Cerebral metabolic deficits in young patients with Tourette Syndrome assessed by proton MRSI

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Introduction: Tourette syndrome (TS) is a chronic, childhood-onset neuropsychiatric illness. It is characterized by motor and vocal tics that fluctuate in severity, and it frequently co-occurs with obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, or other social and behavioural disturbances. Although the neurobiological abnormalities underlying TS remain unknown, various biochemical, neuroimaging, neurophysiological, and genetic studies suggest a role for the basal ganglia and related thalamic and cortical regions (1, 2). Magnetic resonance imaging (MRI) studies of patients with TS have reported volume reductions in the putamen, globus pallidus, and lenticular nucleus (3). Volumetric abnormalities have also been reported in the frontal cortex (3, 4) and white matter (4-6). We previously reported significant localized reductions of NAA in frontal cortex, reduced NAA in left putamen and reduced Cho bilaterally in the putamen of TS patients relative to control children (7). In the present study, we used ^{1}H MRSI and multi-voxel partial volume regression analysis to evaluate global levels of proton MRS metabolites in cortical gray matter and cerebral white matter in the same cohort. We hypothesize that children with TS will exhibit reduced cortical N-Acetylaspartate (NAA) levels, reflecting distributed dysfunction of cortical neurons.

Methods: Twenty-five boys with TS (ages 7-15 years) and 32 healthy boys (ages 6-16 years) were recruited from the local community. The groups did not differ in age, race, or handedness. Patients were interviewed with the Schedule for Affective Disorders and Schizophrenia-Childhood Version (K-SADS) to confirm the diagnosis of TS and also to assess patients for the presence of comorbid psychiatric conditions. At the time of their scans, patients were assessed with the Yale Global Tic Severity Scale (YGTSS) to assess the severity of their tics. Control subjects were also assessed using K-SADS, and personal history of major psychiatric illness was exclusionary. In either group, mental retardation was exclusionary. Experiments were performed late at night while subjects were asleep, and 16 TS patients were imaged under sedation using oral midazolam or oral chloral hydrate; no control subjects were sedated. Parental informed written consent, approved by the local ethics review board, was provided prior to scanning.

A 3.0 T head-only research scanner with a quadrature head coil was used for all imaging experiments in this study. 3-D MP-RAGE image sets (1.2-mm isotropic voxels) were acquired, and used for MRSI partial volume correction and regression analyses. Localized proton spectra were acquired with an interleaved multi-slice spin-echo MRSI sequence (7) using slice-selective adiabatic inversion for extra-cranial lipid nulling (TI/TE/TR=230/135/1800 ms). Two 9-mm thick oblique-axial slices (figure) were excited with numerically optimized RF pulses, yielding nominal voxel size of 8x8x9 mm (~1.2cc after spatial filtering). CHESS water suppression was performed during the inversion time. Flip-angle maps (8) were acquired to correct MRSI signal levels for RF field inhomogeneity. The full examination took approximately 1 hour. MRSI datasets were first processed using *k*-space extrapolation to reduce ringing artifact from residual extra-cranial lipid signal (9). After subtraction of the residual water signal, fit using HSVD, unfiltered complex MRSI data were fit in the time domain using prior knowledge from *in vitro* metabolite solutions using a constrained Marquardt-Levenberg minimization algorithm (10). The metabolite signal amplitudes were corrected for coil load, CSF partial volume and RF field inhomogeneity.

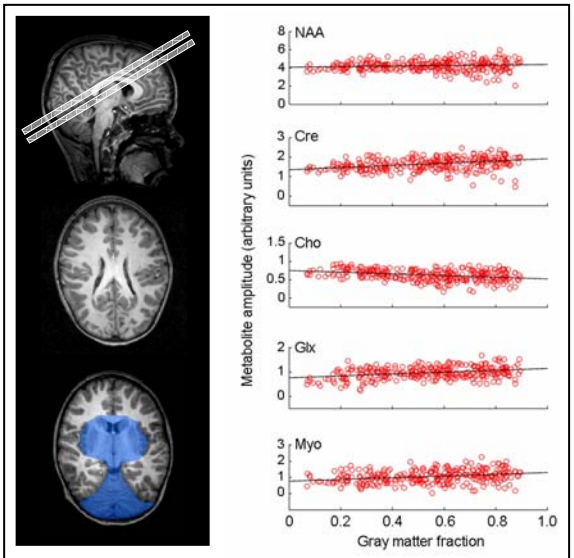

Figure *(left): MRSI slice positions showing manually masked non-cerebral voxels (sub-cortex and cerebellum). (right): multi-voxel partial-volume linear regression results for a patient (~200 valid cerebral MRSI voxels per subject).*

Gray and white matter partial-volume maps were constructed from the segmented MP-RAGE volumes, and used to perform linear regression analysis using all cerebral voxels; voxels with large volume fraction (>25%) arising from cerebellum or subcortical gray matter were excluded from this analysis to obtain estimates of exclusively cortical gray matter and cerebral white matter metabolite levels (figure). Voxels from both slices were pooled, resulting in approximately 200 cerebral voxels per subject. For each participant, fitted metabolite amplitudes for all cerebral voxels were regressed against gray matter fraction, providing estimates of cerebral gray and white matter metabolite levels for each participant (figure).

Results: MANCOVA revealed significant group differences in NAA ($F_{1,54}$=8.5; p=.005) and Glx ($F_{1,54}$=8.1; p=.006). Post-hoc tests revealed significant reduction of NAA in cortical gray matter (p=.029) and cerebral white matter (p=.009) in TS patients relative to controls. Cortical gray matter Glx levels were also reduced in the patient group (p=.024). Metabolite levels did not correlate significantly with symptom severity as assessed by YGTSS.

Discussion: The finding of lower NAA levels in cortical gray matter suggests widespread reductions in cortical neuronal density or function in patients with TS. These observations are complementary to reports of abnormal cerebral volumes in TS patients (3-6), and may reflect a compromised neuronal subpopulation in those regions. Abnormal cortical Glx levels may indicate disruption of the glutamatergic neurotransmitter system, a major component of cortical-striatal interaction. This study is limited by potentially confounding effects of patient sedation, medication and comorbidity with ADHD, and potential effects of group differences in metabolite T_2. Parcellation of the data set into lobar sub-regions may help further localize the observed metabolic deficits, while providing greater sensitivity than single-voxel analyses.

References:

1) Leckman & Riddle, Neuron, 28:349-54, 2000
2) Rauch et al, Adv Neurol, 85:207-24, 2001
3) Peterson et al, Arch Gen Psych, 58:427, 2001
4) Fredericksen, Neurology, 58:85-9, 2002
5) Hong et al., J Korean Med Sci, 17:530-6, 2002
6) Kates et al., Psychiatry Res 116:63-81, 2002
7) DeVito et al., JAACAP 44(12):1301-8, 2005
8) Pan, et al., Magn Res Med, 40:363-369, 1998
9) Haupt, et al., Magn Res Med, 35:678, 1996
10) Bartha, et al., NMR in Biomed, 12:205, 1999

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