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Neural Underpinnings of Autism

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Disclosures

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Disclosures 2023-2026

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American Academy of Child & Adolescent Psychiatry		✓		
American Physician Institute		✓		
Hackensack Meridian Health		✓		
Neuroimmune Institute		✓		
New York University (Grand Rounds)		✓		
Optum Health Education		✓		
Regional Council of Child and Adolescent Psychiatry of Eastern Pennsylvania and Southern New Jersey		✓		
EuMentis Therapeutics			✓	
Mass General Brigham Innovation				✓

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Integration and Segregation of Default Mode Network Resting-State Functional Connectivity in Transition-Age Males with High-Functioning Autism Spectrum Disorder: A Proof-of-Concept Study

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Abstract

The aim of this study is to assess the resting-state functional connectivity (RsFc) profile of the default mode network (DMN) in transition-age males with autism spectrum disorder (ASD). Resting-state blood oxygen level-dependent functional magnetic resonance imaging data were acquired from adolescent and young adult males with high-functioning ASD ($n = 15$) and from age-, sex-, and intelligence quotient-matched healthy controls (HCs; $n = 16$). The DMN was examined by assessing the positive and negative RsFc correlations of an average of the literature-based conceptualized major DMN nodes (medial prefrontal cortex [mPFC], posterior cingulate cortex, bilateral angular, and inferior temporal gyrus regions). RsFc data analysis was performed using a seed-driven approach. ASD was characterized by an altered pattern of RsFc in the DMN. The ASD group exhibited a weaker pattern of intra- and extra-DMN-positive and -negative RsFc correlations, respectively. In ASD, the strength of intra-DMN coupling was significantly reduced with the mPFC and the bilateral angular gyrus regions. In addition, the polarity of the extra-DMN correlation with the right hemispheric task-positive regions of fusiform gyrus and supramarginal gyrus was reversed from typically negative to positive in the ASD group. A wide variability was observed in the presentation of the RsFc profile of the DMN in both HC and ASD groups that revealed a distinct pattern of subgrouping using pattern recognition analyses. These findings imply that the functional architecture profile of the DMN is altered in ASD with weaker than expected integration and segregation of DMN RsFc. Future studies with larger sample sizes are warranted.

Keywords: autism spectrum disorder; default mode network; resting-state fMRI

Resting-State Functional-Connectivity of Default Mode Network (DMN)

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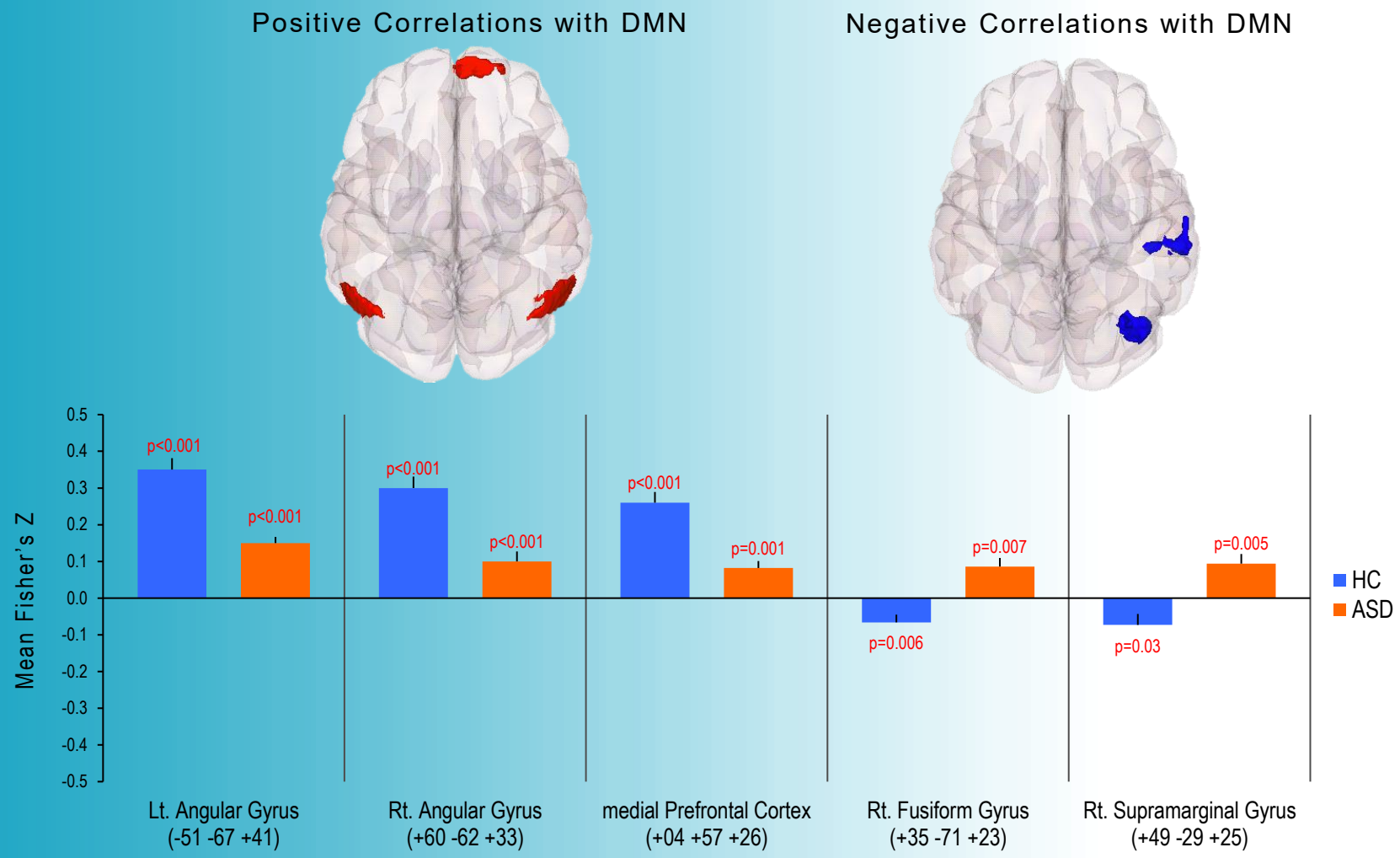

Joshi et al. 2017

Individual Subject RsFc Strength of the ROIs

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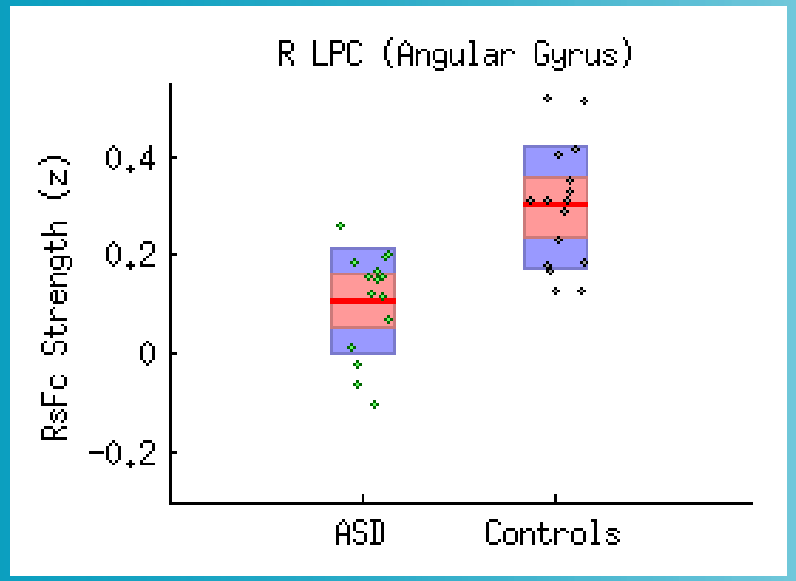

