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GENERAL HOSPITAL

PSYCHIATRY ACADEMY

# Addressing ASD - ADHD comorbidity

*Casting light on where none has cast before*

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# DISCLOSURES\*



Source	Research Support	Employee	BOD Member
Massachusetts General Hospital		✓	
MGH Dept. of Psychiatry	✓		
The Brain Foundation	✓		
The O’Sullivan Foundation	✓		
Gerstner Family Foundation	✓		
Niraxx, Inc.	✓		
Intra-Cellular Therapeutics, Inc.	✓		
Private Practice		✓	
Mass. Council of Gaming and Health			✓

None of the medications or somatic interventions has been approved for use in children

All medication and somatic treatment suggestions in this presentation are off label uses

# Neurodevelopmental Disorders (ASD and ADHD)



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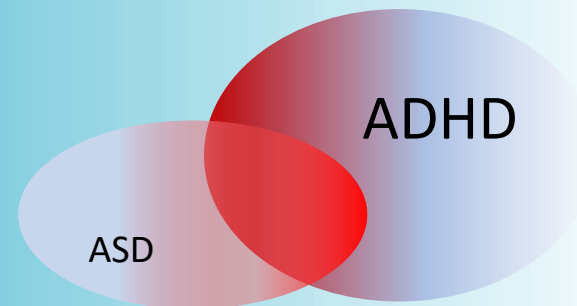
PSYCHIATRY ACADEMY

## Shared Characteristics

	<b>ADHD</b>	<b>ASD</b>
Prevalence in Children	6-8%	2%
Heritability Estimates	75%	90%
Male:Female Ratio	2.5:1	4:1
Manifest early in life	Yes	Yes
Lifelong Disorders	Yes	Yes

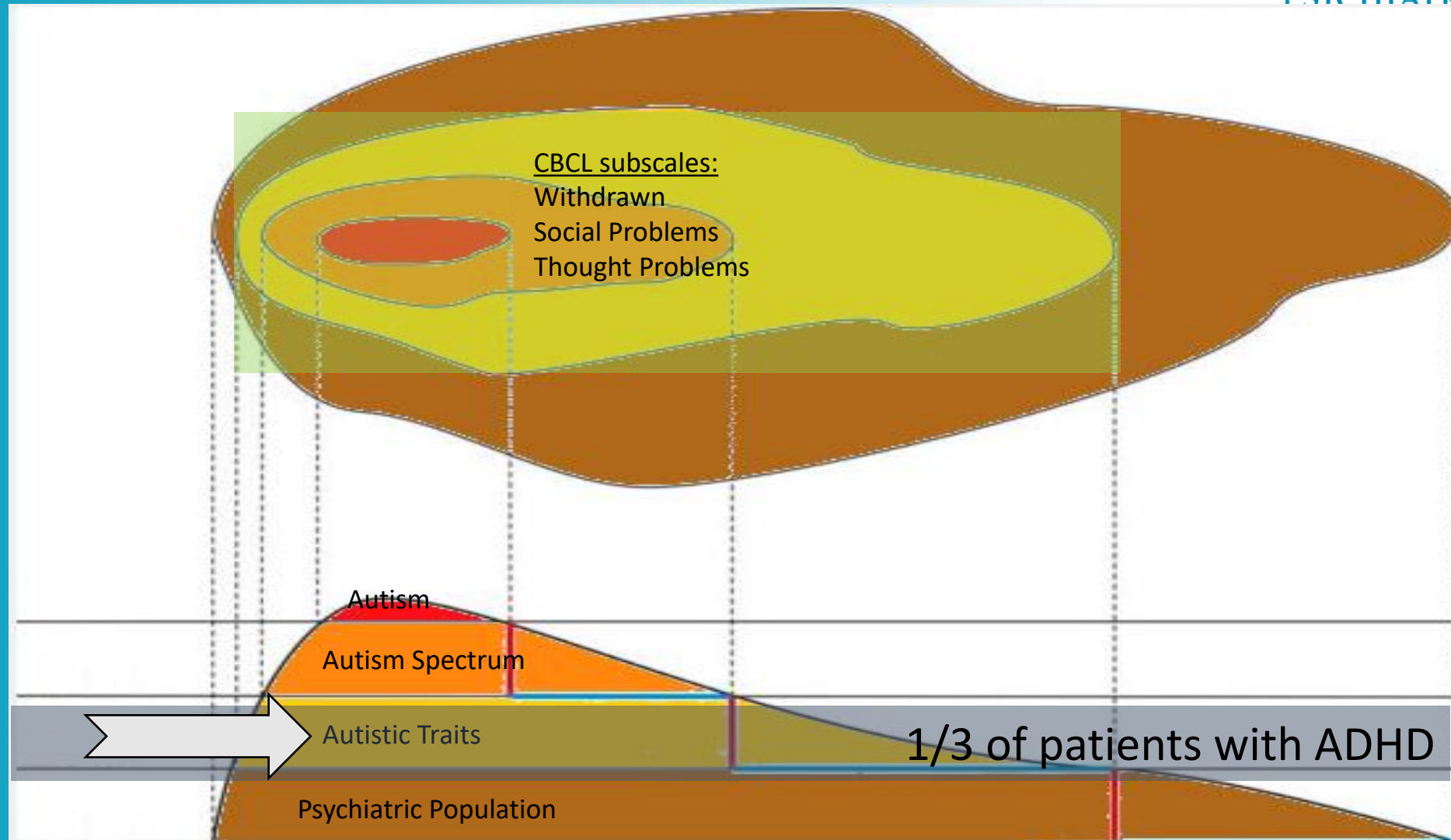
## Distinct Symptom Triad

<b>ASD</b>	<b>ADHD</b>
- Impaired social interaction	- Inattention
- Impaired social communication	- Hyperactivity
- Restricted Repetitive Behaviors	- Impulsivity

