An MR Spectroscopy Examination of Brain Metabolites in Autism

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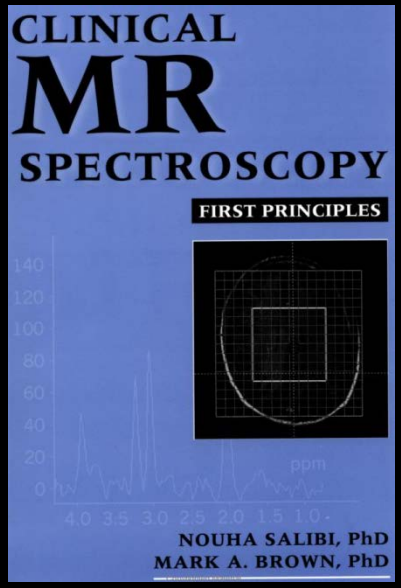
UAB DEPARTMENT OF PSYCHOLOGY
College of Arts and Sciences

UAB CAS Interdisciplinary Team Proposal Presentation
Alumni Auditorium (April 16, 2013)

Interdisciplinary Research Team

Dr. Adrienne Lahti



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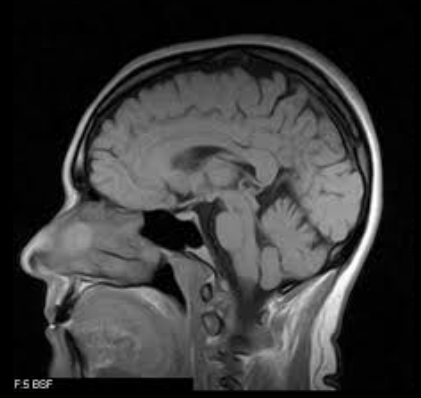

David White

Brain Imaging

Autism: Triad of Impairments

SOCIAL INTERACTION

AUTISM

COMMUNICATION

REPETITIVE BEHAVIOR
RESTRICTED INTERESTS

American Psychiatric Association (1994)

Volume 11, Number 5, 2005 THE NEUROSCIENTIST REVIEW ■

Large Brains in Autism: The Challenge of Pervasive Abnormality

MARTHA R. HERBERT
Pediatric Neurology, Center for Morphometric Analysis
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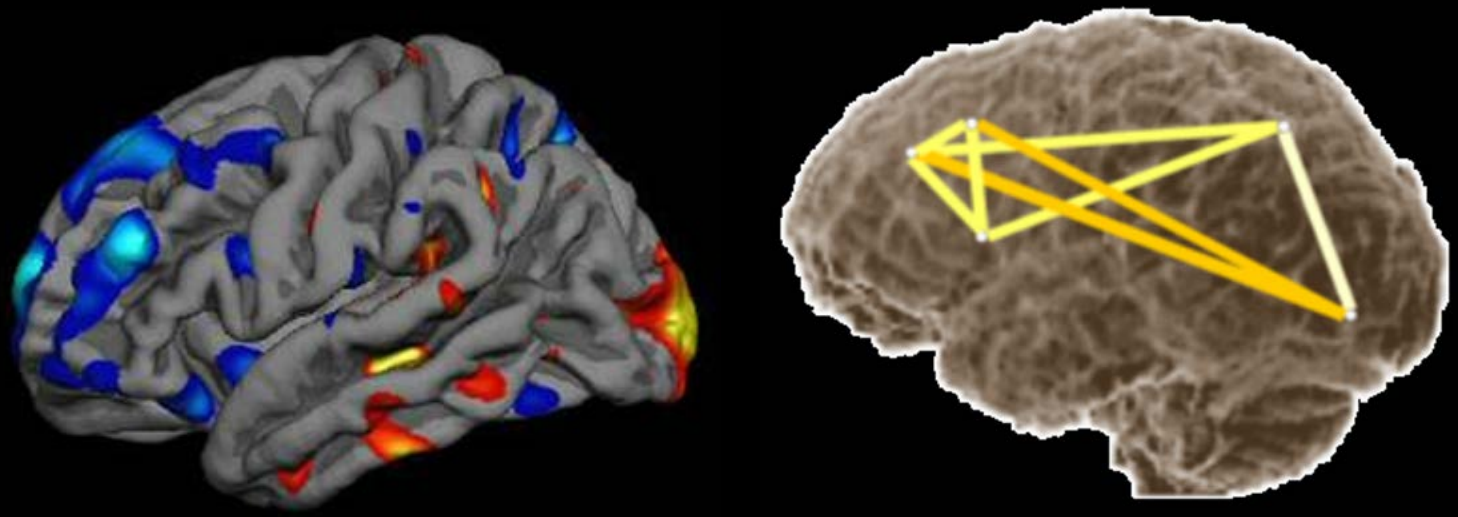
Where in the brain is Autism located?



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PHYSICS of LIFE reviews

Physics of Life Reviews 8 (2011) 410–437

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Disrupted cortical connectivity theory as an explanatory model for autism spectrum disorders

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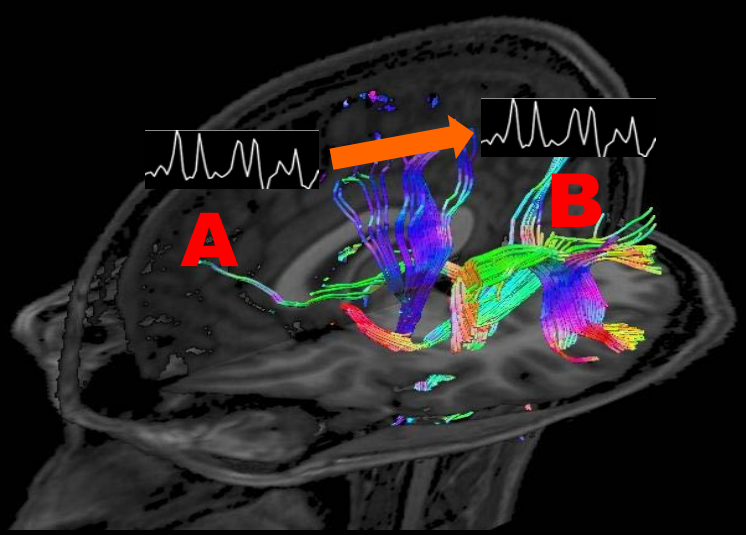

