

# Glutamate and GABA in Children with ADHD and Complex Motor Stereotypies: A 7T <sup>1</sup>H MRS Study

Alena Horska<sup>1</sup>, Xin Wang<sup>1</sup>, Matthew Ryan<sup>2</sup>, Martha B Denckla<sup>2</sup>, Peter B Barker<sup>1</sup>, Harvey S Singer<sup>1</sup>, and E Mark Mahone<sup>2</sup>  
<sup>1</sup>Johns Hopkins University, Baltimore, MD, United States, <sup>2</sup>Kennedy Krieger Institute, Baltimore, MD, United States

## TARGET AUDIENCE

Researchers and clinicians with interest in brain metabolism in pediatric neuropsychiatric disorders.

## PURPOSE

Myelination and maturation of the prefrontal and frontal-striatal systems in children occurs during the crucial period of development of executive functions and self-regulatory skills [1]. Development of several neuropsychiatric disorders of childhood, particularly those with atypical behavioral, emotional, and cognitive regulation, is associated with disruptions of neural circuits including the frontal cortex and its striatal-thalamic-cerebellar connections [2]. The main objective of our high-field <sup>1</sup>H MRS study was to measure the concentrations of the neurotransmitters glutamate (Glu) and GABA, implicated in the neuropathology of several neuropsychiatric disorders, in prefrontal and fronto-striatal regions in children diagnosed with ADHD or non-autistic complex motor stereotypies (CMS).

## METHODS

Three groups of children ages 5-10 years participated in the IRB-approved study: 20 with ADHD (mean age 7.6 ± 1.1 years, 8 girls), 19 with CMS (mean age 6.7 ± 1.3 years, 3 girls), and 24 typically developing children (mean age 7.5 ± 1.4 years, 14 girls). The patients were medication-naïve (ADHD group), or not on medication at the time of MRI (CMS group). MRI/MRS, preceded by a 10-20 minute session in a mock scanner, was performed at 7T using a 32-channel volume head coil. The protocol included 3D-MPRAGE and single voxel <sup>1</sup>H MRS (TR/TE/TM=3000/14/26 ms, SW=3000 Hz, 2048 data points, NS=96 and 4 w/o water suppression). VAPOR was used for water suppression. Spectra were acquired in the left hemisphere in the anterior cingulate (ACC), dorsolateral prefrontal cortex (DLPFC), premotor cortex (PMC) and the striatum (STR), with voxel volumes of 5-9 ml. Spectra were processed using the LCModel with an in-house created basis set including macromolecules. Linear mixed-effects models (LME) analyses with the Fisher's LSD as a post-hoc test were used to examine group differences in regional metabolite concentrations, controlling for age and sex.

## RESULTS

The MRI/MRS protocol (1 hour) was well tolerated in both controls and patients who were included in this study. Figure 1 shows an example of a 7T spectrum acquired in a child with ADHD. The main finding was significantly higher overall GABA/Cr ratio in controls (age-adjusted mean: 0.24 ± 0.07) compared with both patient groups (ADHD: 0.21 ± 0.07, p=0.035; CMS: 0.19 ± 0.06, p=0.004). Within individual regions (Figure 2), significant reductions in the GABA/Cr ratio were observed in the ACC (controls vs. CMS, p=0.009) and STR (controls vs. patients, p<0.015). The differences among groups in the main LME analysis for GABA concentration approached statistical significance (p=0.099); the CMS patients tended to have the lowest mean GABA concentration of the three groups examined. While both ADHD and CMS groups had higher overall Glu concentrations compared with controls (by 14% and 11%, respectively; both p<0.015), they also had higher mean Cr and NAA concentrations, resulting in no group differences in the Glu/Cr (Figure 2) and NAA/Cr ratios. Across groups, among children younger than 8 years, Glu/Cr ratio was 4% higher in boys than in girls (p<0.05).

## DISCUSSION

The finding of reduced GABA in children with ADHD is consistent with the results of a study performed using J-difference-edited MRS at 3T in children 8-12 years of age [3]. In ADHD patients, lower GABA was detected in a region including the primary motor and somatosensory cortices [3]. In our study, which evaluated younger ADHD patients and both cortical and subcortical gray matter, the most pronounced differences between patients and healthy children were obtained in the striatum, while no significant abnormalities were observed in the premotor cortex. Our study also suggests, for the first time, that GABA metabolism may also be impaired, to an even larger extent, in patients with non-autistic CMS. The finding of higher NAA in childhood ADHD is in agreement with results of a recently published meta-analysis [4]. However, we did not detect reduction in Cr levels [5] or abnormalities in Glu (Glx) metabolism reported in earlier studies of older patients, including adults, at lower magnetic fields [6, 7].

## CONCLUSION

High field MRS studies in young pediatric patients with neuropsychiatric disorders may help to reveal the location and extent of neuropathology early in the course of a disease. The data from our study demonstrate feasibility and tolerability of 7T MRS studies in non-sedated healthy children and patients and are encouraging for future 7T projects.

NIH (R21 MH09263; P30 HD-024061) and institutional (BSI, ICTR-UL1 TR 000424) grant support is acknowledged.

Figure 1

7T <sup>1</sup>H MRS in the left ACC  
(8 year-old ADHD patient)

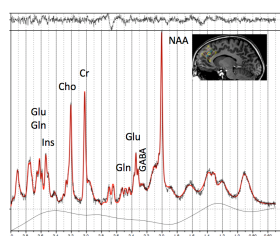


Figure 2

Regional GABA/Cr ratios

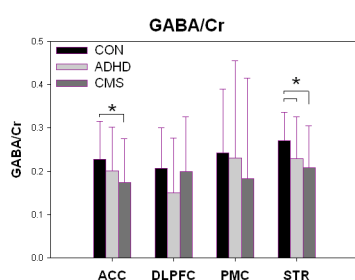
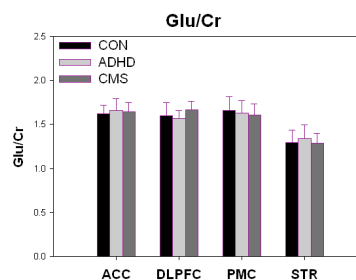


Figure 3

Regional Glu/Cr ratios



## REFERENCES

1. Brocki, KC *et al*: Dev Neuropsychol 26: 571-93 (2004).
2. Marsh, R *et al*: Am J Psychiatry 166:664-74 (2009).
3. Edden, R *et al*: Arch Gen Psychiatry 69: 750-3 (2012).
4. Aoki, Y *et al*: Neurosci Biobehav Rev 8: 1692-701 (2013).
5. Tafazoli, S *et al*: J Psychiatr Res 47: 505-12 (2013).
6. Perlov, E *et al*: J Psychiatr Res 44:938-44 (2010).
7. Arcos-Burgos, M *et al*: ADHD 4:205-12 (2012)