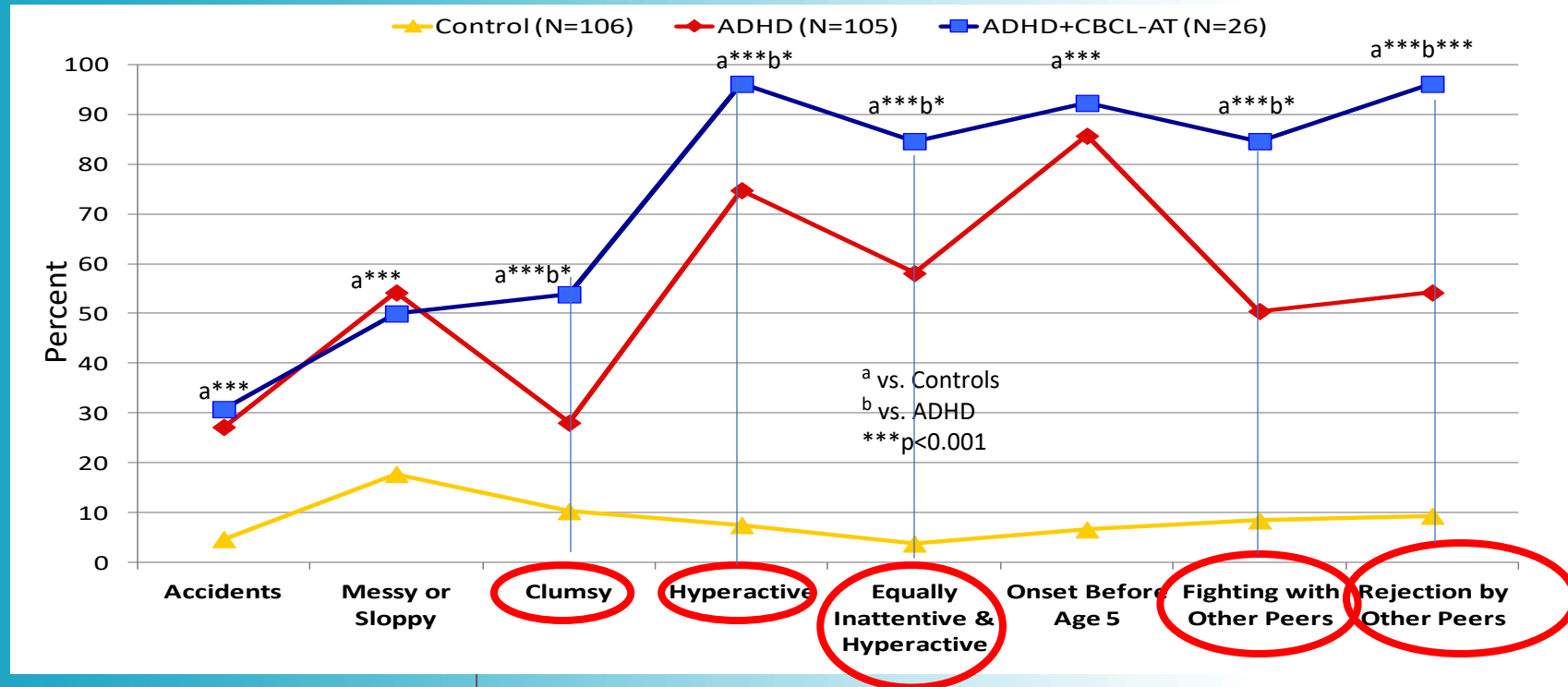


Bailey et al., 1995; Levy et al., 1997; Constantino & Todd, 2000, 2003; Ronald et al., 2005, 2006, 2008; Price et al., 2001; Fombonne, 2003; APA, 1994; MMWR, 2005; Kogan et al., 2009; ADDM Network, 2007, 2009; Bailey et al. 1996

# From Autism to Autistic Traits

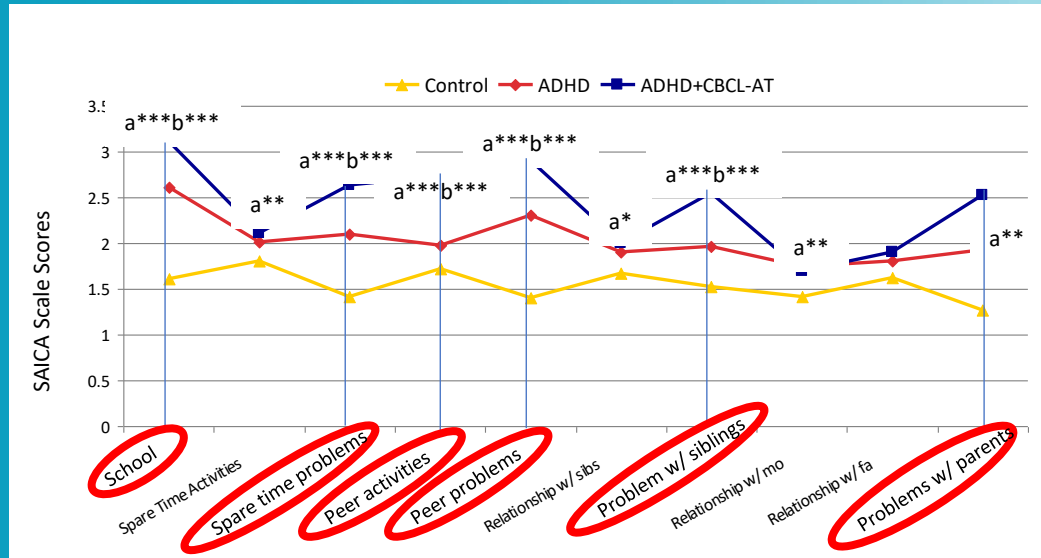


# Additional ADHD-Related Symptoms

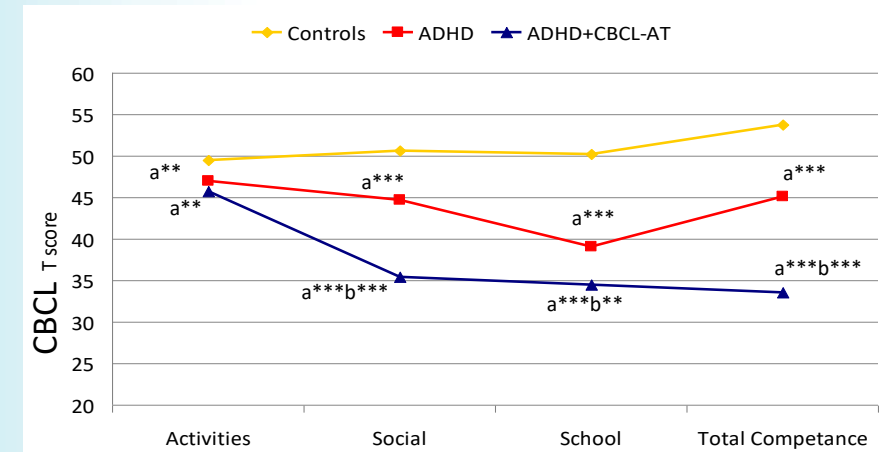


ATs bring on more additional ADHD-related symptoms

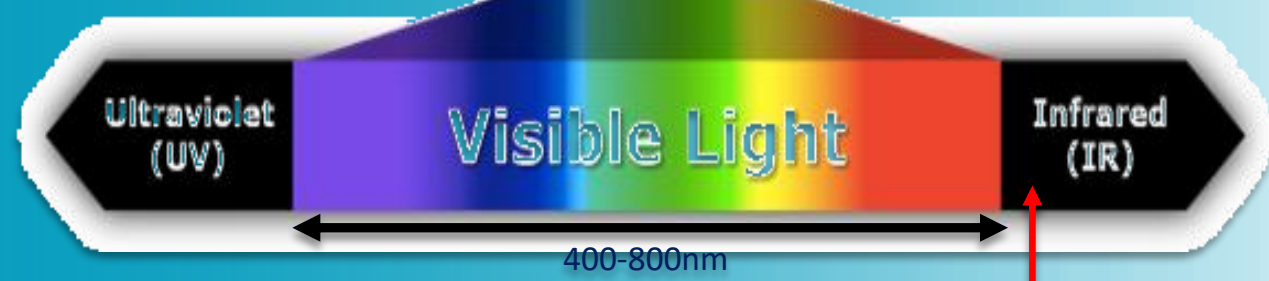
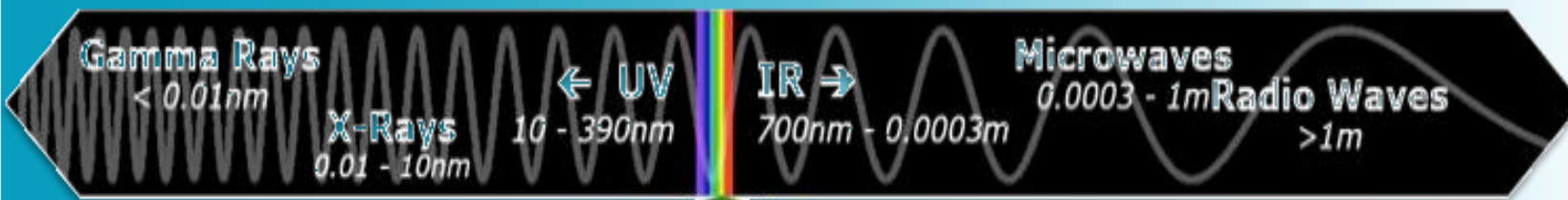
# Social Adaptive Skills



