A combined GABA-MRS and behavioural study in children with Autism Spectrum Disorder

NICOLAAS A PUTS1,2, Taylor Koriakin1, Ericka L Wodka1, Mark Tommerdahl3, Peter B Barker1,2, Stewart H Mostofsky1,3, and Richard A E Edden1,2
1The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, Maryland, United States; 2FM Kirby Centre for functional neuroimaging, Kennedy Krieger Institute, Baltimore, Maryland, United States; 3Kennedy Krieger Institute, Baltimore, Maryland, United States, 1Biomedical engineering, University of North Carolina, Chapel hill, North Carolina, United States, 2School of Medicine, Johns Hopkins University, Baltimore, Maryland, United States

Target audience: This work will be of interest to clinicians and researchers studying Autism Spectrum Disorder, as well as neuroscientists and MR physicists with an interest in GABAergic processing, translational/multi-modal research to investigate specific GABAergic (dys)-function.

Purpose: Impaired sensory processing is a common but poorly understood behavioral trait in Autism Spectrum Disorder (ASD). Recent work suggests that a deficit in cortical inhibitory transmission may contribute to impairments in sensory processing1. The purpose of this study was to combine edited-MRS to non-invasively measure the in vivo concentration of the inhibitory neurotransmitter GABA, with tactile psychophysics to investigate atypical sensory processing in ASD. We tested (1) The ASD population will show reduced GABA concentration compared to typically developing children (TDC), as measured by MRS (2) ASD pediatric population differ in their response to tactile stimuli compared to TDC, which can be characterized by a dysfunction of specific inhibitory cortical mechanisms. (3) This difference in tactile processing can be partly attributed to decreased levels of GABA within the sensorimotor cortex.

Methods: Subject and parental consent were obtained under local IRB approval. Neuroimaging: GABA-edited MR spectra were acquired from (3cm)3 volumes using the MEGA-PRESS J-difference editing method on a 3T Philips ‘Achieva’ scanner (Philips Medical Solutions, Best, the Netherlands) for five participants in each cohort (1 female, all right-handed). Spectra were acquired from two regions: a sensorimotor region (see Figure 1) and an occipital “control” region. The sensorimotor region, as seen in Figure 1a, was centred on the right “hand knob” as identified in axial images and aligned with the cortical surface. The occipital region was positioned on the posterior midline in the occipital lobe and aligned with the cerebellar tentorium. The following experimental parameters were used: 32-channel head coil, TE 68ms; TR 2000ms; 300 transients acquired in 10min scan time. Data was analysed using Gannet (gabamrs.blogspot.com), which uses a Gaussian+baseline model to fit the edited GABA signal and a Lorentz-Gaussian lineshape to fit the unsuppressed water signal. All participants provided good quality spectra (Fig 1b).

Behavioral: 21 TDC and 6 children diagnosed with ASD (all ages 8-12; 2 female, all right-handed) received a battery of vibrotactile tasks. (1) static and a dynamic detection threshold task (DT) (2) Three 2-alternative forced choice (2AFC) amplitude discrimination (AD) tasks (no adaptation, single site adaptation & dual site adaptation) (3) Sequential and simultaneous frequency discrimination tasks (FD).

Results: There was a significant reduction in GABA concentration in the ASD group compared to TDCs (p < 0.05, fig 2A). Preliminary analysis shows a correlation between GABA concentration and FD in the TDC group (R = -0.48, p <0.05; as shown in1), but not in ASD (R =0.28, p > 0.5, fig 2B). Static DT was significantly lower than dynamic DT in TDCs (p < 0.02), but not the ASD group (p>0.2, Figure 2C). AD threshold improved after dual-site adaptation in the TDC group but not in the ASD group (although not significant) and threshold increased after single-site adaptation compared to no-adaptation in the TDC group (p<0.01), but not in the ASD group (p > 0.5, fig 2D). Discussion: GABA concentration in sensorimotor cortex is reduced in children with autism. This study also replicates the previous finding that GABA concentration is correlated with frequency discrimination threshold in TDCs, but finds that this is not the case for ASD, suggesting impaired temporal encoding in autism. The behavioural data is consistent with the presence of reduced GABAergic-mediated inhibition in this population, and further analysis of the behavioural data suggests that autism might be characterised by broad GABAergic impairment (as there is no effect of adaptation or dynamic detection threshold, and frequency encoding seems impaired as well), but the current preliminary data is only from a small cohort. In addition, medication should be taken into account.

Conclusion: In this study of 10 children, reduced GABA concentration is found in children with ASD, which may also be related to differences in tactile processing performance. These results warrant further investigation in a larger cohort of subjects. 1. Tommerdahl et al Brain res. 2007. 18;1154:116-23., 2. Puts et al 2011. J Neurosci. 2011. 16;31(46):16556-60 This work is funded by an Autism Speak translational Fellowship (NAJP) and the Organisation for Autism Research (ELW)