Go/NoGo Performance in Boys with Tourette Syndrome

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Summary

Tourette syndrome has been associated with impairments of performance monitoring and alterations of attentional and executive functions. This impairment has been linked to fronto-striatal dysfunctions, which comprise the same brain circuits that are actively engaged in the suppression of tics. We compared behavioral performance and performance monitoring in nineteen boys with Tourette syndrome (TS) (mean age 12.64 years, ± 2.05) and nineteen age-matched controls (mean age 13.16 years, ± 2.29) in a Go/NoGo paradigm. This paradigm was designed to test for problems with inhibition and attention when withholding the response to NoGo targets following repetitive Go targets. The results indicated similar performance accuracy in the TS group and the control group. TS participants showed the expected pattern of Post-Error Slowing, but responded significantly slower to correct Go trials than the controls. The reaction times (RT) to NoGo targets in commission errors, however, did not differ between the groups. The results suggest that boys with TS develop inhibitory adaptive strategies (overall slower reaction times) to maintain high performance accuracy. These effects may be suspended prior to and during NoGo commission errors.
**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ADHD</td>
<td>Attention-Deficit/Hyperactivity Disorder</td>
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<td>ANCOVA</td>
<td>Analysis of Covariance</td>
</tr>
<tr>
<td>CSTC</td>
<td>Cortico-Striato-Thalamo-Cortical</td>
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<td>DBS</td>
<td>Deep Brain Stimulation</td>
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<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>EEG/ERP</td>
<td>Electroencephalogram/Event-Related Potentials</td>
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<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>GPi/GPe</td>
<td>Globus Pallidus internal portion/ Globus Pallidus external portion</td>
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<tr>
<td>HRT</td>
<td>Habit Reversal Training</td>
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<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Related Health Problems- 10\textsuperscript{th} revision</td>
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<td>IQ</td>
<td>Intelligence Quotient</td>
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<tr>
<td>Kiddie-SADS</td>
<td>Schedule for Affective Disorders and Schizophrenia for School-Aged Children</td>
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<tr>
<td>OCB</td>
<td>Obsessive Compulsive Behaviors</td>
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<td>OCD</td>
<td>Obsessive Compulsive Disorder</td>
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<td>PES</td>
<td>PostError Slowing</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>RT</td>
<td>Reaction Times</td>
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<td>SATO</td>
<td>Speed-Accuracy-Trade-Off</td>
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<td>SDRT</td>
<td>Standard Deviation of Reaction Times</td>
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<td>SLITRK1</td>
<td>Slit and Trk-like 1 gene</td>
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<tr>
<td>SNC</td>
<td>Substantia nigra compacta</td>
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<td>SNR</td>
<td>Substantia nigra reticulate</td>
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<tr>
<td>SPECT</td>
<td>Single-Photon Emission Computed Tomography</td>
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<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
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<td>TS</td>
<td>Tourette Syndrome</td>
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<tr>
<td>WAIS</td>
<td>Wechsler Adult Intelligence Scale</td>
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<td>WISC-III</td>
<td>Wechsler Intelligence Scale for Children – Third Edition</td>
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<tr>
<td>YGTSS</td>
<td>Yale Global Tic Severity Scale</td>
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I. Theoretical Background

1. Tourette Syndrome

1.1. Symptoms

Tourette syndrome (TS) is a neuropsychiatric disorder with a prevalence estimated of 1% for the overall international population (Robertson, 2008). The disorder is characterized by multiple motor tics and at least one vocal tic that have persisted for more than one year as defined in the diagnostic classifications Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (American Psychiatric Association, 1994) and International Statistical Classification of Diseases and Related Health Problems (ICD-10) (WHO, 1992). There should not have been a tic–free period of more than three consecutive months (American Psychiatric Association, 1994) (two months in the ICD-10 classification (WHO, 1992)).

Both motor and vocal tics fluctuate in severity, intensity, frequency, and persist during sleep and change character during childhood and adolescence (Robertson, 2000). Tic severity is often exacerbated by stress, fatigue, anger and changes in temperature (Bloch, 2008). Possibly antecedent streptococcal infections are discussed to be a trigger for the disease (Swain, Scahill, Lombroso, King, & Leckman, 2007). Motor tics are sudden semi-voluntary or involuntary movements and usually begin in the facial region. Motors tics can also involve other regions of the body as well and may be present in a great variety of movement intensities and motor patterns. Motor tics usually manifest between the age of 3 and 8 years (Leckman, 2002), with a peak of onset around 5 to 6 years (Bloch, Peterson et al., 2006). Vocal tics typically follow the onset of motor tics by several years (Leckman, 2002) and are initially often present by coughing, throat clearing or by the production of short and meaningless sounds. Vocal tics frequently worsen in the course of the disease and extend into pronounced symptoms, such as repeating words. Less than one-third of TS patients experience the more seldom vocal tic of involuntary cursing (coprolalia), the symptom for which the condition seems to have become predominantly known (Robertson, 2000). Even though TS core symptoms appear to be of neurologic character, vocal tics in particular can disturb social and
Both motor and vocal tics often are experienced as a response to so-called “premonitory urges”. These sensory phenomena precede tic activity (Leckman et al., 1998) and prompt a moment of relief after performing a tic. Awareness of premonitory urges follow the onset of tics with a lag of around three years and has been reported in a large sample of children and adults with TS (Leckman, 2002). These preceding events are important clues, if patients wish to learn suppression of tics (Himle, Woods, Piacentini, & Walkup, 2006).

The natural course of TS is characterized by an increase of tic severity until the age of 10-12 years and, in most cases, attenuation of tics during or after puberty (Swain et al., 2007). About 20% of children with TS continue to experience a moderate level of impairment due to their tic-symptoms by the age of 20 (Bloch, Peterson et al., 2006). This typical course of improvement during puberty and diminishing after puberty may suggest that the basis of the condition could be considered as a developmental diversification rather than a progressive disorder (Singer & Minzer, 2003). Therefore, the identification of developmental factors and neural mechanisms that help to modulate the severity of tics during adolescence is an important area of research (Spessot, Plessen, & Peterson, 2004).

1.2. Comorbidity

Comorbid disorders are frequent in children with TS and influence their neuropsychological profile. Attention-deficit/hyperactivity disorder (ADHD), characterized by hyperactivity, inattention and impulsivity is a common comorbid condition in children with TS and is observed in about 60% of children with TS syndrome (Robertson, Banerjee, Eapen, & Fox-Hiley, 2002). Problems to control impulsivity and problems of social adjustment are significantly higher in children with TS and comorbid ADHD compared with children who have only TS (A. S. Carter et al., 2000; Sukhodolsky et al., 2003). Therefore, problems with impulsivity control in patients with TS may rather imply a comorbid ADHD condition than
representing typical cases of TS. Moreover, problems in school and academic settings, such as distractibility and problems with executive functions could be primarily originated from the ADHD symptoms. Problems with executive control may not be associated with Tourette syndrome per se. Early reports showing executive function deficits in TS (as reviewed in (Como, 2001)) may not have controlled sufficiently for comorbid ADHD condition (Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2005). Children with TS only show rather internalizing symptoms (A. S. Carter et al., 2000).

Another common comorbid condition in individuals with TS is obsessive compulsive disorder (OCD) or obsessive compulsive behaviors (OCB). More than 50% of all TS patients have obsessive compulsive symptoms (Swain et al., 2007) and the onset of obsessive-compulsive symptoms follows the onset of tic symptoms by about 2 years (Leckman, Walker, Goodman, Pauls, & Cohen, 1994). Although it is widely accepted that obsessive compulsive symptoms often are part of the clinical spectrum of TS, some clinical features of OCD appear quite differently in patients with TS from those seen in patients with OCD (Cath et al., 2001; Como, LaMarsh, & O'Brien, 2005; Eapen, Robertson, Alsobrook, & Pauls, 1997). Symptoms, such as forced touching, counting, repeating, ordering and self-damage compulsions and violent, sexual and symmetrical obsessions are more common in patients in comorbid OCD/TS, whereas contamination obsessions and cleaning compulsions are more common in OCD patients without comorbid TS (Cath et al., 2000; Miguel et al., 1997). Additionally, many patients with TS may experience compulsive symptoms, but the severity of those symptoms may not be sufficient to meet the diagnostic criteria for OCD (Como et al., 2005) and therefore, OCB is the more precise term for this behavioral phenomenon occurring in TS. Obsessive-compulsive symptoms and complex tics are often difficult to distinguish. Compulsive symptoms include premonitory feelings or urges to perform tics or compulsions until they are felt to be “just right”. Although urges to tic are a release to complete a muscular movement and compulsive urges are more a release to perform a specific task, their outcomes are similar in that a feeling of relief is achieved, which could be an intrinsic part of the TS symptomatology (Leckman et al., 1994). Furthermore, adults
with OCD have a hyperactive performance monitoring system (Ursu, Stenger, Shear, Jones, & Carter, 2003), as also described in adults with TS (Johannes et al., 2002; Johannes et al., 2003).

The two disorders may share the same underlying genetic vulnerability (Pauls, 2003) and molecular genetic basis (State et al., 2003). OCD/OCB are often undetected in patients with TS and may over years disturb family interactions and self-esteem of the child. Education of parents and children of this important aspect of TS should therefore constitute an obligatory part of follow-up consultations, especially with regard to the later onset of OCD symptoms (Bloch, Peterson et al., 2006).

Other common comorbid conditions include anxiety, selfinjurious behavior, personality disorders and depression and can detract from the patient’s overall quality of live. Less common, but also important, comorbid conditions are oppositional defiant disorder, conduct disorder, aggression, learning difficulties, rage and autism (A. S. Carter et al., 2000; Robertson, 2000). As well as comorbid depressive symptoms, selfinjurious behavior and anxiety are often related to obsessive-compulsive behavior or comorbid OCD, but exact relationship to TS is unclear (Robertson, 2000). These emotional disturbances also may well be a biological condition independent of the TS condition, or result of psychosocial complications that children with TS may experience in school or academic settings. Finally, depressive symptoms are commonly reported as side effects of neuroleptic medication used in tic treatment.

1.3. Clinical Assessment and Diagnosis

The diagnostic criteria for TS currently in use are described in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and 4th edition text revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Despite some differences in the classifications, both schemes are mostly aligned. Initially, the clinical diagnosis is based on both of the child’s and the caregiver’s observations (Plessen, 2006).
Clinician, family and child together reconstruct the child’s history and present functioning to determine appropriate treatment approaches (Leckman, 2002). However, during medical consultations children often show an absence of tic symptoms due to suppression or inhibition. This absence of tic-symptoms in consultations disappears frequently when the child is becoming more comfortable in the consultation situation. The clinician should not only focus on tics and tic severity, but all competencies and difficulties to get an impression of the global functioning of the child. Moreover, it is important to map how tics interfere with the child’s emotional, social, and familial and school experiences (Leckman, 2002). To get a complete picture, it is very helpful to monitor symptoms, fluctuations, effects on family, and psychosocial situations over a few months with help of records (Leckman & Cohen, 1999a).