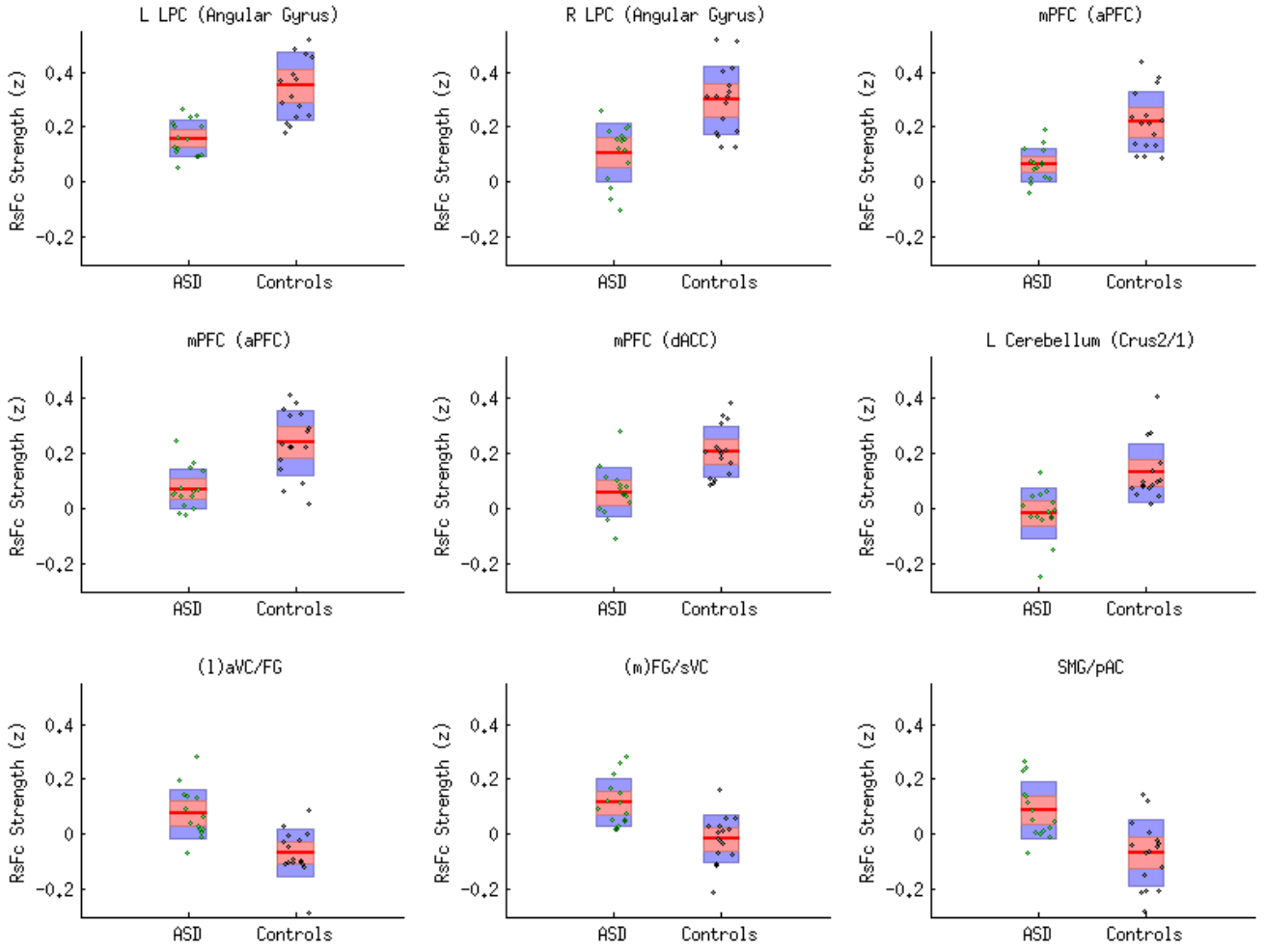

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Diversity in Atypical DMN Profile in Autism

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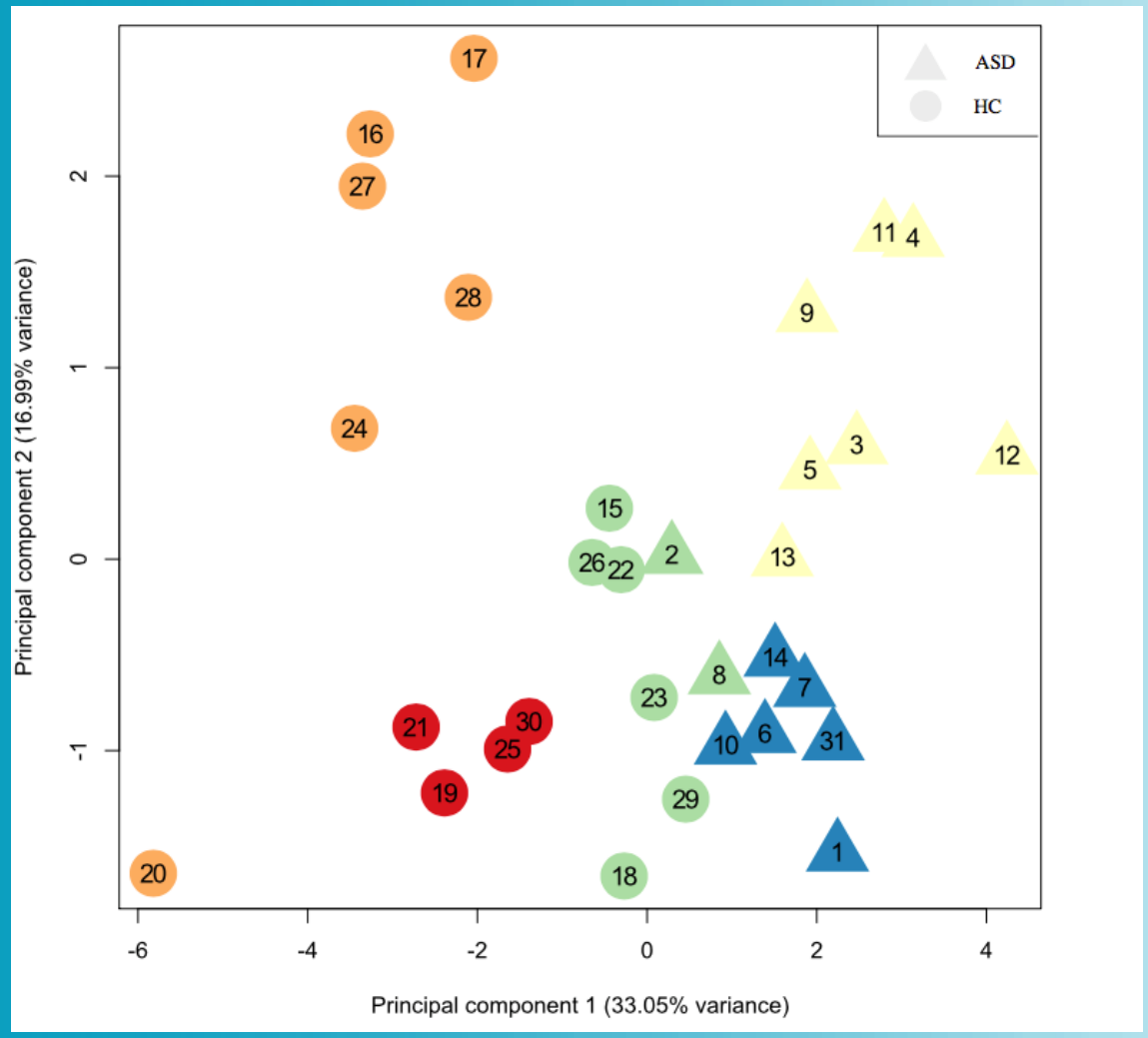

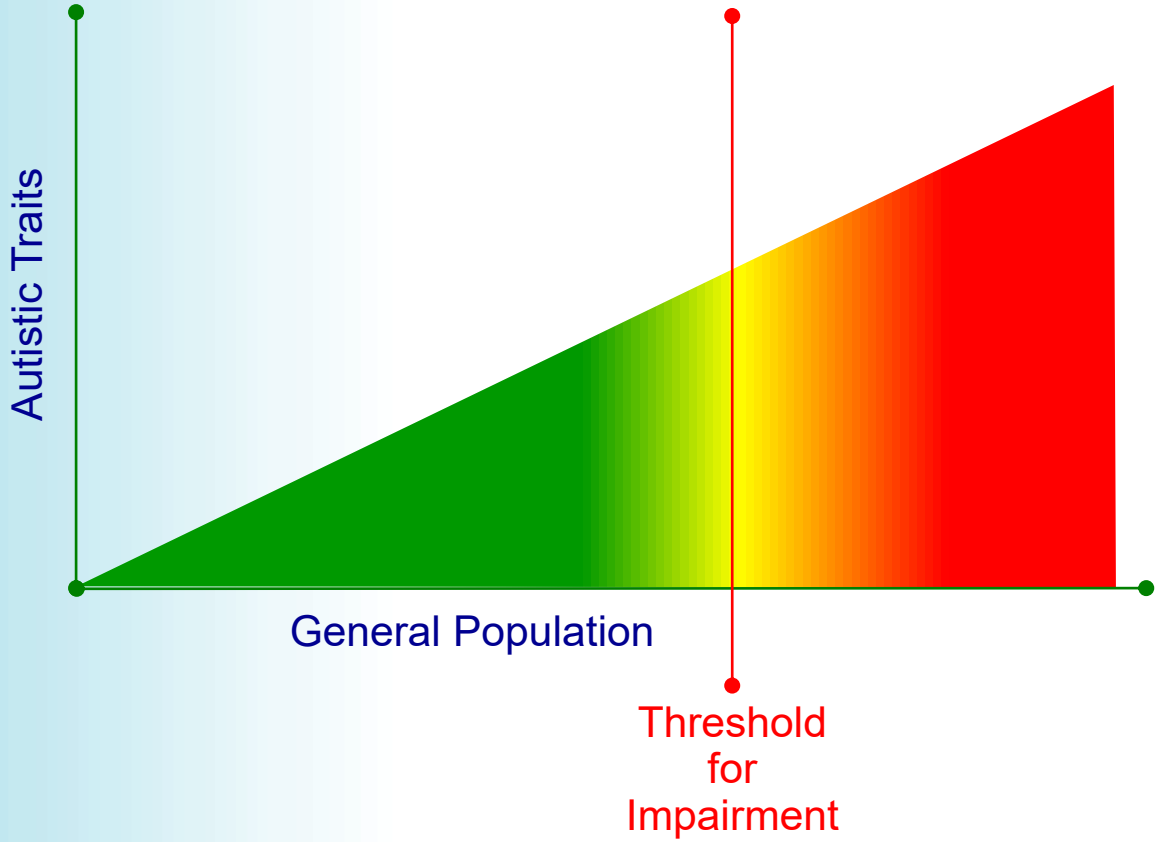

Machine Learning Unsupervised Clustering Analysis

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Inter-ROI Connectivity Patterns in Autism

