



# V. Abnormal Brain Glutamate Activity in Autism

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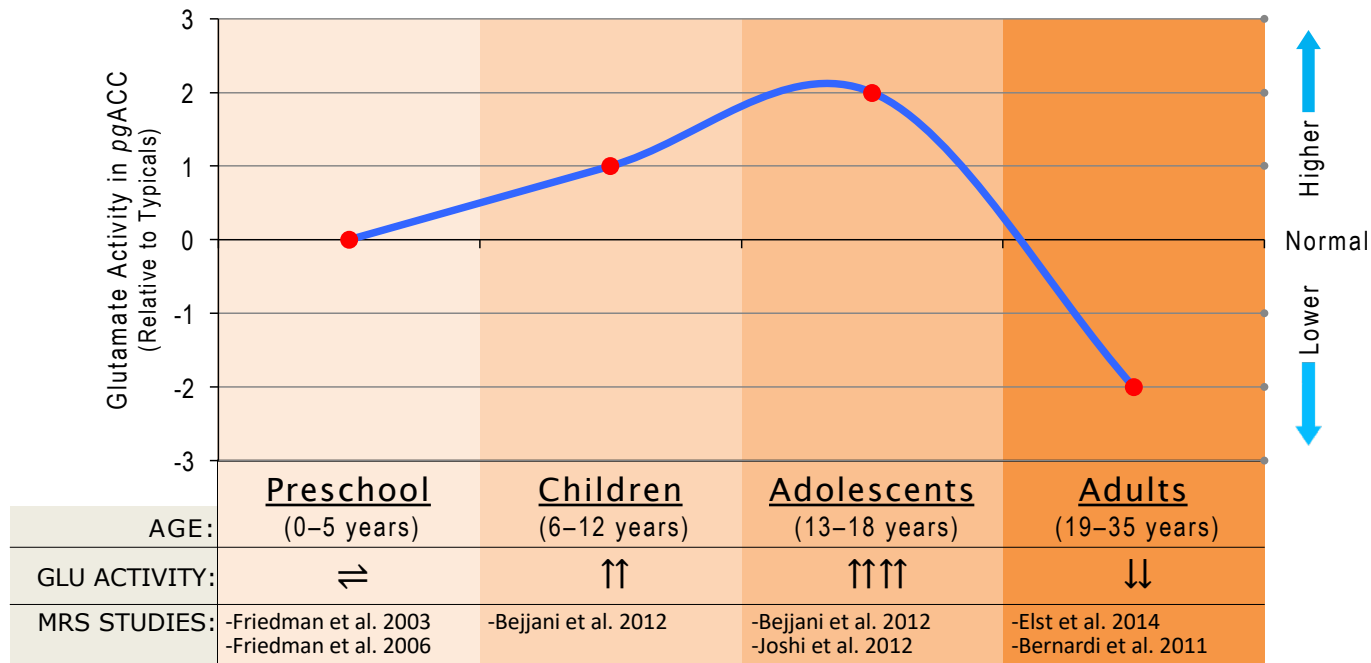
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# MR Spectroscopic Glutamate Activity in Autism

