MM-suppressed GABA concentration correlates with symptom severity and abnormal tactile processing in children with ASD

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

Purpose: Autism Spectrum Disorder (ASD) is a pervasive developmental disorder characterised by impairments in social cognition, disordered communication, and repetitive behaviors[1]. Despite decades of study, the neurophysiological basis of ASD remains poorly understood. Multiple lines of evidence suggest that GABA, the main inhibitory neurotransmitter in the brain, plays a role in the pathophysiology of ASD (e.g[2]). Abnormalities in touch perception are often reported in children with ASD[1]. It is well known that tactile processing is linked to GABAergic function; for instance, detection threshold is related to the expression of the GABRB3 receptor subunit[3]. However, the link between abnormal GABAergic function and tactile abnormalities in ASD is unclear. GABA can be measured using edited Magnetic Resonance Spectroscopy (MRS) but these measurements typically suffer from macro-molecule (MM) contamination (GABA+). The purpose of this study was to use MM-suppressed GABA-edited MRS[4] (removing MM signal using symmetric editing), and vibrotactile psychophysics[5] to investigate atypical sensory processing in children with ASD. We hypothesized that 1) MM-suppressed GABA is reduced in children with ASD; 2) GABA correlates with symptom severity in ASD, as well as with vibrotactile processing.

Methods: Subject and parental consent were obtained under local IRB approval. *Eligibility*; Children with ASD met the DSM-V criteria for ASD (confirmed using the Autism Diagnostic Observation Schedule-Version 2 (ADOS-2)). All Typically Developing Children (TDC) were free of criteria for psychiatric disorders using the Diagnostic Interview for Children and Adolescents. All children had normal IQ and were IQ matched. *Neuroimaging*: MM-suppressed GABA-edited MR spectra were acquired from (3cm)[3] volumes in the right sensorimotor cortex (corresponding to tactile testing on the left hand; Fig. 1A) using the MEGA-PRESS J-difference editing method on a 3T Philips 'Achieva' scanner (Philips Medical Solutions, Best, the Netherlands) for 13 children with ASD and 9 TDC (3 female, all right handed, all ages 8-12 years). Parameters: TE 80ms; 20 ms editing pulse at 1.9 and 1.5 ppm; TR 2000ms; 320 transients (10 min scan time), 32-channel head coil. Data were analysed using Gannet[6] and GABA levels expressed against the unsuppressed water signal measured from the same volume. *Behavioral*: Children received a battery of vibrotactile tasks involving the left hand including[5] (1) Static and Dynamic detection threshold task (linked to $GABA_B$-receptor processes[7]) and (2) Amplitude discrimination tasks with and without adaptation (linked to $GABA_A$-receptor processes[8]).3 ASD/1 TDC were unable to perform all behavioral tasks.

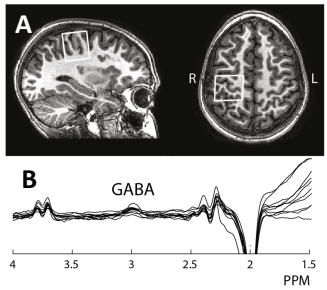

Figure 1. A. SM1 voxel location. B. Example MM-suppressed GABA-edited difference spectra from right sensorimotor cortex for TDC and ASD participants.

Results: There was a near significant reduction in right SM1 MM-suppressed GABA levels in the ASD group compared to TDC ($p < 0.12$, Fig 2A). For children with ASD, SM1 GABA levels correlated negatively and significantly with ADOS-2 total score ($R = -0.43$, $p < 0.05$). Behaviorally, the data were consistent with previous work in separate TDC and ASD cohorts, showing worse baseline detection threshold and amplitude discrimination in ASD, as well as impaired adaptation to weak stimuli and amplitude discrimination. Furthermore, ADOS-2 total score correlated positively with static ($R = 0.66$; $p < 0.01$, Fig 2C and as previously shown[8]) and dynamic detection thresholds ($R = 0.56$, $p < 0.05$). In TDC, GABA levels correlated significantly with $GABA_B$-driven dynamic detection threshold ($R = -0.59$, $p < 0.05$; Fig 2D) and adaptation ($GABA_A$; $R = -0.50$, $p < 0.05$); these correlations were not significant in ASD.

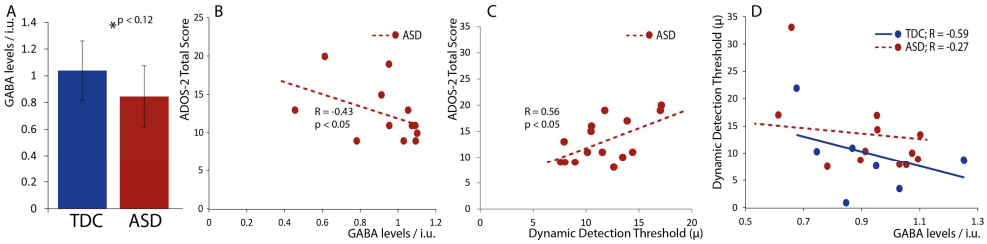

Figure 2 A. Sensorimotor GABA levels is significantly reduced in ASD compared to TDC ($p < 0.12$). B. GABA levels correlate with ADOS-2 scores (a measure of ASD severity). C.ADOS-2 scores correlate with detection threshold in ASD. D. Detection Threshold correlates with GABA levels in TDC, but this correlation is absent in ASD.

Discussion: Our preliminary data suggests reduced MM-suppressed GABA levels in children with ASD, and although this did not reach significance in this relatively small preliminary cohort, it is consistent with previous findings showing reduced GABA+ in ASD[9]. Nevertheless, GABA levels were significantly correlated with autism severity, with participants with a lower GABA levels show higher (more severe) ADOS score. The behavioral data are consistent with reduced GABAergic-mediated inhibition in ASD and consistent with our previous work[10]. The reduction found is this study is near significance, but as can be seen in Fig 2C, a large part of the current sample has relatively low ADOS scores and may be more "typical". Further, ADOS scores were found to correlate positively with both static and dynamic detection thresholds (higher score = worse detection threshold). While GABA levels in TDC correlated with detection threshold, this correlation was not observed in children with ASD, suggesting that regulation of tactile sensory thresholds may be anomalous, and dependent on mechanisms alternative to GABA input. In addition, GABA levels in TDC correlated with tactile adaptation, but this correlation (as well as the effect of adaptation) were absent in ASD. The absence of GABA – tactile correlation could potentially be driven by alterations in GABA receptor subunits. *Conclusion*: In this study we show that reduced GABA levels in children with ASD is associated with ASD severity and that there may be a link between abnormal GABAergic processing and vibrotactile impairments in ASD. These finding provide increased understanding of mechanisms contributing to tactile sensory dysfunction in ASD and may lead to the development of novel therapies or pharmaceutical applications. 1. Rogers et al., 2005. 2. Rubenstein et al., 2003. 3. Tavasolli et al. 2012. 4. Edden et al., 2013. 5. Puts et al. 2014. 6. Edden et al. 2014. 7. Blankenburg et al. 2006. 8. Whitsel et al. 2002. 9. Gaetz et al. 2013. 10. Tavasolli et al. 2012 (IMFAR).