a vs. Controls  
 b vs. ADHD  
 \*p<0.05,  
 \*\*p<0.01,  
 \*\*\*p<0.001



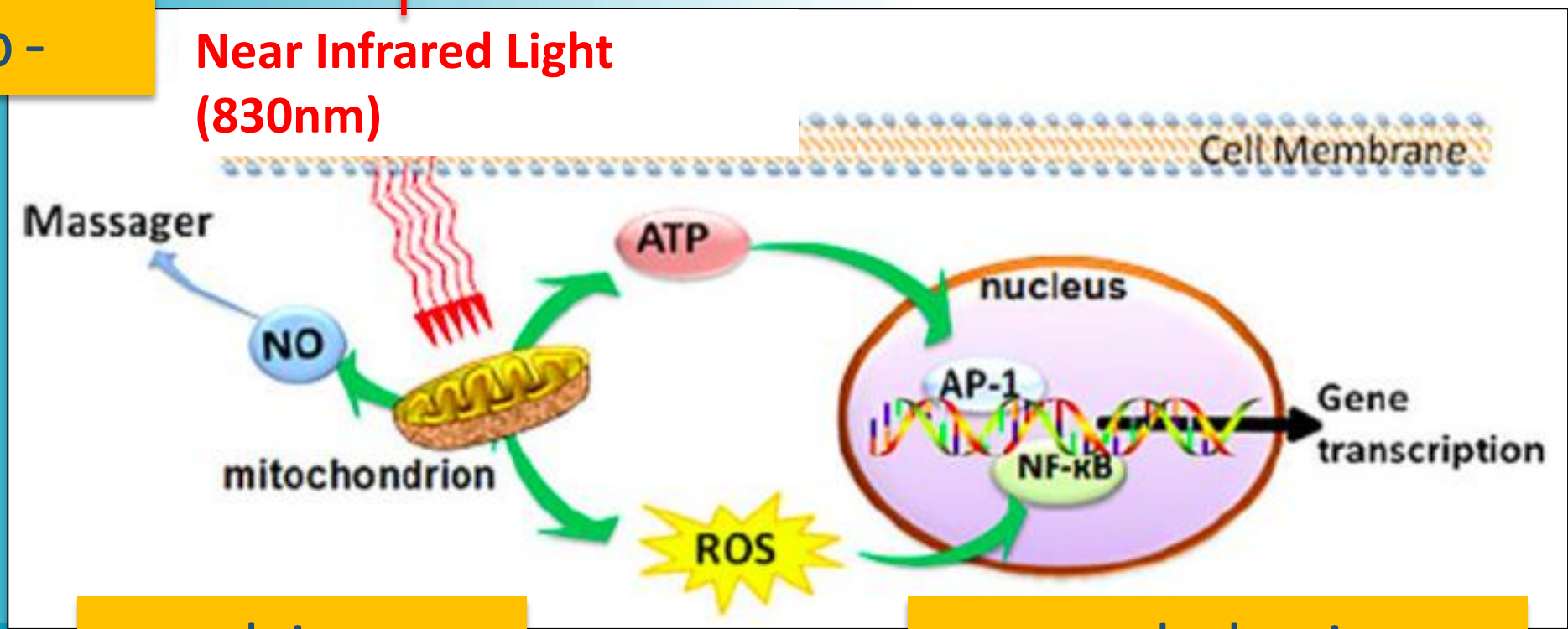
a vs. Controls  
 b vs. ADHD  
 \*p<0.05  
 \*\*p<0.005  
 \*\*\*p<0.0001



$$\text{Energy} = \frac{\# \text{Photons} \times \text{Planck's constant} \times \text{Light speed}}{\text{Wavelength formed by release} (\lambda)}$$

Photo-

Near Infrared Light (830nm)

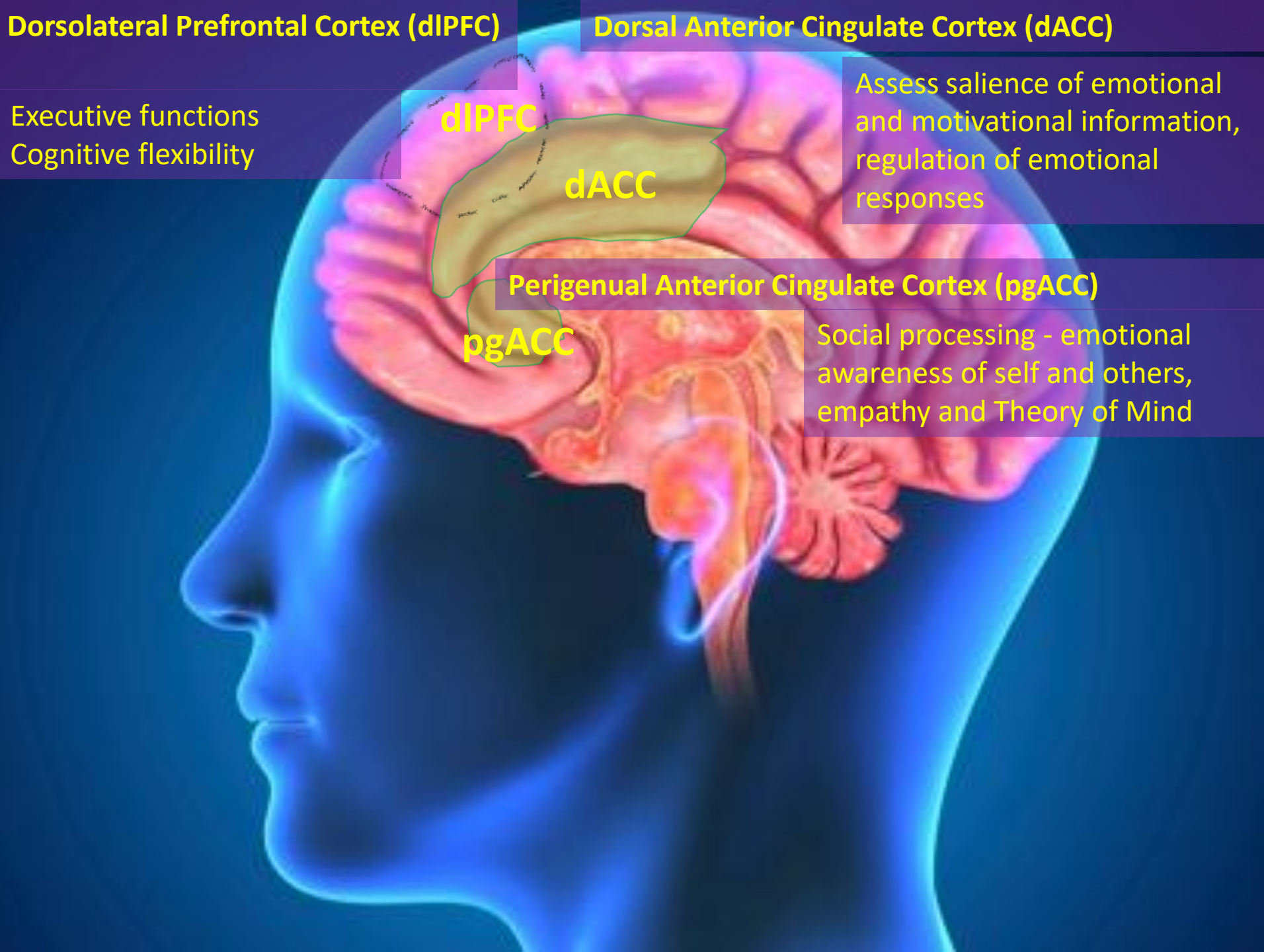


-bio-

-modulation

# Brain Regions Involved in ASD

Posner & Petersen 1990  
Johnson 2002  
Garavan 2002  
Wager & Smith 2003  
Frith & Frith 2003  
Hester 2004  
Milham & Banich 2005  
Ochsner 2005  
Gilbert 2006  
Amodio & Frith 2006  
Curtis 2006  
Weissman 2006  
Nee 2007  
Dosenbach 2008





## Stimulate

### Neurogenesis, neuroprotection

- Increased brain derived neurotrophic factor (BDNF)
- Decreased GSK-3 $\beta$  and proapoptotic molecules

