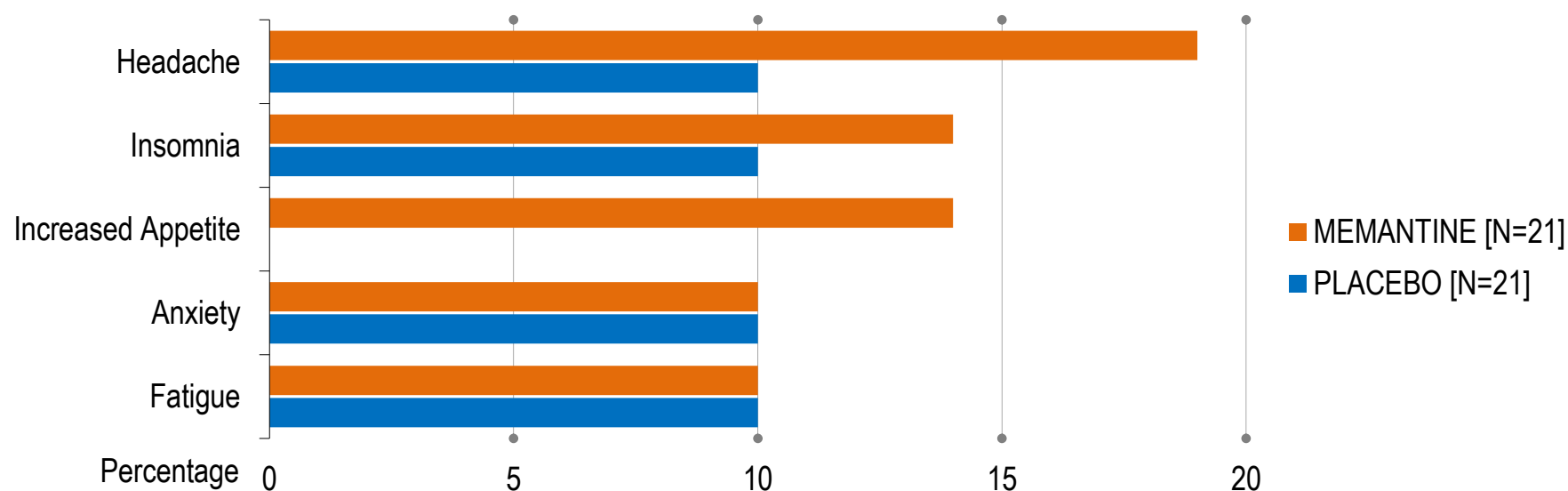
Findings In this randomized clinical trial that included 42 youths with ASD, memantine was well tolerated and significantly improved social impairments, particularly in youths with abnormally high glutamate levels in the pregenual anterior cingulate cortex region of the brain.

Meaning Memantine appears to be safe and effective for treating social impairments in patients with autism, particularly for those with glutamate dysregulation.

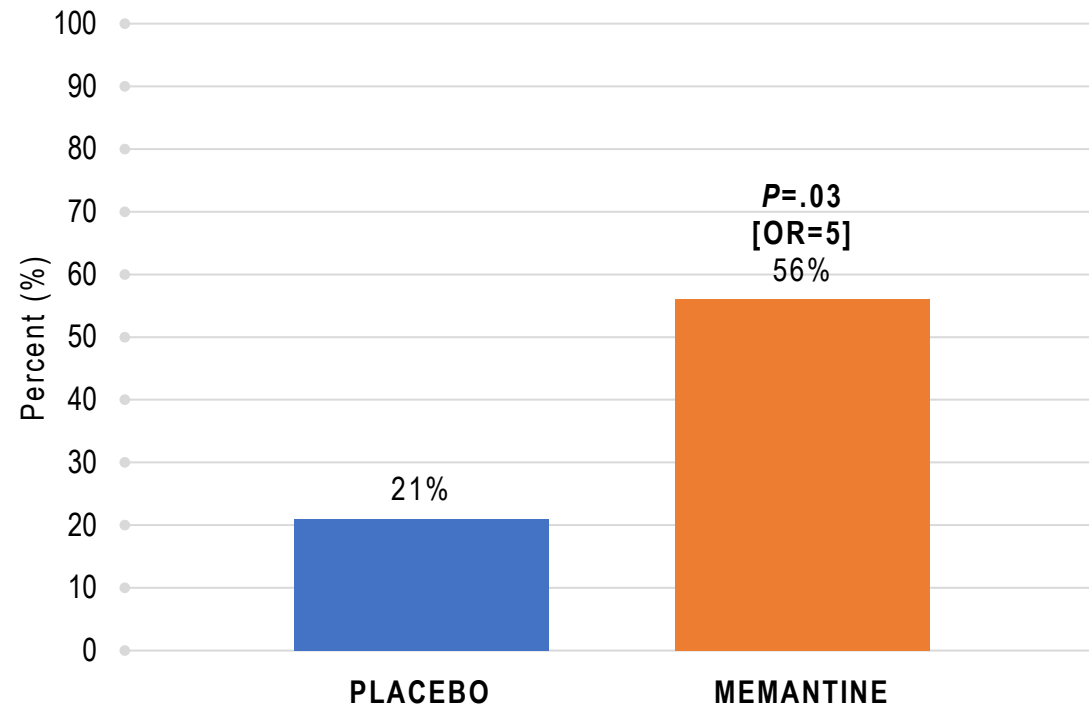
Tolerability

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)