A neurological examination of the child with TS and a clinical medical history may be of great value. Tics are sudden, habit-like movements or utterances that can involve single muscle groups and it is easy to mistake them as fragments of normal behavior, normal coordinated movements or vocalizations (Leckman, 2002). Tics can also be misunderstood as akathisia, tardive dyskinesia, or other hyperkinetic movement disorders (Swain et al., 2007). Patients and parents may therefore need education in order to recognize recurrent behaviors as tic symptoms (Leckman, 2002). The ability of patients to suppress tics helps to differentiate tics from other hyperkinetic movement disorders (Jankovic, 2001).

In addition to the (temporary) suppressibility, both motor and vocal tics persist during all stages of sleep, although much attenuated, and can cause sleep disturbances (Rothenberger et al., 2001). Tics vary by their presentation, complexity, intensity (waxing and waning) and frequency (Swain et al., 2007).

To ascertain all important symptoms and conditions of patients with tics a standardized clinical psychiatric interview (Coffey et al., 2000) should be used. Examples for these interviews are semi-structured interviews, such as the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present/Lifetime (Kiddie-SADS) (Kaufman et al., 1997) (used in the present study), or the Child Assessment Schedule (Hodges, McKnew, Cytryn, Stern, & Kline, 1982),
or other structured interviews, as e.g. the Development and Well-Being Assessment (R. Goodman, Ford, Richards, Gatward, & Meltzer, 2000). To minimize errors in case ascertainment due to waxing and waning of tic severity and tic suppressibility and to estimate tic severity an instrument measuring likelihood of having Tourette syndrome should be used, such as the Diagnostic Confidence Index (Robertson et al., 1999). Moreover, the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) is a semi-structured interview that helps to quantify tics in a dimensional manner and is frequently used in research studies. Tic severity and tic symptoms may also be reported by patients themselves or by caregivers using tables of registration for different specified tics e.g. the Tourette Symptom Self-Report (Cohen, Leckman, & Shaywitz, 1984) or the Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey (Gaffney, Sieg, & Hellings, 1994). Another important aspect of the initial evaluation is to check for the presence and severity of commonly co-occurring disorders like e.g. ADHD, OCD or depression. Those associated disorders often cause disturbing symptoms in children with TS that lead to severe isolation and family problems (Thomsen, 2000). A standard work-up of patients with TS should therefore involve both a standardized diagnostic procedure and dimensional specific questionnaires, such as. the Child Yale-Brown Obsessive Compulsive Scale for OCD symptoms (W. K. Goodman et al., 1989) and the Connors’ Parent rating scales (Conners, 1997) for ADHD symptoms. Those quantify symptoms of these co-occurring disorders after the diagnosis by a standardized interview. It is also important to determine school problems as children with TS tend to have attentional and endurance problems (Burd, Freeman, Klug, & Kerbeshian, 2005) and poor penmanship.

Beyond the importance of a comprehensive clinical evaluation on an individual basis for every patient, the recent focus on genetic psychiatric research into mental disorders additionally increases the need for precise and standardized descriptions of symptoms or “phenotypes” and “endophenotypes” (Gottesman & Gould, 2003).
1.4. Etiology

A number of genetic and non-genetic risk factors are frequently invoked to explain the variable expression of tic disorders. Genetic factors are implicated in vertical transmission in families with vulnerability to TS and related disorders (Pauls, 2003). Originally, heritability was assumed to be autosomal dominant (Pauls & Leckman, 1986), yet more recently, the underlying genetic mechanisms are thought to be more likely heterogeneous and based on a polygenic etiology (Robertson, Althoff, Hafez, & Pauls, 2008). Twin studies revealed genetic and non-genetic factors, genetic association studies have reported interesting findings for chromosomes 2, 3, 4, 5, 8, 9, 10, 11, 13, 17 and 19 (as cited in (Robertson et al., 2008)), however, replication studies with representative samples have so far been elusive. In detail, a promising study (Abelson et al., 2005), could identify one frameshift mutation and sequence variants in Slit and Trk-like 1 (SLITRK1) gene on chromosome 13q31.1. in three of 174 unrelated probands, but in none of 3600 controls. However, several studies (Deng, Le, Xie, & Jankovic, 2006; Verkerk et al., 2006; Wendland, Kruse, & Murphy, 2006) even failed to replicate the finding or, when found, did not segregate with the disorder. These conflicting results lead to the conclusion by some authors that these two DNA changes are unlikely in Tourette syndrome (Keen-Kim et al., 2006; Scharf et al., 2008). A recent study confirmed that SLITRK1 does not account for Tourette Syndrome but does indicate an association with TS (Miranda et al., 2009). More work is needed to explore other genetic and epigenetic mechanisms at work that could mimic the expressions patterns seen in TS.

Many non-genetic factors have been implicated in the pathogenesis of Tourette syndrome. Association between TS symptoms and stressful life situations has been noted since the initial description by Gilles de la Tourette (Gilles de la Tourette, 1885) and often tic symptoms exacerbate following a stressful life-event (Leckman, 2002). Stress-related neurotransmitters and hormones, such as corticotrophin-releasing factor, have also been found in higher concentrations in cerebrospinal fluid of patients with Tourette syndrome (Chappell et al., 1996). These
findings suggest that stress-related neurobiological mechanisms may play a role in the pathobiology of TS.

Other epigenetic factors include gestational and perinatal risk factors. Children with low birthweight, perinatal hypoxic events and maternal stress and extreme nausea during pregnancy are more likely to show more severe tics and an earlier onset of the disorder (Khalifa & von Knorring, 2005). Maternal smoking during pregnancy (Pringsheim, Sandor, Lang, Shah, & O'Connor, 2009), drug abuse, co-existing medical or psychiatric disorders can also be a risk factor (Leckman, 2002).

Moreover, male sex is a risk factor for TS with a male:female ratio of 4.3:1 (Bruun & Budman, 1997; Freeman et al., 2000). The increased prevalence has led to the hypothesis that the presence of androgenic steroids during critical periods in fetal development may play a role in the later development of the illness (Peterson, Zhang, Anderson, & Leckman, 1998) as sex steroid hormones are thought to influence brain areas to respond to changes in postnatal hormone levels (Collaer & Hines, 1995). This theory is supported by several clinical features of TS: 1. tic severity typically increases during puberty, when gonadal androgen production increases in both males and females, 2. androgen drug administration in adults exacerbates tic symptoms and severity (Leckman & Seahill, 1990), and 3. blockade of the androgen receptors attenuates tic symptoms in some individuals (Peterson et al., 1994). Moreover, females with TS showed increased masculine play preferences, more gender dysphoria and a “masculine pattern of performance on sex-typed spatial tasks” (G. M. Alexander & Peterson, 2004). Males with TS showed a increased masculine play pattern which correlated positively with symptom severity (G. M. Alexander & Peterson, 2004). Furthermore, frequent male-to-male transmissions within families seem to rule out the presence of an X-linked vulnerability gene (Leckman, 2002).

The literature regarding the hypothesis that post-infectious autoimmune mechanisms contribute to the pathogenesis of some cases of TS is not clear. It has been suggested that group A β-hemolytic streptococcal infections might be an important trigger for the onset and exacerbation of tics and associated behavior
Performance Monitoring in Tourette Syndrome

(Swedo et al., 1998). However, the biochemical link between autoantibodies and the specific neurochemical changes described involving dopaminergic and possible serotoninergic abnormalities remains a topic of great debate (A. J. Church, Dale, Lees, Giovannoni, & Robertson, 2003; Harris & Singer, 2006; D. S. Wolf & Singer, 2008).

1.5. Pathophysiology: Generation and Suppression of Tics

Tics are stereotyped, repetitive movements that tend to change in type and anatomical location over long periods of time. It is most likely that specific movement patterns result from activation of dopaminergic and serotoninergic neurotransmitter systems within motor portions of cortico-subcortical circuits, especially within the cortical-striato-thalamo-cortical (CSTC) circuits (Albin & Mink, 2006; Leckman, Vaccarino, Kalanithi, & Rothenberger, 2006). The basal ganglia constitute the “fine-tuning station” of the brain for movements and consist largely of five nuclei: the striatum (caudate nucleus + putamen), the subthalamic nucleus, the globus pallidus (devided into the internal portion (GPi) and the external portion (GPe)) and the substantia nigra (substantia nigra compacta (SNC) and reticulata (SNr)). Based on the physiologic nature of basal ganglia neurons, it is most likely that specific movement patterns result from striatal neurons becoming active, but also other basal ganglia parts seem to be involved (Albin & Mink, 2006). Two pathways from cortex to striatum (direct pathway) or the subthalamic nucleus (indirect pathway) are involved in the pathophysiology of TS (Mink, 2006). If neurons in the striatum or the subthalamic nucleus become abnormally active, they cause unwanted inhibition of a group of GPi/SNr output neurons. These GPi/SNr neurons yield reduced inhibition to the thalamus and thereby release thalamo-cortical circuits to the motor cortex, supplementary motor area, and prefrontal cortex and an unwanted motor pattern can be triggered. If striatal or subthalamic nucleus neurons become hyperactive in discrete repeated episodes, the result would be a repeated, stereotyped, unwanted movement (Mink, 2003, 2006). The excitatory input through subthalamic neurons is faster, while the inhibitory input through
striatal neurons to GPi is slower but more powerful than the excitatory input through the subthalamic nucleus (Mink, 2006). This overdriven circuit can be normalized again by receiving a new input (Graybiel, 2008).

CSTC circuits are composed of multiple parallel (partially overlapping) circuits that direct information from the cerebral cortex to the subcortex, and then back again to specific regions of the cortex (G. E. Alexander, DeLong, & Strick, 1986; Leckman & Cohen, 1999b). The number of cortical-subcortical circuits still remains controversial. At least four circuits are acknowledged as important: the motor, the oculomotor, the prefrontal (including the dorsolateral prefrontal and lateral orbitofrontal cortex), and the limbic (including the anterior cingulate and medial orbitofrontal cortex) (G. E. Alexander, Crutcher, & DeLong, 1990). Those fronto-striatal circuits are involved in self-regulatory control in normal cognitive function (Marsh, Zhu, Wang, Skudlarski, & Peterson, 2007). They are also involved in the pathophysiology of TS (J. A. Church et al., 2009; Raz et al., 2009; Singer, 2005; Sowell et al., 2003; Spessot & Peterson, 2006), especially in the suppression of tics (Gerard & Peterson, 2003).

The prefrontal cortex mediates performance on tasks that require decisions of whether, when, and how to act across a time delay, as are needed in working memory, behavioral inhibition, and Go/NoGo tasks (Fuster, 2002). In the case of tic symptoms, prefrontal cortices may inhibit across time a behavioral response to the somatosensory urge to tic, and they probably determine at the same time when to release the tic behavior from controlled suppression (Spessot et al., 2004). Dysfunction of prefrontal regions in TS patients is therefore likely to impair their ability to inhibit tic symptoms (Peterson, Skudlarski et al., 1998; Peterson, Staib et al., 2001).