## Reduce

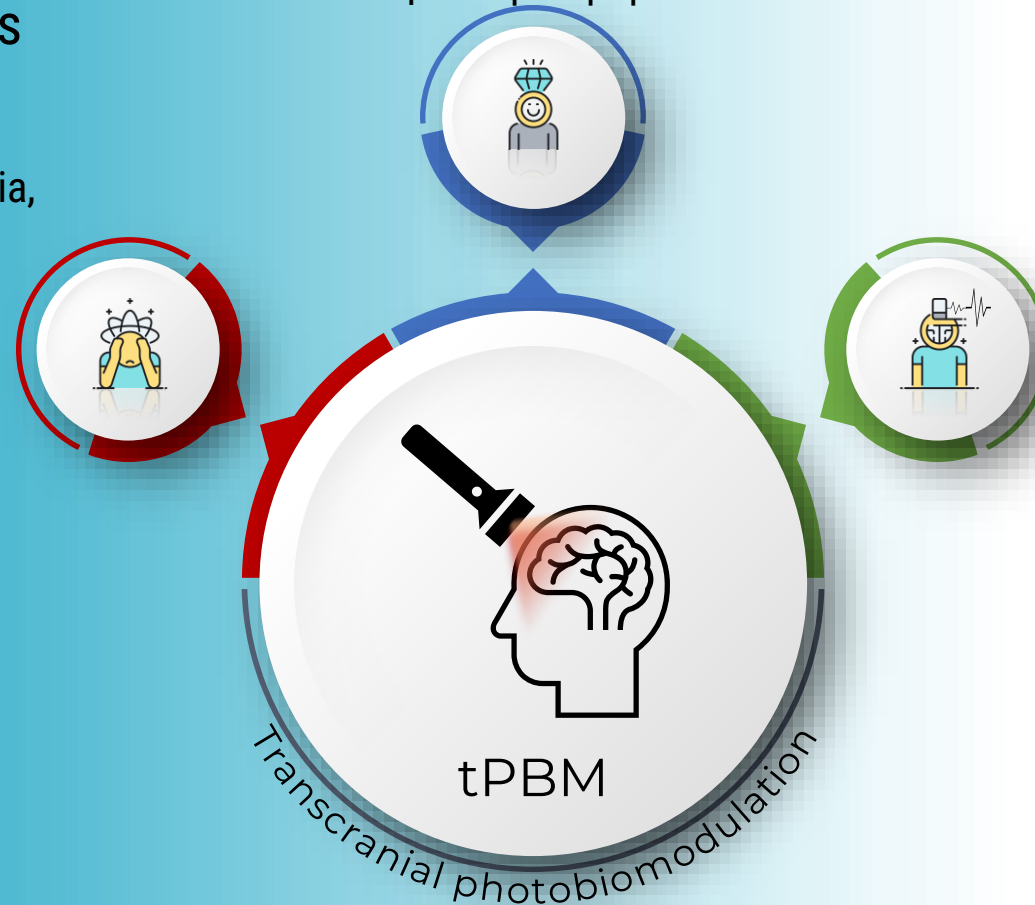
### Proinflammatory cytokines

- Reduced IL-6, TNF- $\alpha$ , IL-1 $\beta$ , IL-8
- Reduced CNS infiltration of macrophages, activated microglia, T-lymphocytes

## Change

### Brain activation pattern

- Reduced delta wave and, increased gamma-wave activity corresponded with reduced CARS score





Photobiomodulation, Photomedicine and Laser Surgery, 2022 Jan;40(1):4-12. doi: 10.1089/photob.2020.4986. Epub 2021 Dec 23.  
<https://doi-org.treadwell.idm.oclc.org/10.1089/photob.2020.4986>

## Transcranial Photobiomodulation in Adults with High-Functioning Autism Spectrum Disorder: Positive Findings from a Proof-of-Concept Study

*T. Atilla Ceranoglu, MD, Paolo Cassano, MD, Barbora Hoskova, BA, Allison Green, BA, Nina Dallenbach, BS, Maura DiSalvo, MPH, Joseph Biederman, MD, and Gagan Joshi, MD*

# tPBM for ASD – *Ceranoglu et al., 2022*



Open label, single group design,  
Core deficits of ASD in adults  
33.2mW/cm<sup>2</sup> @830nm, 20-30 min exposure, x2/wk

## Inclusion Criteria:

- 18-59 year old patients with ASD diagnosis,
- At least moderate severity of ASD (CGI-S  $\geq$  4)

## Exclusion Criteria

- Serious medical or psychiatric concerns
- H/o photosensitivity
- Current treatment with light activated medications

## Primary outcome measurements

- Social Responsiveness Scale, 2<sup>nd</sup> Ed (SRS-2)
- Clinical Global Impression of Improvement (CGI-I)