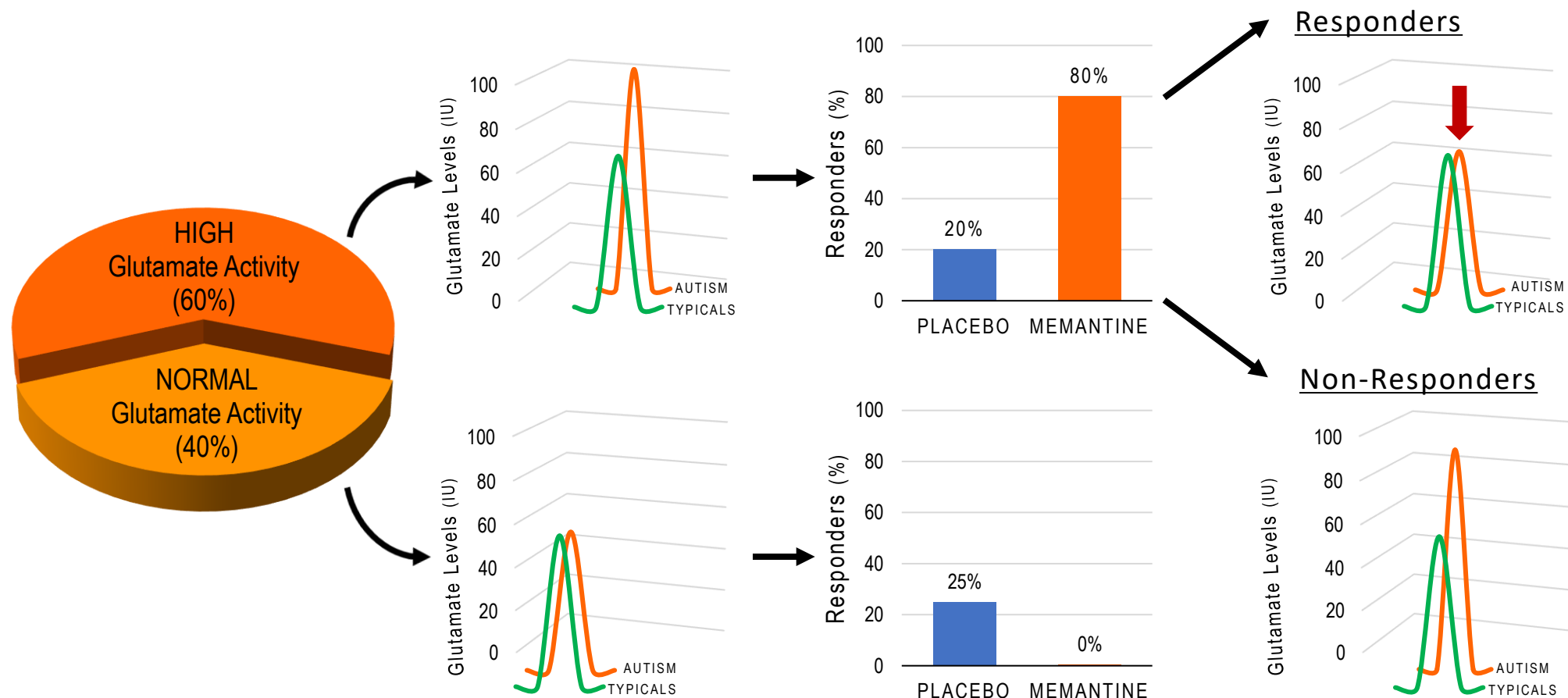
Memantine Treatment Responders



Response criteria: $\geq 25\% \downarrow$ SRS+ASD-CGI-I ≤ 2

Brain Glutamate Activity

Memantine Treatment



A Prospective Open-Label Trial of Memantine Hydrochloride for the Treatment of Social Deficits in Intellectually Capable Adults With Autism Spectrum Disorder

Gagan Joshi, MD,*† Janet Wozniak, MD,*† Stephen V. Faraone, PhD,‡§ Ronna Fried, EdD,*† James Chan, MA,* Stephannie Furtak, BA,* Emily Grimsley, BS,* Kristina Conroy, BA,* J. Ryan Kilcullen, BA,* K. Yvonne Woodworth, BA,* and Joseph Biederman, MD*†

Abstract: This prospective 12-week open-label trial evaluates the tolerability and efficacy of memantine hydrochloride for the treatment of core social and cognitive deficits in adults with high-functioning autism spectrum disorder (ASD). Measures for assessment of therapeutic response included the Social Responsiveness Scale-Adult Research Version (SRS-A), disorder-specific Clinical Global Impression scales, Behavior Rating Inventory of Executive Functioning-Adult Self-Report, Diagnostic Analysis of Nonverbal Accuracy Scale, and Cambridge Neuropsychological Test Automated Battery. Eighteen adults (mean age, 28 ± 9.5 years) with high-functioning ASD (SRS-A raw score, 99 ± 17) were treated with memantine (mean dose, 19.7 ± 1.2 mg/d; range, 15–20 mg), and 17 (94%) completed the trial. Treatment with memantine was associated with significant reduction on informant-rated (SRS-A, -28 ± 25 ; $P < 0.001$) and clinician-rated (Clinical Global Impression-Improvement subscale ≤ 2 , 83%) measures of autism severity. In addition, memantine treatment was associated with significant improvement in ADHD and anxiety symptom severity. Significant improvement was noted in nonverbal communication on the Diagnostic Analysis of Nonverbal Accuracy Scale test and in executive function per self-report (Behavior Rating Inventory of Executive Functioning-Adult Self-Report Global Executive Composite, -6 ± 8.8 ; $P < 0.015$) and neuropsychological assessments (Cambridge Neuropsychological Test Automated Battery). Memantine treatment was generally well tolerated and was not associated with any serious adverse events. Treatment with memantine appears to be beneficial for the treatment of ASD and associated psychopathology and cognitive dysfunction in intellectually capable adults. Future placebo-controlled trials are warranted.

Key Words: autism spectrum disorder, memantine, adults, treatment, psychopharmacology

(*J Clin Psychopharmacol* 2016;36: 00–00)

Journal of Clinical Psychopharmacology • Volume 36, Number 3, June 2016

comorbid psychopathology including attention-deficit/hyperactivity disorder (ADHD), mood and anxiety disorders, and cognitive dysfunction.^{2–4} Although there are drugs to treat irritability and hyperactivity in ASD, to date, no medications have been shown to reliably improve core features of the disorder.^{5,6}

Emerging evidence on the safety and efficacy of glutamatergic agents for the treatment of social deficits in ASD is encouraging. Glutamate (Glu) dysregulation has been documented in ASD. Serological, postmortem brain, genetic, and spectroscopic neuroimaging research suggests increased Glu activity in ASD.^{7–12} Significantly increased spectroscopic levels of Glu have been documented in the anterior cingulate cortex of adolescent males with high-functioning ASD (HF-ASD) versus controls.¹³ The empirical evidence of Glu-modulating agents lamotrigine, amantadine, and D-cycloserine as potential treatments for the core symptoms of ASD is modest at best.^{14–16} Memantine hydrochloride is a moderate-affinity, noncompetitive, N-methyl-D-aspartate receptor antagonist. Memantine is approved by the US Food and Drug Administration to treat moderate to severe Alzheimer disease.¹⁷ Memantine has also been explored as a treatment for psychiatric disorders including obsessive-compulsive disorder (OCD), bipolar disorder, and ADHD.¹⁸ Open-label trials (OLTs) of memantine report improvement in symptoms of ADHD and executive dysfunction (ED) in adults with ADHD.^{19,20} To date, with the exception of a single pediatric trial that included a small number of adults,²¹ memantine trials in ASD are limited to children and adolescents; these trials report acceptable tolerability with improvement in attention, hyperactivity, irritability, language, social interaction, and repetitive behaviors.^{22–25} Evidence in intellectually capable populations of adults with ASD is lacking. The primary aim of this study was to evaluate the efficacy, safety, and tolerabil-