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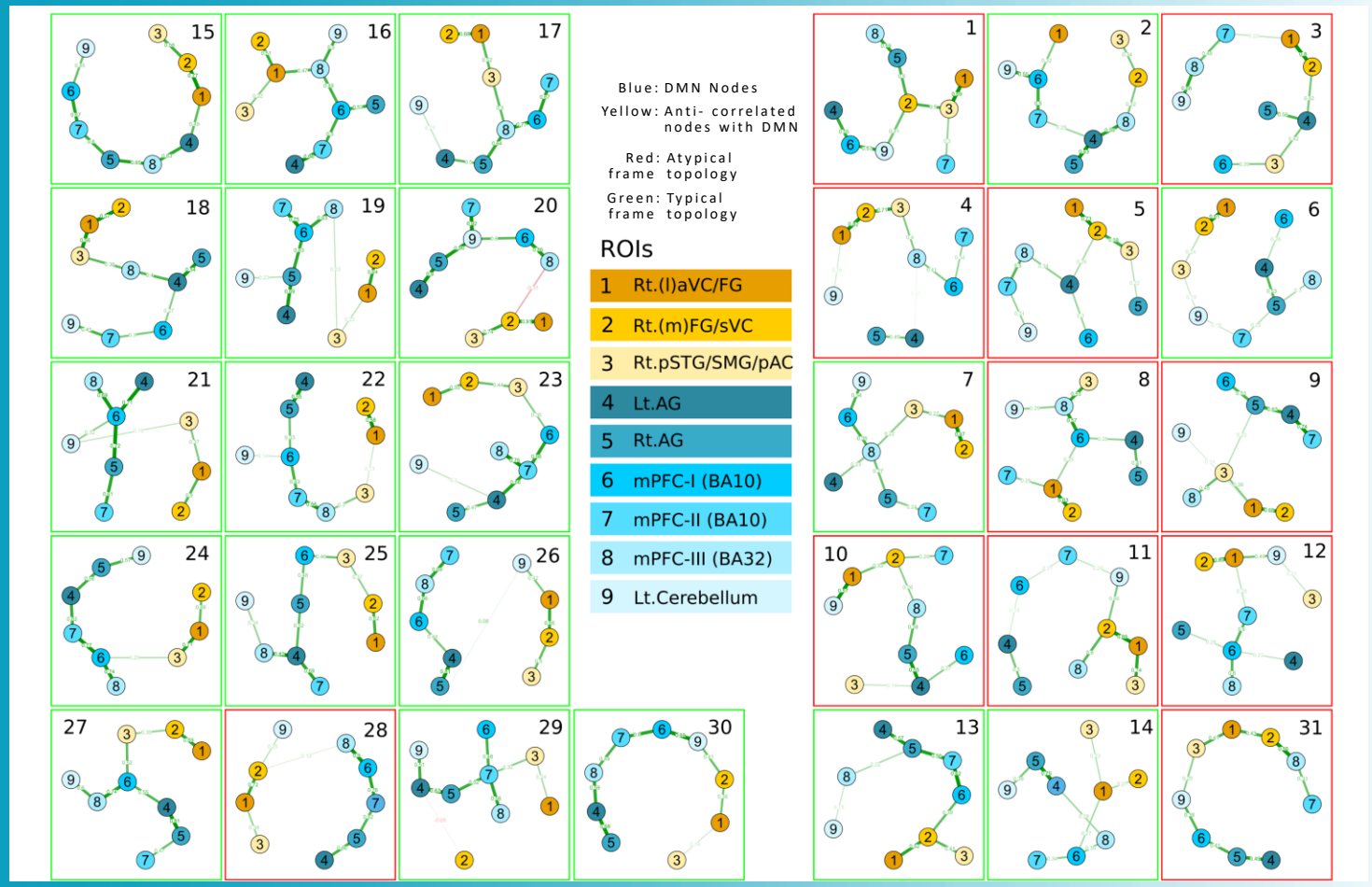
HC
(Specificity = 94% [15/16])

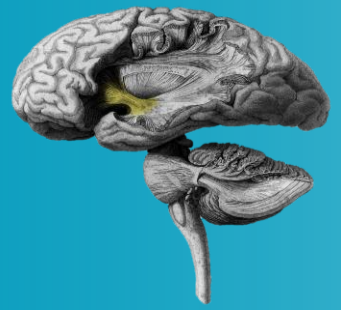
ASD
(Sensitivity = 67% [10/15])



Graph Theoretical
Minimum Spanning Tree Analysis

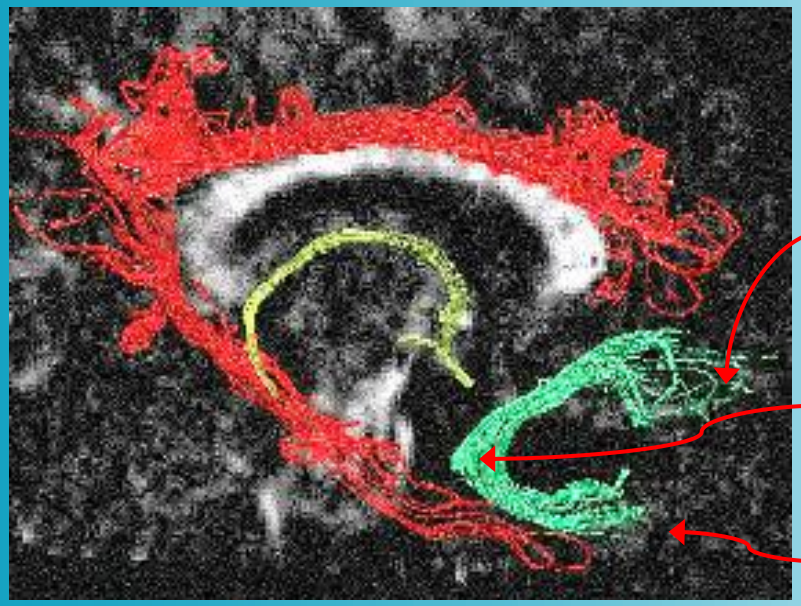
Joshi et al. 2017.

Diffusion Tensor Imaging Tractography



Left Uncinate Fasciculus Abnormality in ASD

- Connects Amygdala & Hippocampus (MTL) with Orbitofrontal Cortex
- Uncinate fibers form the "Amygdalo-orbitofrontal circuit" (involved in theory of mind, social cognition, stereotypies)



Left Uncinate Fasciculus

	ASD	Control
Fiber Length max	187.92	200.43
Fiber Length mean	65.25	72.70
FA mean	0.36	0.46

FA=Fractional anisotropy (a measure of microstructural integrity)

Neurotransmitter – Glutamate

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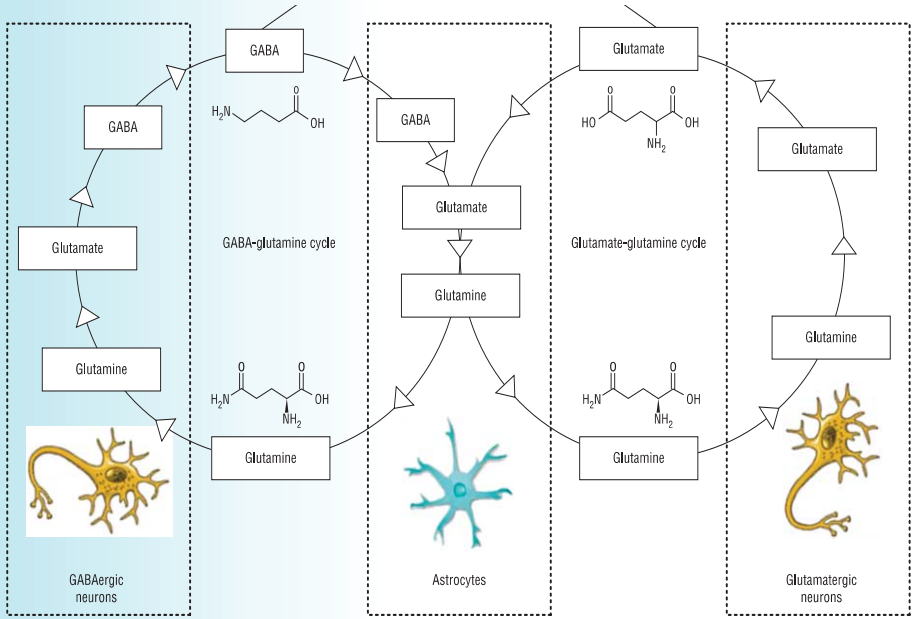
Glutamate

- Primary excitatory neurotransmitter in brain
- Most abundant central neurotransmitter
- Crucial for neurodevelopmental processes (neuronal plasticity and higher cognitive function)
- Glutamate, through its activity on N-methyl-D-aspartate (NMDA) receptor, plays a critical role in cognition and neuronal plasticity
- Over-activity is associated with excitotoxicity (neuronal injury) & apoptosis (cell death)