## Response Definition (*both required*)

- $\geq$ 25% reduction in SRS-2 at endpoint
- Endpoint CGI-I  $\leq$ 2

## Secondary outcome measurements

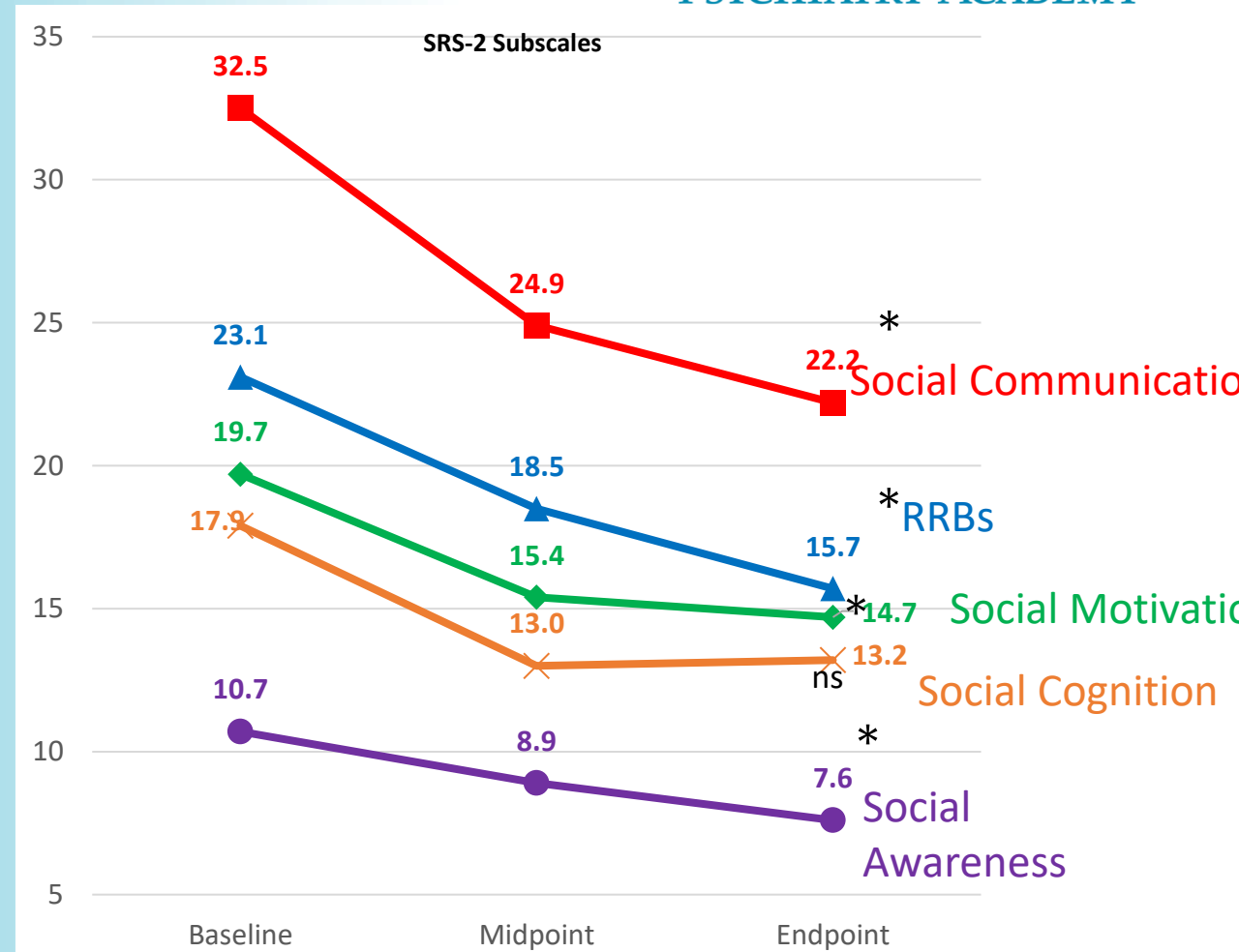
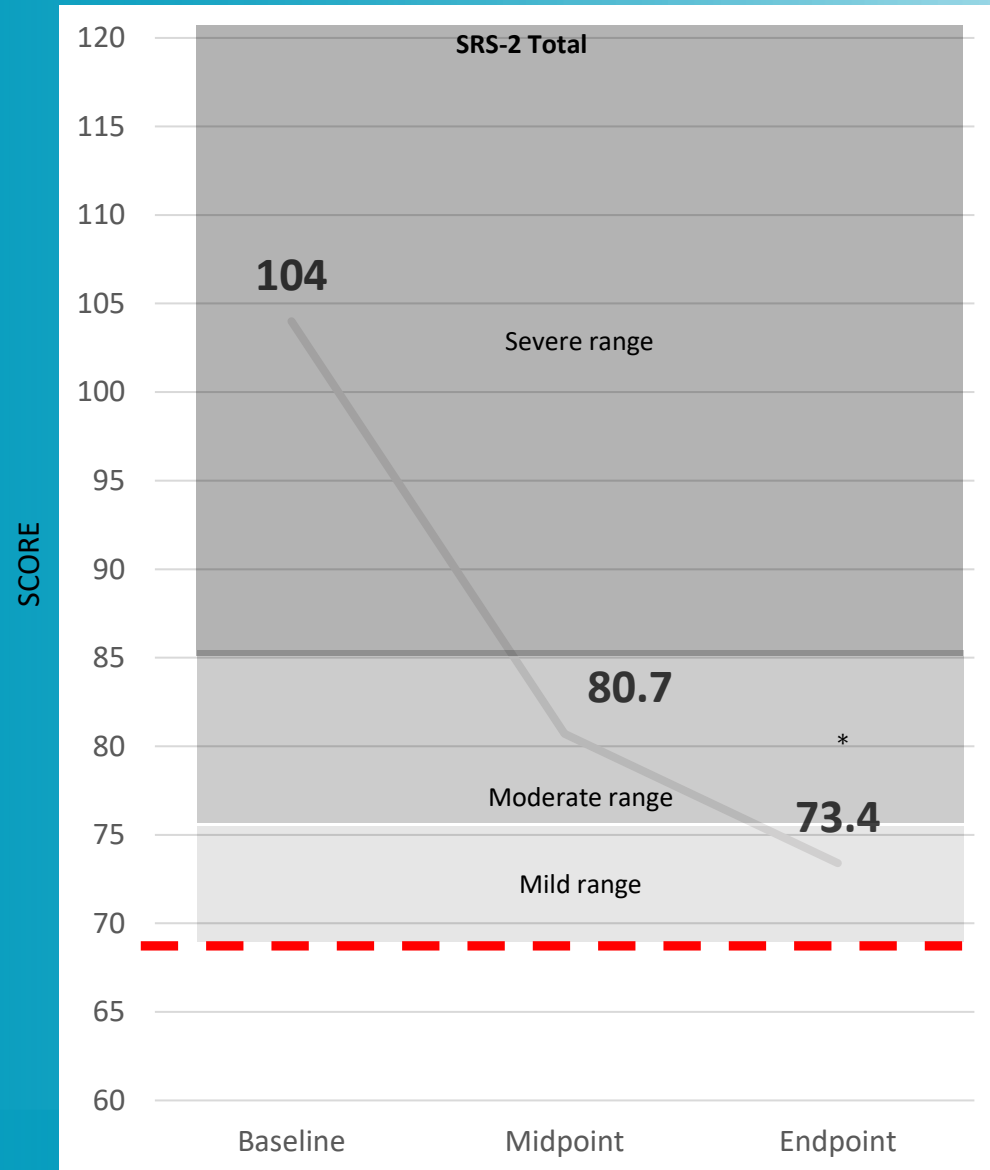
- Global Assessment of Functioning (GAF)
- Adult ADHD Self Rating Scale (ASRS)
- Behavior Rating Inventory of Executive Function-Adults (BRIEF-A)