12-week Open-label Trial

Demographic Characteristics

Participants

Total participants	18
Gender (<i>male</i>)	14 (78%)
Ethnicity (<i>Caucasian</i>)	18 (100%)

Age (*years*)

Mean	28 ±9.6
Range	18-47

Full Scale IQ

Mean	106 ±15
Range	75 - 125

Study Medication

- Memantine: 5 mg & 10 mg tablets
- Taken in divided dosage (AM & Afternoon)

Flexible Dose Titration Schedule

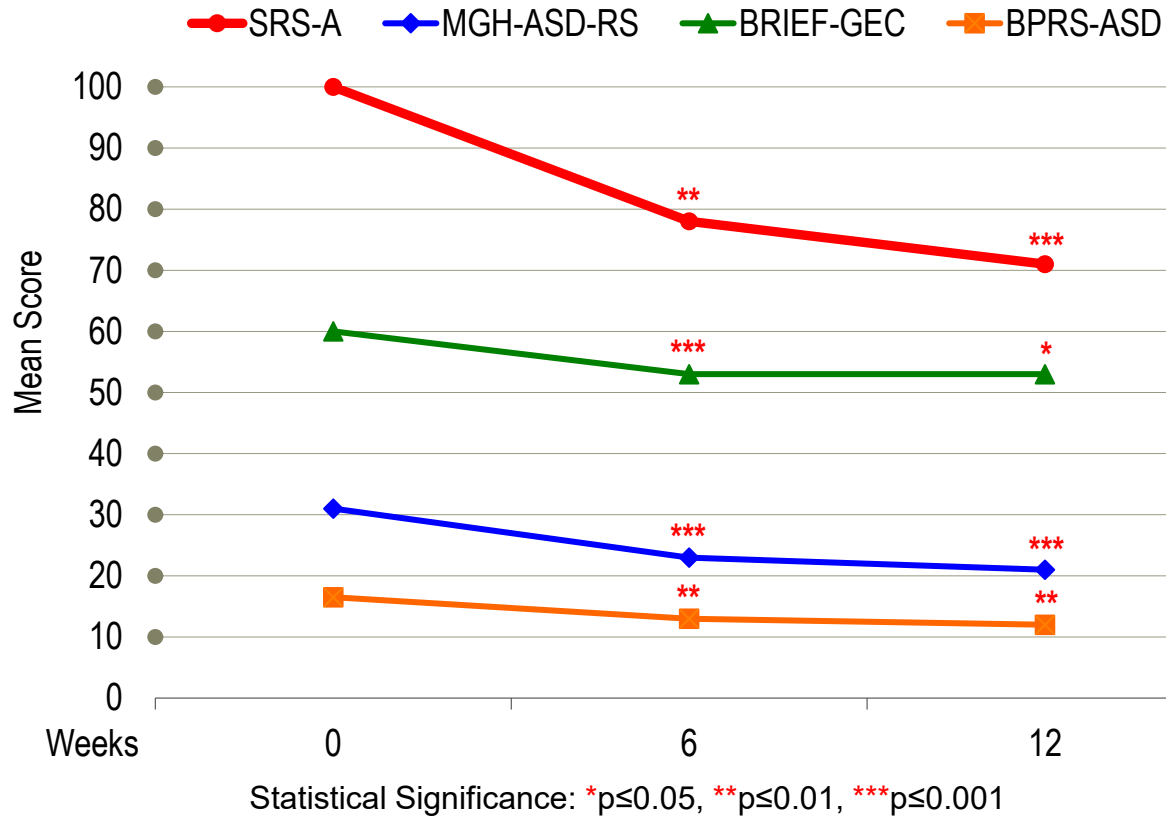
Duration (<i>Weeks</i>)	Maximum Dose
0-1	5 mg/day
1-2	10 mg/day
2-3	15 mg/day
4-12	20 mg/day

Study Medication (Memantine)

Mean dose [Range]	19.7 ±1.2 [15-20] mg/day
At dose 20 mg/day	17 (94%)
At dose 15 mg/day	01 (6%)

AUTISM Features: Treatment Response

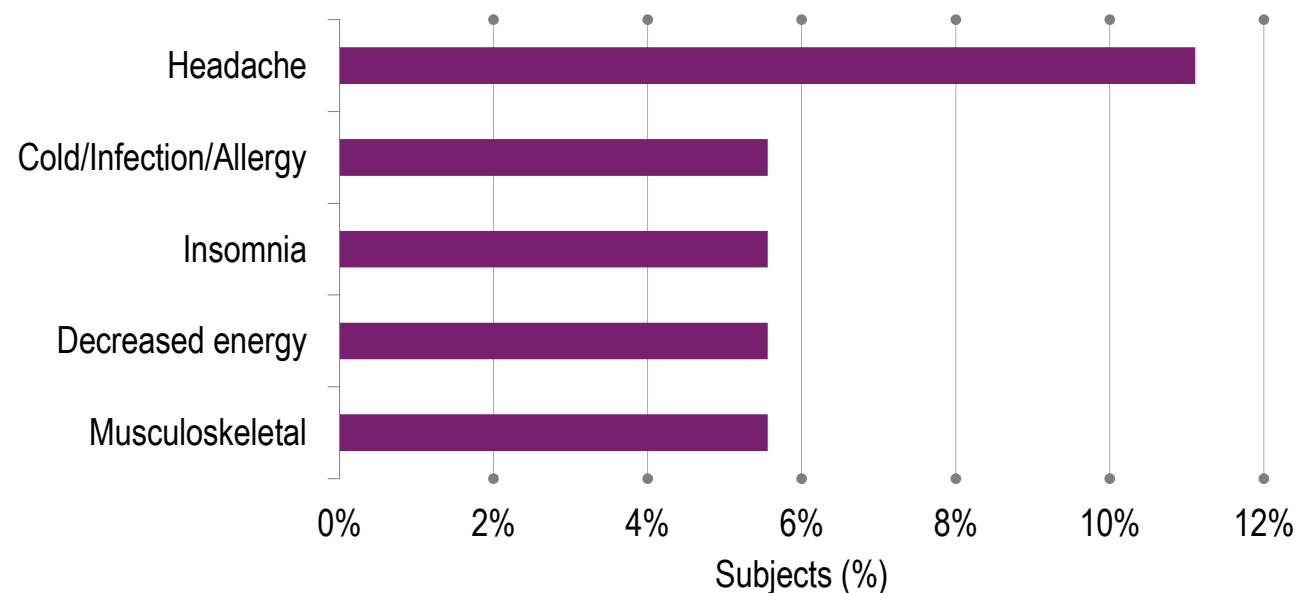
Self-, Informant-, & Clinician-Rated Measures