1.6. Treatment

Despite some advances during the past decade, ideal anti-tic treatment is not available so far. Current treatment options are only partially effective and have often crucial side effects. The goal of the treatment for children with Tourette syndrome
should thus not be the complete elimination of tics, but to maximize social functioning and to relieve pain. The decision to begin treatment should be based on symptom severity with provision for the waxing and waning nature of the tic symptoms, and the evidence that the tics are an important source of interference with daily life as reflected in self-esteem, interpersonal relationships and ability to perform in school settings (Swain et al., 2007). Therefore, in milder cases, educational interventions, lifestyle adjustments and information concerning the nature of tic symptoms to the child, the parents and the teachers is most important and often proves a sufficient intervention.

TS is usually diagnosed in childhood and the following paragraph deals therefore predominantly with children. Adult individuals with TS, however, may also need help in adapting their professional life to the condition. Parents and children may need help to get hold of the available information, when the disorder initially presents. Information is available through the National Tourette Association (Tourette-Gesellschaft Deutschland e.V.: http://www.tourette-gesellschaft.de) that is an important source for parents, teachers and individuals with TS, who wish to keep updated about research advances or who wish to get into contact with other families in a similar situation. Education of the wider family, teachers, friends and peers about the condition may help the child to feel more relaxed in social situations. Accommodations in school settings should be considered as tics occasionally can be disruptive or distract other children. Children with TS have a higher percentage of learning difficulties, although this may partly be attributed to a comorbid ADHD condition (Abwender et al., 1996; Debes, Hjalgrim, & Skov, 2009; Erenberg, Cruse, & Rothner, 1987). Therefore it is important to assess reading and writing abilities in children with TS (Plessen, 2006). Another important point is the relationship between children with TS and their peer group to detect signs for bullying. Education of school teachers about the involuntary nature of the tics is important as especially vocal tics can attract attention of the class and thereby cause academic disturbances. In such cases, an extra room for the child with the feasibility to tic free could be a helpful solution.
However, pharmacological treatment should be considered, if the tics are so severe that the child is not able to concentrate at school, if tics cause physical pain (as e.g. seldom may be the case in severe motor tics) or if the child itself experiences the tics as very disturbing in social settings. In an overview (Swain et al., 2007), it has been recommended to start pharmacological treatment with low dose α-2 adrenergic agonists as clonidine, guafacine, baclofen and clonazepam, especially in case of milder tics. Side effects as sedation and mid-sleep waking often can be minimized by adjusting the dose schedule. Although α-2 adrenergic agonists have shown to be effective for treating Tourette syndrome, antipsychotic drugs are the most effective agents. Due to unfavorable side effects, the use of antipsychotic drugs as haloperidol and pimozide rather should be reserved to suppress severe tic behavior. Thus, if α-2 adrenergic medications have been found ineffective, the newer atypical antipsychotic drugs as e.g. olanzapine, risperidone and quetiapine usually are the medication to consider. This class of medication blocks both dopamine and serotonin receptors. This appears to be protective against the neurological adverse effects patients with TS usually experience with typical antipsychotics, which are primarily dopamine blockers. Generally, due to the side-effect profile and the dynamic symptom patterns in TS, pharmacotherapy should be evaluated closely and drug holidays for patients receiving medication may be an easy way to re-evaluate the indication of the drug (Plessen, 2006).

Other pharmacological treatment such as local injections of Botulinum toxine have shown to decrease simple motor tics in a randomized, double-blind study (Marras, Andrews, Sime, & Lang, 2001). Botulinum toxine may also be effective in treating vocal tics and coprolalia with decrease in frequency and interference from vocal tics and decline in premonitory urges as shown in a large case study (Porta, Maggioni, Ottaviani, & Schindler, 2004). However, in clinical practice Botulinum toxine are most commonly used in patients with sustained, single, and bothersome tics in a single muscular group, especially when tics involve strong, forced movements of the neck that can cause physical trauma (Bloch, 2008)).

Neurosurgery treatment like Deep Brain Stimulation (DBS) has been used for other movement disorders in adults as Parkinsons disease, tremor and dystonia
for many years. With the increased successful use, DBS has been become a treatment option for medically intractable tics in adults with Tourette syndrome. A study of 18 therapy-refractory patients with TS showed an overall reduction in tic severity of 62% (Servello, Porta, Sassi, Brambilla, & Robertson, 2008). However, since TS often spontaneously resolves by adolescence, using a surgical intervention like DBS for tics is presently only recommendable for the most severely affected adults with TS (Mink et al., 2006).

The emergence of effective, nonpharmacologic treatments for TS has been in advancement over the last decade. Habit reversal therapy (HRT) is the first cognitive-behavioral intervention that clearly reduces tic severity in patients with Tourette syndrome. HRT has been shown to significantly reduce tic severity in adults in randomized, blinded, clinical trials (Deckersbach, Rauch, Buhlmann, & Wilhelm, 2006; Wilhelm et al., 2003), and has shown similar effects in trials among children with TS (Himle et al., 2006). HRT trains awareness and competing response practice and offers a potentially effective treatment option for individuals with TS (Himle et al., 2006). Further standardization and validation of methods for behavioral treatments of tics is important and considered as useful by all involved parties. HRT seem to bee an especially attractive treatment option for patients with premonitory urges and a set of discrete, but bothersome tics. However, other researchers found that the ability to suppress tics is not dependent on the awareness of premonitory urges (Banaschewski, Woerner, & Rothenberger, 2003). This is especially important for younger children, who may not yet be aware of this sensory phenomena (Leckman, Walker, & Cohen, 1993). In general, individuals with TS learn to be aware of their ability to suppress tics, even though the capability to suppress tic may vary individually and at different points in time. During the tic suppression training, it is important to keep in mind the involuntary nature of the tics. An exhibition of tics should not be proscribed, which would attribute a form of stigmatization to the tics.

Children with comorbid conditions should be referred to a specialist in child- and adolescent psychiatry. The treatment of comorbid conditions should be
prioritized, because tics diminish often after treatment of comorbid conditions (Leckman, 2002).

For the treatment of associated OCD/OCB, beside a pharmacological treatment with a selective serotonin reuptake inhibitor (SSRI), cognitive behavioral therapy should be considered as a first-line intervention (Debes et al., 2009; The Pediatric OCD Treatment Study (POTS) Team, 2004). However, tics with comorbid OCD/OCB appear to be less responsive to pharmacotherapy with selective serotonin reuptake inhibitors and more responsive to antipsychotic augmentation than tics without comorbid OCD/OCB (Bloch, Landeros-Weisenberger et al., 2006). A recent meta-analysis of the dose-response relationship of SSRI suggested that a higher doses of SSRI should be considered before the addition of antipsychotic agents to SSRI treatment for those patients not responding to selective serotonin reuptake inhibitors (Bloch, McGuire, Landeros-Weisenberger, Leckman, & Pittenger, 2009). The combination, however, of pharmacological treatment and cognitive behavioral therapy performed by a well-trained therapist seems to be the most effective treatment especially for OCD (Shprecher & Kurlan, 2009).

The treatment of comorbid ADHD has been object of controversy because in some cases the stimulants have worsened the tics (Robertson, 2000). This resulted in recommendations to avoid treatment with stimulants in TS patients with comorbid ADHD. However, double-blind trials did not replicate this phenomenon and The Tourette Syndrome Medical Advisory Board Practice Committee currently recommends α2 agonists or stimulants as first-line medication for comorbid ADHD in patients with tics (Scahill et al., 2006), whenever a child with a comorbid ADHD diagnosis needs pharmacological treatment (Leckman, 2002). The combination of an α2 agonist and a stimulant may even improve treatment results (Debes et al., 2009).

1.7. Observations from Neuroimaging

In the last two decades, researchers have turned increasingly to neuroimaging proceedings to localize, quantify, and characterize neuroanatomic, functional and neurochemical distinctions in patients with TS. Studies of neuronal synaptic activity
can be performed with radiotracer imaging techniques, like Positron emission tomography (PET) of glucose metabolism or cerebral blood flow, and single-photon emission computed tomography (SPECT). PET and SPECT have the advantage of sampling the entire brain on high anatomic level of resolution; however, they have the disadvantage of localization ambiguity and the need to expose the patients to ionizing radiation. PET and SPECT studies suggest that dopamine D2 receptors are excessively sensitive in Tourette syndrome (S. S. Wolf et al., 1996; Wong et al., 1997). These findings, together with reports that the administration of dopamine antagonists reduces tic severity (Scahill, Leckman, Schultz, Katsovich, & Peterson, 2003), suggest that hyperinnervation of the striatum by dopaminergic neurons may contribute to the difficulties of individuals with Tourette syndrome in regulating their tics (Marsh, Maia, & Peterson, 2009).

More recently, techniques have been introduced that allow for indirectly imaging neuronal function based on magnetic resonance imaging (MRI). The most widely adopted blood oxygenation level-dependent functional MRI (fMRI) procedure localizes changes in cerebral perfusion associated with changes in neuronal activity. Neuroimaging evidence from those studies of children and adults with Tourette syndrome suggests the presence of both anatomical (Peterson, Staib et al., 2001; Peterson et al., 2003) and functional (Marsh et al., 2007; Peterson, Skudlarski et al., 1998) abnormalities in the frontostriatal circuits that conduct self-regulatory control processes. Anatomical studies have found abnormal thinning of the sensorimotor, primary motor, and premotor cortices in children with Tourette syndrome, with the degree of thinning proportional to the severity of their tics (Sowell et al., 2008), as well as hypoplasia of the caudate nucleus in children and adults with the disorder (Peterson et al., 2003). “Together, these findings suggest that abnormal maturation of specific pathways in portions of cortico-striato-thalamo-cortical circuits, particularly those involving sensorimotor pathways looping between the cortex and basal ganglia, may contribute to the genesis of tic behaviors” (Marsh et al., 2007). These interpretations are consistent with a report (Bohlhalter et al., 2006) that activation of supplementary motor area, paralimbic regions (including
the anterior cingulate and insular cortices), and parietal operculum accompanies the experience of the sensory cues that precede tics (Marsh et al., 2009).

Other anatomical findings include decreased caudate volumes in children and adults (Peterson et al., 2003), smaller corpus callosum sizes in children with TS (Plessen et al., 2004) and larger dorsolateral prefrontal cortices in children but not in adults who have the disorder (Peterson et al. 2001) and larger hippocampus and amygdala (Peterson et al. 2008). Those findings were significantly correlated with tic symptom severity and may represent a compensatory or adaptive process that attenuates tics (Peterson, Staib et al., 2001), consistent with the role of the prefrontal cortex in inhibiting inappropriate impulses or behaviors.