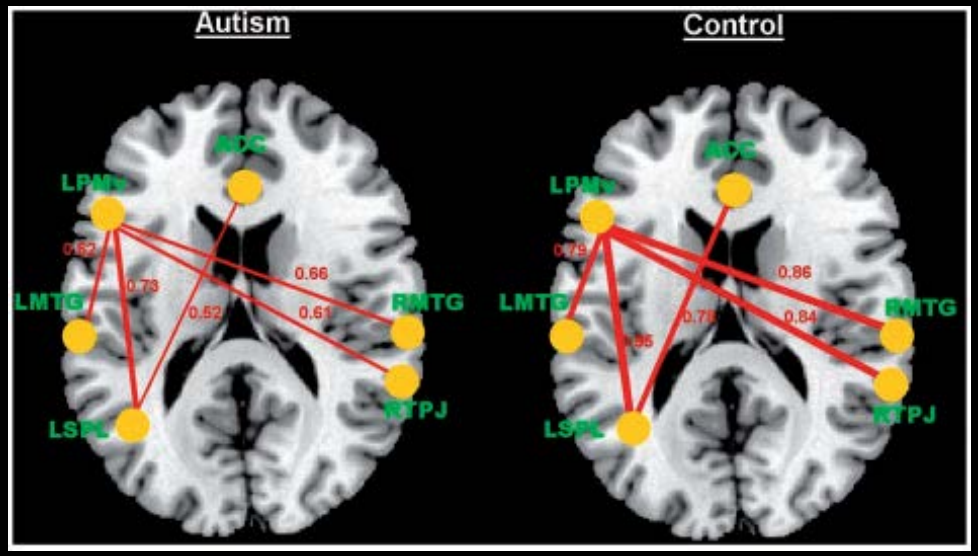

PRELIMINARY COMMUNICATION

Neuron Number and Size in Prefrontal Cortex of Children With Autism

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Peter R. Mouton, PhD
Michael E. Calhoun, PhD
Katerina Semendeferi, PhD
Clelia Ahrens-Barbeau, BS
Melodie J. Hallet, MS
Cynthia Carter Barnes, PhD
Karen Pierce, PhD

Context Autism often involves early brain overgrowth, including the prefrontal cortex (PFC). Although prefrontal abnormality has been theorized to underlie some autistic symptoms, the cellular defects that cause abnormal overgrowth remain unknown.

Objective To investigate whether early brain overgrowth in children with autism involves excess neuron numbers in the PFC.

Design, Setting, and Cases Postmortem prefrontal tissue from 7 autistic and 6 control male children aged 2 to 16 years was examined by expert anatomists who were blinded to diagnostic status. Number and size of neurons were quantified using stereological methods within the dorsolateral (DL-PFC) and mesial (M-PFC) subdivisions of the PFC. Cases were from the eastern and southeastern United States and died between 2000 and 2006.

Main Outcome Measures Mean neuron number and size in the DL-PFC and M-PFC were compared between autistic and control postmortem cases. Correlations of neuron number with deviation in brain weight from normative values for age were also performed.

Results Children with autism had 67% more neurons in the PFC (mean, 1.94 billion; 95% CI, 1.57-2.31) compared with control children (1.16 billion; 95% CI, 0.90-1.42; $P=.002$), including 79% more in DL-PFC (1.57 billion; 95% CI, 1.20-1.94 in autism cases vs 0.88 billion; 95% CI, 0.66-1.10 in controls; $P=.003$) and 29% more in M-PFC (0.36 billion; 95% CI, 0.33-0.40 in autism cases vs 0.28 billion; 95% CI, 0.23-0.34 in controls; $P=.009$). Brain weight in the autistic cases differed from normative mean weight for age by a mean of 17.6% (95% CI, 10.2%-25.0%; $P=.001$), while brains in controls differed by a mean of 0.2% (95% CI, –8.7% to 9.1%; $P=.96$). Plots of counts by weight showed autistic children had both greater total prefrontal neuron counts and brain weight for age than control children.

Conclusion In this small preliminary study, brain overgrowth in males with autism involved an abnormal excess number of neurons in the PFC.

JAMA. 2011;306(18):2001-2010 www.jama.com

CLINICAL SIGNS OF AUTISM ARE often preceded by or emerge concurrently with a period of abnormal brain and head overgrowth.[1-12] This early neurobiological signal of abnormal development has been reported to begin at 9 to 18 months of age.[2,9-11]

Overgrowth[13] and neural dysfunction[14,15] are evident at young ages in multiple brain regions, including the prefrontal cortex (PFC),[3,6,7,11,12] that are involved in higher-order social, emotional, communication, and cognitive development. Therefore, knowledge of the neural basis of overgrowth could point to early causal mechanisms in autism and elucidate the neural func-

Figure 1. Schematic of Dorsolateral Prefrontal Cortex and Mesial Prefrontal Cortex