Glutamate Cycle

GABA ⇄ Glutamate ⇄ Glutamine Cycle



Excitatory-Inhibitory Imbalance in Autism

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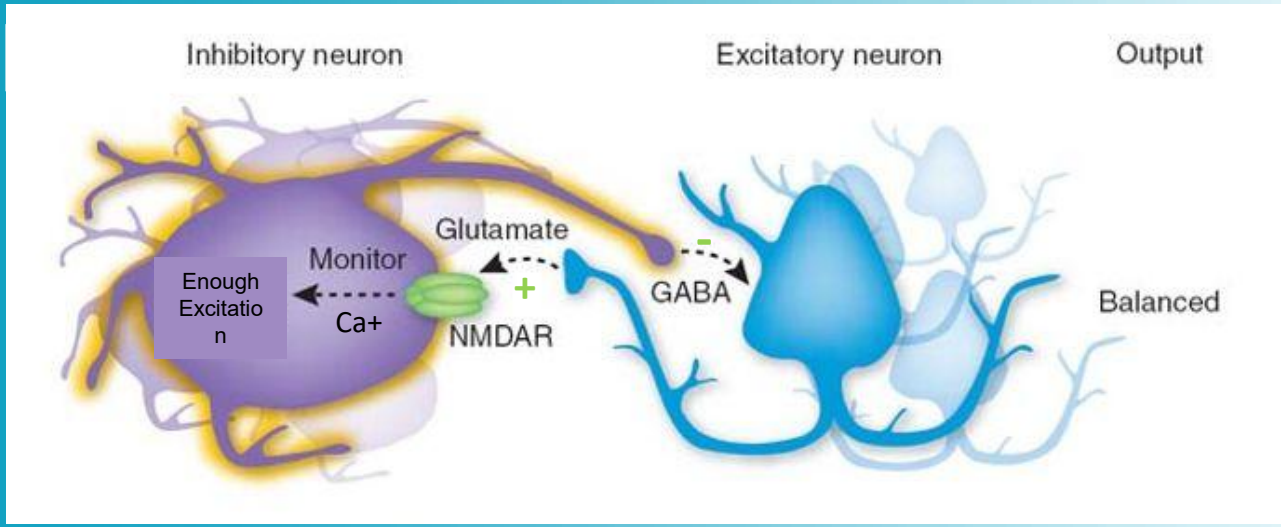
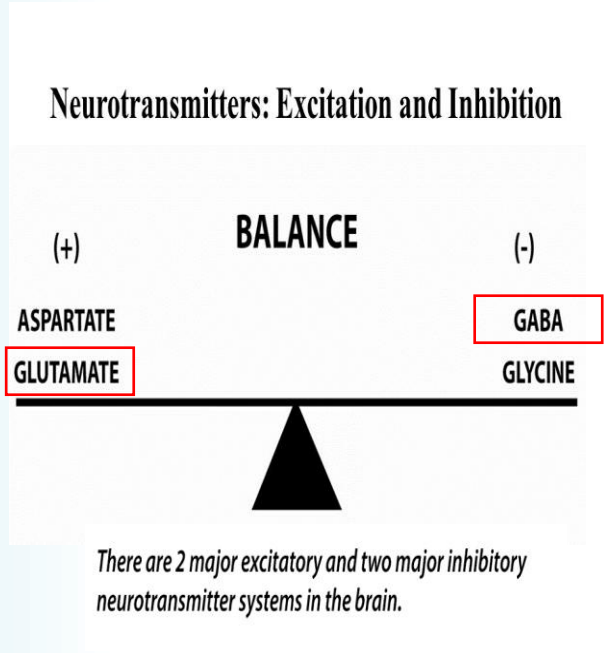
Brain Glutamate – GABA Activity





Glutamate Dysregulation in Autism

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Evidence Supporting

Increased Glutamate Activity in Autism

- Elevated Glu in:
  - Plasma
  - Cerebral spinal fluid
- Affected postmortem brains have:
  - Increase in NMDA receptors
  - Decrease in glutamic acid decarboxylase proteins
- Autism associated with single-nucleotide polymorphisms (SNPs) in glutamatergic genes encoding for:
  - Kainite, ionotropic, & metabotropic Glu receptors
  - Mitochondrial aspartate/glutamate carrier
  - Astrocytic Glu transporter proteins

Shimmura et al. 2011. Lappalainen et al. 1999. Fatemi et al. 2002. Jamain et al. 2002. Shuang et al. 2004. Serajee et al. 2003. Ramoz et al. 2004. Reichert et al. 2004. Purcell et al. 2002.

Proton Spectroscopy at 4T

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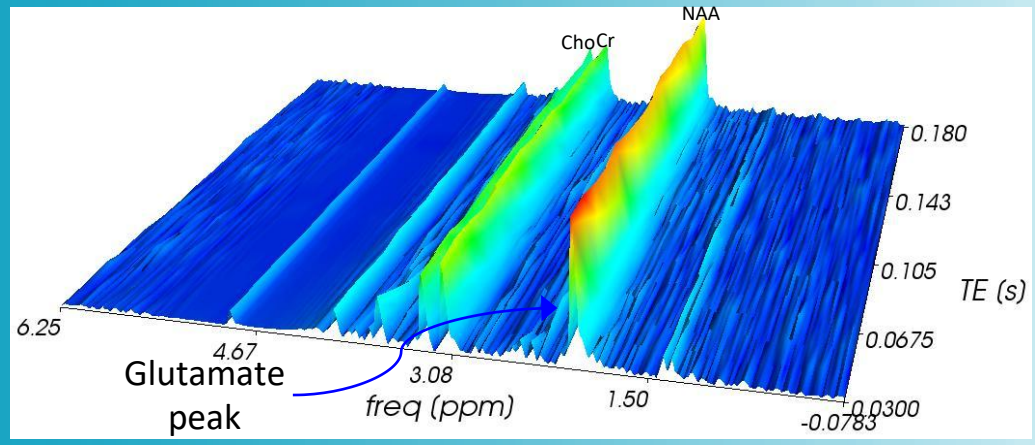
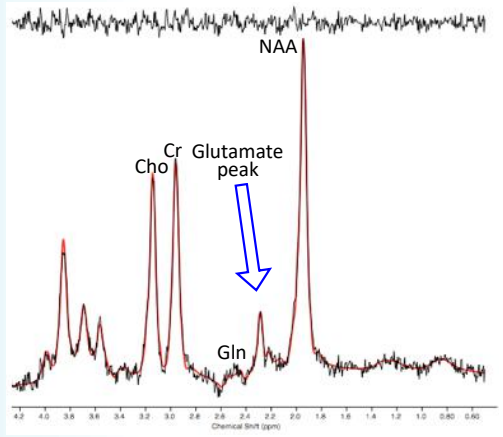
TE - Stepped (J-PRESS) Spectrum



TE-Averaged Spectrum



Differentiation & quantification of Glu from Glx spectra (Glu+Gln+GABA) is achieved by acquiring proton spectra @ 4 Tesla (4T) & by applying multi-echo two-dimensional J-resolved (2D-JPRESS) ^{1}HMRS protocol

Voxel Placement: Social Brain Regions

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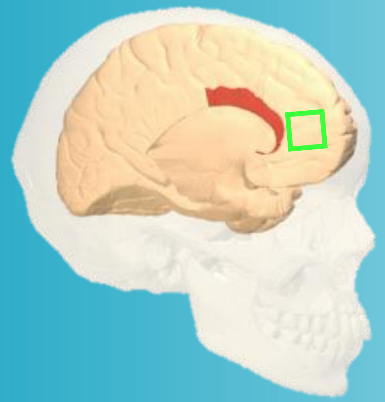
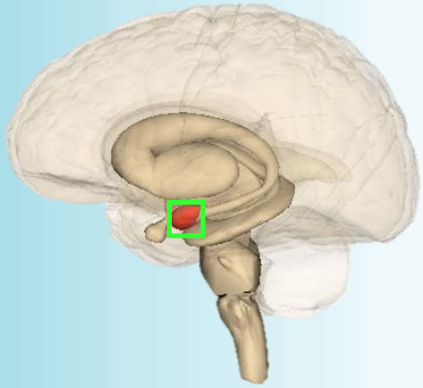
Anterior Cingulate Cortex (ACC)

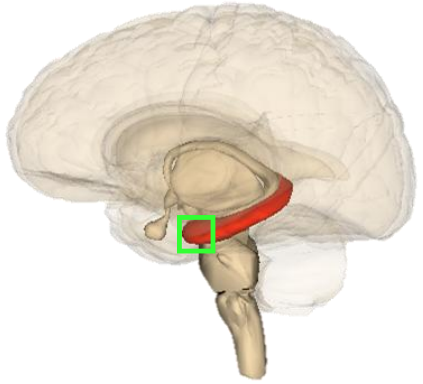


Pregenual ACC [*pg*ACC]

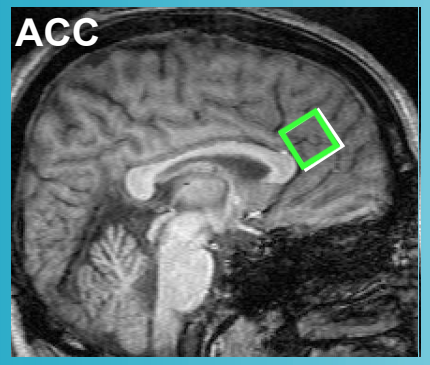
Bilateral Medial Temporal Lobes (MTLs)