## ACC Glutamate Activity in ASD Across The Lifespan

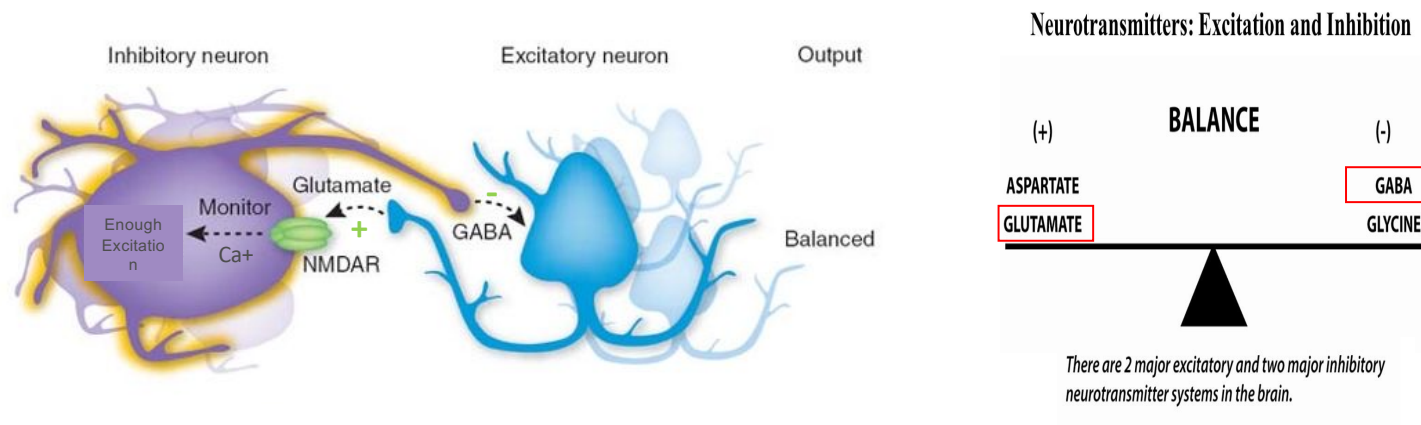


**Higher than expected brain glutamate activity in youth with Autism**



# Excitatory-Inhibitory Imbalance in ASD

## Brain Glutamate – GABA Activity

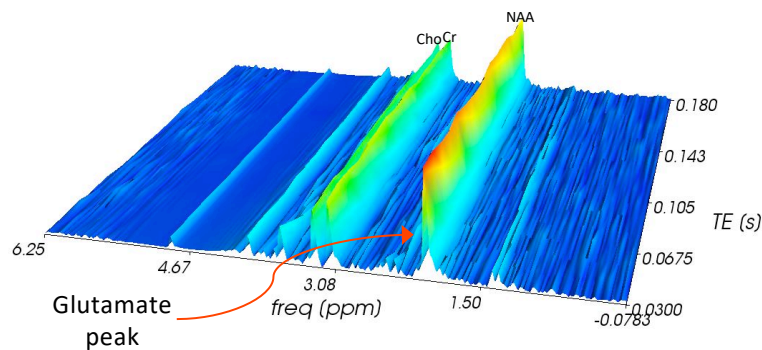


## **Imbalance in Glutamate–GABA activity reported in Autism**



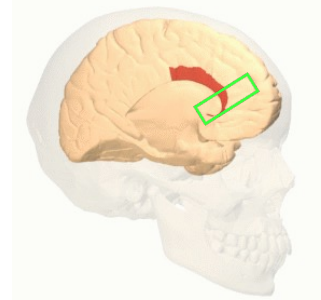
# Proton Spectroscopy at 4T

## TE - Stepped (J-PRESS) Spectrum

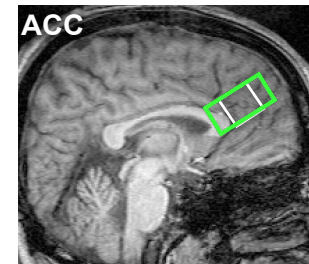


Differentiation & quantification of Glu from Glx spectra (Glu+Gln+GABA) is achieved by acquiring proton spectra @ 4 Tesla (4T) & by applying multi-echo two-dimensional J-resolved (2D-JPRESS)  $^1\text{H}$ MRS protocol

## Anterior Cingulate Cortex (ACC)



### Pregenual ACC [pgACC]



*pgACC* regulates the interaction between cognitive and affective processes



## Magnetic resonance spectroscopy study of the glutamatergic system in adolescent males with high-functioning autistic disorder: a pilot study at 4T

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Rachel L. Goldin · Dave Crowley · Stephannie Furtak ·  
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**Abstract** The pilot study aimed at examining the neural glutamatergic activity in autism. Seven adolescent males (mean age:  $14 \pm 1.8$ ; age range: 12–17 years) with intact intellectual capacity (mean IQ:  $108 \pm 14.26$ ; IQ range: 85–127) suffering from autistic disorder and an equal number of age- and sex-matched healthy controls underwent a two-dimensional magnetic resonance spectroscopy scan at 4T. Results indicated significantly high glutamate (Glu) levels in the anterior cingulate cortex of autistic disorder versus control subjects (paired *t* test  $p = 0.01$ ) and a trend for lower Glu in the right medial temporal lobe, which was not statistically different between the groups (paired *t* test  $p = 0.06$ ). These preliminary findings support the glutamatergic dysregulation hypothesis in autism and need to be replicated in a larger sample.