Significant improvement in social behaviors with memantine treatment

Adverse Events

Adverse Events (reported >1 visit)



Experienced any AEs: 6 (33.3%)

Serious AEs: None

Treatment Limiting AEs: N=1
*Decreased energy,
emotional numbness,
feeling dissociated,
feeling on edge
(resolved on d/c)*

Memantine treatment was very well tolerated by adults with AUTISM

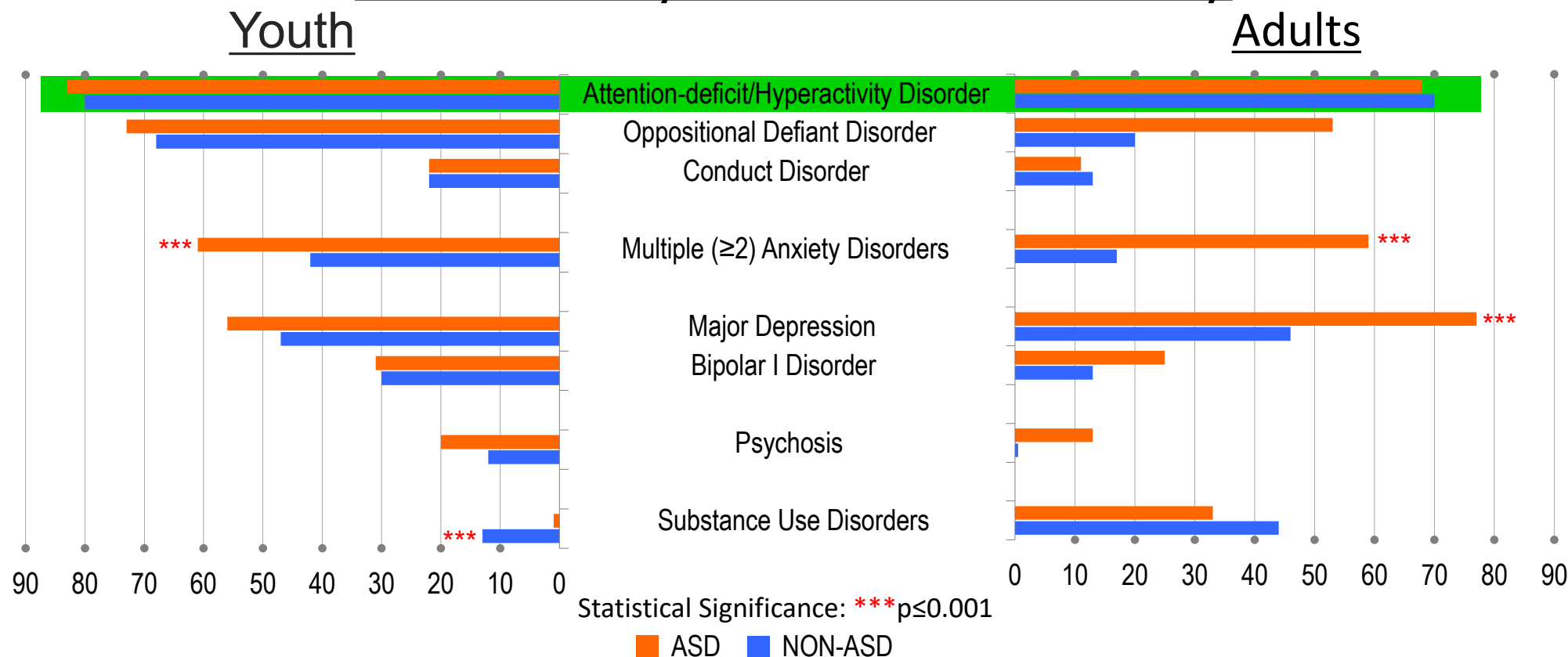
Memantine Response with Age

ASD-CGI-Improvement Score @ Endpoint

Subject	Age (yrs.)	Sex	ASD-CGI-I @ Endpoint
1	18	M	Much Improved
2	19	M	Much Improved
3	20	M	Much improved
4	20	M	Very much improved
5	20	M	Very much improved
6	22	M	Much Improved
7	23	M	Much improved
8	24	M	Very much improved
9	24	M	Much Improved
10	24	F	Much improved
11	29	M	Much improved
12	31	F	No change
13	31	M	Much Improved
14	33	F	Very Much Improved
15	38	M	Much Improved
16	43	F	(D/O @ Week-9) Minimally worse
17	45	M	Much improved
18	47	M	(D/O @ Week-1) No Change
19	47	M	Much Improved

