Proton MRSI of Tourette Syndrome at 3.0 Tesla: Abnormalities of the Cortico-Striato-Thalamo-Cortical Circuit

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Synopsis
Eight boys with Tourette Syndrome and a control group of twelve healthy boys were scanned using proton magnetic resonance spectroscopic imaging (MRSI) at 3.0 tesla. Localized spectra were acquired with a multislice inversion-recovery spin-echo MRSI sequence (TI/TE/TR=230/135/1800 ms) (~1-cc voxels). Patients with Tourette Syndrome showed increased NAA in the left caudate (p=0.02), and decreased NAA in left frontal grey matter (p=0.05) relative to controls. No differences were observed in left or right thalamus. These results are consistent with previous reports of a dysfunctional cortico-striato-thalamo-cortical circuit in Tourette Syndrome, and suggest abnormalities of neuronal density in parts of this circuit.

Introduction
Tourette Syndrome 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 Tourette Syndrome 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 Tourette Syndrome is associated with a failure to inhibit subsets of the CSTC mini-circuits (1,2). Magnetic resonance imaging (MRI) studies of patients with Tourette Syndrome 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, the neuronal abnormalities within these regions remain unknown. Through the measurement of N-acetylaspartate (NAA), a neuronal marker, proton magnetic resonance spectroscopic imaging (MRSI) provides a unique opportunity for the in vivo investigation of neuronal abnormalities from numerous brain regions in a single experiment. To date, however, there have been no published studies of NAA or proton MRSI in Tourette Syndrome.

In the present study, children and adolescents with Tourette Syndrome and a control group of healthy children were imaged using 1H MRSI to evaluate levels of NAA in components of the CSTC circuit, specifically, left and right caudate nuclei, thalamus, and frontal grey matter. We hypothesize that children with Tourette Syndrome will exhibit abnormalities in neuronal density, as assessed by NAA measurement, in some or all of these regions reflecting an aberrant CSTC circuit.

Methods
Eight boys with Tourette Syndrome (ages 7-15 years) and 12 healthy boys (ages 6-15 years) were recruited from the local community. The groups did not differ in age, sex, race, or handedness. Patients were interviewed with the Schedule for Affective Disorders and Schizophrenia-Childhood Version (K-SADS) to confirm the diagnosis of Tourette Syndrome and also to assess patients for the presence of comorbid psychiatric conditions. At the time of their scans, patients were assessed using the Yale Global Tic Severity Scale 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 Tourette Syndrome patients were imaged under sedation using oral midazolam or oral chloride hydrate. Parental informed written consent, approved by the local Research Ethics Review Board, was provided prior to scanning.

A 3.0 T head-only research scanner (IMRIS, Winnipeg, Canada) with a quadrature head coil was used for all imaging experiments in this study. Standard T1-weighted localized images and axial multi-echo images for radiological assessment were initially acquired. This was followed by a 3-D DP-MRAGE acquisition (1.2-mm isotropic resolution, 0.5-mm inter-slice and 12-degree slice angle TI=350 ms, TR=2000 ms, inter-segment repeat time 5.3 s), to be used for extra-cranial lipid nulling (TI/TE/TR=230/135/1800 ms, FOV=280 mm, 35x35 circularly bounded k-space 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 10-mm thick oblique-axial slices were excited (Figure 1a) with numerically optimized RF pulses, yielding nominal voxel size of 8x8x10 mm (~1.0 cc effective voxel size after filtering). Water suppression was performed during the inversion time, using the adiabatic WASHCODE technique (9), providing good insensitivity to RF inhomogeneity, and eliminating the time-consuming task of optimizing the water-suppression pulses for each subject. T1-weighted images were acquired at the same slice positions as the MRSI acquisition for anatomical correlation, and B1-maps (10) were acquired to correct MRSI signal levels for RF field inhomogeneity. The full examination took approximately 1 hour.

Using the T1-weighted anatomical correlation images, voxels were selected for spectral analysis from left and right caudate nuclei, medial thalamus, and frontal grey matter (Figure 1b). After subtraction of the residual water signal, fit using HLSVD, unfiltered spectra were fit in the time domain using prior knowledge from in vivo metabolite solutions using a constrained Marquardt-Levenberg minimization algorithm (11). The metabolite signal amplitudes were corrected for coil load (12) and compared between groups.

Results
Patients exhibited abnormalities in components of the CSTC circuit relative to controls (Figure 2). Specifically, increased NAA was observed in the left caudate (p=0.02), and reduced NAA was found in left frontal grey matter (p=0.05). In addition, the asymmetry index for frontal grey matter NAA, defined as (left-right)/(left+right), was reversed in Tourette patients (right>left) relative to controls (p=0.05). In addition, the asymmetry index for frontal grey matter NAA, defined as (left-right)/(left+right), was reversed in Tourette patients (right>left) relative to controls (p=0.05). No differences were observed in the thalamus, or in any right-sided structure investigated.

Discussion
Given that NAA is regarded as a marker of functional neurons, these preliminary findings suggest that there may be abnormalities in neuronal density or function in components of the CSTC circuit in patients with Tourette Syndrome; this provides further support for the hypothesis of a dysfunctional CSTC circuit associated with this disorder. This is the first study to report metabolic abnormalities in the CSTC circuit in Tourette Syndrome using proton MRSI. The study is limited by small sample size, lack of female subjects, and potentially confounding effects of patient medication and comorbidity; these limitations will be addressed in upcoming data collection.

References
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Figure 1: MP-RAGE images showing (a) MRSI slice positions, (b) lower slice showing voxels in caudate nuclei, thalamus, and frontal grey matter

Figure 2: Mean NAA levels (arbitrary units) for Tourette syndrome and control subjects from left and right caudate nuclei, thalamus, and frontal grey matter, showing significant differences (*p<0.05) in components of the CSTC circuit

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