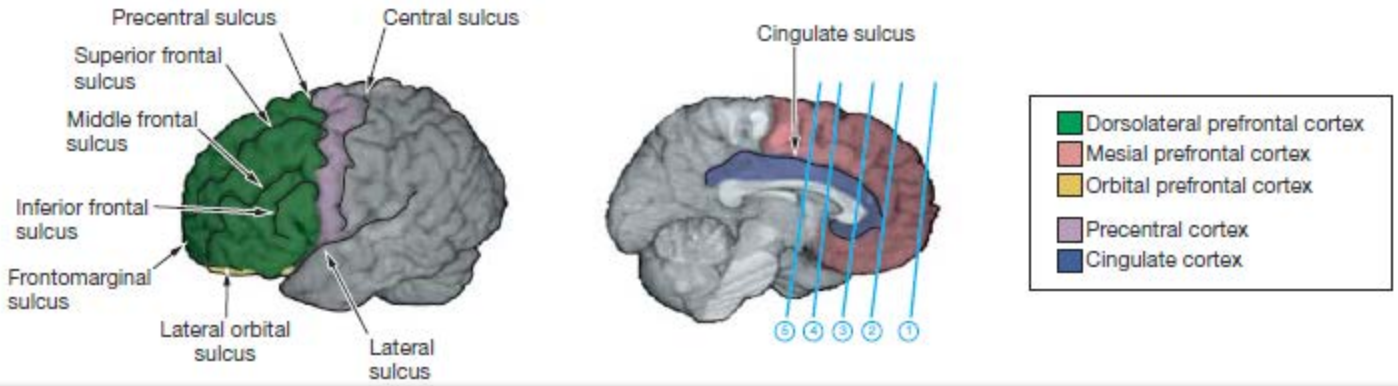
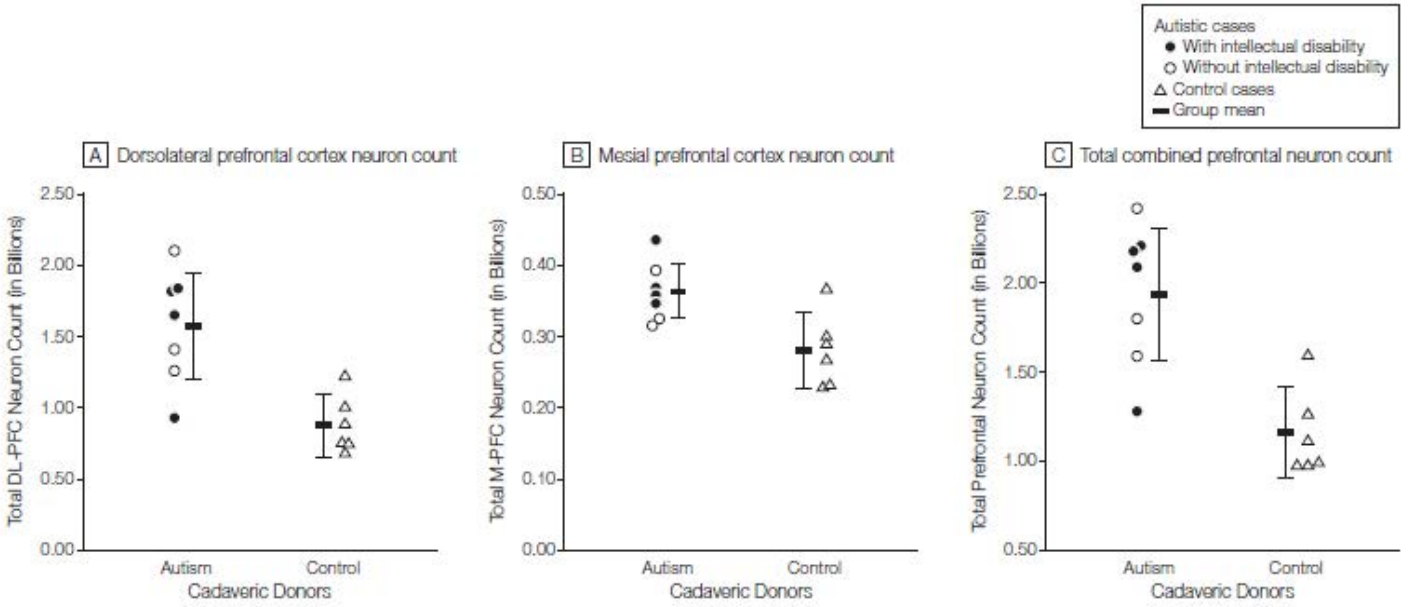
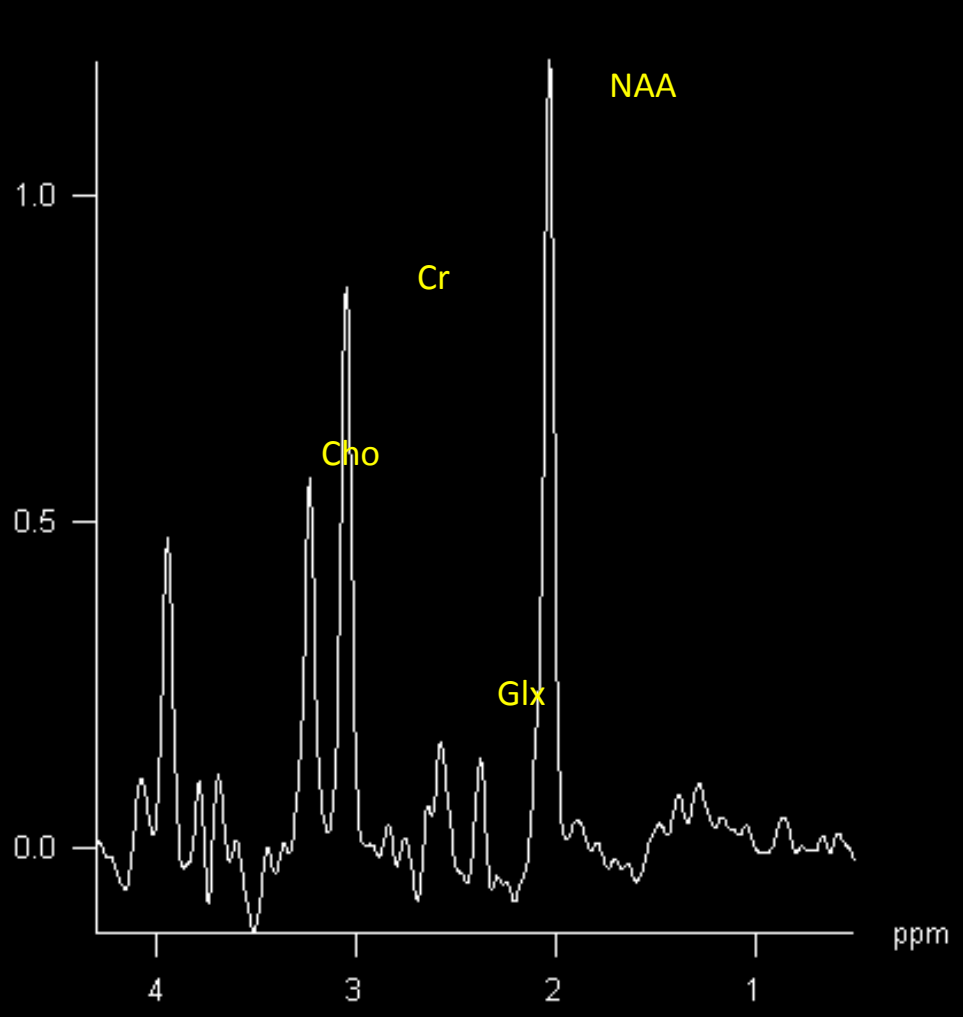


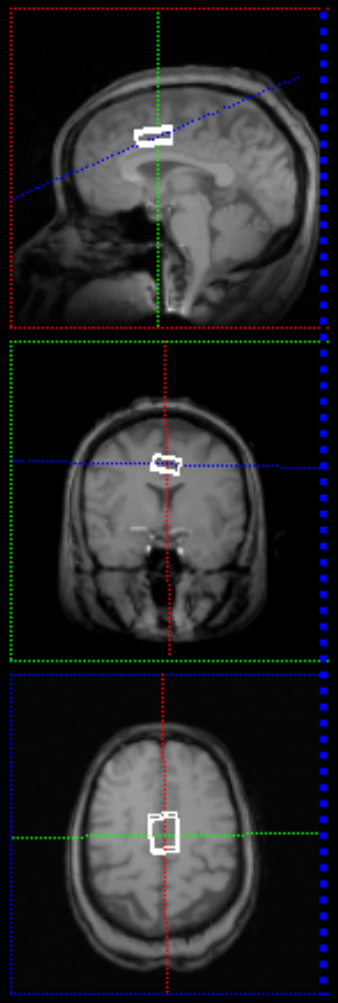
Figure 3. Dorsolateral (DL-PFC) and Mesial Prefrontal Cortex (M-PFC) Neuron Counts in Autism vs Control Group Cases



Error bars indicate 95% CIs. For between-group comparisons, statistical tests were as follows: $P = .003$ for panel A, $P = .009$ for panel B, and $P = .002$ for panel C. Autistic case with lowest neuron count value in panels A and C had a seizure disorder, adverse perinatal medical conditions, and intellectual disability.

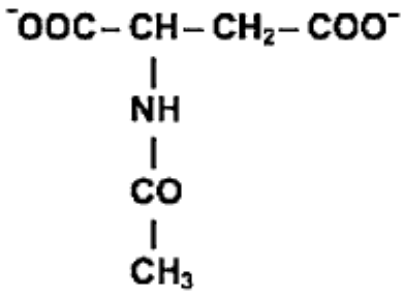
MR Spectroscopy (^{1}H-MRS)