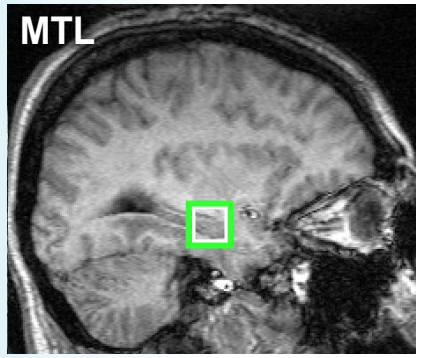
Amygdala



Anterior Hippocampus



***pg*ACC regulates interaction of Cognitive and Affective processes**



MTLs integrate Social and Emotion processes

Glutamate Activity in *pg*ACC & MTL

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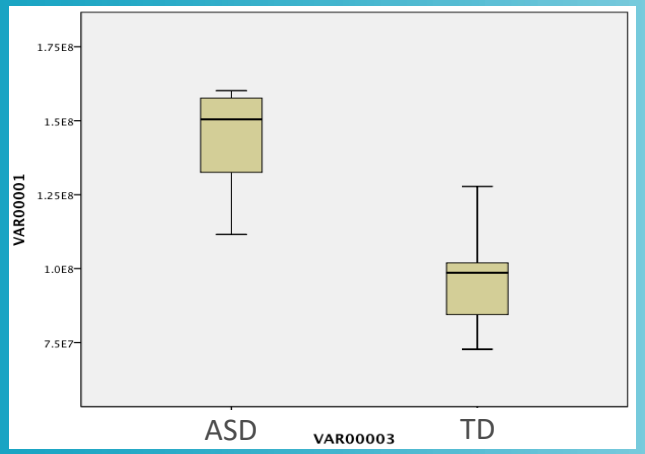
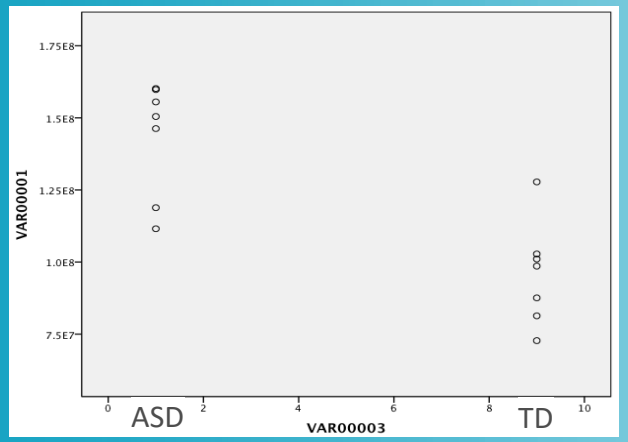
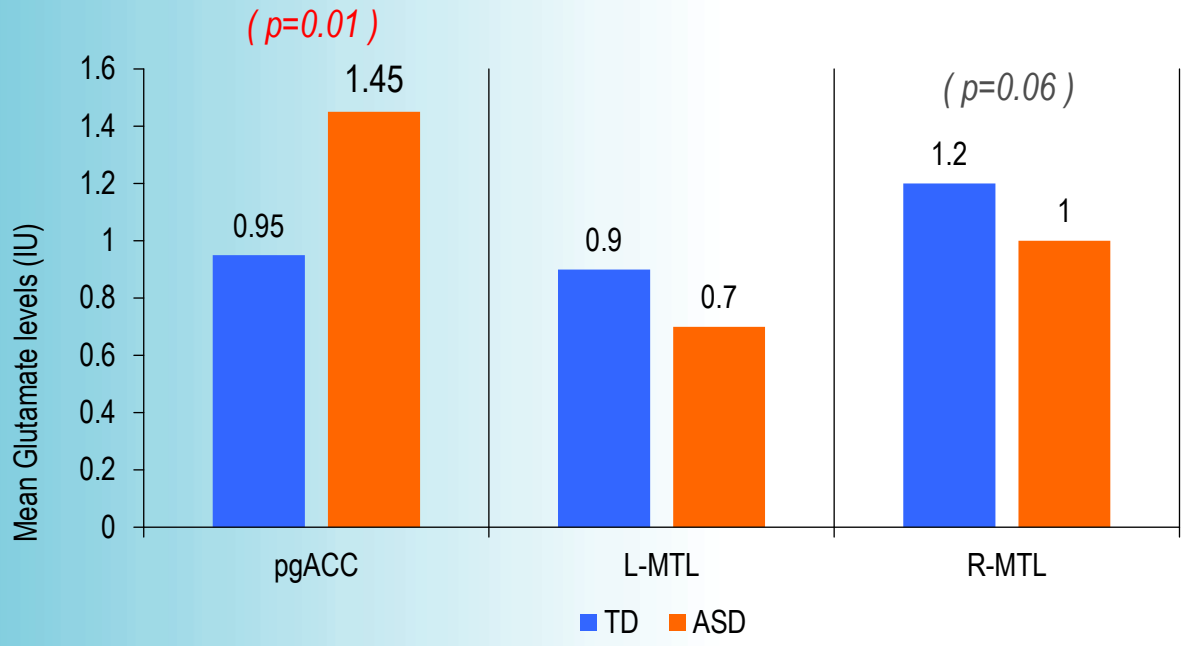
*pg*ACC







Brain Region	GLU Levels (x10⁸) (IU) ASD	HCS	T-statistic	P-value
*pg*ACC	1.43 ±0.20	0.96 ±0.18	3.413	**0.01**
L-MTL	0.72 ±0.08	0.89 ±0.16	1.937	0.101
R-MTL	0.98 ±0.06	1.21 ±0.20	2.242	0.066

Joshi et al. 2012.

MR Spectroscopic Glutamate Activity in Autism

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Study	Age Group	Brain Region	GLX* Levels	GLU Levels
Friedman et al., 2003, 2006	Preschoolers	**ACC (Global)**, Temporal lobes	⇌	
Corrigan et al., 2013	Preschoolers	White matter (Global)	⇊	
Harada et al., 2010	Children	Frontal lobe, Lenticular nuclei (L)		⇋
Hardan et al., 2008	Youth	Thalamus	⇋	
DeVito et al., 2007	Youth	Frontal-Occipital Grey matter	⇊	
Kubas et al., 2012	Youth	Frontal lobe	⇊	
Doyle-Thomas et al., 2014	Youth	Putamen	⇈	
Bejjani et al., 2012	Youth	**ACC (Pregenual)**	⇈	
Cochran et al., 2015	Adolescents	**ACC (Pregenual)**	⇋	
Joshi et al., 2012	Adolescents	**ACC (Pregenual)**		⇈
Elst et al., 2014	Adults	**ACC (Pregenual)**	⇊	⇊
Bernardi et al., 2011	Adults	**ACC (Dorsal)**	⇊	
Page et al., 2006	Adults	Amygdalo-Hippocampus (R)	⇈	
Brown et al., 2012	Adults	Auditory Cortex (BL Temporal region)	⇈	⇈

Preschoolers = 0-5 years; Children = 6-12 years; Adolescents = 13-17 years; Youth = 6 – 17 years; Adults=≥18 years
*GLX = Glutamate + Glutamine + GABA; GLU=Glutamate; ACC=Anterior Cingulate Cortex

MR Spectroscopic Glutamate Activity in Autism

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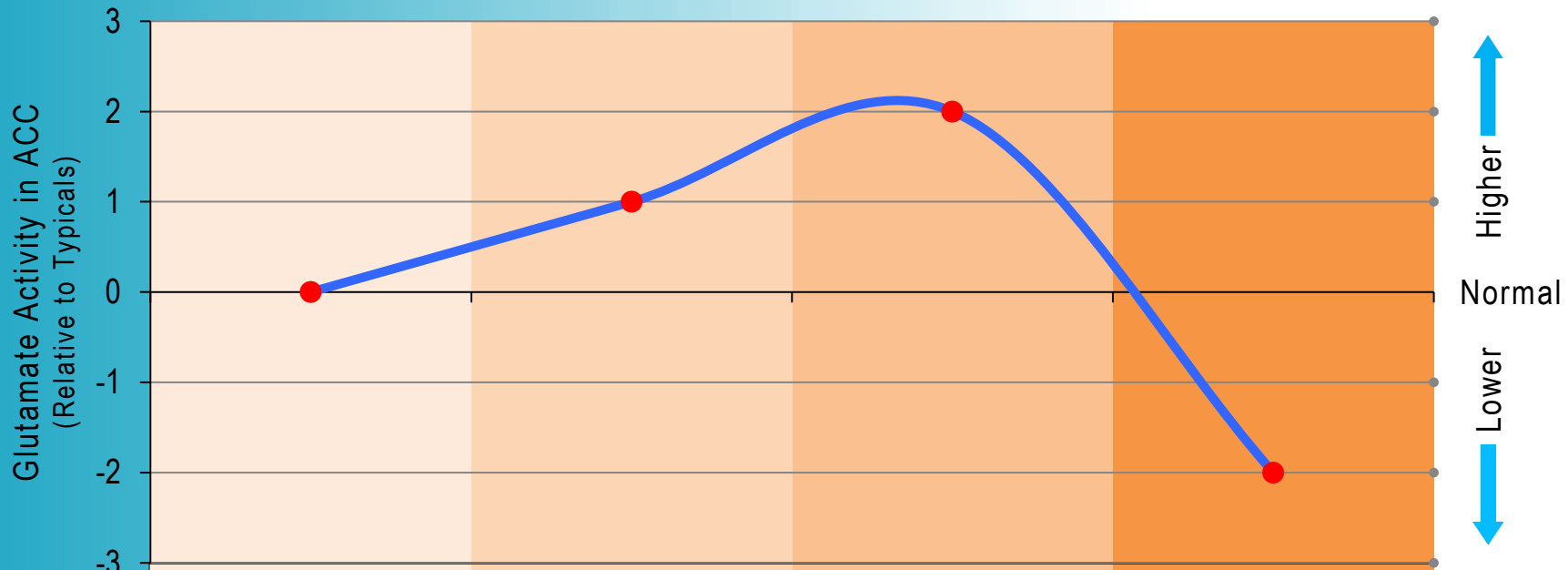
ACC Glutamate Activity in ASD Across the Lifespan



