

Proton MRS Reveals Striatal and Anterior Cingulate GABA Deficits in Adolescents with Tourette's Disorder

V. Gabbay¹, B. Coffey¹, X. Mao², B. Ely¹, A. Panzer¹, J. S. Babb³, N. Weiduschat², and D. C. Shungu²

¹Child Study Center, New York University School of Medicine, New York, NY, United States, ²Radiology, Weill Cornell Medical College, New York, NY, United States, ³Radiology, New York University School of Medicine, New York, NY, United States

Background

Converging lines of evidence derived from postmortem¹ and animal² studies implicate γ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system, in the pathophysiology of Tourette's disorder (TD), an inherited neuropsychiatric disorder of childhood onset characterized by multiple physical (motor) tics and at least one vocal (phonic) tic¹. However, no study to date has examined *in vivo* concentrations of brain GABA in TD. In this pilot study, we used ¹H MRS to measure GABA levels in two brain regions that have been strongly implicated in TD¹, the anterior cingulate cortex (ACC) (Fig. 1A) and the striatum (Fig. 1B), in adolescents with TD and matched healthy controls (HC). Based on prior preclinical data, we hypothesized that adolescents with TD would have significantly decreased ACC and striatal GABA compared to HC.

Methods

A. Patient Population Twelve medically healthy adolescents with TD and 20 HC subjects, ages 12-17, were enrolled in the study. Diagnosis of TD was established with the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL), and severity of tics was assessed by the Yale Global Tic Severity Scale (YGTSS). All participants were right-handed, were psychotropic medication-free, had negative day-of-scan urine toxicology, and the TD group had YGTSS scores > 10. GABA levels were obtained in the ACC of 12 TD and 20 HC subjects, and in the striatum of 8 TD and 8 HC subjects.

B. In Vivo Brain GABA Measurements by ¹H MRS All *in vivo* brain GABA spectra were recorded in 15 min from single 2.5x2.5x3.0-cm³ ACC and 1.5x2.0x3.0-cm³ striatal voxels on a GE 3.0 T "EXCITE" MR system, using the standard J-edited spin echo difference method and an 8-channel phased-array head coil, with TE/TR 68/1500 ms and 240 interleaved excitations (580 total). Fig. 1 illustrates the editing method and the resulting difference spectrum, which includes a co-edited glutamate+glutamine (Glx) resonance. The areas under the GABA and Glx peaks were obtained by frequency-domain spectral fitting (Fig. 1D) and expressed as ratios relative to the area of simultaneously acquired unsuppressed voxel tissue water (w) peak. Mean GABA/w values in each voxel for the two groups were compared using rank-based analysis of covariance, with age and sex as covariates.

Results and Discussion

To the best of our knowledge, this is the first study to investigate the postulated cortical GABA abnormalities in TD *in vivo*. Consistent with previous postmortem¹ and animal studies², we found significantly decreased mean GABA levels in TD subjects compared to HC, both in the ACC ($2.38 \pm 0.31 \times 10^{-3}$ vs. $2.66 \pm 0.27 \times 10^{-3}$, $p < 0.02$) and in the striatum ($3.13 \pm 0.62 \times 10^{-3}$ vs. $3.70 \pm 0.54 \times 10^{-3}$, $p < 0.04$), providing the first direct *in vivo* evidence of GABA alterations in fronto-striatal circuits in TD. The scatter plots in Fig. 2 show the individual GABA changes for the two regions. These promising preliminary results suggest further investigations in larger samples to (a) confirm the present finding of a significant decrease of cortical GABA in TD, (b) investigate the extent of this neurotransmitter abnormality in other brain regions that may be implicated in the disorder, and (c) assess for associations with clinical characteristics, such as comorbid mood and anxiety symptoms and disease chronicity, which may be impacted by dysregulated neurotransmitter function in TD.

Conclusion

Our finding of decreased GABA levels in adolescent TD is potentially consistent with a pathophysiological role for dysregulated striatal and ACC neurotransmitter function, and provides further evidence for possible dysfunction of the central GABAergic system in TD.

References

1. Kalanithi PS, Zheng W, Kataoka Y, DiFiglia M, Grantz H, Saper CB, Schwartz ML, Leckman JF, Vaccarino FM. Altered parvalbumin-positive neuron distribution in basal ganglia of individuals with Tourette syndrome. *Proc Natl Acad Sci* 102,13307-13312 (2005).
2. Veliskova J, Moshe SL. Sexual dimorphism and developmental regulation of substantia nigra function. *Ann Neurol* 50, 596-601 (2001).

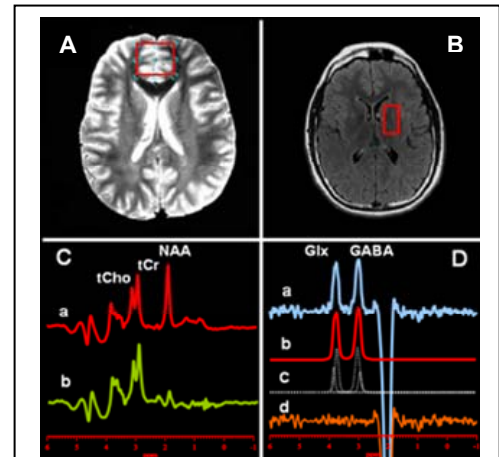


Fig. 1: [A] and [B] Axial images showing, respectively, the ACC and striatal voxel sizes and locations; [C] PRESS ¹H MR spectra with the editing rf pulse (a) off and (b) on. [D] The difference of the spectra in [C] showing (a) the detected GABA and Glx peaks, with (b-d) best-fit model curves and residuals.

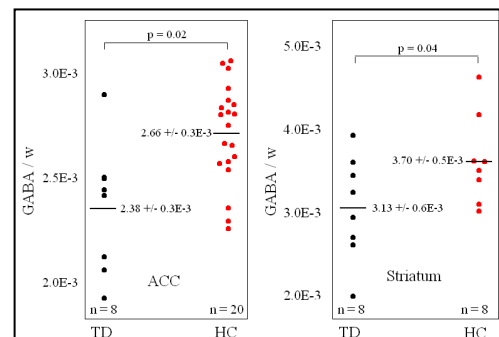


Fig. 2: ACC (left) and striatal (right) GABA scatter plots for TD and HC.