20 mins  
x3 weeks

25 mins  
x2 weeks

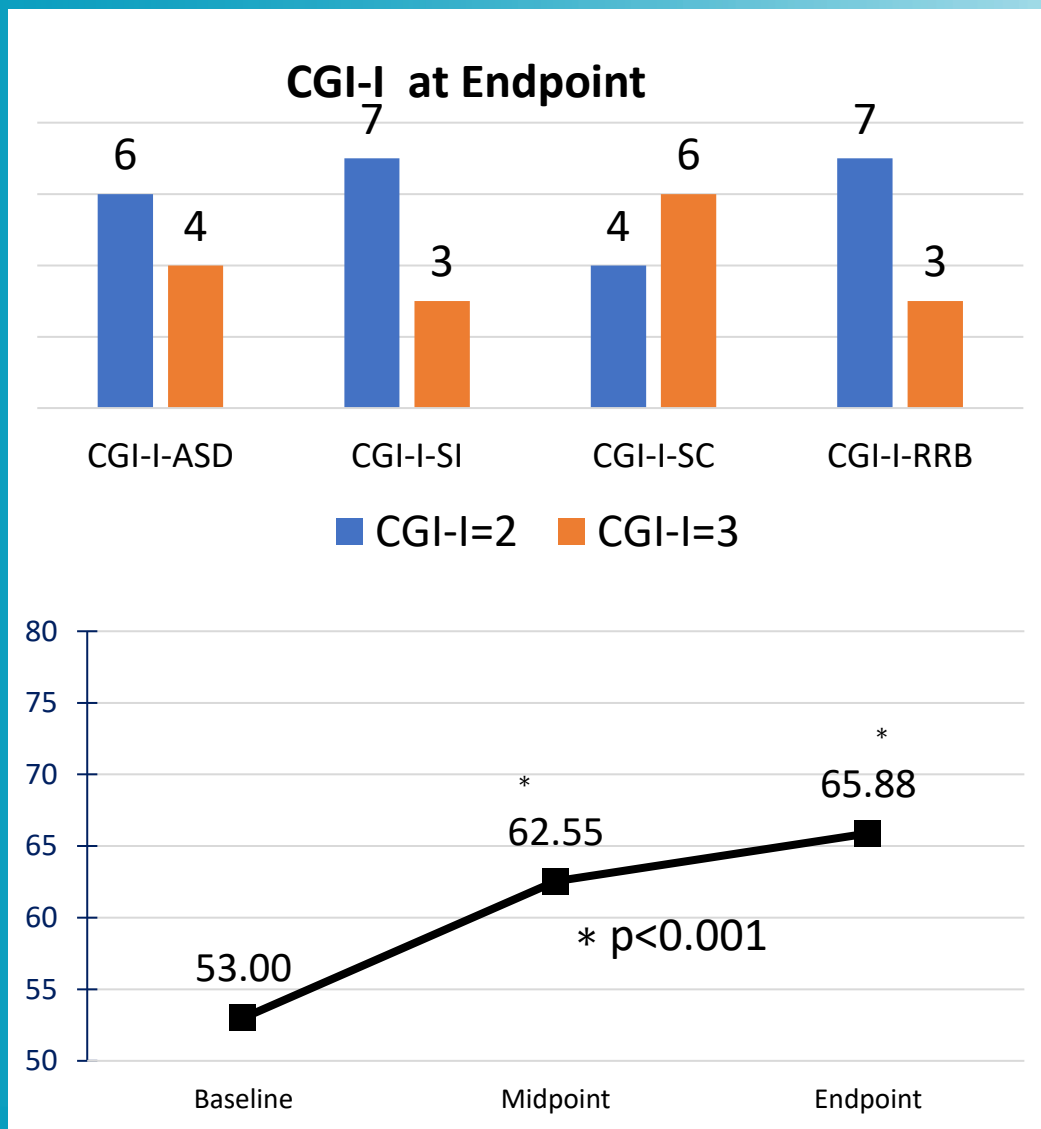
30 mins  
x3 weeks

# tPBM effect on core features of ASD



Ceranoglu et al., Photobiomodul Photomed Laser Surg 2022

# tPBM in ASD - Outcome Measures



### Behavior Rating Inventory of Executive Function-Adult (BRIEF-A)

	Baseline Mean ± SD	Endpoint Mean ± SD	Difference Mean ± SD	Cohen's d (95% CI)	p
Inhibit	60.4 ± 14.4	51.2 ± 11.7	-9.2 ± 11.6	0.70 (0.07, 1.33)	0.01
Shift	68.0 ± 16.0	57.9 ± 13.1	-10.1 ± 17.6	0.69 (-0.11, 1.49)	0.07
Emotional Control	65.9 ± 17.6	55.5 ± 12.1	-10.4 ± 14.9	0.69 (0.02, 1.36)	0.03
Self Monitor	61.0 ± 11.9	51.7 ± 12.8	-9.3 ± 15.1	0.75 (-0.09, 1.59)	0.05
Initiate	59.2 ± 14.1	53.3 ± 9.8	-5.9 ± 13.7	0.49 (-0.24, 1.22)	0.16
Working Memory	65.3 ± 14.3	58.8 ± 13.7	-6.5 ± 13.9	0.46 (-0.19, 1.11)	0.10
Plan/Organize	63.7 ± 17.4	53.8 ± 10.0	-9.9 ± 14.2	0.70 (0.03, 1.37)	0.03
Task Monitor	62.0 ± 17.1	51.9 ± 12.5	-10.1 ± 17.1	0.67 (-0.09, 1.43)	0.05
Organization of Materials	53.5 ± 17.0	47.8 ± 12.3	-5.7 ± 6.9	0.38 (0.11, 0.65)	0.01
Behavioral Regulation Index	67.1 ± 16.8	55.1 ± 13.5	-12.0 ± 15.9	0.79 (0.05, 1.53)	0.02
Metacognitive Index	62.5 ± 15.7	53.5 ± 11.5	-9.0 ± 13.0	0.65 (0.003, 1.30)	0.03
Global Executive Composite	65.3 ± 15.8	54.5 ± 12.5	-10.8 ± 14.9	0.76 (0.03, 1.49)	0.02



# tPBM for Autistic Traits in ADHD

Open label, single group design to test safety and efficacy in Autistic Traits in children with ADHD

- 9-17 years old
- ADHD diagnosis (DSM-5)
- At least moderate severity of Autistic Traits (SRS-2 raw score  $\geq 75$ , or CGI-AT  $\geq 4$ )
  - No serious medical or psychiatric concerns
  - No h/o photosensitivity
- Fixed dose titration of daily tPBM at home

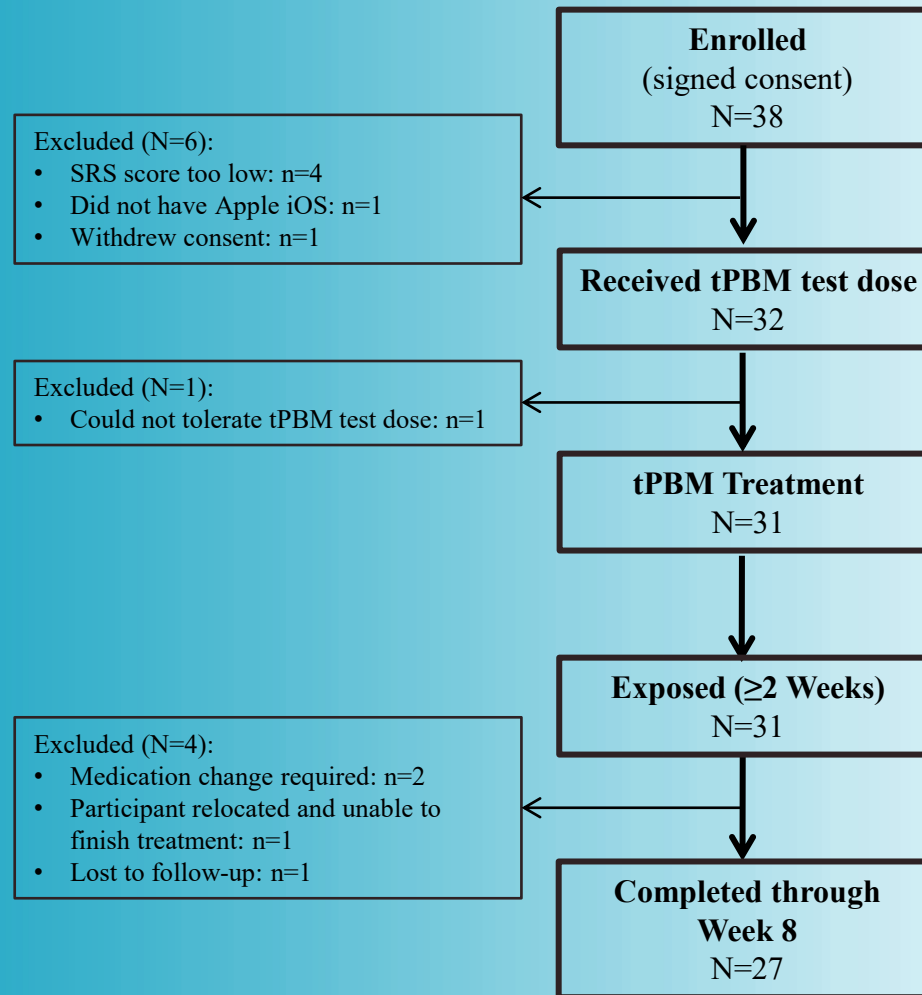


10 min/d  
x1 week

20 min/d  
x1 week

30 min/d  
x1 week

40 min/d  
x5 weeks



# Study Population Characteristics



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Demographic characteristics	
	tPBM Treatment N=31
	Mean ± SD
Age (years)	12.5 ± 3.0
	N (%)
Gender	
Female	7 (23)
Male	24 (77)
Race	
Asian/Native Hawaiian/Pacific Islander	1 (3)
Black/African American	0 (0)
White/Caucasian	24 (77)
More than one	1 (3)
Other	4 (13)
Unknown/Not reported	1 (3)
Ethnicity	
Hispanic/Latino	4 (13)
Not Hispanic/Latino	27 (87)

## Baseline clinical characteristics

	tPBM Treatment N=31
	Mean ± SD
Baseline SRS raw score	104.3 ± 24.6
Baseline clinician-rated MGH-SEC score	177.3 ± 24.5
Baseline CGI-Severity for ASD	4.5 ± 0.6
	N (%)
Baseline SRS T-score ≥66	29 (94)
Baseline CGI-S for ASD markedly ill or higher (≥5)	15 (48)