AGE:	Preschool (0–5 years)	Children (6–12 years)	Adolescents (13–18 years)	Adults (19–35 years)
GLU ACTIVITY:	⇌	↑↑	↑↑↑	↓↓
MRS STUDIES:	-Friedman et al. 2003 -Friedman et al. 2006	-Bejjani et al. 2012	-Bejjani et al. 2012 -Joshi et al. 2012	-Elst et al. 2014 -Bernardi et al. 2011

MRS Glutamate Activity in *pg*ACC

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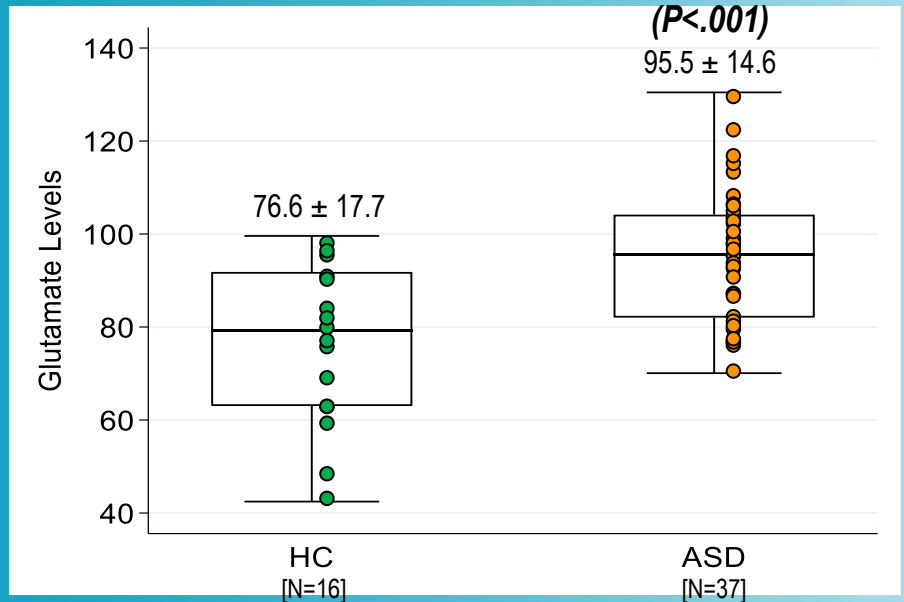
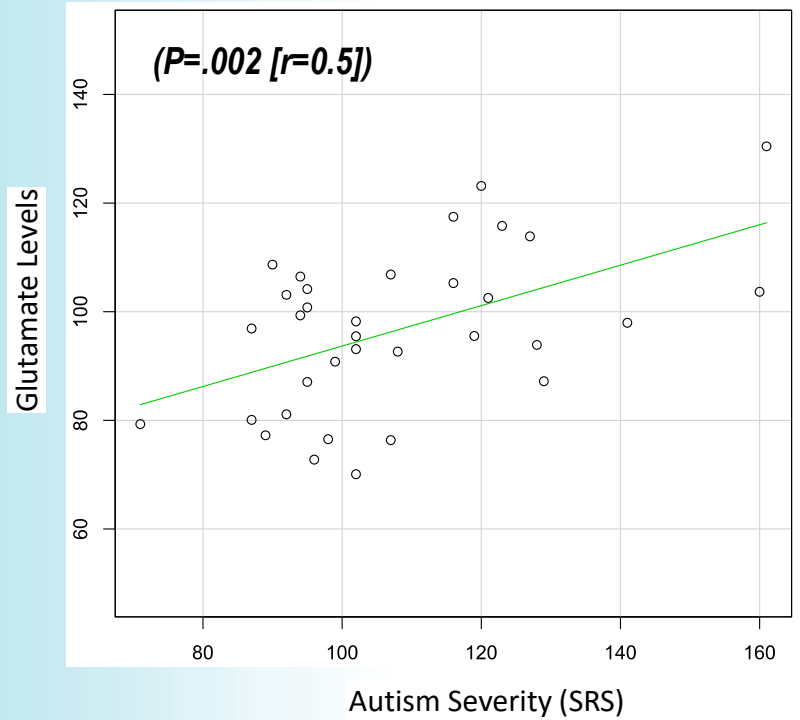
Spectroscopy in Adolescents with HF-ASD

Baseline Glutamate Levels in *pg*ACC



Correlation Between ASD Severity and *pg*ACC Glutamate Levels



Abnormally High *pg*ACC Glutamate activity in ASD correlated with severity of Autism

[NIMH CDA #K23MH100450]

MRS Glutamate Activity in *pg*ACC

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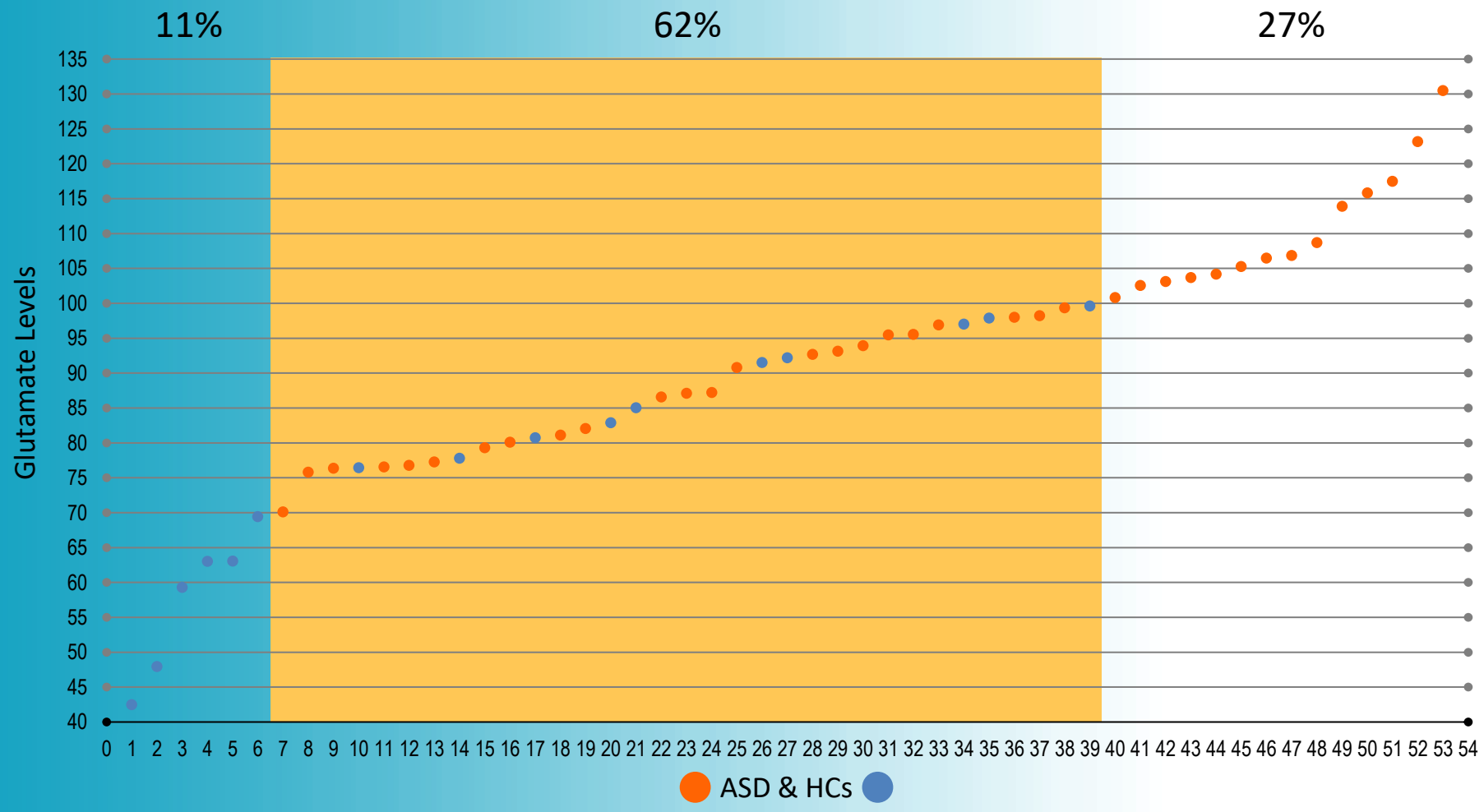