Psychopathology Associated with ASD In Psychiatrically Referred Populations

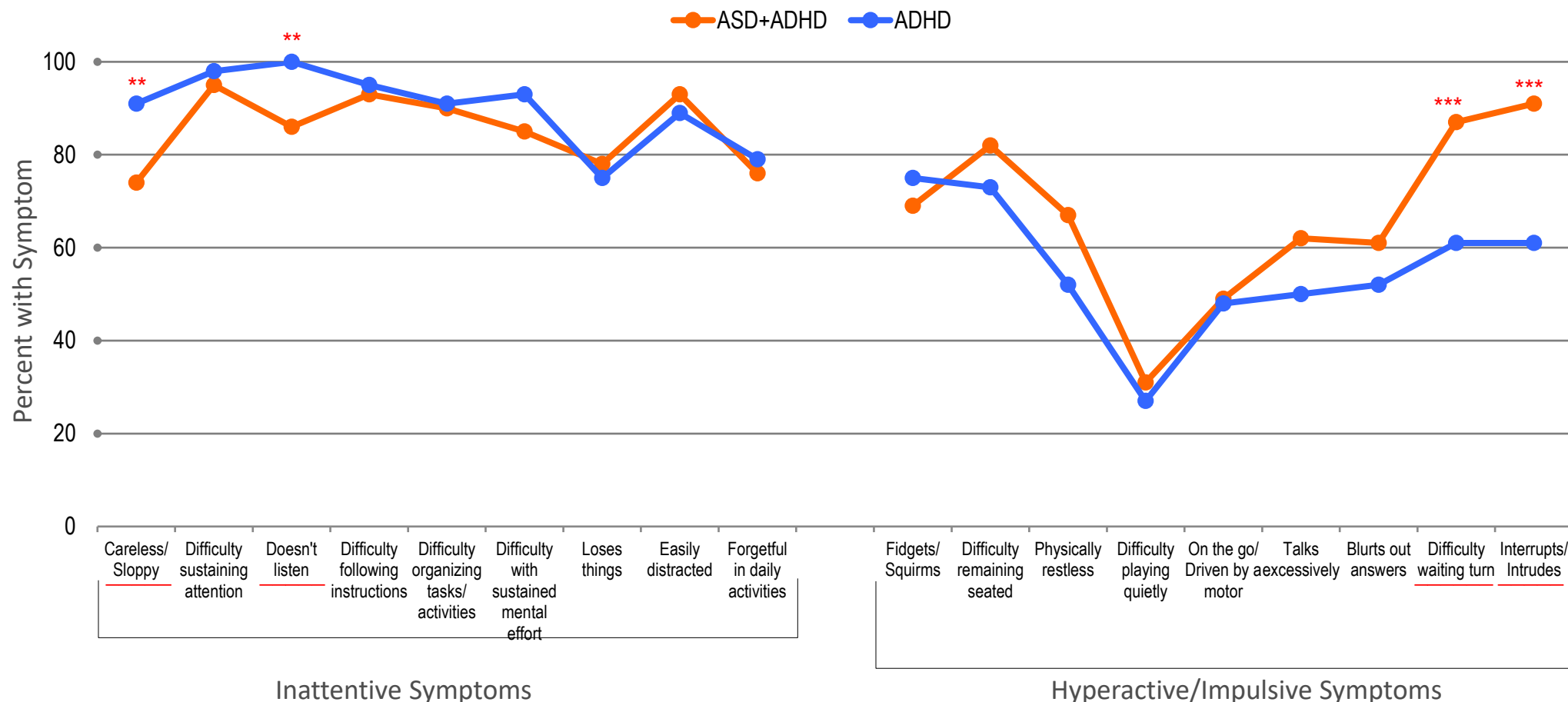
Lifetime Psychiatric Comorbidity



ADHD is the most frequent psychiatric disorder associated with AUTISM

Joshi et al., 2010, 2013

ADHD Symptom Profile in ASD



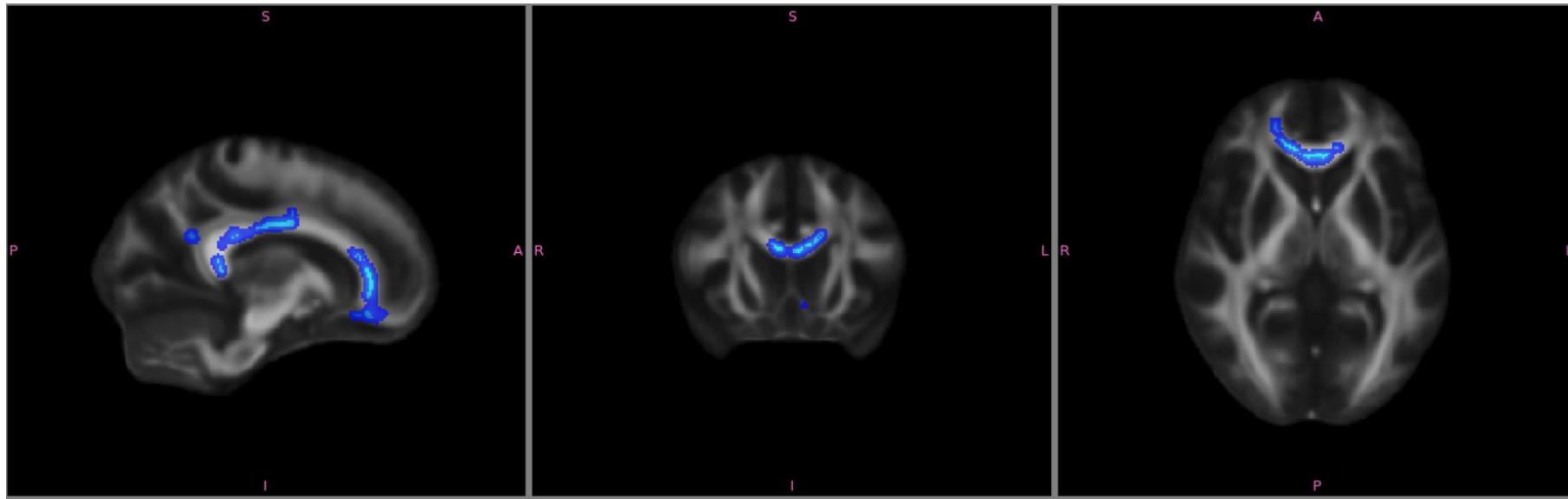
Statistical Significance: *p<0.05, **p<0.01, ***p<0.001

Typically expected presentation of ADHD in youth with Autism

Joshi et al., 2014

Diffusion Tensor Imaging Findings in ADHD $\pm$ ASD

Typical ADHD Profile of DTI Underconnectivity Observed in ASD Youth with ADHD



Cingulum-Corpus Callosal tracts DTI underconnectivity shared between ADHD youth with and without ASD

Hung, Joshi et al., 2023

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
- No controlled trials in Adults with ASD

Campbell et al., 1972 & 1976; Handen et al., 2000; Stigler et al., 2004



The World Journal of Biological Psychiatry

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A prospective open-label trial of long-acting liquid methylphenidate for the treatment of attention deficit/hyperactivity disorder in intellectually capable adults with autism spectrum disorder

Gagan Joshi, Maura DiSalvo, Janet Wozniak, T. Atilla Ceranoglu, Amy Yule, Craig Surman, Ronna Fried, Maribel Galdo, Barbora Hoskova, Abigail Belser & Joseph Biederman

OLT of MPH in Adults with AUTISM

Participant Characteristics (N=15)

- Adults aged 19-34 years (Mean age: 25 $\pm$ 4.5 years)
- Intact intellectual ability (IQ Range: 99 – 144)
- Met the DSM-5 criteria for ASD and ADHD
- At least moderate level of severity for ASD and ADHD (SRS= $\geq$ 85; AISRS= $\geq$ 24; & respective CGI-S $\geq$ 4)
- Not experiencing sign. symptoms of anxiety or mood dysregulation