Another fMRI study of 22 adults with TS compared brain activation in a condition when individuals with TS were instructed to suppress voluntary tics with a resting condition when individuals with TS were allowed to tic spontaneously (Peterson, Skudlarski et al., 1998). The findings revealed that CSTC circuits are involved in the suppression of tics resulting in increased activation in the caudate and decreased activation in the basal ganglia. Those signal changes in the frontal brain correlated positively with measures of tic severity for the last month preceding the task. Those results suggest that tic severity might depend on the neuroplastic ability of the brain that compensate by hypertrophy for the inhibitory problems in patients with TS (Peterson, Skudlarski et al., 1998). As opposed to the larger prefrontal cortices, the smaller prefrontal volumes in adults with TS may reflect an inability to produce this activity-dependent plastic response to repeated attempts to control tics (Peterson, Staib et al., 2001). Those adults may be the minority of TS patients that still continue to experience tics in adulthood (Bloch, Leckman, Zhu, & Peterson, 2005), which was true of the adults in these imaging studies. Other fMRI studies have reported that adults with TS are dependent on immoderate activation of fronto-striatal circuits in order to achieve normal performance on the Stroop task (Marsh et al., 2007) or a Simon task (Raz et al., 2009). Those findings point to a need for increased functional recruitment of these cortices in order to overcome enduring difficulties with selfregulation during performance of self-regulation tasks (Marsh et al., 2007; Raz et al., 2009). A recent resting-state functional connectivity
MRI study confirmed those findings by spotting out immature and anomalous connections in the fronto-parietal networks that are important for online adaptive control (J. A. Church et al., 2009).

2. Performance Monitoring

2.1. Overview

Performance monitoring is a broad term that includes among others error monitoring and the development of adaptive behavior that is necessary to prevent undesirable actions and to optimize task performance (Wiersema, van der Meere, & Roeyers, 2007). The capability to monitor performance usually refers to the ability to guide information processing and behavior in the service of a specific goal by continuous checking whether the action goals have been reached and adjusting behavior to optimize action outcome (C. S. Carter & van Veen, 2007; Ullsperger, 2006). This system tracks unfavorable outcomes and signals the need for appropriate behavioral adjustments (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007). Such adjustments are initiated by enhancing and updating context and rule representations, thereby optimizing goal-directed behavior (Botvinick, Cohen, & Carter, 2004; Holroyd et al., 2004). Brain activation studies using event related potentials (ERP), neuroimaging with functional magnetic resonance imaging, single- and multunit recordings of performance monitoring have shown that the frontal lobes, in particular the rostral part of the anterior cingulate gyrus, the pre-supplementary motor area, and the mesial cortical area 8 produce error-related signals and play key roles for momentary adaptations such as Post-Error Slowing and post-error reduction of interference (Ullsperger, 2006), whereas right inferior frontal and midline parietal regions can be associated with longer scale (tonic) maintenance of effort (Eichele et al., 2008).
2.2. Performance Monitoring in Patients with Tourette Syndrome

The presence of inhibitory impairment in patients with TS is a matter of discussion and several studies reported variable results. In a flanker task (Crawford, Channon, & Robertson, 2005) children with TS were inferior to an age matched control group in the interference condition. Children with TS, however, were not impaired in accurately discriminating target and non-targets in a continuous performance task, but showed slower reaction times (RT) compared to a control group (Shucard, Benedict, Tekok-Kilic, & Lichter, 1997). Inhibitory control, when measured with the Go/NoGo task was not impaired in adults with TS (Hershey et al., 2004; Watkins et al., 2005), and the Go/NoGo performance in children with TS was comparable to age matched peers (Ozonoff, Strayer, McMahon, & Filloux, 1994; Roessner, Albrecht, Dechent, Baudewig, & Rothenberger, 2008). Moreover, several lines of research suggest that children with TS even may exert enhanced inhibitory control in situations that require performance monitoring. Children with TS perform superior to controls in directing their eye-movements (Jackson, Mueller, Hambleton, & Hollis, 2007; Mueller, Jackson, Dhall, Datsopoulos, & Hollis, 2006). In addition, tic suppression may involve elements of performance monitoring, because it activates the same prefrontal brain regions as in experimental tasks of inhibitory function requiring performance monitoring (Peterson, Skudlarski et al., 1998). Further, the increase in size of the dorsolateral prefrontal cortex and its inverse correlation to tic-severity in children with TS (Peterson, Staib et al., 2001) suggests that parallel processes may be involved in performance monitoring and in tic-suppression. Behavioral patterns relating performance monitoring and tic-suppression, however, have not been demonstrated yet and existing studies have not examined measures of performance monitoring such as Post-Error Slowing as an equivalent to error adaption in persons with TS.

Deficiencies in inhibitory control in patients with TS have, been linked to comorbid disorders, including attention-deficit/hyperactivity disorder and obsessive–compulsive disorder and it thus remains unclear if those findings reflect deficits specific to TS or due to comorbidity (Verte et al., 2005). Consistent with the typical symptoms of ADHD a number of studies have revealed deficits of attention
in patients with TS with comorbid ADHD (Dooley, 2006; Leckman, 2003) and the action monitoring system in children with ADHD is altered (Albrecht et al., 2008). Patients with TS, without comorbid ADHD are not impaired in their ability to perform easy visual attentional tasks, but perform worse in more complex settings (Johannes et al., 2002; Johannes et al., 2003).

None of these studies, however, has focused on measures of performance monitoring such as Post-Error Slowing as a surrogate for error adaption in individuals with TS.

2.3. Post-Error Slowing

When subjects commit errors in reaction time tasks, they temporarily pause and slow down their responding on the trial following the error (Rabbitt, 1977). Post-Error Slowing (PES) has been extensively studied in adults, but relatively little is known about the development of error monitoring systems in children. PES has been interpreted to be an indicator of error detection emerging at the age of about 4 years (Jones, Rothbart, & Posner, 2003). Previous studies investigated the development of the error-related negativity in 7-25 year old participants, and they found no differences between age groups in PES (Davies, Segalowitz, & Gavin, 2004; Wiersema et al., 2007). Investigations of post-error adjustments in children with Tourette syndrome are lacking so far.

2.4. Speed-Accuracy Trade-Off

Individuals participating in a task need to bargain between the competing needs of response speed and response accuracy, a tight spot known as the so-called speed-accuracy trade-off (SATO). The SATO has been considered as a built-in trade-off and should be considered when interpreting performance of a task requiring both speed and accuracy. The SATO has been used as an indicator for concentration and attention, impulsivity and reflection, extraversion and neuroticism, anxiety and intelligence, but also as a diagnostic tool for developmental coordination
disorder (Maruff, Wilson, Trebilcock, & Currie, 1999). For nearly a century, the SATO has been studied almost exclusively using abstract mathematical models. Although those models provide a good description of behavioral data, they do not provide knowledge about the structures and underlying mechanisms by which the SATO is carried out in the brain. Recently, researchers started to study the neural basis of the SATO. The most direct evidence concerning the neural basis of SATO comes from fMRI studies. It was found that the SATO is controlled in CSTC circuits (Forstmann et al., 2008; Ivanoff, Branning, & Marois, 2008; van Veen, Krug, & Carter, 2008), but also regions of higher decision making as the dorsolateral prefrontal cortex (Gold & Shadlen, 2007; Heekeren, Marrett, & Ungerleider, 2008; Schall, 2001), regions that are involved in the pathology of the Tourette syndrome. Thereby, studying SATO in children with TS is important to elucidate the mechanisms that may differ in children with disorders, such as TS.

2.5. The Go/NoGo Task

Go/NoGo tasks are used in psychological research to measure a participant’s capacity for sustained attention and response control. A participant responds to an action given certain stimulus (e.g., press a button - Go) and inhibit that action under a different stimuli (e.g., not press that same button - NoGo). The conflict during the Go/NoGo task occurs between selecting a prepotent (frequent, automated) speeded response to a designated “Go” stimulus, and withholding a response to a “NoGo” stimulus (Hester, Fassbender, & Garavan, 2004). Typically, in our task setup, response accuracy (ACC) to NoGo stimuli is lower than the ACC to Go, and erroneous responses during NoGo trials show faster reaction times than Go responses (Li, Yan, Bergquist, & Sinha, 2007). Further, RT in trials preceding an error response (PreError) may be shorter than RT in trials preceding a correct response (PreError Speeding) (Gehring & Fencsik, 2001), and RT succeeding an error response (PostError) are longer than RT in trials succeeding a correct response (PostError Slowing) (Jentzsch & Leuthold, 2006; Ridderinkhof, 2002). Go/NoGo paradigms are sensitive to fronto-striatal dysfunction and provide measures of
inhibitory control mechanisms that may be deviant in disorders like TS (Durston et al., 2002; Levin et al., 1991).
II. Objectives of the Thesis

Studying performance monitoring in children with TS is important in order to elucidate the mechanisms that allow children with TS to exert self-regulatory control. Such studies can inform the further development and evaluation of the neural effect of non-pharmacological therapies, such as HRT (Himle et al., 2006). We tested the performance accuracy and reaction times in boys with TS in a Go/NoGo experiment and compared them to an age- and gender-matched control group. In particular, we analyzed differences in the pattern of reaction times in correct Go responses, responses preceding commission errors, NoGo commission errors per se, and RT after errors. We expect that the general pattern consist of slightly speeded responses prior to errors, fast commission errors, and subsequent Post-Error Slowing. Based on the evidence of adaptive mechanisms that enhance prefrontal function in children with TS, we hypothesized a) that participants with TS would perform more accurate in a Go/NoGo task and b) that they exhibit more prominent PES compared to age-matched controls due to their enhanced ability of performance monitoring.
III. Methods

1. Participants

Participants with TS were recruited from the Department of Child- and Adolescent Psychiatry, Haukeland University Hospital, and from outpatient clinics in the greater Bergen area in the Hordaland County, Norway. Controls were recruited by randomly contacting local schools in the same geographic regions as the subjects with TS. Written informed consent was obtained from all participants and the study was approved by Regional Committee for Medical Research Ethics of western Norway.

Individuals who were included in the TS group met all DSM-IV criteria (American Psychiatric Association, 1994) for TS. Controls were matched for gender and age. Exclusion criteria for the control group were a lifetime history of Tic disorder, OCD, ADHD, or a current DSM-IV Axis I disorder. Additional exclusion criteria for both groups were epilepsy, head trauma with loss of consciousness, former or present substance abuse, prematurity (gestational age < 36 weeks) or an IQ below 70, measured by WISC-III (Wechsler, 1996) or the WAIS (Wechsler, 1981). Participants were right-handed as measured by the Edinburgh handedness inventory (Oldfield, 1971), except for two left-handed individuals in each group. The diagnostic procedure consisted of a semi-structured interview, the Kiddie-SADS (Kaufman et al., 1997) and “a best-estimate consensus procedure” that considered all available study materials (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982). Tic symptoms were measured with the YGTSS (Leckman et al., 1989) and OCD symptoms were measured with the Children Yale Brown Obsessive Compulsive scale (W. K. Goodman et al., 1989). Socioeconomic status was estimated by measuring the parental level of education in four categories, dependent on their school and higher education (JAACAP, 2005). All instruments were translated into Norwegian.