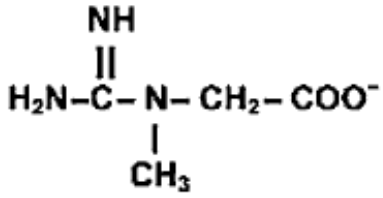


The molecular structures of 6 brain metabolites commonly studied with 1H-MRS

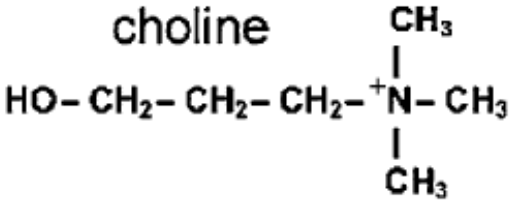
N-acetylaspartate



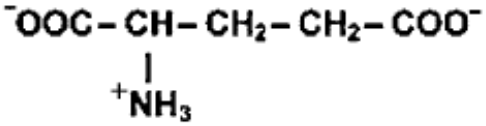
creatine



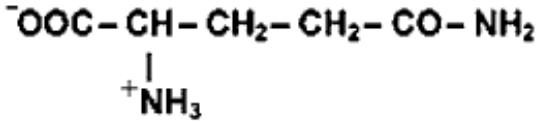
choline



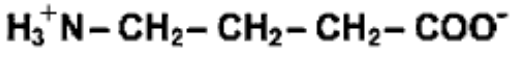
glutamate



glutamine



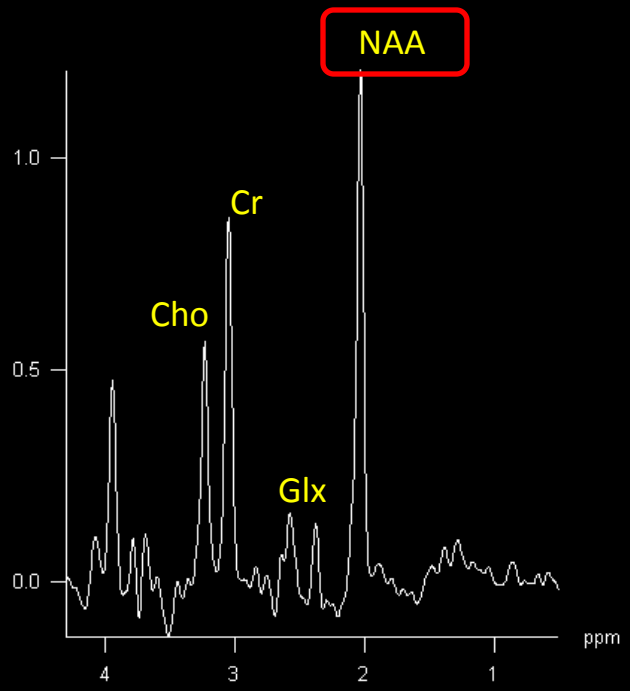
gamma-aminobutyric acid



Maddock & Buonocore (2012); Curr. Topics in Beh. Neur.

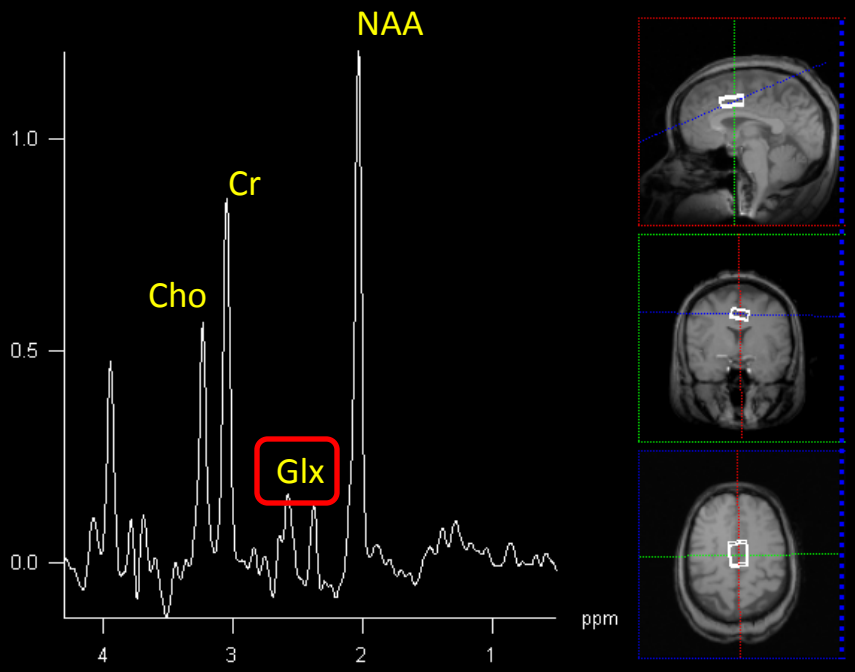
N-Acetyl Aspartate

- Amino acid synthesized in mitochondria of neurons
- Marker of neuronal integrity
- Robust signal in ^{1}H-MRS studies
- Correlates with cognitive function



Glutamate/Glutamine

- Glutamate is the major excitatory neurotransmitter
- Direct precursor for GABA, the major inhibitory neurotransmitter
- Glutamine synthesized from glutamate in astrocytes & broken down to glutamate in neurons
- Complex ^{1}H-MRS spectra



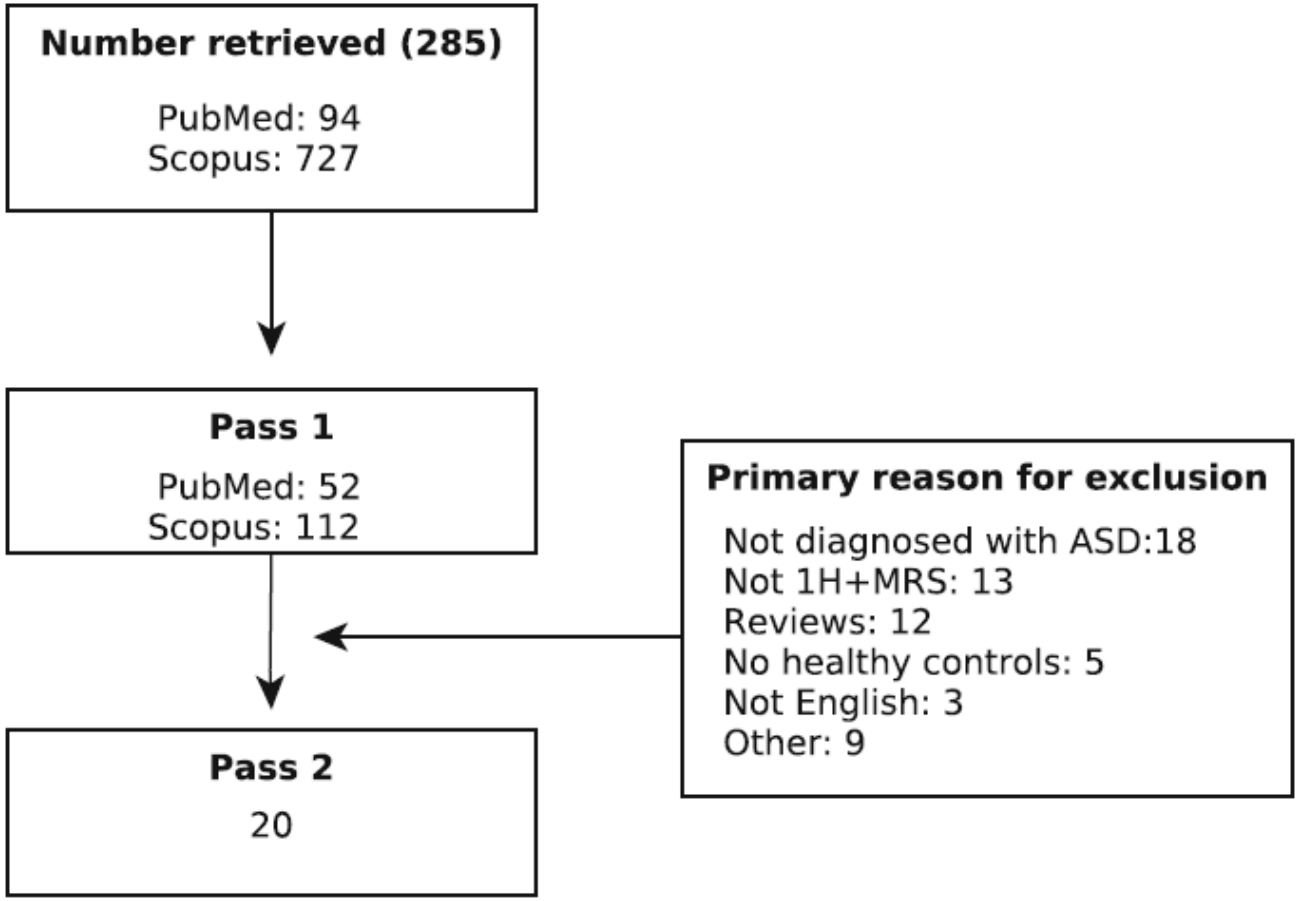
Metab Brain Dis
DOI 10.1007/s11011-012-9293-y