[NIMH CDA #K23MH100450]

Prevalence of HIGH-Glu Activity in Intellectually Capable AUTISM

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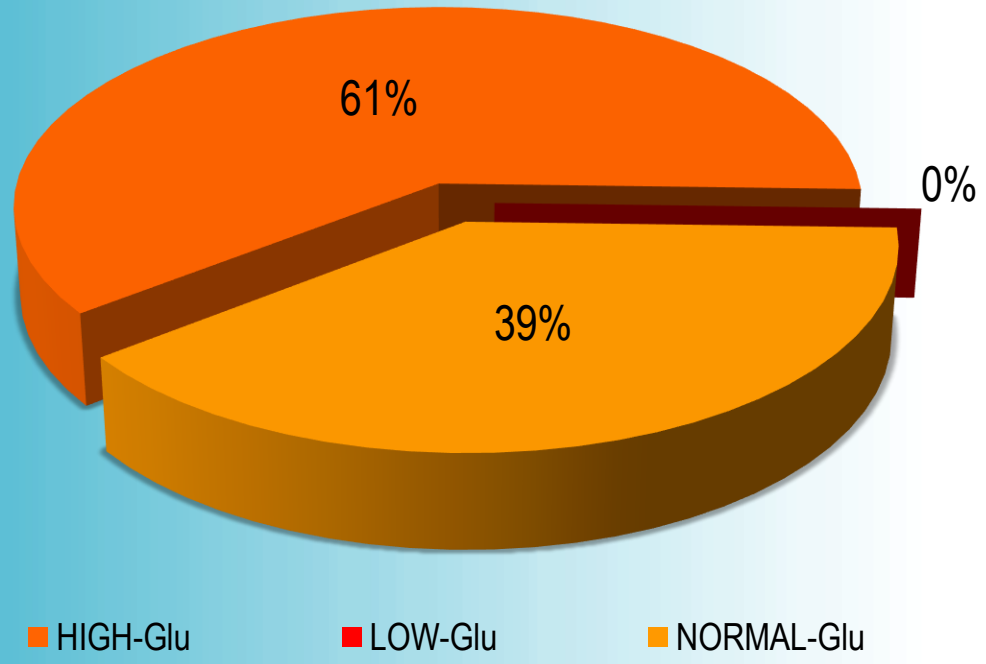

More than a Half of the Youth with AUTISM suffer from abnormally High Brain Glutamate Activity

Behavioral & Neural Response to Memantine in Adolescents with HF-ASD. [NIMH CDA #K23MH100450]

In Summary

- The neurochemical and functional connectivity profile in Autism reflects clinical heterogeneity associated with the disorder
- Selectively, abnormally high Glu activity in *pg*ACC brain region in Autism
- *pg*ACC glutamate activity positively correlates with symptom severity of Autism and ED
- Identified a subtype of autism based on *pg*ACC Glu activity in more than a half of intellectually-capable autism population

12-Week Randomized-Controlled Trial of Memantine Hydrochloride (Namenda) in Adolescents with High-Functioning Autism Spectrum Disorder

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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

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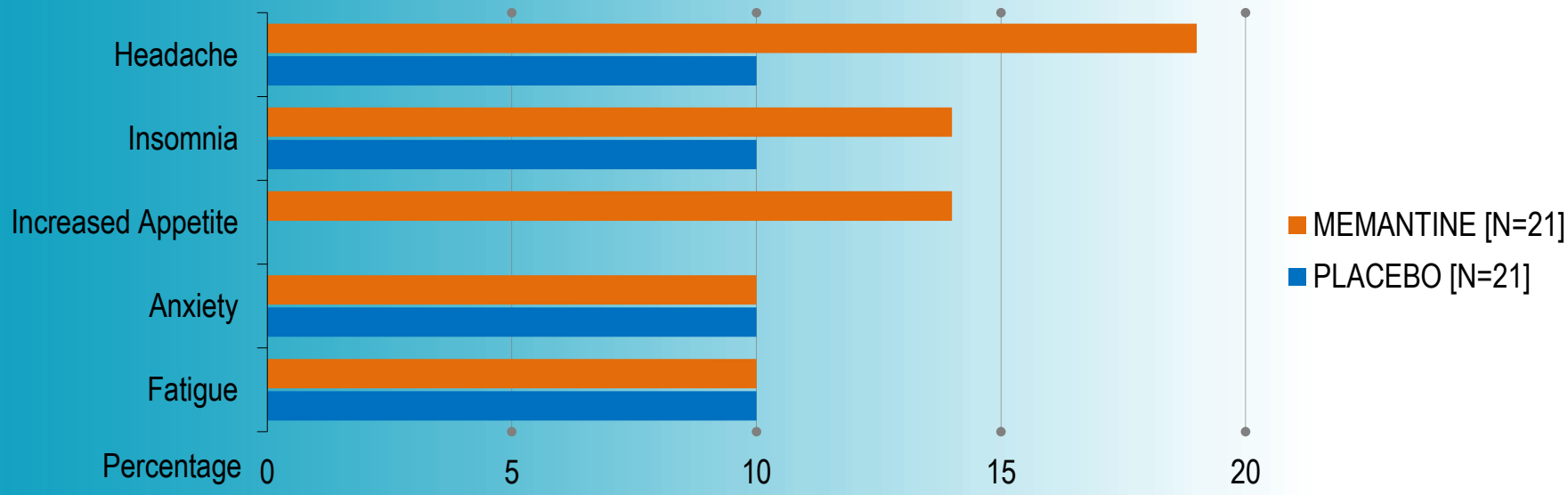
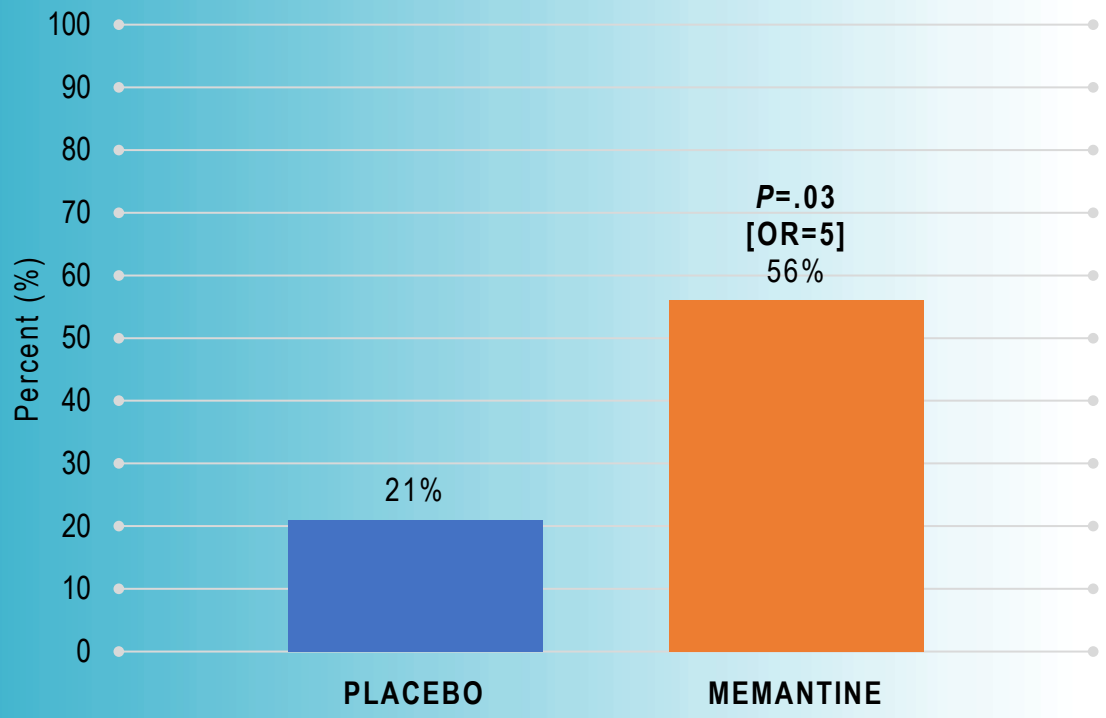
STUDY MEDICATION	MEM[N=21]	PBO[N=21]	p-value [t-statistic]
Dose[Range] *(mg/day)*	19.7 ±1 [15-20]	19 ±3 [10-20]	0.35 [t_{38}=0.94]
@ Maximum Study Dose (20mg/day)	18 (86)	19 (95)	

Adverse Events (Mild-Moderate Severity)



[NIMH CDA #K23MH100450]

Memantine Treatment Responders



Response criteria: ≥25%⇊SRS+ASD-CGI-I≤2

[NIMH CDA #K23MH100450]