Sample size was limited to the first 20 subjects with TS who were referred consecutively to the study and who met the criteria for inclusion. 20 age-matched
peers were recruited for the control group. After inspection of the Go/NoGo results, two subjects, one from each group, were identified and excluded, one due to fast RT at too low NoGo-ACC (25%) and one due to too slow RT at low NoGo-ACC (70%). Thus, the reported data consist of two male groups: 19 boys with TS and 19 control boys, 9 to 17 years of age. The groups were of comparable age (TS = 12.64 years, ± 2.05; controls = 13.16 years, ± 2.29; t36 = .74; p = .46, d = .24) and socioeconomic status.

Five of the participants in the TS group had comorbid combined-type ADHD, four others had comorbid OCD, none had both conditions. At the time of testing, nine subjects in the TS group were taking medication, either neuroleptics (n= 4), alpha agonists (n = 2), selective serotonin uptake inhibitors (n = 1), or stimulants (n = 2), all on monotherapy. Controls were free of any psychotropic medications. The groups differed significantly in full-scale IQ (TS = 93.58 ± 9.72; controls = 105.68 ± 9.49; t36 = -3.88; p < .01, d = 1.26) (Figure 10), and IQ was therefore employed as a covariate of no interest in the analyses of group differences. Tic severity at the time of investigation in the TS group was 11.6 ± 2.9 for motor and 9.3 ± 3.5 for phonic tics, with lifetime-worst ever scores 15.2 ± 5.1 for motor and 13.5 ± 5.6 for phonic tics (possible range 0 to 25 in each category).

2. Experimental Setup

After verbal and written instruction the test subjects performed a PC-based test (platform: E-Prime 1.0, PST): on a screen pink (Probability 75%) and blue (Probability 25%) circles appeared in random order. Participants were instructed to press a key with the appearance of a pink circle as fast as possible (Go), and to withhold the prepotent response with the appearance of a blue circle (NoGo). Stimuli were presented in four blocks with 48 trials and varying interstimulus intervals between 500 and 1250 ms. On-screen stimulus duration was 150 ms.
3. Statistical Analyses

All statistical procedures were performed in Statistica v. 8 (StatSoft, 2008) or SPSS v. 15 (SPSS, 1999). The first a priori hypothesis was tested using a general linear model (GLM) Analysis of variance (ANOVA) with repeated measures over the reaction times of four different trial types. The model included the within-subjects factors Trial with 4 levels (RT Go, RT PreError, RT NoGo Error, RT PostError) and the between-subjects factor Group (TS or controls). Moreover, the subject’s age was included as a continuous covariate in the model. Full IQ was also considered as a covariate in the GLM model, because the TS and controls significantly differed in this respect.

In addition to the independent variables described above, all two-and three-way-interactions of Group (TS and controls), Trial, and Age were tested. Interactions that were not statistically significant were hierarchically eliminated via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well-formulated (i.e. all possible lower order terms had to be included in the model, regardless of their statistical significance) (Morrell, Pearson, & Brant, 1997). Differences in Post-Error Slowing between groups were tested with assessment of the statistical significance of the Group-by-Trial term in the model. Whether these regional differences varied with age was tested with the Group-by-Trial-by-Age, 3-way interaction term. All tests for significance were of the 2-sided type.

Additionally, between-groups analyses of covariance (ANCOVA) were used to test our main hypotheses for potential differences in the groups in the Go/NoGo measures while controlling for age.

4. Exploratory Analyses

4.1. Go/NoGo Measures across all Participants

We compared the reaction times and response accuracy producing Go trials and erroneous NoGo trials of all subjects in a t-test for independent samples using
the within subjects factor condition between Go and NoGo. Additionally, we provide the F-statistic from the corresponding analysis of variance.

4.2. Potential Confounds

In order to assess the effects on our findings of comorbidity and medication in the TS group, the analysis was repeated while restricted to all subjects with TS, excluding those with comorbid ADHD (remaining n= 14) or OCD (remaining n=15), and excluding those on medication (remaining n=10), compared with the original control sample (n= 19).

4.3. Association with Age

Correlations of NoGo accuracy Go and NoGo reaction times with age were explored separately in each group by calculating the Pearson correlation coefficient $r$.

4.4. Association with Symptom Severity

Correlations of RT and accuracy with symptom severity in the TS group were investigated by calculating the Pearson correlation coefficient $r$.

4.5. Speed-Accuracy Trade-Off

Using the Pearson correlation coefficient, we explored the presence of a Speed-Accuracy Trade-Off in both groups, in order to gather information concerning adaptive mechanisms.

4.6. IQ Differences between the Groups

We used an ANCOVA to explore verbal IQ, performance IQ and full-scale IQ differences between the groups. The analysis was repeated while restricted to all
subjects with TS, excluding those with comorbid ADHD (remaining n= 14) or OCD (remaining n=15), and excluding those on medication (remaining n=10), compared with the original control sample (n= 19) to assess the effects on our findings of comorbidity and medication in the TS group.
IV. Results

1. Accuracy of NoGo Measures

As predicted, the ANCOVA revealed no difference of Accuracy on NoGo trials between the two groups ($F_{1,35} = 1.95$, $p = .17$, $\eta^2 = .04$), with an average of $62.8\% \pm .04$ in the controls and $68.0\% \pm .04$ in the TS group and a significant effect of age ($F_{1,35} = 12.64$, $p < .01, \eta^2 = .25$). Additionally, the accuracy of Go trials did show a significant effect of the age covariate ($F_{1,34} = 5.93$, $p = .02, \eta^2 = .14$), but did not differ between the groups ($F_{1,34} = .04$, $p = .84, \eta^2 < .01$), with an average of $94.9\% \pm .02$ in the controls and $94.7\% \pm .02$ in the Tourette group (Table 1).

Table 1. Results of the between-group analyses of covariance (ANCOVA) in accuracy with the covariate age. Mean and standard error of the mean (SEM), F value, p value and eta squared.

<table>
<thead>
<tr>
<th></th>
<th>TS (Mean±SEM)</th>
<th>Control (Mean±SEM)</th>
<th>Between-Group ANCOVA</th>
<th>Age covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC Go</td>
<td>94.7 % ± .02</td>
<td>94.9% ± .02</td>
<td>$F_{1,35} = .04$, $p = .84, \eta^2 &lt; .01$</td>
<td>$F_{1,35} = 5.93$, $p = .02, \eta^2 = .14$</td>
</tr>
<tr>
<td>ACC PreError</td>
<td>91.1 % ± 1.89</td>
<td>87.5% ± 1.89</td>
<td>$F_{1,35} = 2.53$, $p = .12, \eta^2 = .06$</td>
<td>$F_{1,35} = 3.73$, $p = .06, \eta^2 = .09$</td>
</tr>
<tr>
<td>ACC NoGo Error</td>
<td>68.0 % ± .04</td>
<td>62.8% ± .04</td>
<td>$F_{1,35} = 1.95$, $p = .17, \eta^2 = .04$</td>
<td>$F_{1,35} = 12.64$, $p &lt; .01, \eta^2 = .25$</td>
</tr>
<tr>
<td>ACC PostError</td>
<td>81.8 % ± 3.27</td>
<td>84.0% ± 3.27</td>
<td>$F_{1,35} = .02$, $p = .89, \eta^2 &lt; .01$</td>
<td>$F_{1,35} = 8.28$, $p &lt; .01, \eta^2 = .19$</td>
</tr>
</tbody>
</table>
2. Post-Error Slowing

The model revealed a non-significant trend of Group (F\(_{1,35} = 3.02\); \(p = .09\), \(\eta^2 = .05\)), and a non-significant interaction between Trial-by-Group (Figure 1). Moreover, Age was retained in the final model (F\(_{1,35} = .08\); \(p = .77\), \(\eta^2 < .01\)). Age of the subject showed an interaction with Trial (F\(_{3,105} = 3.04\); \(p < .05\), \(\eta^2 = .02\)). IQ was eliminated from the model, because it did not reach significance as a main-effect or in interaction with Group or Age. Also, the Group-by-Trial-by-Age interaction was not significant (at the point of elimination n.s.), indicating that the findings were stable across the age range of children studied.

**Figure 1. Post-Error Slowing (PES).** Reaction times on RT Go, RT PreError, RT NoGo Error, and RT PostError show that the subjects increase their speed before an error (RT NoGo Error) and slow it down after an error. The reaction times in the dotted line represent the Tourette group; the reaction times in the solid line represent the control group.
A post-hoc assessment of the origin of the trend of a difference between groups, using a test of differences in least-square means, demonstrated that the boys with Tourette showed a trend toward slower reaction times (RT Go \( p = .06 \), RT PostError \( p = .07 \)), but that this effect was not specific for the RT following an error.

Table 2. Results of the between-group analyses of covariance (ANCOVA) in reaction times with the covariate age. Mean and standard error of the mean (SEM), F value, p value and eta squared.
Comparison in a ANCOVA showed a significant difference in Go reaction times between the groups ($F_{1,35} = 4.44; p < .05, \eta^2 = .11$) (Figure 2) and did not show effects of the covariate age ($F_{1,35} < .01, p = .96, \eta^2 < .01$). Moreover, the average Go reaction time variability (SDRT) showed a non-significant trend of Group ($F_{1,35} = 3.65; p = .06, \eta^2 = .07$) with $86.78 \text{ ms} \pm 4.83$ in controls vs. $102.67 \text{ ms} \pm 4.83$ in TS and a significant effect of the age covariate ($F_{1,35} = 10.18; p < .01, \eta^2 = .21$). The average NoGo SDRT showed no effect of the age covariate ($F_{1,35} = .92; p = .34, \eta^2 = .03$) and no difference between the groups ($F_{1,35} = .76; p = .39, \eta^2 < .02$) with $64.07 \text{ ms} \pm 7.54$ in controls vs. $75.29 \text{ ms} \pm 7.54$ in TS (Table 2).

**Figure 2. Go and NoGo Reaction Times.** Differences between Go RT between both groups, no significant differences between NoGo RT between the groups.
3. Exploratory Analyses

3.1. Go/NoGo Measures across all Participants

Participants responded more correctly in the Go trials compared with the NoGo trials ($94.81\% \pm 7.17$ vs. $65.41\% \pm 18.81$; $t_{74} = 9.00; p < .01, d = 2.26; F_{1,37} = 114.5, p < .01, \eta^2 = .52$) (Figure 3).

**Figure 3. Go and NoGo Accuracy across all Participants.** Go and NoGo accuracy differed significantly across all participants.
The Go reaction times were longer than the erroneous NoGo reaction times, (339.99 ms ± 47.31 vs. 275.23 ms ± 40.89; $t_{74} = 6.38$; $p < .01$, $d = 1.47$; $F_{1,37} = 201.90$, $p < .01$, $\eta^2 = .36$) (Figure 4).