ORIGINAL PAPER

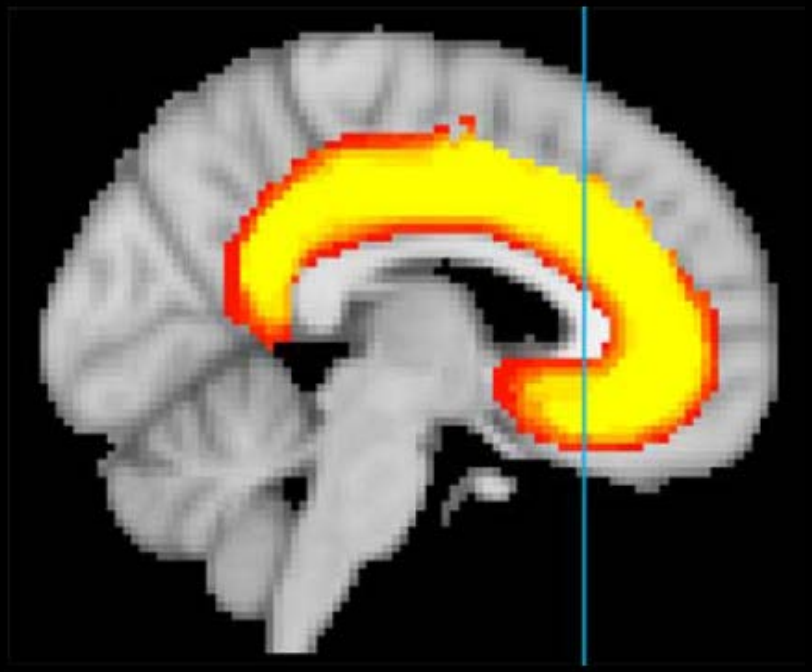
1H-MRS in autism spectrum disorders: a systematic meta-analysis

Jonathan C. Ipser · Supriya Syal · Judy Bentley · Colleen M. Adnams · Bennie Steyn · Dan J. Stein

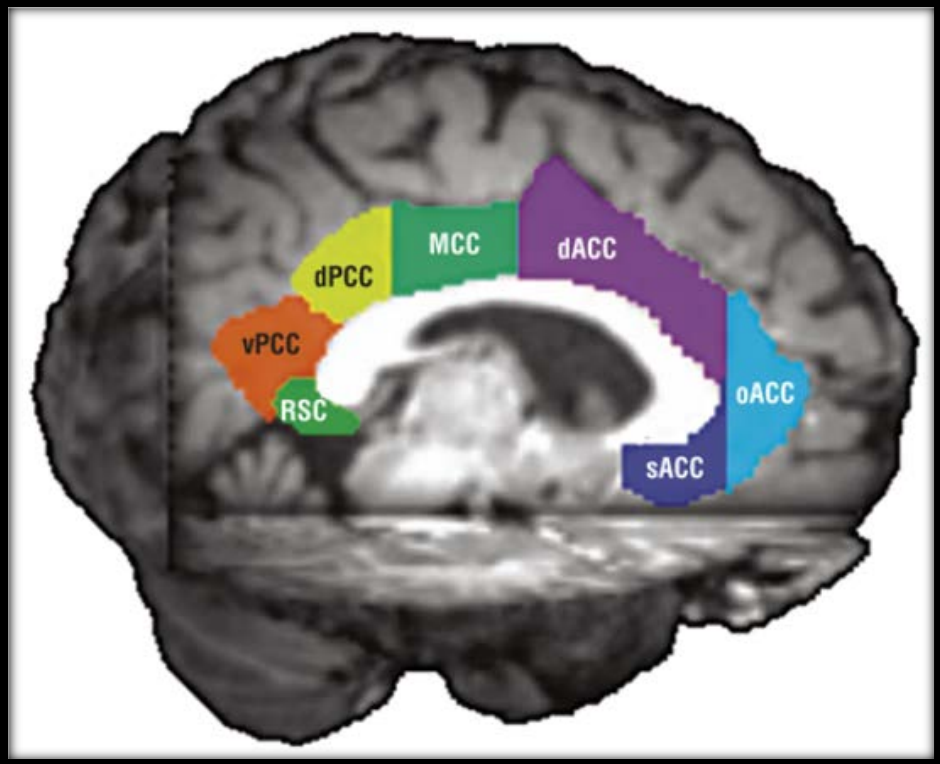
Published online: 18 March 2012



Subdivisions of the Human Cingulate Cortex



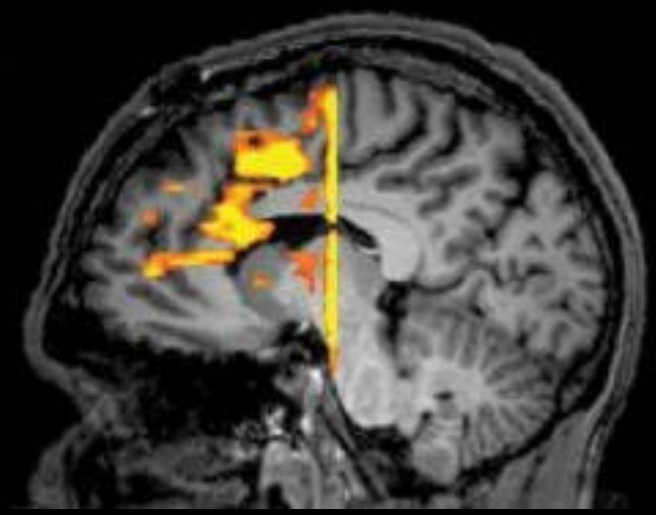
Beckman et al. (2009); J. Neuroscience



Hong et al. (2009); JAMA Psychiatry

Dorsal Anterior Cingulate

- Part of a functional network
- Works together with DLPFC
- dACC involved in both monitoring & control
- dACC also has a role in reward-based decision making
- Specific mechanisms not well understood
- No theory fully explains the cognitive/emotional division



Posterior Cingulate Cortex

- Part of the Default mode Network (DMN)
- Self-reflection and Autobiographic memory (Spreng et al., 2009)
- Visuospatial orientation and navigation of the body in environmental space (Vogt & Laureys, 2005)

