



## Fronto-striatal glutamate in children with Tourette's disorder and attention-deficit/hyperactivity disorder<sup>☆</sup>



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### ABSTRACT

**Objective:** Both Tourette's disorder (TD) and attention-deficit/hyperactivity disorder (ADHD) have been related to abnormalities in glutamatergic neurochemistry in the fronto-striatal circuitry. TD and ADHD often co-occur and the neural underpinnings of this co-occurrence have been insufficiently investigated in prior studies.

**Method:** We used proton magnetic resonance spectroscopy (1H-MRS) in children between 8 and 12 years of age (TD  $n = 15$ , ADHD  $n = 39$ , TD + ADHD  $n = 29$ , and healthy controls  $n = 53$ ) as an in vivo method of evaluating glutamate concentrations in the fronto-striatal circuit. Spectra were collected on a 3 Tesla Siemens scanner from two voxels in each participant: the anterior cingulate cortex (ACC) and the left dorsal striatum. LC-model was used to process spectra and generate glutamate concentrations in institutional units. A one-way analysis of variance was performed to determine significant effects of diagnostic group on glutamate concentrations.

**Results:** We did not find any group differences in glutamate concentrations in either the ACC ( $F_{(3132)} = 0.97$ ,  $p = 0.41$ ) or striatum ( $F_{(3121)} = 0.59$ ,  $p = 0.62$ ). Furthermore, variation in glutamate concentration in these regions was unrelated to age, sex, medication use, IQ, tic, or ADHD severity. Obsessive-compulsive (OC) symptoms were positively correlated with ACC glutamate concentration within the participants with TD ( $\rho = 0.35$ ,  $p_{uncorrected} = 0.02$ ).

**Conclusion:** We found no evidence for glutamatergic neuropathology in TD or ADHD within the fronto-striatal circuits. However, the correlation of OC-symptoms with ACC glutamate concentrations suggests that altered glutamatergic transmission is involved in OC-symptoms within TD, but this needs further investigation.

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### 1. Introduction

Tourette's disorder (TD) and attention-deficit/hyperactivity disorder (ADHD) are early onset neurodevelopmental disorders affecting approximately 1% (Robertson, 2008) and 5% (Polanczyk et al., 2007) of children and adolescents, respectively. While TD is characterized by the presence of motor and vocal tics (American Psychiatric Association, 2013) there are also psychiatric comorbidities present in

up to 86% of those with TD during their lifetime (Hirschtritt et al., 2015). ADHD is the most common, occurring in approximately 40% of cases (Rickards, 2011) and even more TD patients have ADHD symptoms that do not meet the threshold for diagnosis (Robertson, 2000). Conversely, the presence of tics within patients with ADHD has been estimated at 20% (Roessner et al., 2007). ADHD itself is characterized by age inappropriate inattention and/or hyperactivity/impulsivity leading to impaired functioning (American Psychiatric Association, 2013).

Both disorders have been associated with abnormalities in fronto-striatal circuits (Leisman and Melillo, 2013; Mink, 2006), although the overlap in conditions has confounded research to date. Structural and functional neuroimaging studies have reported alterations in the caudate nuclei, putamen, and anterior cingulate cortex (ACC) in TD (Peterson et al., 2003; Ganos et al., 2013) and ADHD (Frodl and Skokauskas, 2012; Nakao et al., 2011; Hart et al., 2013) relative to controls, although not always consistently. It has been proposed that excitatory abnormalities in the striatum cause erroneous inhibition of neurons in the globus pallidus (GP) internus, which in turn leads to

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disinhibition of prefrontal neurons which results in tic phenomena (Albin and Mink, 2006). These striatal abnormalities may also underlie the high rate of comorbidity with other disorders, like ADHD and obsessive compulsive disorder (OCD) (Hirschtritt et al., 2015) due to the aberrant integrative interplay of different fronto-striatal circuits including connections with the ACC (Albin and Mink, 2006; Mink, 2001). Dopamine dysfunction within the fronto-striatal circuit has long been considered the primary cause of tics (Singer et al., 1982) and has been related to difficulties with attention and impulsivity (Swanson et al., 2007). However, as glutamatergic, GABAergic, serotonergic, cholinergic, and opioid as well as dopaminergic systems all operate within the fronto-striatal circuits it is plausible that multiple neurotransmitter systems may be involved in TD and ADHD (Singer et al., 2010). Glutamate is the primary excitatory neurotransmitter found in the brain (Monaghan et al., 1985; Pittenger et al., 2011), essential in fronto-striatal transmission and often co-transmitted with dopamine (Chuhma et al., 2009). Post-mortem analysis of a small number of brains from people who had TD corroborates the view that glutamate is involved in TD as reduced levels of glutamate were seen in the GP and substantia nigra of the TD brains compared to control brains (Anderson et al., 1992).

Additional insights into the underlying neurobiology of TD and ADHD can be found by investigating brain neurochemistry. This can be achieved by using proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) which allows for non-invasive *in vivo* quantification of specific neurometabolites. There have been just four MRS studies of TD to date, three of which focused on GABA concentrations either in the primary and secondary motor areas (Draper et al., 2014) or the sensory motor cortex (Tinaz et al., 2014; Puts et al., 2015). DeVito et al. (2005) on the other hand investigated multiple neurochemicals including Glx, the combined signal from glutamatergic compounds (glutamate + glutamine), within multiple regions; premotor cortex, caudate nucleus, putamen and thalamus with a 3 Tesla scanner in a sample of 25 (male only) children and adolescents with TD in comparison to controls. No group differences were seen in Glx in any of the regions. Within the putamen lower creatine (Cre) levels bilaterally and lower *N*-acetyl aspartate and choline in the left putamen were found. Reduced Cre bilaterally in the caudate nucleus was also seen but this did not reach significance.