**Figure 4. Reaction Times across all Participants.** Go and NoGo RT differed significantly across all participants.
Moreover, the average SDRT was higher than the NoGo SDRT, (94.73 ms ± 24.66 vs. 69.69 ms ± 34.61; \(t_{74} = 3.63; p < .01, d = .84\); \(F_{1,37} = 26.19, p < .01, \eta^2 = .15\)) (Figure 5).

![Go and NoGo Variability (SDRT)](image)

**Figure 5. Go and NoGo Variability across all Participants.** Go and NoGo SDRT differed significantly across all participants.

### 3.2. Potential Confounding Variables

Excluding subjects with comorbid ADHD (n = 5), subjects with OCD (n = 4), and without subjects on medication (n = 9), the model showed the same pattern, *Group* was non-significant (without ADHD: \(F_{1,30} = 2.67, p = .11, \eta^2 = .05\), without medication: \(F_{1,26} = 1.53, p = .22, \eta^2 = .04\), without OCD: \(F_{1,31} = 2.15, p = .15, \eta^2 = .05\)), same as *Trial-by-Group* (without ADHD: \(F_{3,90} =1.36, p = .26, \eta^2 = .01\),
without medication: $F_{3,78} = 1.56$, $p = .20$, $\eta^2 = .01$, without OCD: $F_{3,93} = .18$, $p = .91$, $\eta^2 < .01$). IQ as a covariate in the model did not show a significant influence on RT at the different trial types (at the point of elimination n.s.).

3.3. Correlations with Age

In both groups, the accuracy of NoGo trials was correlated with age ($r = .48$, $p = .04$, $r^2 = .23$ in TS, $r = .55$, $p = .02$, $r^2 = .3$ in controls) (Figure 6), while reaction times of Go and erroneous NoGo trials were not age-correlated.

![Figure 6. Age Dependence of NoGo Accuracy](image-url)

**Figure 6. Age Dependence of NoGo Accuracy.** The accuracy of NoGo correlated positively in both groups with age.
3.4. Associations with Tic Severity

NoGo accuracy correlated positive with current motor symptom severity on a trend level of statistical significance ($r = .4; p = .09, r^2 = .16$).

3.5. Speed-Accuracy Trade-Off

The overall sample showed a significant correlation between accuracy and reaction times (overall: $r = .46, p = .01, r^2 = .21$; controls: $r = .52, p = .02, r^2 = .27$), while only reaching trend levels in the Tourette group ($r = .39, p = .1, r^2 = .15$) (Figure 7).

![Speed-Accuracy Trade-Off (SATO)](image)

**Figure 7. Speed-Accuracy Trade-Off.** The RT NoGo Error correlated with ACC NoGo in both groups.
3.6. IQ Differences between the Groups

The groups differed in full-scale IQ (TS = 93.58 ± 2.09; controls = 105.68 ± 2.09; F₁,₃₅ = 15.02, p < .01, η² = .29) (Figure 10), verbal IQ (TS = 93.37 ± 2.36; controls = 104.11 ± 2.36; F₁,₃₅ = 8.18, p < .01, η² = .20) and performance IQ (TS = 95.0 ± 2.5; controls = 106.42 ± 2.5; F₁,₃₅ = 10.26, p < .01, η² = .20). The results did not show effects of the covariate Age. The model showed the same pattern when excluding subjects with comorbid ADHD (n = 5) (full-scale IQ 96.78 ± 2.27, performance IQ 97.37 ± 3, verbal IQ 96.78 ± 2.64) and subjects with OCD (n = 4) (full-scale IQ 94 ± 2.65, performance IQ 94.26 ± 3.12 and verbal IQ 94.6 ± 2.81), with slightly lower IQ scores in TS subjects when a comorbid OCD condition was excluded vs. exclusion of a comorbid ADHD condition. Excluding subjects on medication (n = 9), the model revealed a significant difference in full-size IQ (TS = 97.2 ± 2.88; controls = 105.68 ± 2.09; F₁,₂₆ = 5.75, p = .02, η² = .18), but not in verbal IQ and performance IQ.
V. Discussion

Patients with TS report continuous urges of exerting tic behavior which build-up over time and they feel in many situations a need to suppress such impulses. The underlying circuitry that mediates performance monitoring is a relevant topic for understanding tic behavior and self-regulatory control. Several lines of research suggest that children with TS may exert enhanced inhibitory control in performance monitoring. Children with TS are superior than controls in controlling their eye-movements (Jackson et al., 2007; Mueller et al., 2006) and recent fMRI studies showed that children with TS show stronger prefrontal cortex activation than controls during a cognitively engaging task (Baym, Corbett, Wright, & Bunge, 2008; Marsh et al., 2007), whereas performing on the same level of accuracy. Frontal regions of the brain have been implicated in the suppression of tics in adults with TS (Peterson, Skudlarski et al., 1998) and children with TS have larger dorsal prefrontal regions (Peterson, Staib et al., 2001) and a smaller corpus callosum (Plessen et al., 2004). These anatomical features have been understood to reflect neural plasticity that helps to attenuate the severity of tics (Plessen et al., 2006) by training inhibitory loops (Peterson, Staib et al., 2001; Stern, Blair, & Peterson, 2008). These changes in brain function and neuroanatomy may be part of a prefrontal control system that is frequently active in order to monitor and to suppress unwanted tic activity (Leckman et al., 2006; Plessen, Royal, & Peterson, 2007; Spessot et al., 2004).

Here, we tested behavioral correlates of performance monitoring in a Go/NoGo task in children with TS and a matched control group. Our findings indicate that patients diagnosed with TS seem to adjust their performance monitoring system to levels with higher control and correspondingly slower response times, putatively to maintain high performance accuracy.

The discussion is organized in separate sections that address the meaning and relevance of the results from the tests for the Accuracy of NoGo Measures, PostError Slowing, Go/NoGo Measures across all Participants, Potential...
Confounding Variables, Correlations with Age, Associations with Tic Severity, Speed-Accuracy-Trade-Off and IQ Differences between the Groups.

1. Accuracy of NoGo Measures

Confirming our first hypothesis, we found that children with TS were not impaired in their accuracy of withholding a response in the more demanding NoGo trials compared to age matched peers, thus children with TS were capable of inhibiting an automated response. Problems of attention and inhibition as measured in a Go/NoGo tasks are not part of the TS profile in our study. These findings are in line with other investigations showing that children with TS have a comparable or even enhanced ability of cognitive control (Como, 2001; Mueller et al., 2006; Ozonoff, Strayer, McMahon, & Filloux, 1998; Plessen et al., 2007; Verte et al., 2005). Along the same lines, several recent functional magnetic resonance imaging studies showed that children with TS, although showing comparable performance to a matched control group, activated the left prefrontal cortex more than the control group during a cognitively demanding task (Baym et al., 2008; Hershey et al., 2004; Marsh et al., 2007). However, because adults with TS were found impaired in inhibitory tasks (Hershey et al., 2004; Muller et al., 2003), it is uncertain whether the deviating electrophysiological correlates of error monitoring are due to a hyperactive performance monitoring or rather the result of dysfunctional fronto-striatal interactions (Ullsperger, 2006). Prior studies dealing with error monitoring in TS have, however, mainly included adults with TS, although several cross-sectional neuroimaging studies in TS have revealed that adult- and children population differ widely with respect to structure and activation patterns of the brain (Gerard & Peterson, 2003). Those patients with TS who even experience tics in adulthood may be a subsample of the TS population, who has not developed the otherwise typical compensatory mechanisms that usually help to suppress tics during development and lead to the common amelioration of tics during adolescence.
2. Post-Error Slowing

The reaction times after an error (RT PostError) were comparable in the children with TS and the controls, but children with TS had a trend toward longer reaction times across all types of trials. Hence the second hypothesis was not confirmed. Boys with TS were not specifically slower in post-error trials and we thus did not find a particularly well adapted strategy for error correction, which we suspected due to the frequent training of inhibitory fronto-striatal loops in the patient group. The adaptive mechanisms after an error are similar across the groups, and the supposed additional inhibitory adaptation (for tic suppression) is momentarily suspended for the Tourette group. In tasks performed with accentuation of response speed, PES can be decreased or absent, as a result of time pressure (Ullsperger, 2006). Future studies should therefore, consider different feed-back experimental paradigms and feedback manipulation that allow for error corrections such as second key presses after erroneous responses. Instructions to correct errors influence reaction times and lead to an increase in slow error corrections, which are appropriate performance monitoring results (Fiehler, Ullsperger, & von Cramon, 2005; Ullsperger & von Cramon, 2006).

Other paradigms than the GoNoGo task yield often stronger post-error slowing and should be considered in future studies. The reason for the is the probabilistic structure of the NoGo stimuli that appear less frequently than the Go stimuli, i.e. participants can form a prediction that likelihood of a repeated NoGo is low and in effect not require a post-error speed adjustment. In particular, equiprobable choice response times with speeded responses such as the Eriksen-Flanker task (Eriksen & Eriksen, 1974) and more complex sequential movement tasks (Gehring & Fencsik, 2001) might be used to differentiate between TS and control groups. Post-error slowing should be regarded as a relatively indirect measure when trying to understand adaptive effects in performance monitoring. It would be preferable to record event-related electrophysiological measures concurrently, specifically the N2- and error-related-negativity-component of the ERP. Even in the possible absence of behavioral differences these more direct measures of performance monitoring on a neuronal level may allow to map changes
in adaptation to errors on a more subtle level. The sources of the event-related-negativity are relatively well understood, and the link between event-related-negativity and PES has been established. Group level differences between controls and TS in the electrophysiological and possibly concurrent hemodynamic dimensions during such tasks could thus help to better understand underlying mechanisms specific to TS. Adults with TS show increased error-related-negativity amplitudes and a more prominent frontal negativity component during response conflicts (Johannes et al., 2002; Johannes et al., 2003), which suggests a hyperactive (and/or hypertrophic) performance monitoring system.

3. Exploratory Analyses

3.1. Go/NoGo Measures across all Participants

In our task setup, ACC to NoGo stimuli is lower than the ACC to Go, and erroneous responses during NoGo trials show faster reaction times than Go responses. Further, RT in trials preceding an error response (PreError) have been shorter than RT in trials preceding a correct response (PreError Speeding). RT succeeding an error response (PostError) are longer than RT in trials succeeding a correct response (PostError Slowing). This effect was expected and has been confirmed in several other studies (Gehring & Fencsik, 2001; Jentzsch & Leuthold, 2006; Li et al., 2007; Ridderinkhof, 2002).

3.2. Potential Confounding Variables

The sample of boys with TS was not restricted to individuals without comorbid disorders. Hence it appeared important to disentangle the effect of TS itself and the comorbid disorders (ADHD and OCD). Repeating the main analyses after excluding individuals with comorbid conditions and those on medication did not alter our main findings and the primary findings remain stable.
3.3. Correlations with Age

Further, we found higher reaction time variability in the children with Tourette syndrome with a significant effect of the age covariate. This variability in the group could indicate that the noise in the system does not fade out with higher age as it does with the control group (Figure 8).