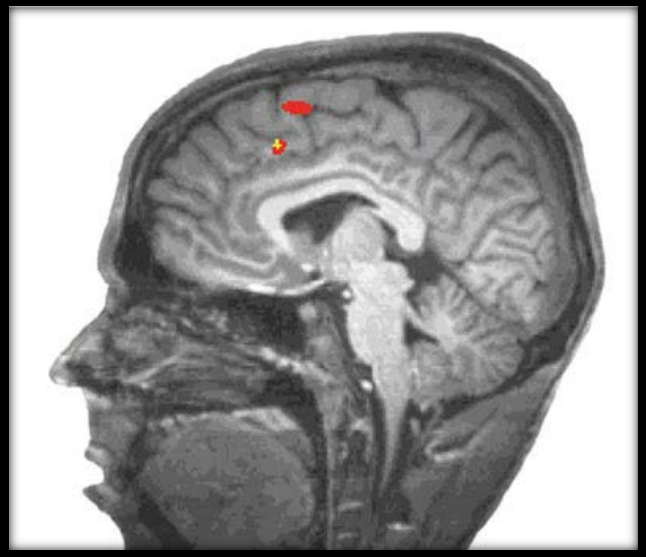
MRS Data Acquisition & Analysis

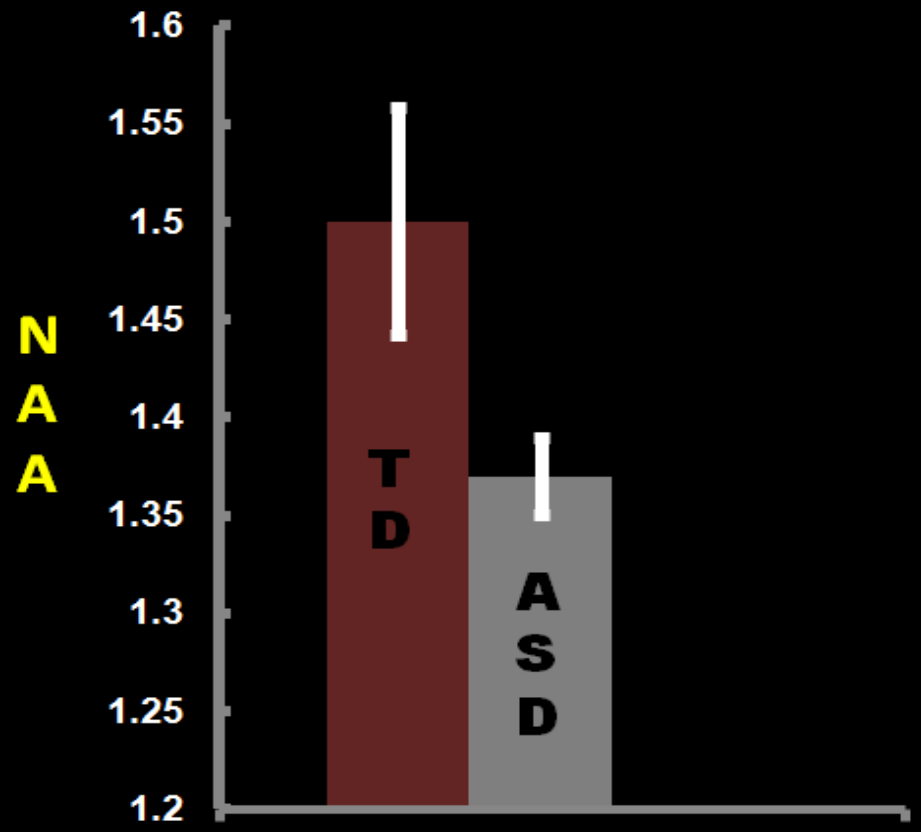
- A series of sagittal, coronal, and axial T1-weighted anatomic scans serving as MRS-localizers (TR/TE = 250/3.48 ms, flip angle = 70°, 5 mm slice thickness, 1.5 mm gap, 512 x 512 matrix) will be acquired for spectroscopic voxel placement. The MRS voxel will be placed in a region of the bilateral ACC and PCC

- Manual shimming will be done to optimize field homogeneity across the voxel, and chemical shift selective (CHESS) pulses will be used to suppress the water signal.

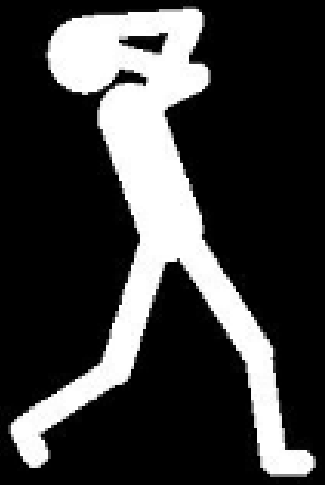
- Spectra will be acquired using the point-resolved spectroscopy sequence (PRESS; TR/TE = 2000/80 ms, number of averages = 256 (scanning time = 8 min 32 s), voxel size 2.7 x 2 x 1 cm3). MRS data will be analyzed in jMRUI (www.mrui.uab.es/mrui) (Naressi, 2001).

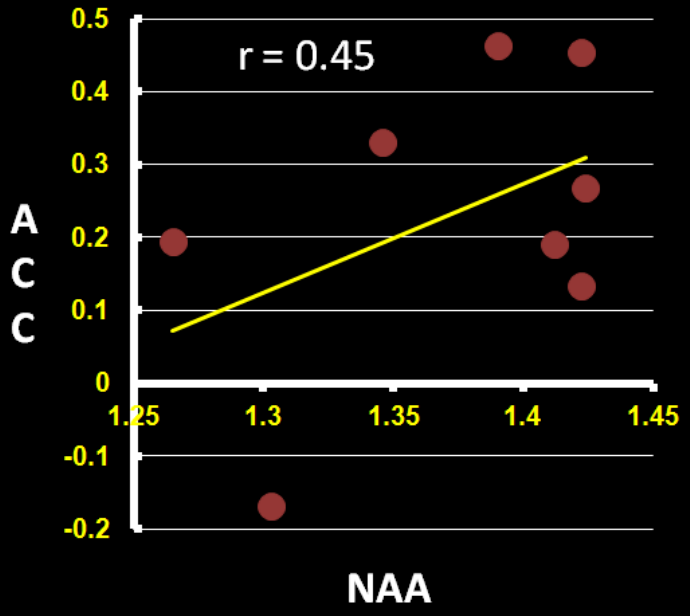
Reduced NAA Level in dorsal ACC in Autism