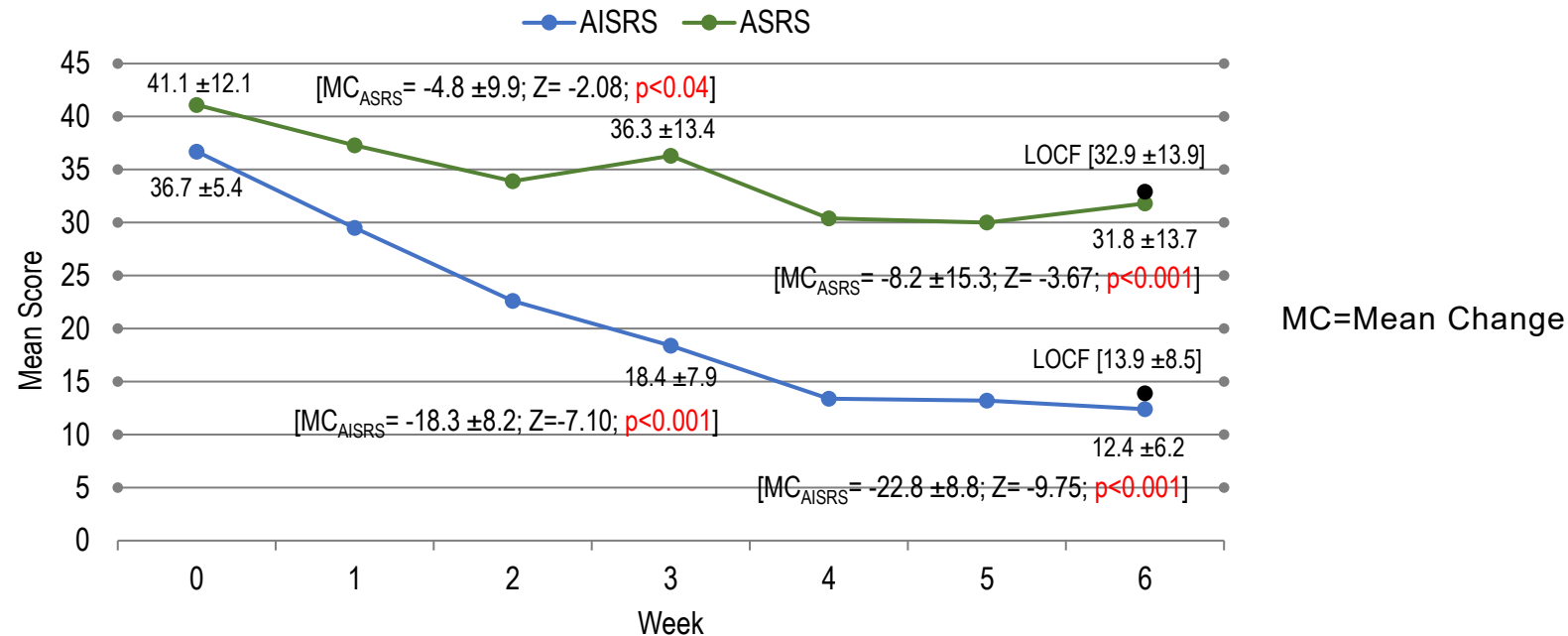
Study Medication (MPH-ER Liquid Formulation: 25mg/5mL)

Flexible Dose Titration Schedule		Study Medication (MPH-ER)	
Duration	QAM Dose	Mean dose: 49 $\pm$ 15 mg/day	
Initial dose:	5 mg/day	At Dose:	60 mg/day 08 (53%)
Titration phase (0-3 weeks):	5-60 mg/day		50 mg/day 02 (13%)
Maintenance phase (4-6 weeks):	Max. achieved dose		20-40 mg/day 05 (33%)

Treatment Response: ADHD Symptoms

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

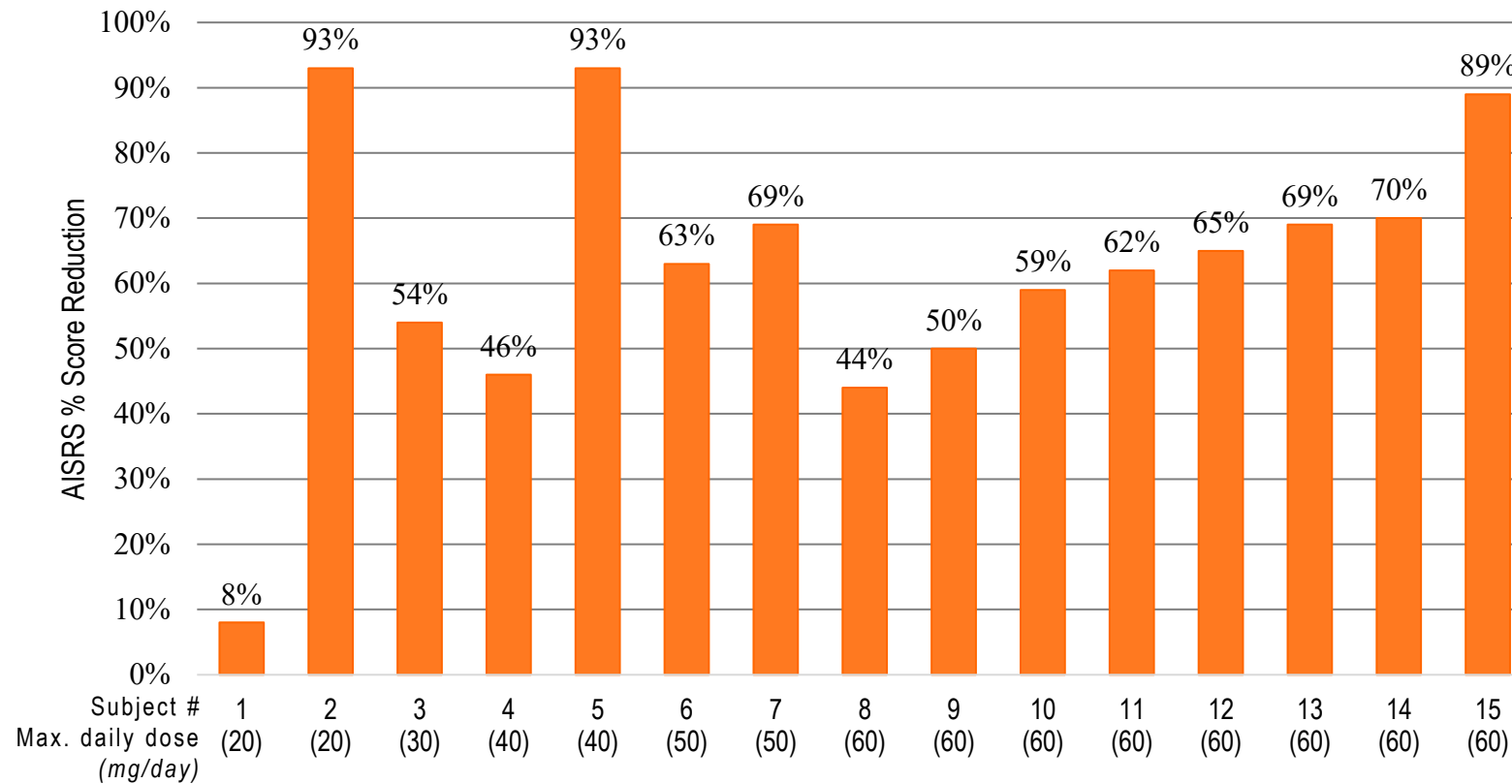
Patient-Rated: Adult Self-Report Scale (ASRS)