# Primary Outcome Measures

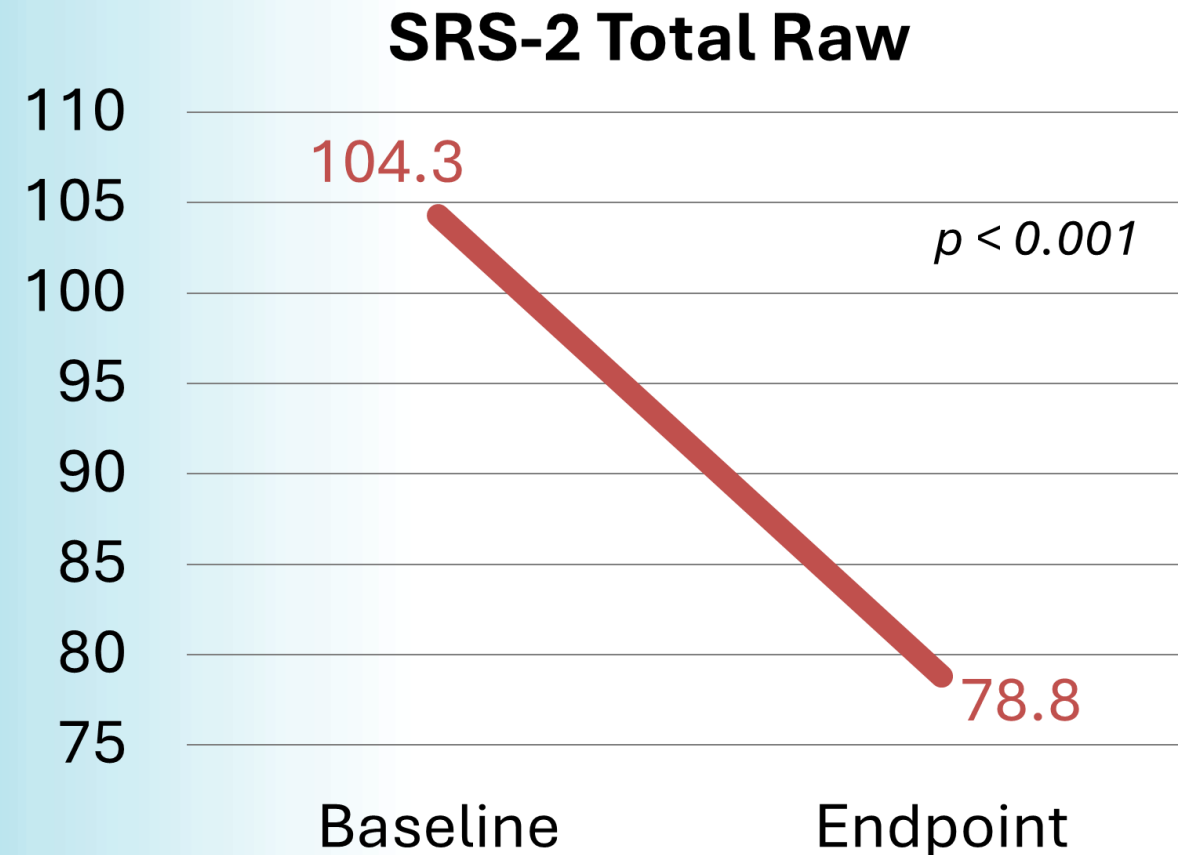
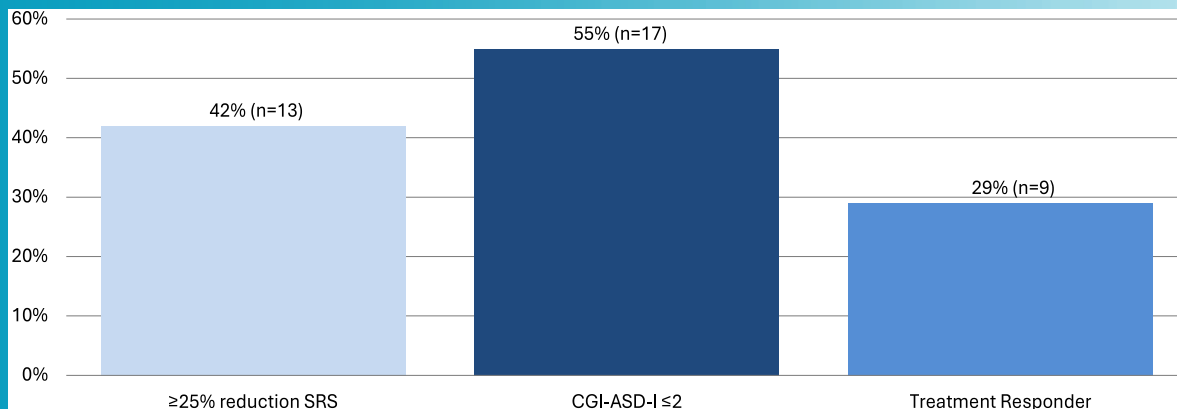


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tPBM Treatment (N=31)					
	Baseline	Endpoint <sup>†</sup>	Difference	Effect Size <sup>‡</sup>	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	SMD (95% CI)	
SRS Total raw score	104.3 ± 24.6	78.8 ± 21.9	-25.5 ± 26.4	1.09 (0.60, 1.58)	<0.001
	N (%)				
≥25% reduction SRS	13 (42)		n/a		
CGI-ASD-I ≤2	17 (55)		n/a		
Responder	9 (29)		n/a		

<sup>†</sup> Endpoint score uses last observation carried forward for those who dropped prior to week 10.  
<sup>‡</sup> Positive SMD indicates improvement



# Safety and Tolerability



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Adverse Events	
	tPBM Treatment N=31
	N (%)
Participants reporting any AEs	27 (87)
Participants reporting severe AEs	0 (0)
Participants reporting serious AEs	0 (0)
AEs reported $\geq 2$ times	
Warmth at application site	3 (10)
Headache	2 (6)
Nose bleeding	1 (3)
Middle Insomnia	1 (3)
Sweating	1 (3)
Mean number of AEs reported	2.4 $\pm$ 2.1
Median (IQR) number of AEs	2 (2)