Many more MRS studies of disorders related to TD, such as ADHD and OCD, have been conducted. For a review of these studies in ADHD, OCD and autism spectrum disorder (ASD) see Naaijen et al. (2015). However, findings were inconsistent, plagued by heterogeneous methodologies, sample selection (i.e., child or adult, inclusion or exclusion of comorbidities), voxel placement, and often inadequate field strengths to distinguish glutamate from glutamine (Naaijen et al., 2015). Despite these issues the review tentatively summarized that increased striatal Glx levels are associated with both ADHD and OCD and increased ACC Glx levels with pediatric ADHD.

In the current study we assessed a large number of children between the ages of 8 and 12 years which allowed us to focus on a group where tics are most frequently observed and not limit ourselves to the subset of patients whose tics persist into adulthood (Bloch and Leckman, 2009). Furthermore we directly addressed the confounds of comorbidity rampant in previous studies by including a TD + ADHD group in addition to ADHD, TD, and healthy control (HC) groups. Based on previous findings in childhood ADHD (Naaijen et al., 2015), we expected increased glutamate concentrations in both regions of interest. This is the first study to investigate fronto-striatal glutamate in children with TD. Given the theory that excitatory abnormalities in the striatum result in tics, we expected to observe raised glutamate in the striatum of TD patients.

## 2. Method

### 2.1. Participants

Participants with TD and/or ADHD: TD with/without ADHD  $n = 60$ , ADHD without TD  $n = 60$  were recruited via child and adolescent

psychiatry departments and patient associations throughout the Netherlands, while healthy controls (HC;  $n = 60$ ) were found mainly through schools. The final numbers included for analysis (i.e. with usable data) can be found in Section 3.1 and Table 1 ( $n = 136$  for the ACC and  $n = 125$  for the striatum). Written informed consent was provided by the parents/guardians of all participants and written assent was also given by participants who were 12 years of age. This study was approved by the regional ethics board (CMO Regio Arnhem-Nijmegen, numbers: NL42004.091.12 & NL48377.091.14).

Inclusion criteria for all participants included being aged 8–12 years, IQ > 70, Caucasian decent, no previous head injuries or neurological disorders, no contraindications for MRI assessment, and no major physical illness. Inclusion criteria for ADHD and TD were meeting DSM-5 criteria for these disorders. Those with sub-threshold ADHD (Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS Kaufman et al., 1997) score of 4 or 5 on either subscale) were also included. Persistent Motor or Vocal Tic Disorder (Motor type) was also allowed for the TD group. Common psychiatric comorbidities like oppositional defiant disorder were not excluded. Within the TD group, ADHD, and OCD were not excluded, while in the ADHD group those with tics and/or OCD were excluded. Within the HC group no psychiatric disorders were allowed, as determined by screening questionnaires (Child Behavior Checklist [CBCL] and Teacher Report Form [TRF] Bordin et al., 2013). Subjects were divided into four groups; HC, TD, ADHD, and TD + ADHD, see Table 1 for demographics. Participants were required to refrain from consuming caffeine on the day of testing. Medications for tics were continued as normal while stimulant medication was withheld for 48 h before testing.

### 2.2. Phenotypic information

TD diagnosis was confirmed, and tic severity rated, by diagnostic interview with parent(s) and child present using the Yale Global Tic Severity Scale (YGTSS Leckman et al., 1989). To determine the presence of ADHD and/or other psychiatric disorders the K-SADS (Kaufman et al., 1997) interview was administered to the parent(s). All interviews were conducted by experienced researchers who were trained and overseen by a child- and adolescent psychiatrist (JKB). The screening module was used, followed if needed by disorder-specific modules. If participants screened positive for possible OCD the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS Scahill et al., 1997) was administered with both parent(s) and child present. The CY-BOCS interview was conducted with each participant of the TD group due to the relatedness of symptoms and common co-occurrence of OCD and TD.

Full-scale IQ was estimated by four subtests of the Wechsler Intelligence Scale for Children-III (WISC-III Wechsler, 2002): Vocabulary, Similarities, Block design, and Picture completion. Questionnaires were further used to assess phenotypic traits. The Conners' Parent Rating Scale – Revised Long version (CPRS-RL Conners et al., 1997) was used to rate ADHD severity. Additional questionnaires were used to assess the presence of autistic symptoms and compulsive behaviors; the Children's Social Behavioral Questionnaire (CSBQ Luteijn et al., 2000) and Repetitive Behavior Scale (RBS-R Lam and Aman, 2007). Information about medication history was gathered from parental report which has previously been shown to correlate well with pharmacy records (Kuriyan et al., 2014). Interviews on psychiatric symptoms were conducted about an unmedicated period.

### 2.3. T1-weighted MRI acquisition

All MRI datasets were acquired on the same 3 T Siemens Prisma (Siemens, Erlangen, Germany) scanner located in the Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands. T1-weighted anatomical images were acquired with a transversal, 3D magnetization prepared rapid gradient echo (MPRAGE) parallel imaging sequence with the following parameters: TR = 2300 ms, TE = 2.98 ms, TI =

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