Significant improvement with treatment in the symptom severity of ADHD, as reported by participants and clinicians

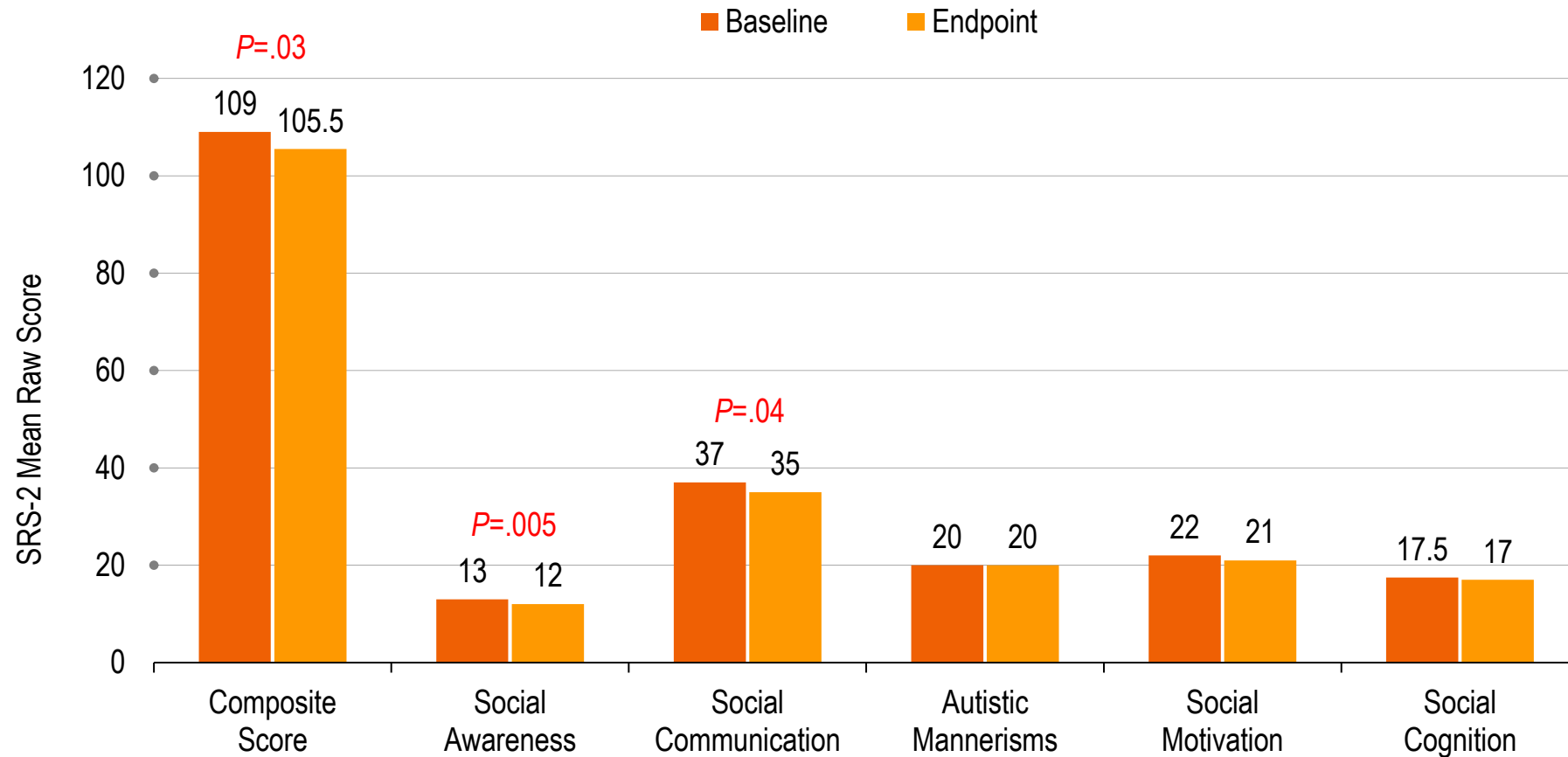
Treatment Response: ADHD Symptoms

AISRS % Score Reduction at Trial Completion

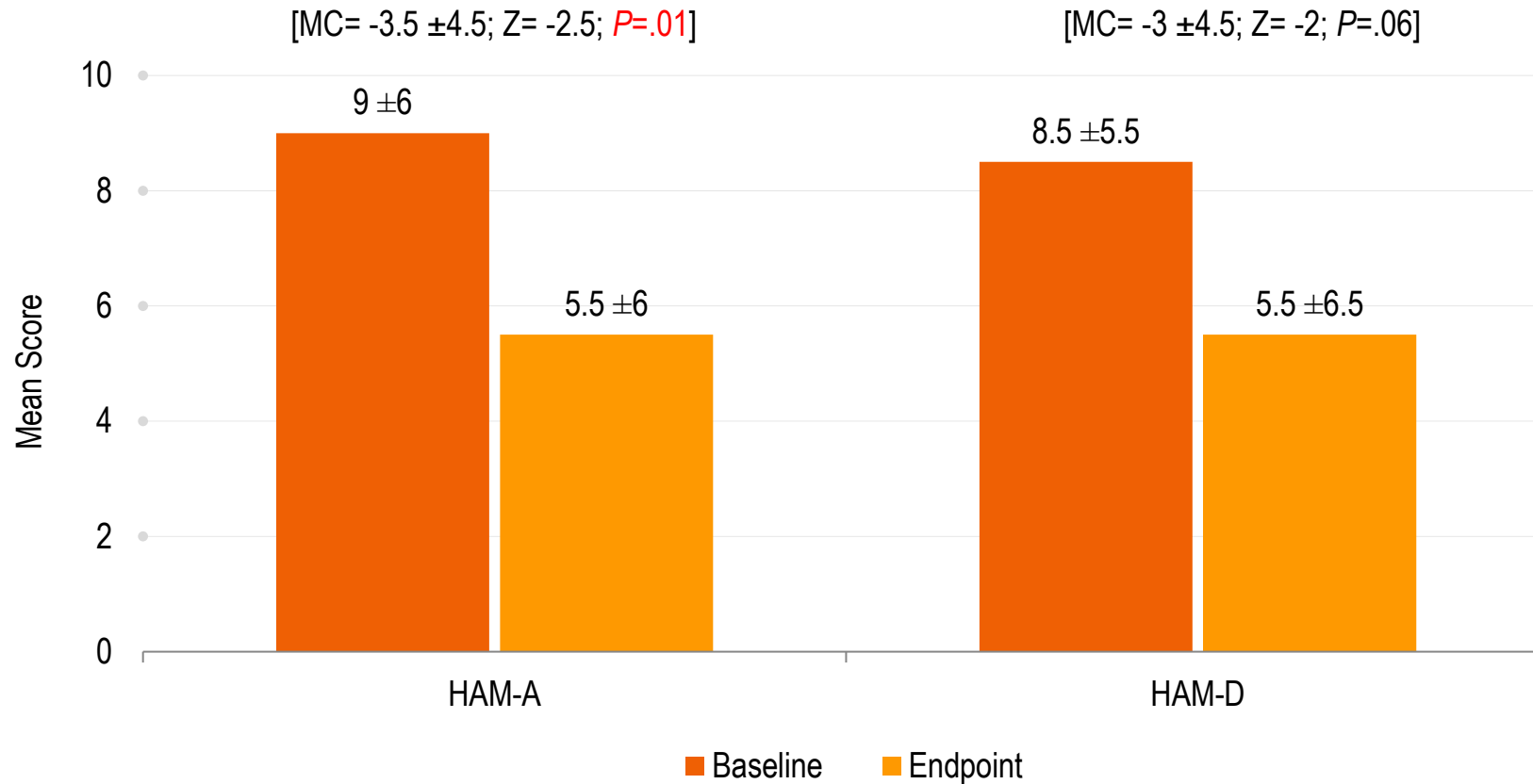


Treatment Response: Autism Traits

Social Responsiveness Scale (SRS-2)



Treatment Response: Associated Psychopathology

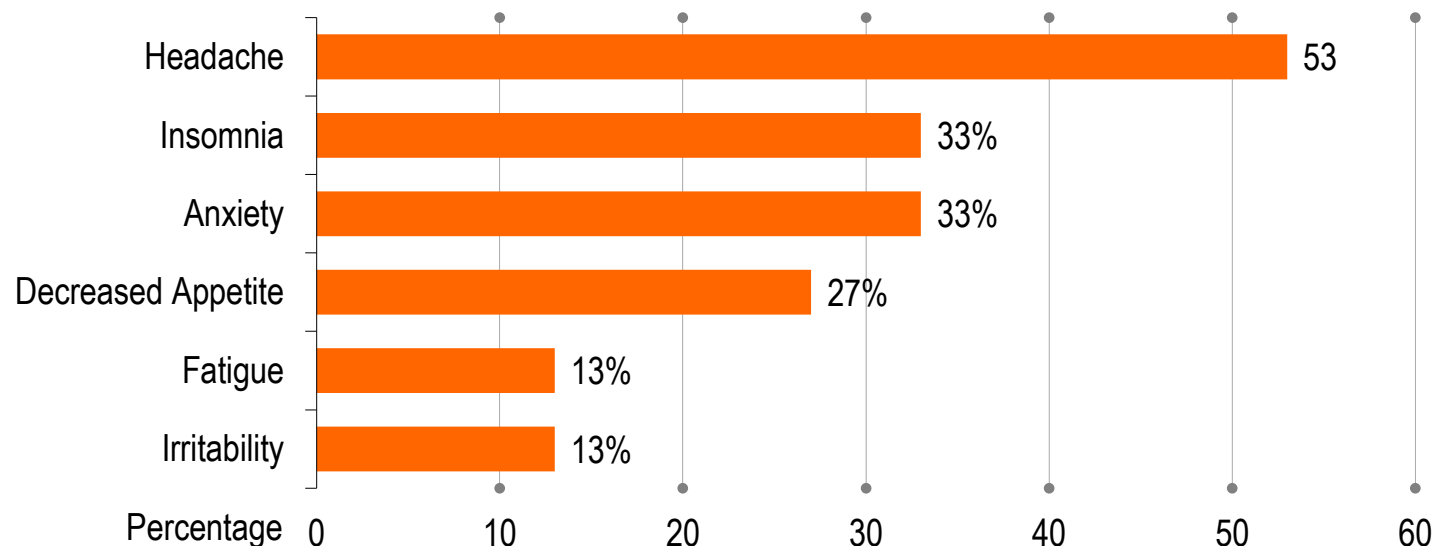


MC=Mean Change; HAM=A=Hamilton Anxiety Scale; HAM-D=Hamilton Depression Scale

No worsening of Anxiety and Depression with treatment

Adverse Events

Adverse Events (Mild-Moderate Severity)



Experienced any AEs: N=13 (87%)

Serious AEs: N=1 (Report of OD on Benadryl [suicide attempt] at week-6. Prior h/o SI. [Upon completion continued tx. with study medication])

Treatment Limiting AEs: N=1 (Terminated at week-3 @ 20 mg/day d/t AEs: headaches, palpitations, jaw pain, & insomnia [resolved on d/c])

Treatment was very well tolerated

In Summary....

- Increasingly greater prevalence of AUTISM
- Greater than expected burden of psychopathology associated with autism
- Tools available for screening and assessment of AUTISM in clinic setting
- Abnormally high levels of Glu activity in *pgACC* brain region in AUTISM
- Promising role of glutamate modulating agents in the management of AUTISM
- Typically expected pharmacological treatment response of ADHD in intellectually capable adults with AUTISM

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