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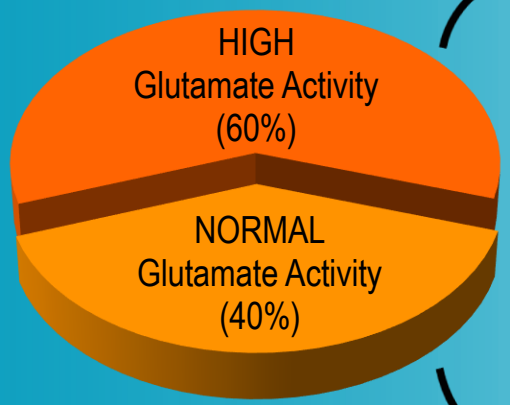
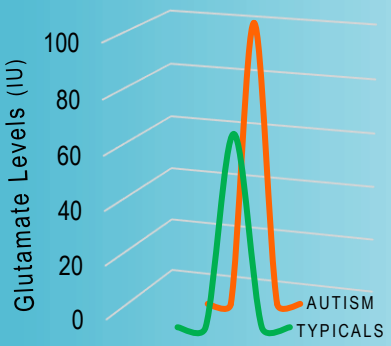
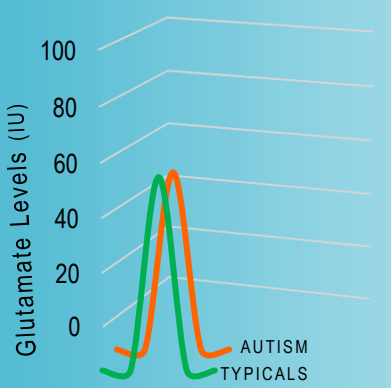
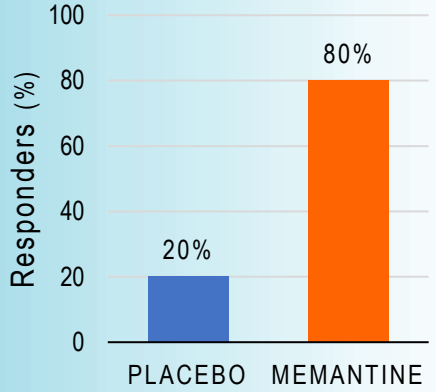
Brain Glutamate Activity

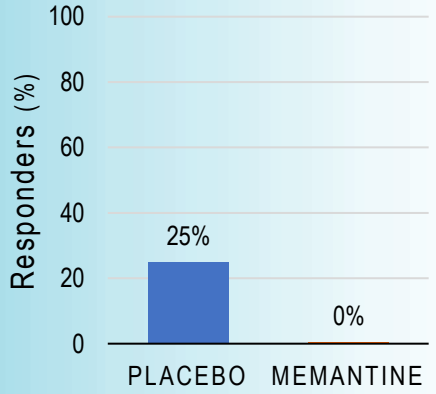




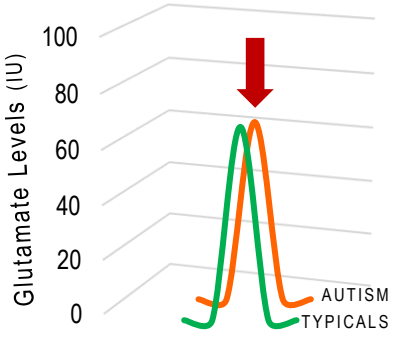


Memantine Treatment

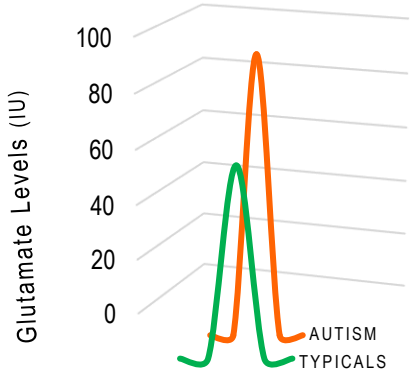




Responders



Non-Responders



[NIMH CDA #K23MH100450]

Moderating Effect of Baseline *pg*ACC Glutamate Level on Tx. Response

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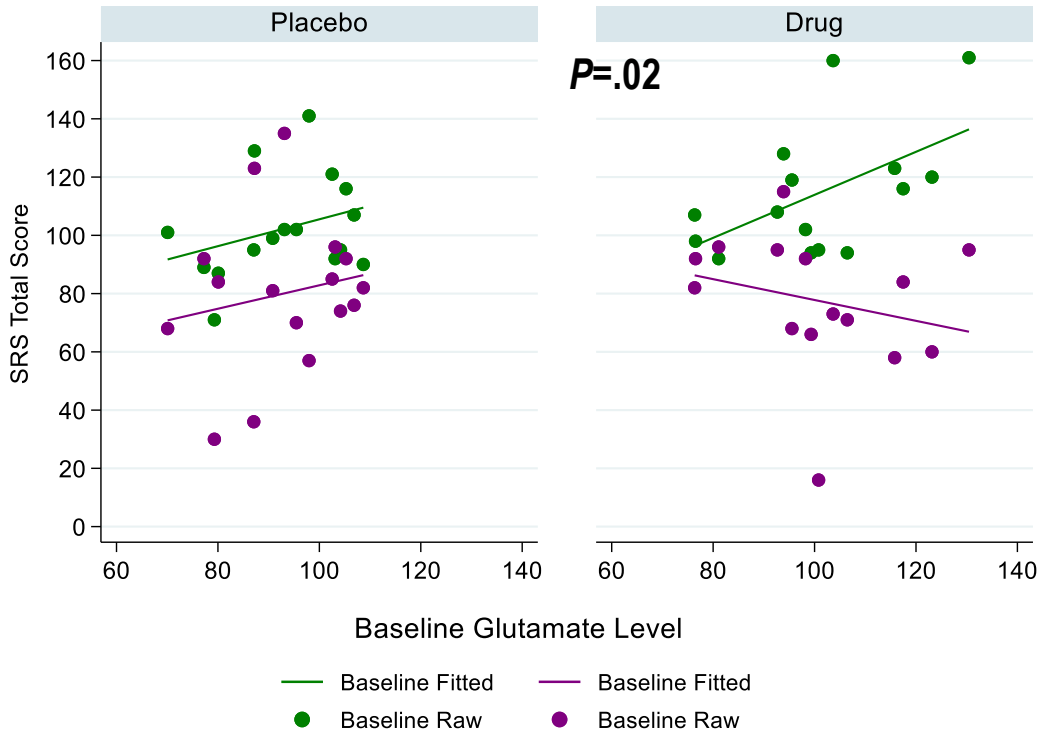
Treatment Response of Autism Severity (SRS)



[NIMH CDA #K23MH100450]

*pg*ACC Glu Activity as Predictor of Response to Memantine Treatment

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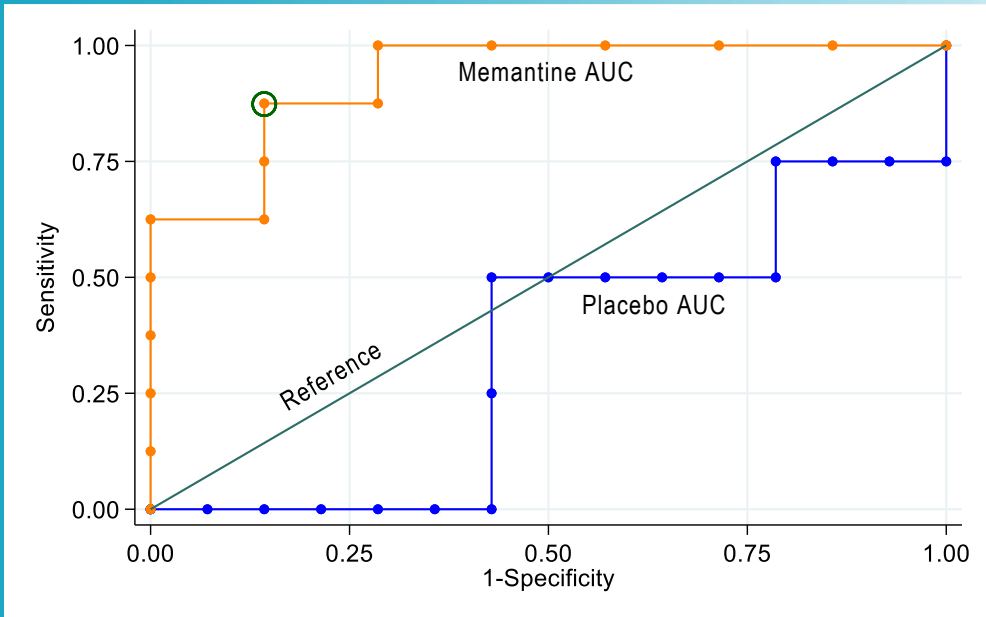
ROC Curve Analysis



	MEM [N=15]	PBO [N=18]	*P*-Value
AUC (95% CI)	0.93 (0.80, 1.00)	0.34 (0.02, 0.66)	<.001

	Optimal Cut-point	Sensitivity	Specificity	PPV	NPV	% Correctly Classified
MEM	99	88%	86%	88%	86%	87%
PBO	97	50%	57%	25%	80%	50%

PPV=Positive Predictive Value; NPV=Negative Predictive Value

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In Summary

- The neurochemical and functional neural connectivity profile in Autism reflects clinical heterogeneity associated with the disorder
- The structural neural connectivity profile associated with ADHD is expressed in HF-ASD youth with comorbid ADHD
- Selectively, abnormally high Glu activity in *pg*ACC brain region in Autism
- Additionally higher *pg*ACC glutamate activity in the presence of ED
- High *pg*ACC Glu activity in more than a half of HF-ASD population that is associated with therapeutic response to Memantine.

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