

Reduced GABA concentration in children with Tourette's Syndrome is linked to sensory impairments and tic severity

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Target audience: This work will be of interest to clinicians and researchers studying Tourette's Syndrome, 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: Tourette's Syndrome (TS) is characterised by the presence of chronic tics. Individuals with TS often report difficulty with ignoring (habituating or adapting to) tactile sensations and perceive that this contributes to a "premonitory urge" to tic. Despite this, impaired sensory processing, particularly tactile processing, is a common but poorly understood behavioral trait in TS¹. Recent work has suggested that a deficit in cortical GABAergic inhibitory transmission may contribute to symptoms found in Tourette's²⁻⁴. The purpose of this study was to combine GABA-edited MRS to measure the concentration of the inhibitory neurotransmitter GABA *in vivo*, with vibrotactile psychophysics⁵ to investigate atypical sensory processing in children with TS. We hypothesized that: (1) Children with TS population would show reduced GABA concentration compared to typically developing children (TDC), as measured by MRS; (2) that reduced GABA concentration would correlate with tic severity and premonitory urge scores; and (3) Children with TS would differ in their response to tactile stimuli compared to TDC, characterized by a dysfunction of specific inhibitory cortical mechanisms.

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 19 children with TS and 16 TDC (3 female, all right handed, all ages 8-12 years). Spectra (Figure 1) were acquired from right primary sensorimotor (SM1) cortex, corresponding to vibrotactile testing of the left hand. The sensorimotor voxel was centred on the right "hand knob" and aligned with the cortical surface. The following experimental parameters were used: 32-channel head coil, TE 68ms; TR 2000ms; 300 transients acquired in 10 min scan time. Data were analysed using Gannet⁵. 5 TS spectra were rejected due to poor quality. **Behavioral:** 23 children diagnosed with TS (1F) received the Yale Global Tic Severity Score. 23 TS and 67 TDC (7 female, all 8-12, all IQ matched) received a battery of vibrotactile tasks involving the left hand including⁶ (1) reaction time (2) static and a dynamic detection threshold task (DT) (3) Amplitude discrimination (AD) tasks with and without adaptation.

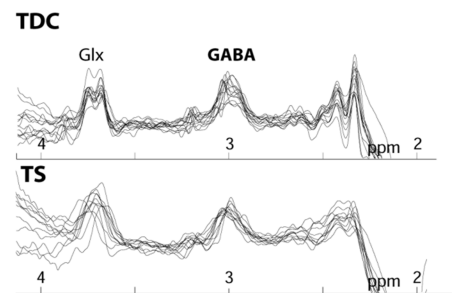


Figure 1. All GABA-edited difference spectra from right sensorimotor cortex for TDC and TS participants. Most participants provided good quality data.

Results: There was a significant reduction in right SM1 GABA concentration in the TS group compared to TDCs ($p < 0.01$, fig 2a). TS were significantly faster in the RT task than TDC ($p < 0.05$). Static DT was significantly lower than dynamic DT in TDCs ($p < 0.02$), but not in TS ($p > 0.5$, Figure 2b). AD threshold increased after single-site adaptation compared to no-adaptation in the TDC group ($p < 0.01$), but not in the TS group ($p > 0.5$). GABA concentration correlated significantly ($r = -0.62$, $p < 0.01$) with motor tic severity (Figure 3), but not with global tic severity.

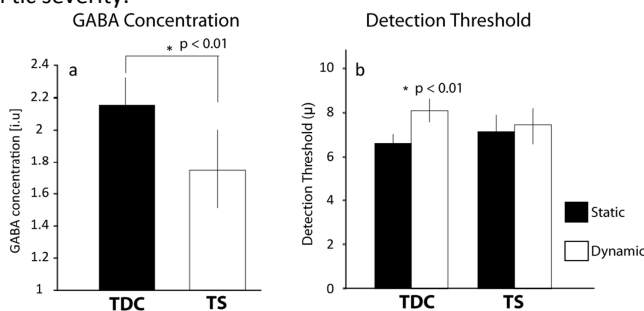


Figure 2 a. Sensorimotor GABA concentration is significantly reduced in TS compared to TDC ($p < 0.01$). b. Dynamic detection is significantly higher than static detection in TDC ($p < 0.01$), but not in TS ($p > 0.5$). Modulation of amplitude discrimination through single-site adaptation is also absent in TS (not shown).

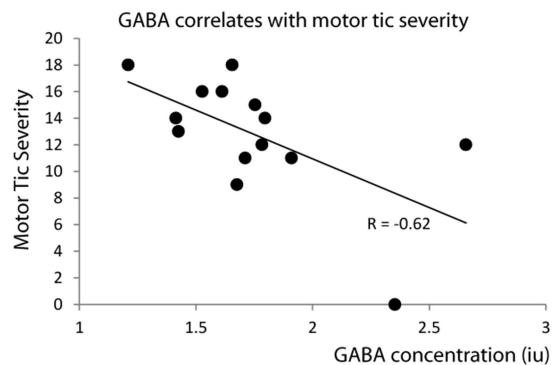


Figure 3. Sensorimotor GABA concentration correlates significantly with motor tic severity in children with TS. More GABA is linked to lower tic severity.

Discussion: GABA concentration in SM1 is reduced in children with TS. The behavioral data are consistent with reduced GABAergic-mediated inhibition in this population, and further analysis of the behavioral data suggests that TS might be characterised by specific sensorimotor inhibitory impairment (as there is no effect of adaptation or dynamic detection threshold, which have been linked to habituation and filtering of sensory input). Furthermore, GABA correlates with tic severity, with lower sensorimotor GABA concentration correlating with greater motor tic severity, possibly reflecting the disinhibition that is thought to be one of the underlying causes of tics. **Conclusion:** In this study we show for the first time that GABA concentration is reduced in children with TS, and that differences in inhibitory processing may contribute to impairments in tactile processing. Furthermore, we show that there is a link between tic severity and GABAergic inhibition. Understanding these mechanisms may lead to development of novel therapies for TS. 1. Cohen and Leckman, 1992. 2. Tian et al., 2011. 3. Lerner et al., 2012. 4. Kalanithi. 2005. 5. Edden et al (in press). 6. Puts et al. 2013 Sponsored by Autism Speaks, NIH: P41 EB015909, NIH / NINDS: R01 NS048527; R01 MH078160, R21 MH098228; R01 EB016089; Local UL1 RR025005