Brain Magnetic Resonance Spectroscopy in Tourette's Syndrome

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Introduction Tourette's 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 cortical and thalamic structures (1). These regions are connected by multiple parallel cortico-striato-thalamo-cortical (CSTC) circuits that subserve a wide variety of motor, association, and inhibitory neural systems, and it has been hypothesized that TS is associated with a failure to inhibit subsets of the CSTC mini-circuits (1,2). Magnetic resonance imaging (MRI) studies of patients with TS have reported volume reductions in the putamen, globus pallidus, and lenticular nucleus and an absence or reversal of the normal volumetric asymmetry of basal ganglia structures (3). Volumetric abnormalities have also been reported in the frontal lobe (3,4). In addition to this, functional neuroimaging studies have noted reduced metabolism and blood flow in the ventral striatum (5), and have also demonstrated an association between tics and brain activity in the prefrontal cortex, thalamus, basal ganglia, and primary motor cortex (6,7). While functional and structural neuroimaging studies implicate CSTC circuits, potential metabolic abnormalities within these regions remain unknown. Proton magnetic resonance spectroscopic imaging (MRSI) provides a unique opportunity for the *in vivo* investigation of metabolic abnormalities from numerous brain regions in a single experiment. To date, however, there have been no published studies of metabolite levels using proton MRS in TS.

In the present study, children and adolescents with TS and a control group of healthy children were imaged using ^{1}H MRSI to evaluate levels of proton MRS metabolites in components of the CSTC circuit, specifically putamen, caudate nuclei, thalami, and frontal grey matter. We hypothesize that children with TS will exhibit reduced N-Acetylaspartate (NAA) levels, reflecting dysfunctional neurons in some or all of these regions.

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 Research Ethics Review Board, was provided prior to scanning.

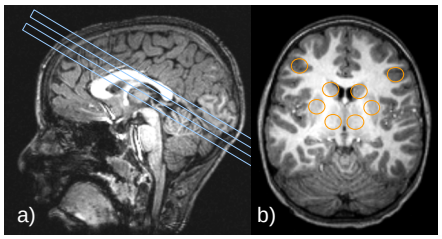

Figure 1: MP-RAGE images showing (a) MRSI slice positions, (b) lower slice showing voxels in putamen, caudate nuclei, thalami, and frontal cortex

A 3.0 T head-only research scanner with a quadrature head coil was used for all imaging experiments in this study. Standard T_1-weighted localizer images and axial multi-echo images for radiological assessment were initially acquired. This was followed by a 3-D MP-RAGE acquisition (1.2-mm isotropic voxels, TI/TE/TR=200/5/11 ms, flip angle 12 degrees, inter-segment repeat time 3.3 s), to be used for segmented regional volumetric analysis and MRSI partial volume correction. Localized proton spectra were acquired with an interleaved, multi-slice spin-echo MRSI sequence using slice-selective adiabatic inversion for extra-cranial lipid nulling (TI/TE/TR=230/135/1800 ms, FOV=280 mm, 35x35 circularly bounded k-space acquisition, 30 minute scan time). Two 9-mm thick oblique-axial slices were excited (Figure 1a) with numerically optimized RF pulses, yielding nominal voxel size of 8x8x9 mm (~1.2 cc effective voxel size after filtering). CHESS water suppression was performed during the inversion time (8). T_1-weighted images were acquired at the same slice positions as the MRSI acquisition for anatomical correlation, and B_1-maps (9) 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 (10). Using the T_1-weighted anatomical correlation images, voxels were selected for spectral analysis from left and right putamen, caudate nuclei, thalami, and frontal grey matter (Figure 1b). After subtraction of the residual water signal, fit using HSVD, unfiltered spectra were fit in the time domain using prior knowledge from *in vitro* metabolite solutions using a constrained Marquardt-Levenberg minimization algorithm (11). The metabolite signal amplitudes were corrected for coil load (12), CSF partial volume contamination and B_1 inhomogeneity before being compared between groups. MANCOVA was carried out using age as a covariate on each region examined, with NAA, creatine + phosphocreatine (Cre), choline-containing compounds (Cho) and glutamate + glutamine (Glx) used as dependent variables. Regions showing significant MANCOVA test were followed up with post-hoc ANCOVA to determine which metabolite(s) differ between groups.

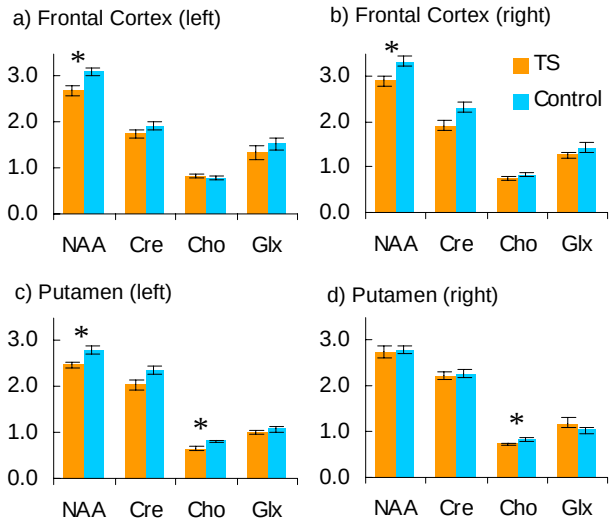

Figure 2: Mean (±SE) metabolite concentrations in arbitrary units for frontal cortex ((a) and (b)) and putamen ((c) and (d)). Significant post-hoc tests are indicated by an asterisk.

Results MANCOVA revealed significant group differences in frontal cortex ($F_{8,44}$=2.34; p=.035) and putamen ($F_{8,47}$=2.25; p=.040). Post-hoc tests revealed significant reduction of NAA in left (p=.003) and right (p=.003) frontal cortex in TS patients relative to controls (Figure 2). TS patients also exhibited significantly reduced levels of NAA in left putamen (p=.029), and reduction of Cho levels in left (p=.001) and right (p=.036) putamen. MANCOVA did not detect group differences in metabolite levels in the caudate nuclei or thalami. Metabolite levels did not correlate significantly with symptom severity as assessed by YGTSS.

Discussion The finding of lower NAA levels in frontal cortex and putamen suggest that there may be abnormalities in neuronal density or function in components of the CSTC circuit in patients with TS. The significantly reduced Cho levels observed bilaterally in the putamen may indicate disruption of membrane metabolism, or a decreased density of glial cells. These observations provide further support for the hypothesis of a dysfunctional CSTC circuit associated with TS. This study is limited by potentially confounding effects of patient medication and comorbidity, and potential effects of group differences in metabolite T_2.

References

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