Correlation between NAA level and Dorsal ACC activation in Autism



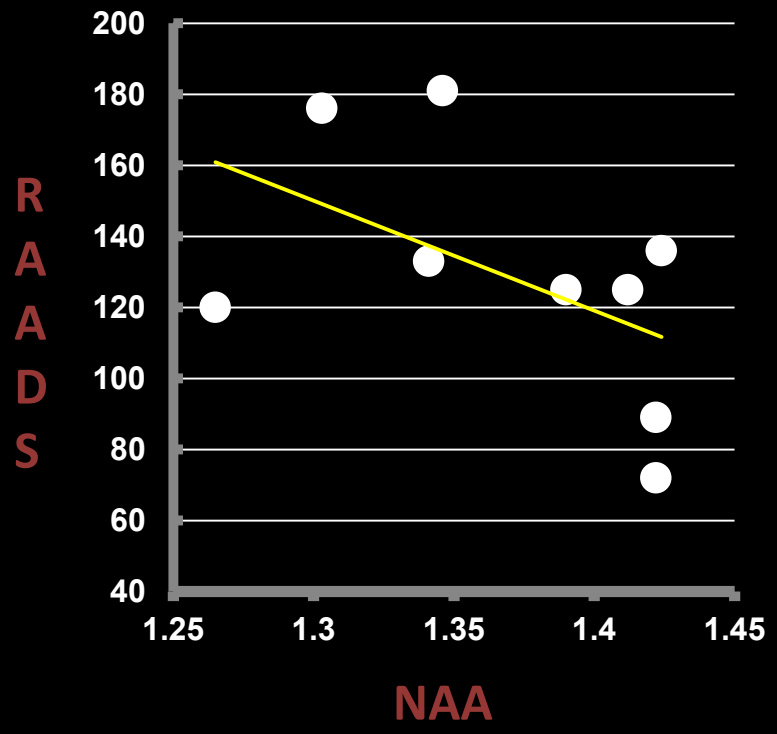


The Ritvo Autism Asperger Diagnostic Scale

Symptom severity and Neurochemical Level

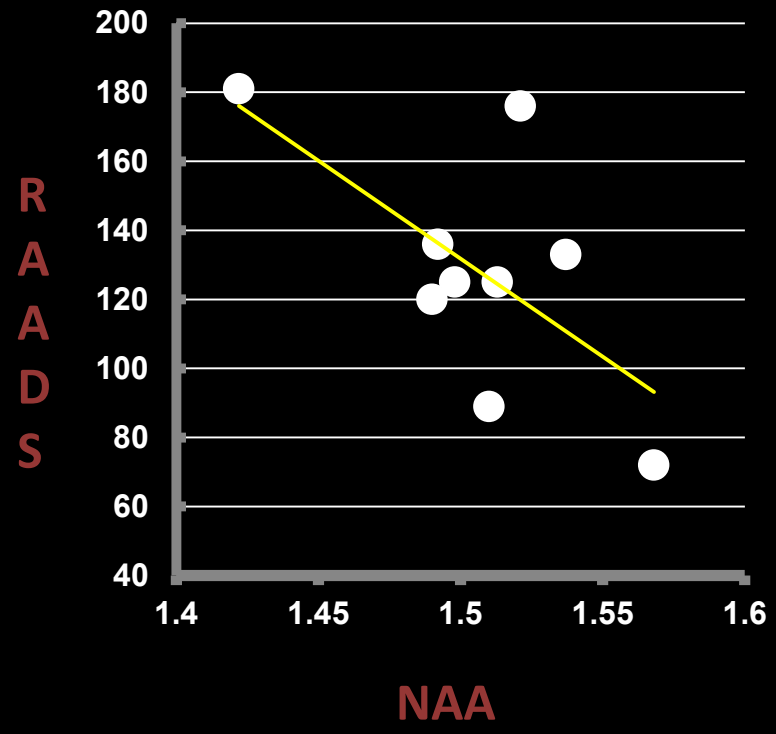
Dorsal ACC

r = -0.51

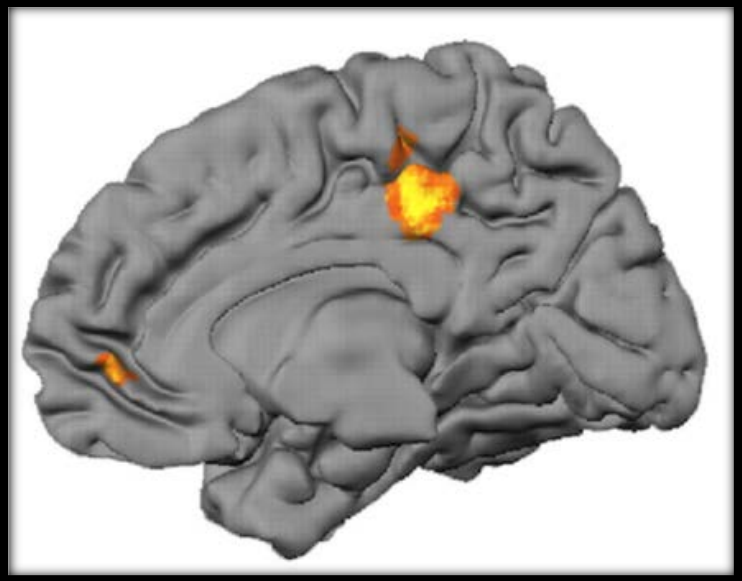


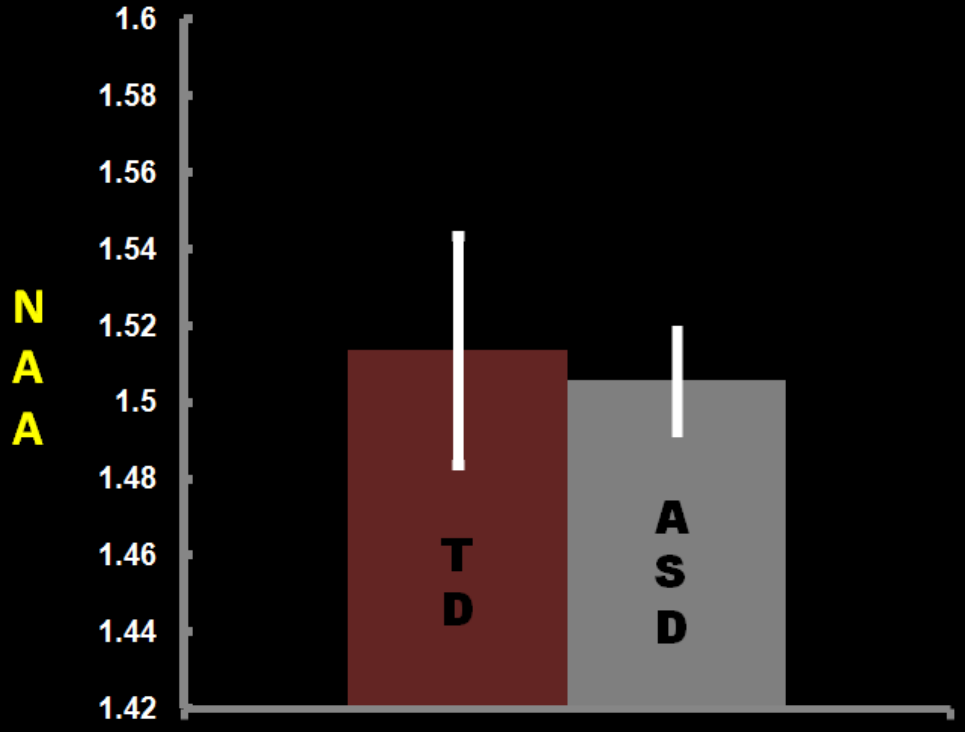
PCC

r = -0.64

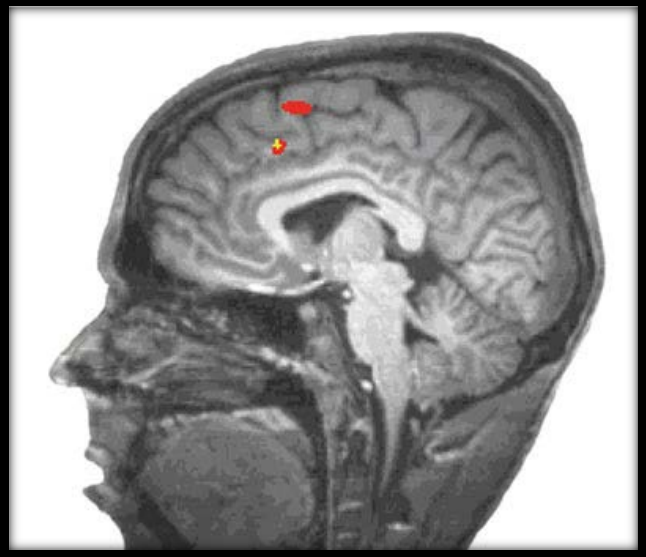


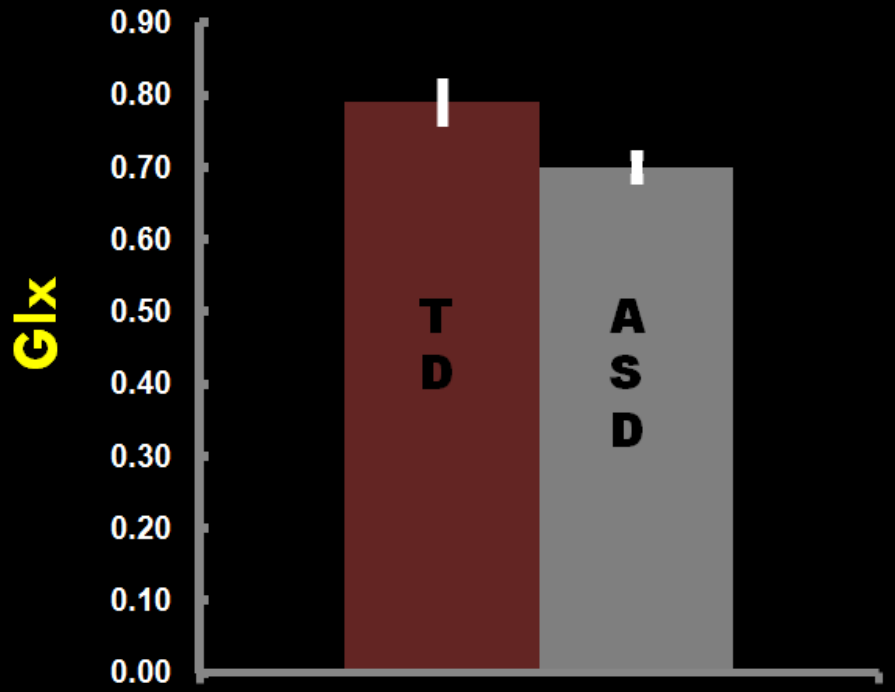
No Group Difference in NAA levels in PCC





Reduced Glutamine/Glutamate level in dorsal ACC in Autism

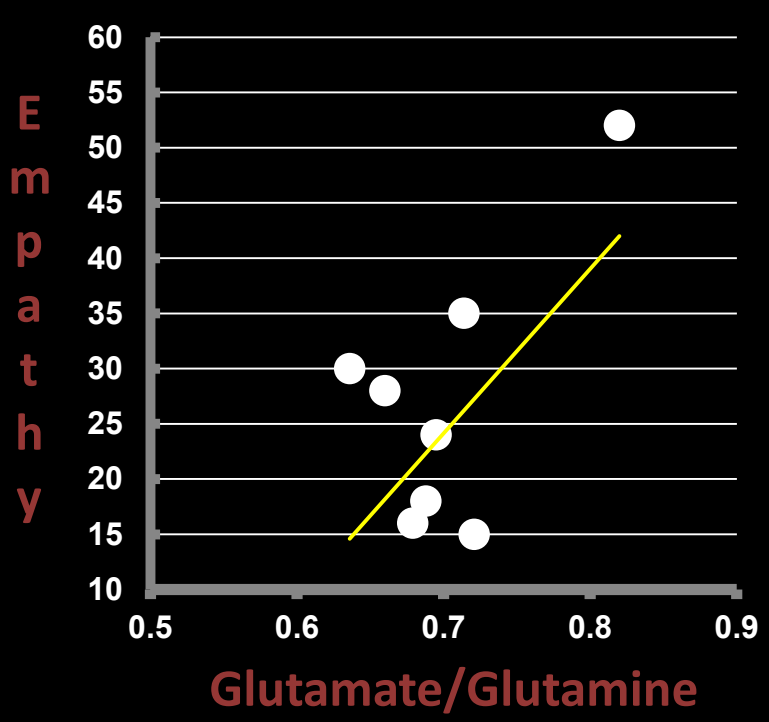




Correlation between Empathy Quotient & Glx in Autism

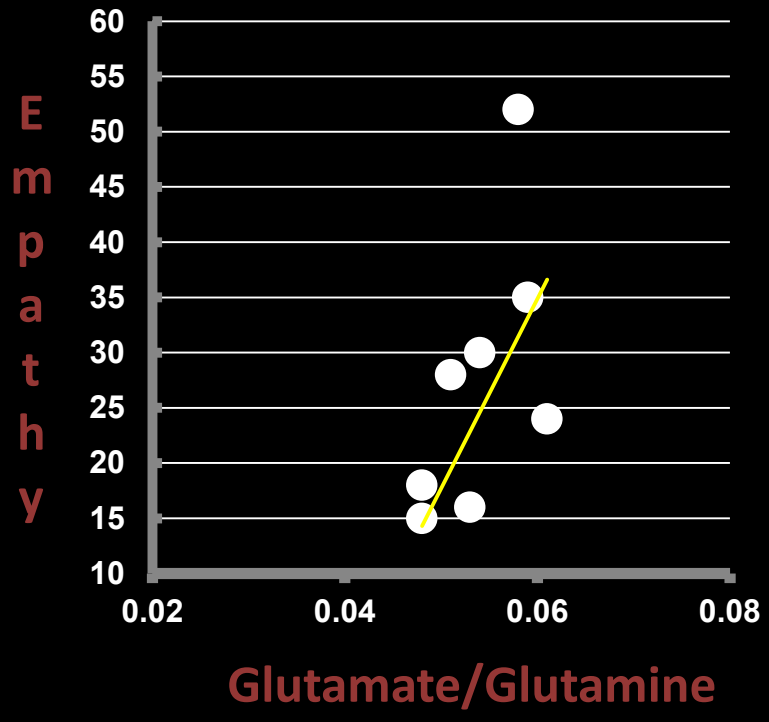
Dorsal ACC

r = 0.62



PCC

r = 0.82



Summary & Future Plans

- Patterns of neurochemical alterations in ASD may suggest differences in tissue chemical composition OR neuronal integrity
- Plan to continue data collection and correlating MRS measures with different brain and behavioral findings
- Findings will be presented at the Society for Neuroscience (SfN) Annual Meeting, 2013 and at the International Meeting for Autism Research (IMFAR), 2014
- NIMH R01 proposal submission : June 2013 Cycle

Co-investigators & Collaborators

- Adrienne Lahti, M.D. (UAB)
- Nouha Salibi, Ph.D. (Auburn University)
- Lauren Libero
- Keya Kuruvilla
- Rishi Deshpande
- Meredith Reid
- David White

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UAB College of Arts & Sciences Interdisciplinary Innovation Award

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