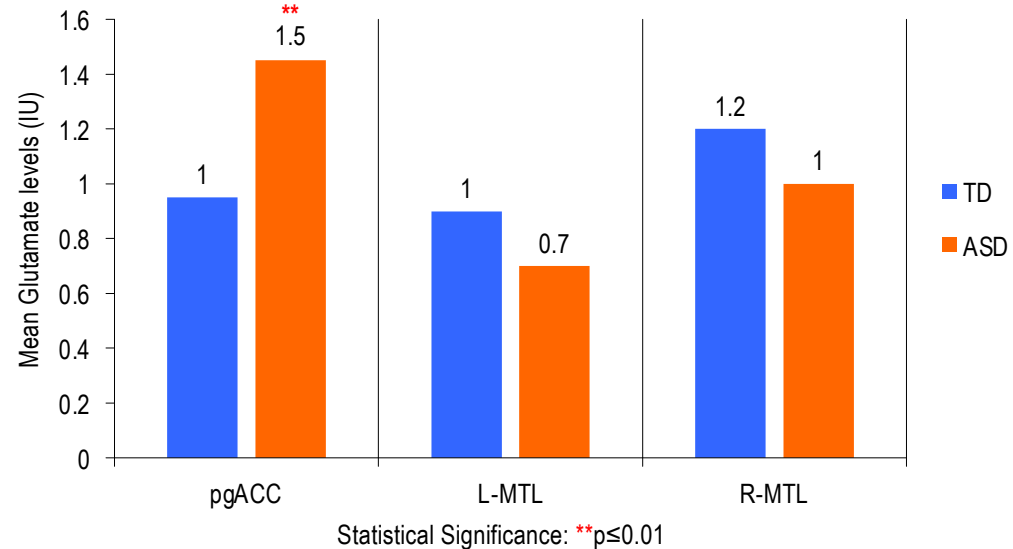
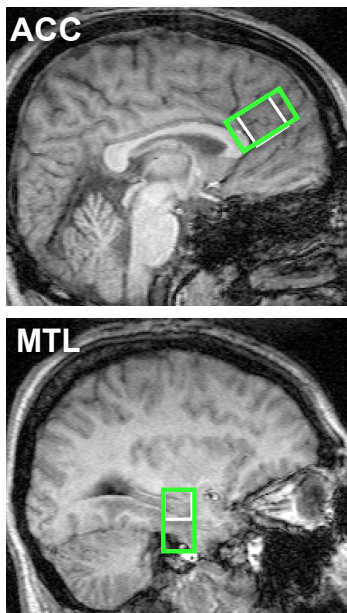
**Keywords** Autistic disorder · Youth ·  
Magnetic resonance spectroscopy · Glutamate

### Introduction

Glutamate (Glu) is the most abundant central neurotransmitter and is crucial for many neurodevelopmental processes, including synapse induction, cell migration, and synapse elimination. Over-activation of Glu is associated with excitotoxicity (neuronal injury) and apoptosis (cell death). Aberrant glutamatergic functioning early in development could have significant subsequent effects on brain development. Dysregulation in glutamatergic activity has been hypothesized in the pathophysiology of several neuropsychiatric disorders including autism spectrum

# Glutamate Activity in *pregenua*ACC & Medial Temporal Lobes

Spectroscopy in Adolescent Males with HF-Autistic Disorder



**Abnormally high glutamate activity in *pgACC*, though not in MTLs**



# A Magnetic Resonance Spectroscopy Study of the Anterior Cingulate Cortex In Youth with Emotional Dysregulation

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## ABSTRACT

**Background:** The main aim of this study was to use proton Magnetic Resonance Spectroscopy (MRS) to identify brain biomarkers for emotional dysregulation in youth as measured by subscales of the Child Behavior Checklist (CBCL).