Figure 8. Age Dependence of Go Reaction Time Variability (SDRT). We found significant age-effects in our exploratory analyses in children and adolescents between the ages of 10-18 years. Even though those effects were not specific for the children with TS, knowledge about age-related changes for the development of self-regulation is important. The ability of performance monitoring develops continuously during the age-range of the included individuals. Although elementary forms of inhibitory control and error monitoring are present as early as
about the age of 4 (Jones et al., 2003), the self-regulatory and performance-monitoring functions appear not to be fully matured until midway into adolescence (Rubia, Smith, Taylor, & Brammer, 2007). However, at around the age of 12 years, the development of selective motor response inhibition in the Go/NoGo task has shown to reach its peak (Levin et al., 1991), with performance- and error-monitoring functions developing into late of the second decade (Davies et al., 2004). The delay of development of inhibitory control processes have been allocated to the relatively late anatomical maturation of the frontal lobes (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Durston et al., 2002; Toga, Thompson, & Sowell, 2006). Those findings have been confirmed by anatomical functional imaging findings of inhibitory control (Durston et al., 2002; Rubia et al., 2001; Rubia et al., 2007; Tamm, Menon, & Reiss, 2002).

3.4. Associations with Tic Severity

The trend-level positive correlation of NoGo accuracy with RT fits with the notion that patients with more prominent tics develop prefrontally mediated cognitive control mechanisms that in turn help them to withhold an automated response in the Go/NoGo task better than those individuals with a lower tic severity. However, this trend should be regarded as preliminary until replicated in a larger sample with higher statistical power.

3.5. Speed-Accuracy-Trade-Off

Comparing reaction times of the two groups, the Tourette group overall had slower reaction times in all four trial types compared to the control group, an effect that only reached trend level. This main effect could be weakened by the relatively faster NoGo trials in the Tourette group which might indicate an intermittent suspension of the inhibitory mechanisms in the Tourette group. A SATO should be considered when interpreting performance of a task requiring both speed and accuracy. Based on the evidence that TS patients have deficits in suppressing
unwanted responses and in a situation where the experimental paradigm requires performing at high accuracy, TS subjects might adjust the SATO to slower reaction times to maintain the same or even better accuracy. As shown in Figure 8, more boys in the TS group had a higher accuracy (above 80%) and also a higher proportion in the TS group had slower RT (above 300 ms). The effect was, however, not significant due to high within-subject reaction time variability in the TS group (Figure 9).

Figure 9. Differences in Go and NoGo Reaction Time Variability (SDRT) between the groups.

Our results show a weak SATO in the TS group, similar to a previous report, which used a continuous performance test (Shucard et al., 1997). The SATO-effect, however, was present to a stronger degree in the control group (Figure 7). Future studies could specifically focus on this measure using other paradigms that induce
stronger SATO, such as the Eriksen flanker task with speed feedback (Eriksen & Eriksen, 1974) in this group of patients. A higher SATO could explain the frequent clinical perception of slowness in children with TS.

3.6. IQ Differences between the Groups

We found that children with TS had lower full scale IQ scores (Figure 10) than the control group.

![Differences in IQ](image)

**Figure 10. Differences in IQ.** The groups differed significantly in full-scale IQ.

Additionally, children with TS showed significantly lower scores on performance IQ and verbal IQ. The literature concerning IQ scores of individuals with TS is contradictory. Some studies found higher IQ scores of TS subjects with
without comorbidity (Hagin, Beecher, Pagano, & Kreeger, 1982; Roessner et al., 2008; Schuerholz, Baumgardner, Singer, Reiss, & Denckla, 1996). Other studies found lower IQ scores for TS subjects with or without comorbid ADHD/OCD (Baym et al., 2008; Bornstein, 1991; Ozonoff et al., 1998) compared to a control group. However, there are many factors that could have influence on this result.

TS itself could be the cause for a lower IQ in children with TS and we compared therefore the TS group with the control group. The control group was matched only partly to the TS group since a life-time history of OCD or ADHD was an exclusion criterion for the control group. This exclusion of a comorbid condition could have contributed to higher IQ scale levels in the control group.

Surprisingly, the presence of comorbidity did not significantly influence IQ scores in our study. A post-hoc analysis revealed a slightly higher IQ scores in TS comorbid with OCD. This effect was also seen in other studies that found positive correlations between obsessive-compulsive symptoms in individuals with TS and IQ measures (Bloch, Peterson et al., 2006; Peterson, Pine, Cohen, & Brook, 2001). The influence of a comorbid ADHD condition in subjects with TS is contradictory. Some studies found that patients with TS and comorbid ADHD had a lower performance IQ (Dykens et al., 1990), full scale IQ (Faraone et al., 1993), another study found no difference in children with TS and ADHD concerning full scale IQ, verbal IQ and performance IQ (Yeates & Bornstein, 1994).

Socio-economic status has an influence on cognitive performance. The TS group and the control group in our study were matched for SES and we found no statistically differences in SES between the groups.

Moreover, some studies suggest an association between tic severity and cognitive performance (Bornstein, 1991; Ozonoff et al., 1998; Peterson, Pine et al., 2001) but those results are not definite (Hagin et al., 1982) and in our study, we did not find a correlation between tic severity and IQ.

Children with TS without medication showed a difference in full-scale IQ score, but they scored not significantly different compared to the control group in performance IQ and verbal IQ. This replicates previous investigations on TS which suggest that medication does not improve cognitive performance on
neuropsychological test (Bornstein, 1991; Bornstein & Yang, 1991; Ferrari, Matthews, & Barabas, 1984).

However, small sample size and thus low statistical power may explain the differences between the TS and the control group.
4. Conclusion and Suggestion for Future Research

This study confirms that children with TS perform on the same level of inhibitory control as matched controls. Although boys with TS in this study showed a trend toward slower reaction times compared to controls, we did not find a statistical difference for the specific measure of PES. Slower reaction times in the TS group may be the result of a SATO toward slower reaction times in order to maintain same performance. Identification of deviant measures in the performance monitoring system and mechanisms of adaptation in children with TS is relevant for understanding the course of the disorder and for developing appropriate therapies and such studies should in the future include larger samples and more sensitive measures, such as EEG/ERP measures or fMRI.

Treatment decisions in psychiatry per today are almost always based on patient symptoms reports. In TS, most treatment options in TS have considerable side-effects and the patients frequently stop their medication due to these unwanted effects. Lately, evidence is emerging that other, none-drug, cognitive-behavioral treatment options may have good effect in certain patients; however, the field lacks algorithms that help to evaluate the patients’ eligibility for one or the other treatment option. To reach this long time goal of developing better treatment decisions, we propose the exploration of a combination of (endo)phenotypes in Tourette syndrome, which seem promising for predicting treatment approaches. Mapping these underlying mechanisms in children with TS will in the future hopefully contribute to develop and to measure treatment approaches that take into account the child's ability of self-regulation, which in the case of TS consists of tic-suppression. Specifically in the case of TS, we see the clinical relevance of studies combining clinical information with behavioural performance, electrophysiological and imaging data for the following areas:

1. Knowledge of these measures may help to develop more adequate treatment algorithms. Patients that have good cognitive control functions may respond better to cognitive-behavioral treatment approaches that require a high amount of self-monitoring, such as habit reversal training (Himle et al., 2006).
2. Establishing a baseline and gathering information concerning cognitive control processes may be important for the evaluation of drug-treatment (e.g. to test the clinical impression that certain drugs, such as neuroleptics may worsen cognitive control in children with TS (Jocham & Ullsperger, 2009). Further we want to propose the use of questionnaires, which help to correlate data from the endophenotypes with clinical measures. Finally, we aim to classify patients and non-patients with help of multimodal models that take into account the whole spectrum of the collected data, in a translational approach ranging from clinical data to electrophysiology and imaging.
VII. References


event-related brain potentials show similar mechanisms [correction of mechanisms] of frontal inhibition but dissimilar target evaluation processes. 

*Behavioural Neurology, 14*(1-2), 9-17.


Proceedings of the National Academy of Sciences of the United States of America, 100(8), 4684-4689.


VIII. Appendix

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4. Reference Notice

Parts of the present work were published in the paper below:

5. Eidesstattliche Erklärung

Hiermit erkläre ich, daß ich die vorliegende Dissertation selbständig verfaßt und keine anderen als die angegebenen Hilfsmittel benutzt habe.

Die Dissertation ist bisher keiner anderen Fakultät vorgelegt worden.

Ich erkläre, daß ich bisher kein Promotionsverfahren erfolglos beendet habe und daß eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

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**Submitted/In preparation**


**Conference presentation**


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GO/NOGO PERFORMANCE IN BOYS WITH TOURETTE SYNDROME

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This study compared performance and performance monitoring in 19 boys with Tourette syndrome (TS) (12.64 years, ± 2.05) and 19 age-matched controls (13.16 years, ± 2.29) using a Go/NoGo task. The results indicated similar performance accuracy in the TS group and the control group. TS participants showed slower correct responses than the control group, whereas error response times were not different between the groups. The results are discussed with reference to inhibitory adaptive effects that may be employed by TS participants to maintain high accuracy at the cost of overall slower performance. These effects may be suspended prior to errors.

Keywords: Children; Tourette syndrome; Cognitive control; Inhibition.

INTRODUCTION

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by multiple motor tics and at least one vocal tic that have persisted for more than one year (American Psychiatric Association, 1994). Tic severity usually increases until 10–12 years of age and is followed by an attenuation of symptoms during or after puberty (Swain, Scahill, Lombroso, King, & Leckman, 2007), parallel with an increase in self-regulatory control in other domains during adolescence.

Literature regarding performance in inhibitory control tasks in patients with TS is not definite. Children with TS were inferior to an age-matched control group in the interference condition of a flanker task (Crawford, Channon, & Robertson, 2005). Deficiencies in inhibitory control have, however, been linked to comorbid disorders, including attention deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) and it remains unclear how far those findings reflect deficits specific to

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TS or due to comorbidity (Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2005). Children with TS were not impaired in discriminating targets and nontargets in a continuous performance test; although they showed slower reaction times (RT) compared to a control group (Shucard, Benedict, Tekok-Kilic, & Lichter, 1997). Several other studies have found comparable inhibitory control in children and adults with TS and in controls (Hershey et al., 2004; Ozonoff, Strayer, McMahon, & Filloux, 1994; Plessen et al., 2007; Roessner, Albrecht, Dechent, Baudewig, & Rothenberger, 2008; Watkins et al., 2005).

Moreover, several lines of research even suggest that children with TS may exert enhanced inhibitory control in performance monitoring. Children with TS are superior than controls in directing their eye movements (Jackson, Mueller, Hambleton, & Hollis, 2007; Mueller, Jackson, Dhall, Datsopulos, & Hollis, 2006). In addition, tic suppression may involve elements of performance monitoring, because it activates the same prefrontal brain regions as in typical inhibitory tasks requiring performance monitoring (Peterson et al., 1998). Further, the increased dorsolateral prefrontal cortices and their inverse correlation to tic severity in children with TS (Peterson et al., 2001) suggest that parallel processes may be involved in performance monitoring and in tic suppression. Specific mechanisms relating performance monitoring and tic suppression, however, have not been demonstrated yet and existing studies have not examined measures of performance monitoring such as PostError slowing (PES) as an equivalent to error adaption in persons with TS.