*No severe or serious adverse events were reported.*

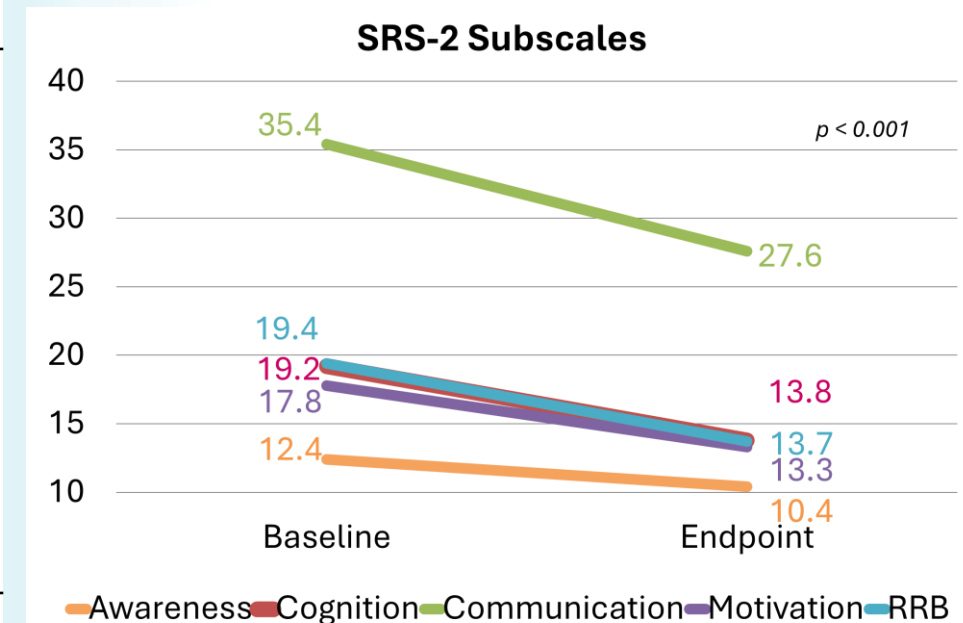
*98% Adherence rate*

# Secondary Outcome Measures



	tPBM Treatment (N=31)				
	Baseline Score	Endpoint <sup>†</sup>	Difference	Effect Size <sup>‡</sup>	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	SMD (95% CI)	
SRS [Raw Scores]					
Awareness	12.4 ± 2.8	10.4 ± 3.0	-2.0 ± 3.0	0.69 (0.30, 1.08)	<0.001
Cognition	19.2 ± 6.4	13.8 ± 5.7	-5.4 ± 5.7	0.89 (0.50, 1.28)	<0.001
Communication	35.4 ± 9.7	27.6 ± 8.0	-7.8 ± 9.8	0.88 (0.43, 1.33)	<0.001
Motivation	17.8 ± 5.5	13.3 ± 4.8	-4.6 ± 4.2	0.89 (0.54, 1.24)	<0.001
RRB	19.4 ± 6.0	13.7 ± 6.0	-5.6 ± 7.0	0.93 (0.46, 1.40)	<0.001
Clinician-rated MGH-SEC <sup>n=30</sup>	177.1 ± 24.9	146.5 ± 22.1	-30.6 ± 22.6	1.30 (0.83, 1.77)	<0.001
Parent-rated MGH-SEC <sup>n=29</sup>	111.9 ± 30.3	94.0 ± 34.9	-17.8 ± 25.6	0.54 (0.23, 0.85)	<0.001
GAF	54.1 ± 2.9	63.6 ± 6.2	9.5 ± 6.4	1.96 (1.29, 2.63)	<0.001
ADHD-SC	33.0 ± 9.4	24.6 ± 11.2	-8.5 ± 8.8	0.82 (0.47, 1.17)	<0.001
	N (%)				
CGI-I-ADHD ≤2	11 (35)				n/a

<sup>†</sup> Endpoint score uses last observation carried forward for those who dropped prior to week 8. <sup>‡</sup> Positive SMD indicates improvement



# Secondary Outcomes



## BRIEF-P T-Scores

	tPBM Treatment (N=31)				
	Baseline	Endpoint <sup>†</sup>	Difference	Effect Size <sup>‡</sup>	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	SMD (95% CI)	
BRIEF [T-score]					
Inhibit	62.2 ± 13.5	60.3 ± 12.1	-1.9 ± 9.9	0.15 (-0.12, 0.42)	0.15
Shift	70.5 ± 14.6	65.5 ± 13.2	-5.0 ± 8.5	0.36 (0.12, 0.60)	0.001
Emotional control	61.4 ± 13.1	58.6 ± 12.2	-2.8 ± 8.4	0.22 (-0.02, 0.45)	0.05
Initiate	66.7 ± 11.9	65.1 ± 12.5	-1.6 ± 8.3	0.13 (-0.11, 0.37)	0.15
Working Memory	69.1 ± 12.4	68.3 ± 12.5	-0.8 ± 6.0	0.06 (-0.10, 0.22)	0.28
Plan/Organize	67.2 ± 11.5	65.0 ± 11.9	-2.2 ± 7.8	0.19 (-0.05, 0.43)	0.06
Organization of Materials	58.1 ± 9.5	56.6 ± 11.1	-1.5 ± 8.0	0.15 (-0.12, 0.42)	0.20
Task Monitor	66.3 ± 11.5	62.2 ± 10.9	-4.1 ± 9.3	0.37 (0.06, 0.68)	0.01
MI	68.3 ± 11.6	65.9 ± 12.0	-2.4 ± 7.9	0.20 (-0.04, 0.44)	0.05
BRI	66.3 ± 13.1	62.6 ± 11.4	-3.7 ± 9.1	0.30 (0.03, 0.57)	0.02
Total	68.9 ± 11.9	65.8 ± 11.1	-3.1 ± 8.4	0.27 (0.02, 0.52)	0.02

<sup>†</sup> Endpoint score uses last observation carried forward for those who dropped prior to week 8. <sup>‡</sup> Positive SMD indicates improvement.

# Secondary Outcomes



Child Behavior Checklist (CBCL)					
	tPBM Treatment (N=31)				
	Baseline	Endpoint †	Difference	Effect Size‡	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	SMD (95% CI)	
CBCL [T-score]					
Anxious/Depressed	62.3 ± 11.3	60.2 ± 10.7	-2.0 ± 7.0	0.18 (-0.06, 0.42)	0.04
Withdrawn/Depressed	62.0 ± 9.7	61.5 ± 9.3	-0.5 ± 7.8	0.05 (-0.24, 0.34)	0.38
Somatic Complaints	58.0 ± 8.5	57.8 ± 8.4	-0.2 ± 5.8	0.02 (-0.22, 0.26)	0.63
Social Problems	63.9 ± 9.5	61.4 ± 7.9	-2.5 ± 6.4	0.29 (0.04, 0.54)	0.02
Thought Problems	63.8 ± 7.3	60.2 ± 8.0	-3.6 ± 7.8	0.47 (0.10, 0.84)	0.003
Attention Problems	68.3 ± 10.0	63.8 ± 6.5	-4.5 ± 8.3	0.53 (0.18, 0.88)	<0.001
Rule-Breaking Behavior	55.5 ± 6.9	55.1 ± 7.2	-0.4 ± 5.4	0.06 (-0.21, 0.33)	0.29
Aggressive Behavior	57.9 ± 7.9	57.6 ± 9.1	-0.3 ± 6.4	0.04 (-0.21, 0.29)	0.53
Internalizing Problems	61.2 ± 10.2	59.9 ± 10.6	-1.3 ± 7.4	0.12 (-0.13, 0.37)	0.17
Externalizing Problems	55.0 ± 10.3	53.2 ± 12.1	-1.8 ± 8.3	0.16 (-0.09, 0.41)	0.10
Total Problems	62.0 ± 8.7	59.6 ± 8.5	-2.4 ± 6.7	0.28 (0.01, 0.55)	0.01
Composite Scales					
CBCL Autistic Traits score	189.8 ± 21.4	183.1 ± 20.3	-6.7 ± 18.1	0.32 (0.006, 0.63)	0.01

† Endpoint score uses last observation carried forward for those who dropped prior to week 8. ‡ Positive SMD indicates improvement.



# Primary Outcomes in Patients With and Without an ASD Diagnosis

	Patients without ASD Diagnosis N=11				Patients with ASD Diagnosis N=20				Between Group Analysis	
	Baseline	Endpoint <sup>†</sup>	Difference	Effect Size <sup>‡</sup>	Baseline	Endpoint <sup>†</sup>	Difference	Effect Size <sup>‡</sup>	Effect Size <sup>‡</sup>	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	SMD (95% CI)	Mean ± SD	Mean ± SD	Mean ± SD	SMD (95% CI)	SMD (95% CI)	
SRS Total raw score	91.0 ± 27.3	78.8 ± 15.7	-12.2 ± 26.3	0.55 (-0.18, 1.28)	111.6 ± 20.1	78.8 ± 25.1	-32.8 ± 24.0	1.44 (0.79, 2.09)	0.83 (0.06, 1.59)	0.006
	N (%)				N (%)				OR (95% CI)	
≥25% reduction SRS	2 (18)				11 (55)				3.81 (0.51, 46.98)	0.26
CGI-ASD-I ≤2	5 (45)				12 (60)				5.50 (0.94, 32.21)	0.06
Responder	1 (9)				8 (40)				4.17 (0.40, 206.48)	0.36

<sup>†</sup> Endpoint score uses last observation carried forward for those who dropped prior to week 10. <sup>‡</sup> For within group analyses, a positive SMD indicates improvement. For between group analysis, positive SMD and OR>1 favor patients with an ASD diagnosis. All between group analyses control for baseline SRS Total raw score.



# Summary

Daily tPBM treatment was,

- Safe and feasible
- Associated with improvement in autistic traits and executive function deficits in patients with ADHD

Further research into efficacy of tPBM as an adjunct treatment in ADHD and for treatment of core features of ASD is warranted.

- Placebo/sham controlled RTCs
- Target different brain regions?



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# THANK YOU!

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