**Methods:** We measured glutamate (Glu) concentrations in the anterior cingulate cortex (ACC) of 37 pediatric subjects (aged 6-17 years) using high field (4.0 Tesla) proton Magnetic Resonance Spectroscopy (MRS). Subjects were grouped based on combined T scores on three subscales (Anxiety/Depression, Aggression and Attention) of the CBCL previously associated with deficits in the regulation of emotion. Subjects were stratified into those with high (>180) (N=10) and low (<180) (N=27) scores.

marker of emotional dysregulation in youth. Further investigation into the causality, time line and utility as a predictive metric is warranted.

**Limitations:** Limitations include small sample size, wide age range studied, focus on Anterior Cingulate Cortex (ACC) only, and that some subjects received psychopharmacological treatments.

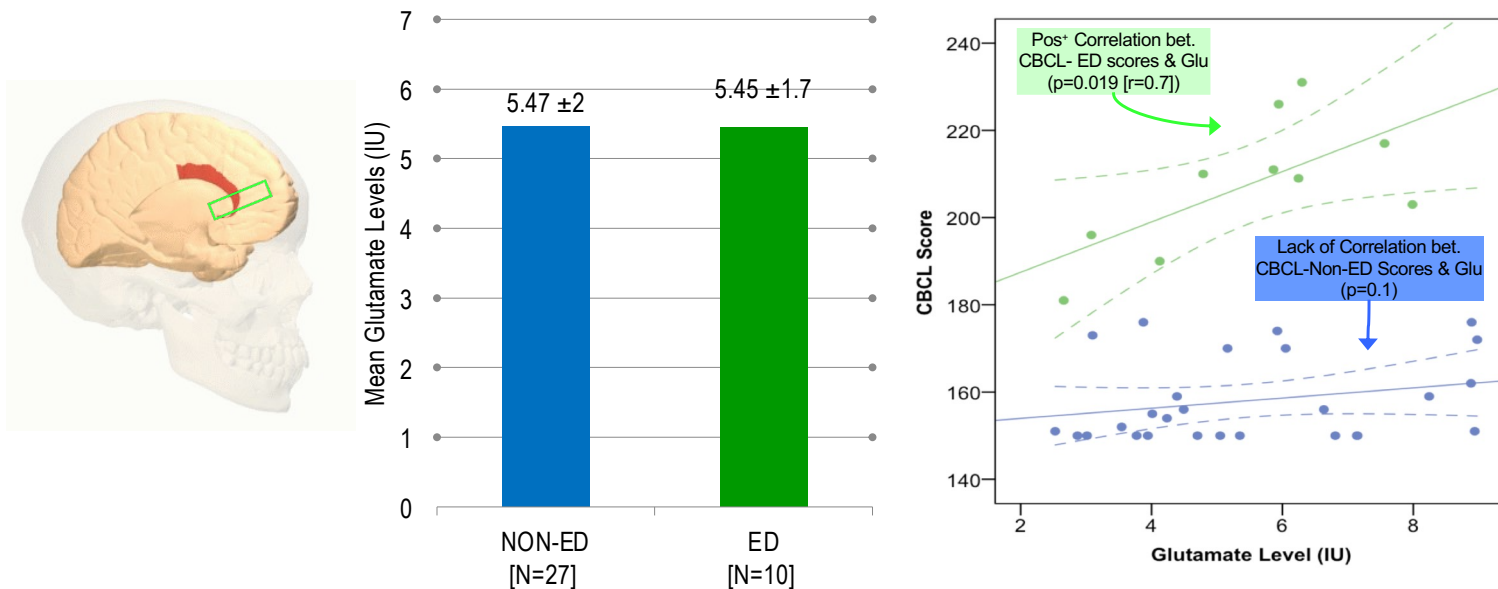
**Results:** We found a statistically significant correlation between Glu levels in the ACC and CBCL dysregulation profile scores among subjects with high dysregulation profile scores.