The capability to monitor performance usually refers to the ability to guide information processing and behavior in the service of a specific goal by continuously checking whether the action goals have been reached and adjusting behavior to optimize action outcome (Carter & van Veen, 2007; Ullsperger, 2006). This error-monitoring system tracks unfavorable outcomes and signals the need for appropriate behavioral adjustments (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007) to optimize goal-directed behavior (Botvinick, Cohen, & Carter, 2004; Holroyd et al., 2004).

We thus tested performance accuracy and RT in a group of young TS patients compared with a matched control group with a Go/NoGo paradigm. We hypothesized (a) that participants with TS would perform more accurate in a Go/NoGo task and (b) that they would exhibit more prominent PES compared to age-matched controls as a result of enhanced performance monitoring.

METHODS

Participants with TS were recruited from the Department of Child and Adolescent Psychiatry, Haukeland University Hospital, and from outpatient clinics in the greater Bergen area in the Hordaland County, Norway. Controls were matched for age and gender and recruited from local schools in the same geographic regions as the subjects with TS. The study was approved by the Regional Committee for Medical Research Ethics, West-Norway. The diagnostic procedure consisted of a semi-structured interview, the Kiddie-SADS (Schedule for Affective Disorders and Schizophrenia for School-Aged Children; Kaufman et al., 1997) in all participants. Children with TS met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria (DSM-IV; American Psychiatric Association, 1994) for TS. Tic symptoms were measured with the Yale Global Tic Severity scale (YGTSS; Leckman et al., 1989).

Comorbid disorders in the TS group were ADHD (n = 5) and OCD (n = 4). Nine boys in the TS group were taking medication, either neuroleptics (n = 4), alpha agonists (n = 2), selective serotonin uptake inhibitors (n = 1), or stimulants (n = 2). Controls were free of any
psychotropic medications. The groups differed in full-scale IQ (TS = 93.58 ± 9.72; Controls = 105.68 ± 9.49; t(36) = −3.88; p < .001, d = 1.26), and IQ was therefore employed as a covariate in the statistical analyses of group differences. Tic severity at the time of investigation in the TS group was 11.6 ± 2.9 for motor and 9.3 ± 3.5 for phonic tics, with lifetime-worst ever scores 15.2 ± 5.1 for motor and 13.5 ± 5.6 for phonic tics (possible range 0 to 25 in each category).

Sample size was limited to the first 20 subjects with TS who were referred consecutively to the study and who met the criteria for inclusion. After inspection of the Go/NoGo results, two outlying subjects, one from each group, were excluded, one due to fast RT at too low NoGo response accuracy (ACC) (25%) and one due to too slow RT at low NoGo ACC (70%). Thus, we included 19 boys with TS and 19 control boys with comparable age (TS = 12.64 years, ± 2.05; Controls = 13.16 years, ± 2.29; t(36) = 0.738; p = .46, d = 0.24) and with socioeconomic status.

After verbal and written instruction, participants performed a PC-based test (platform: E-Prime 1.0, PST): where pink (75% frequency) and blue (25% frequency) circles appeared in random order on a PC screen. On-screen stimulus duration was 150 ms. Participants were instructed to press a key with the appearance of a pink circle as fast as possible (Go) and to withhold the response with the appearance of a blue circle (NoGo). Stimuli were presented in four blocks with 48 trials/block and with varying interstimulus interval (ISI) between 500 and 1250 ms.

All statistical analyses were performed in Statistica v. 8 (StatSoft, 2008) or SPSS v. 15 (SPSS, 1999). Accuracy was tested using a univariate analysis of covariance (ANCOVA) with accuracy of the NoGo response as a dependent variable, “Diagnosis” as a between-groups factor, and “Age” as a covariate.

Group differences in PES times were tested using a general linear model (GLM) with repeated measures using a model that included the within-subjects factors “Trial” with four levels (RT Go, RT PreError, RT NoGo Error, RT PostError) and the between-subjects factor “Group” (TS, Controls) and “Age” as a continuous covariate. Full IQ scores were also considered as a covariate in the GLM. All two-and three-way-interactions of “Group,” “Trial,” and “Age” were tested. Differences in PES between groups were tested with the “Group-by-Trial” term in the model. Age variations of group-differences in RT time were tested with the “Group-by-Trial-by-Age” interaction term.

In order to assess the effects of comorbidity and medication in the TS group, the analyses were repeated while excluding participants in the TS group that had a comorbid ADHD (remaining n = 14) or OCD (remaining n = 15), and excluding participants with TS on medication (remaining n = 10), compared with the control sample (n = 19).

Correlations of NoGo ACC, “Go,” and “NoGo Error” RT with age were explored separately in each group by calculating the Pearson correlation coefficient r.

Using the Pearson correlation coefficient, we explored the presence of a Speed-Accuracy Trade-Off (SATO) in both groups, in order to gather information concerning adaptive mechanisms.

RESULTS AND DISCUSSION

Accuracy of NoGo Measure

The ANCOVA revealed no difference of accuracy on NoGo trials between the two groups, F(1, 35) = 1.96, p = .17, η = 0.04, with an average of 62.8% ± 0.038 in the Controls.
and 68.0% ± 0.038 in the TS group, and a significant covariation with age, $F(1, 35) = 12.6; p < .01, \eta^2 = 0.25$.

**PostError Slowing**

The model revealed a nonsignificant trend of “Group,” $F(1, 35) = 3.02 ; p = .09, \eta^2 = 0.05$, and a nonsignificant interaction between “Trial-by-Group” (see Figure 1A). Moreover, “Age” was retained in the final model, $F(1, 35) = 0.08; p = .77, \eta^2 = 0.001$. “Age” and “Trial” had a significant two-way interaction, $F(3, 105) = 3.04; p < .05, \eta^2 = 0.02$. “IQ” was eliminated from the model, because it did not reach significance as a main-effect or in interactions with “Group” or “Age.” The “Group-by-Trial-by-Age” interaction was not significant.

A post hoc assessment revealed that the boys with TS showed a trend toward slower RT (RT Go $p = .06$, RT PostError $p = .07$). Direct comparison in a two-sample $t$-test with unequal variances showed a significant difference in Go RT between the groups, $t(1,36) = -2.1; p < .05, d = 3.0$, with slower RT for the TS group (see Table 1).

Excluding participants with comorbid ADHD, those on medication and with OCD did not alter main results. “Group” and “Trial-by-Diagnosis” remained nonsignificant. IQ as a covariate in the model did not show a significant influence on RT at the different trial types.

ACC for NoGo trials was correlated with age in both groups ($r = .48, p = .04, r^2 = .23$ in TS, $r = .55, p = .015, r^2 = .3$ in controls), whereas RT for Go trial and erroneous NoGo trials were not age correlated. (see Figure 1B).

For the SATO, the overall sample showed a significant correlation of ACC and RT (overall sample: $r = .46, p = .004, r^2 = .21$; Controls: $r = .52, p = .022, r^2 = .27$), while only reaching trend levels in the TS group ($r = .39, p = .099, r^2 = .15$) (see Figure 1C).

We found that children with TS were capable of inhibiting an automated response tendency but not better than control group. Second, the RT after an error were comparable in the children with TS and the controls, but children with TS had a trend toward a longer RT across all types of trials.

Boys with TS had a slower RT for all four trial types compared with the control group. This main effect was weakened by the relatively faster NoGo trials in the TS group, which may indicate an intermittent suspension of the inhibitory mechanisms in this group. Boys with TS, however, were not specifically slower in postError trials, resulting in no distinct effects on postError adaptation. In tasks performed with accentuation to response speed, however, PES can be decreased or absent, as a result of time pressure (Ullsperger, 2006). Future studies should, therefore, consider different feedback manipulations and paradigms that allow for corrective behavior such as second key presses after erroneous responses.

Adjusting the SATO to slower response times to maintain the same or even better accuracy in cognitive demanding situations is an adaptive mechanism in inhibitory experiments. The less pronounced SATO in our sample with TS may be a result of high variability of performance in the TS group. As shown in Figure 1C, more boys in the TS group had a higher accuracy (above 80%) and a higher proportion in the TS group had slower RT (above 300 ms). The effect was, however, cancelled out due to high variability in the group. Thus a subgroup of children with TS had a higher SATO compared to the controls, which goes well along with the frequent clinical perception of slowness in children with TS. It would be important to identify this subgroup with respect to indication
Figure 1 (A) PostError slowing (PES). Reaction times on RT Go, RT PreError, and RT PostError show that the subjects increase their speed before an error (RT NoGo Error) and slow it down after an error. The RT in the solid line represents the TS group; the RT in the dotted line represents the control group. (B) Dependence of NoGo Accuracy. The accuracy of NoGo correlated positively in both groups with age. (C) Speed-Accuracy Trade-off (SATO). The RT NoGo Error correlated with ACC NoGo in both groups.
for nonpharmacological therapies, such as Habit Reversal Training (Himle, Woods, Piacentini, & Walkup, 2006) that depend on performance monitoring.

In conclusion, boys with TS perform on the same level of inhibitory control as the controls but do not exert more corrective behavior, such as PostError slowing. Slower RTs may be the result of a SATO effect toward a slower RT in a subgroup of boys with TS to maintain the same performance level. Along the same lines, a recent functional magnetic resonance imaging (fMRI) study showed that children with TS, although showing an equal behavioral performance, activated the left prefrontal cortex more than the controls during a cognitive demanding task (Baym, Corbett, Wright, & Bunge, 2008). Exploration of the performance monitoring system and mechanisms of adaptation in children with TS is relevant for understanding for developing appropriate therapies. In the future, the integration of more sensitive measures, such as EEG/ERP measures or fMRI, could contribute to defining the mechanisms of performance monitoring in TS beyond behavioral characteristics.

Table 1 Reaction Times in Children with Tourette Syndrome (TS) and Control Children (Mean and Standard Error of the Mean [SEM]).

<table>
<thead>
<tr>
<th></th>
<th>TS (mean ± SEM)</th>
<th>Controls (mean ± SEM)</th>
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<tbody>
<tr>
<td>RT Go</td>
<td>355.77 ms ± 10.55</td>
<td>324.22 ms ± 10.55</td>
</tr>
<tr>
<td>RT NoGo</td>
<td>284.65 ms ± 9.35</td>
<td>265.81 ms ± 9.35</td>
</tr>
<tr>
<td>RT PreError</td>
<td>335.03 ms ± 13.35</td>
<td>311.39 ms ± 13.35</td>
</tr>
<tr>
<td>RT PostError</td>
<td>359.72 ms ± 14.31</td>
<td>328.84 ms ± 14.31</td>
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REFERENCES


