Reduced Sensorimotor GABA in Attention-deficit Hyperactivity Disorder

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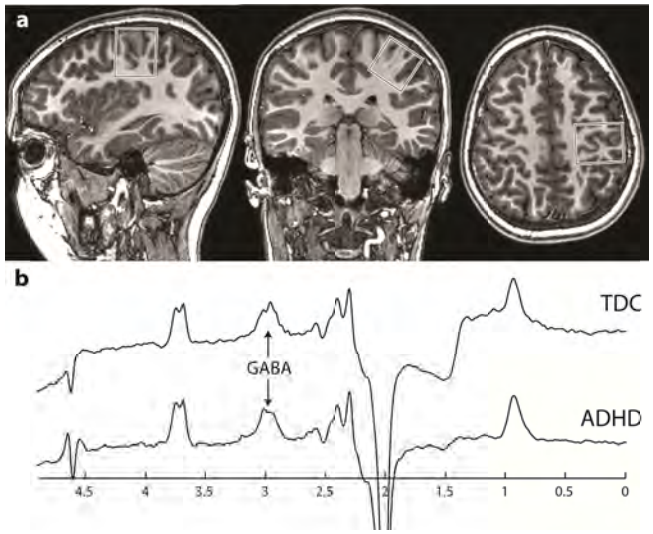
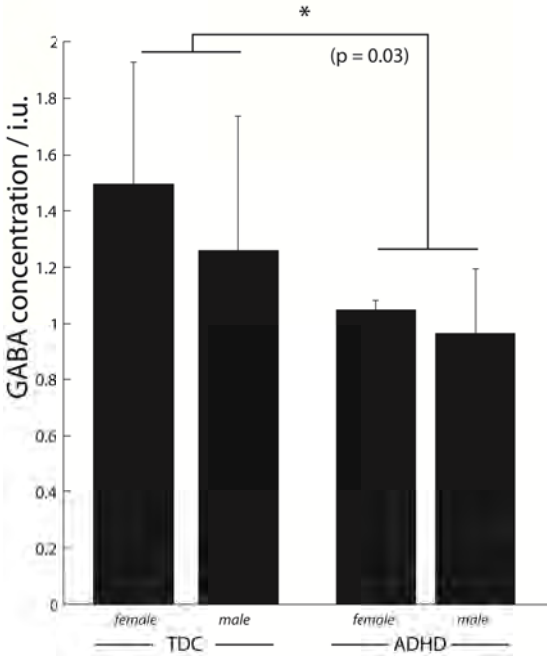
Introduction Cerebral cortical inhibitory function, via gamma-aminobutyric acid (GABA)ergic transmission, may be vital for filtering sensory information and selecting appropriate behavioral responses. As such, understanding and quantifying GABAergic function in children developing motor and behavioral control could provide vital insights into the neurobiological underpinnings of attention deficit hyperactivity disorder (ADHD). GABA-A agonists increase short interval cortical inhibition (SICI)[1,2], and thus we would hypothesize on the basis of recent findings of reduced SICI in children with ADHD[3] that GABAergic function may be altered in children with ADHD. We employed edited 1H-MRS to evaluate cerebral cortical GABA in ADHD. This technique allows us to gain more direct information about neural transmission at the motor cortex node where SICI is evoked, anchoring this biomarker in inhibitory neural transmission, and thereby providing a foundation for linking brain physiology and behavioral dysfunction. We hypothesized that children with ADHD would exhibit reduced motor cortex GABA concentration as compared to aged-matched typically developing (TDC) children.

Methods Edited Magnetic Resonance Spectroscopy (MRS) data was acquired in children (13 ADHD, 19 TDC) using a 3T Philips Achieva. Magnetization Prepared Rapid Gradient Recalled Echo (MP-RAGE) images were acquired at 1mm^3 isotropic resolution using the following parameters: TR=8ms; TE=3.76ms, TI=843ms, Flip Angle=8°; FOV= 25.6cm. GABA-edited MR spectra was acquired from a 3x3x3 cm^3 volume using the MEGA-PRESS Method.[4] The voxel was positioned using the MPRAGE anatomical scan, centered on the 'handknob' as identified in axial images, and aligned so that one face of the voxel lies on the cortical surface as shown right. The following experimental parameters were used: TE=68 ms; TR=2000 ms; 332 transients of 2048 datapoints acquired in 10 min experiment time; a 16 ms Gaussian editing pulse was applied at 1.9 ppm in alternate scans. Concentration measurements in institutional units were derived from the ratio of the edited GABA signal to the unsuppressed water signal in the same volume, accounting for the editing efficiency and the T1 and T2 relaxation times of water and GABA. The integral of the GABA peak was calculated automatically using a model that consisted of a linear baseline plus a Gaussian to fit the peak itself. All analyses were performed blinded to diagnosis.





Results Good quality edited spectra were acquired in ADHD and TDC children (as seen above). Linear regression analysis revealed a significant effect of diagnosis on GABA concentration within SM1 (β_1=-0.34; p=0.03) but not gender (β_2=-0.16; p=0.33) as seen left. The average ± standard deviation for the four groups were: ADHD male 0.96±0.23 i.u.; ADHD female 1.05±0.03 i.u.; TD male 1.26±0.47 i.u.; TD female 1.49±0.43 i.u.

Discussion These data reveal children with ADHD show decreased motor cortex MRS GABA compared with TD children, with no evidence of a gender effect. With additional data, we will be able to examine associations of MRS GABA levels with SICI as well as behavioral measures. This may provide a foundation for identifying SICI/MRS GABA based clusters or profiles within ADHD. These clusters in turn may segregate ADHD into groups with differing long-term treatment responses, helping to predict groups at high risk for adverse outcomes and generating clues to future rational, biologically based interventions.

References 1. Di Lazzaro V, et al. Clin Neurophys 2007;118:2207. 2. Ziemann U et al. Exp Brain Res 1996;109:127. 3. Gilbert DL et al. Neurology 2011 67:7615. 4. Mescher M et al. NMR Biomed 1998;11:266.