**Conclusions:** These results suggest that glutamatergic dysregulation in the ACC may represent a useful bio-



# Emotional Dysregulation and MRS Glutamate Activity in *pgACC*

Youth (6-17 yrs.) with and without Emotional Dysregulation



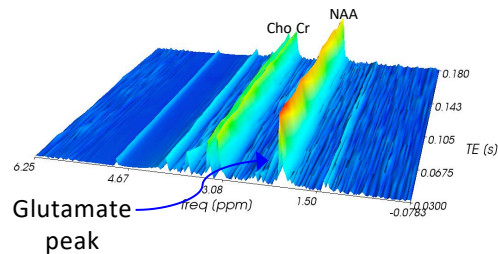
Severity of emotional dysregulation correlates with higher levels of *pgACC* glutamate activity in the brain



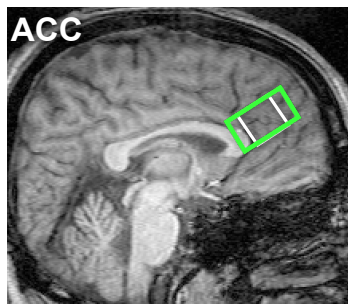


# MRS Glutamate Activity in Pregenual Anterior Cingulate Cortex Proton Spectroscopy in Youth with HF-ASD

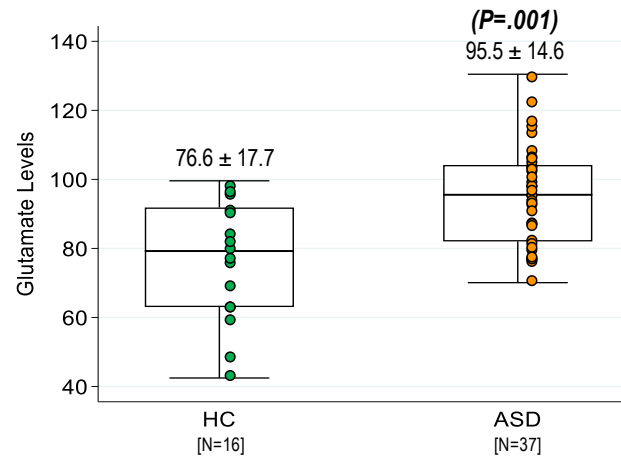
TE - Stepped (J-PRESS) Spectrum



Voxel Placement at Pregenual ACC



Baseline Glutamate Levels in pgACC



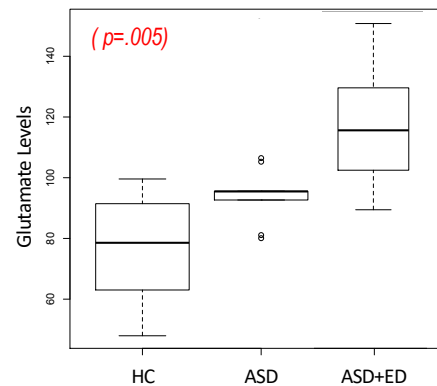
**Abnormally High *pgACC* Glutamate Activity in ASD**



# Emotional Dysregulation and Brain Glutamate Activity in *pgACC*

## Spectroscopy in Adolescents with HF-ASD $\pm$ ED

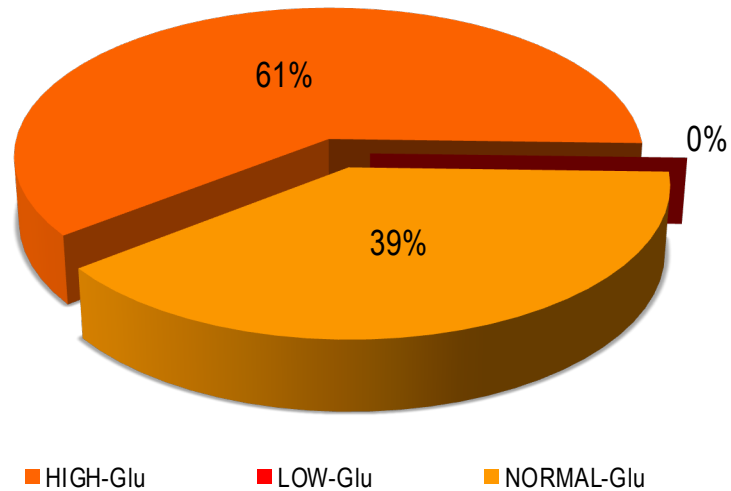
Glutamate Levels in *PgACC*



**Additionally, higher *pgACC* glutamate activity in the presence of emotional dysregulation in ASD**



## Prevalence of HIGH-Glu Activity in HF-ASD



**More than half of the intellectually intact youth with ASD present with abnormally high *pgACC* glutamate activity in the brain**

