

Electrophysiological Correlates of Performance Monitoring in Children with Tourette Syndrome

A developmental perspective

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Scientific environment

During my work with this thesis, I have been part-time employed as a PhD student at the Department of Biological and Medical Psychology, University of Bergen. I have been enrolled in the International Graduate School on Integrated Neuroscience *IGSIN* at the Faculties of Psychology and Medicine, University of Bergen.

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My main supervisor has been Kerstin von Plessen, with co-supervisors Kenneth Hugdahl and Ingvar Bjelland. Kerstin von Plessen is affiliated with the Child and Adolescent mental Health Centre, Mental Health Services Capital Region, Copenhagen, Denmark and Department of Clinical Medicine, Faculty of Health and Medical Science, University of Copenhagen, Denmark.

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Abstract

Tourette syndrome (TS) is a neuropsychiatric disorder with childhood onset, characterized by chronic motor and vocal tics. Typically, tic symptoms attenuate during adolescence in parallel with the emerging self-regulatory control during brain development. The voluntary control over thought and action provides the ability to withhold unwanted behaviour and an association between cognitive control and tic control has been suggested. This attenuation of tic symptoms also suggests that neuroplasticity may play an important role in this process. The work discussed herein is centred on how compensatory mechanisms may affect dysfunctional neurocognitive processes, specifically performance monitoring deficits in children and adolescents with TS.

In **paper I**, we have summarized current knowledge on neural plasticity in children and adolescence with TS. To present the current understanding of dysfunctional neurocognitive processes seen in functional magnetic resonance imaging and possible compensatory effects seen in anatomical magnetic resonance imaging in TS, we conducted an overview of data from studies comparing children with TS to healthy peers. In order to assess the importance of possible adaptive effects in paediatric TS, we reviewed with special attention to covariation with tic severity. The summary revealed differences in brain regions representing the tic origin along with deviations in other regions that might represent activity-dependent activation that help to modulate tic severity in TS compared with controls. Age, comorbidity with other developmental disorders, especially with attention deficit/hyperactivity disorder (ADHD), medication use, and intelligence were identified as factors that potentially influence the development of adaptive changes. Comparative analyses or meta-analytic approaches are thus far difficult due to inherent differences in study-design, magnetic resonance imaging techniques for acquisition, and analysis of primary data. The paper highlights the importance of studying cognitive control and adaptive effects in TS, while also revealing the scarcity of studies with longitudinal design and other modalities, as e.g. electrophysiology.

The two next papers are based on the electrophysiological data collected to better understand the origins of cognitive control and performance monitoring deficits in TS. The main aim of **paper II** was to test an established experimental setup of performance monitoring in order to identify if behavioural and electrophysiological performance monitoring differences occur in children with TS when compared to controls and a contrast group with children with ADHD at the age of 8-12 years. We employed event-related potentials (ERP) in order to monitor stimulus-related and response-related components elicited during a flanker task. The main findings of this investigation indicate that the children with TS and children with ADHD and healthy controls behaviourally performed much the same regarding reaction times, accuracy and response variability when controlling for covariates. However, when not controlling for relevant covariates, children with TS and children with ADHD performed on a slightly lower level. ERP results showed higher amplitudes of an early P3 component of the stimulus-locked potentials in ensemble averages and in separate trial outcomes, as well as a slightly higher positive complex before the motor response, likely reflecting a late P3 in children with TS when compared to controls and children with ADHD. We interpreted the differences as mainly caused by heightened attentional resource allocation during stimulus evaluation. Groups did not differ in post-response components. These findings thus suggest that children with TS may employ additional attentional resources as a compensatory mechanism to maintain equal behavioural performance.

While paper II focused on disentangling the role of sub-processes of performance monitoring in children with TS, **paper III** was more focused on the developmental changes in performance monitoring which might help the understanding of tic regulation and attenuation over time in children and adolescents with TS. To this end, we compared task performance and ERP components from the first assessment with a follow-up ERP study administered on average 4.5 years later in the same population using regression models. The results from this investigation indicated that cognitive measures of children with TS approached the values found in controls at the second assessment while differences between children with ADHD and controls largely persisted. ERP measures related to orienting and sustained

attention, that developed earlier in children with TS compared with controls at the first assessment converged with maturation and correlated with worst-ever tic scores.

In summary, the research described in this thesis contributes to the further understanding of *electrophysiological correlates of performance monitoring in children with Tourette syndrome* in several ways. In **paper I**, we found the current literature to implicate dysfunctional neurocognitive processes and possible compensatory effects in children with TS. The use of a neurocognitive model of performance monitoring in **paper II** suggested heightened orienting and/or attention requirements during stimulus evaluation as a compensatory mechanism to maintain equal behavioural performance. The developmental approach in **paper III** allowed us to find evidence of converging cognitive and electrophysiological measures over time in children with TS when compared with controls as well as correlation between ERPs and worst-ever tic scores. The main results from each of the papers presented continue to implicate compensatory self-regulation mechanisms during early adolescence, probably facilitating tic suppression. Correlations between ERP amplitudes and tic scores also support this notion.

List of publications

- Eichele, H., & Plessen, K. J. (2013). Neural plasticity in functional and anatomical MRI studies of children with Tourette syndrome. *Behavioural Neurology*, *27*(1), 33-45. doi:10.3233/BEN-120294
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List of abbreviations

ADHD	attention-deficit/hyperactivity disorder
CBIT	comprehensive behavioural intervention for tics
CBT	cognitive behavioural therapy
CSTC	cortical-striato-thalamo-cortical
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
EEG	electroencephalogram
ERN	error-related negativity
ERP	event-related potential
fMRI	functional magnetic resonance imaging
FSIQ	full-scale intelligence quotient
HRT	habit reversal training
ICA	independent component analysis
IQ	intelligence quotient
LPC	late positive complex
MeSH	Medical Search Headings
MRI	magnetic resonance imaging
OCB	obsessive-compulsive behaviour
OCD	obsessive-compulsive disorder

Pe	error positivity
RT	reaction time
SDRT	reaction time variability
SMA	supplementary motor area
SSRI	selective serotonin reuptake inhibitor
TMS	transcranial magnetic stimulation
TS	Tourette syndrome
YGTSS	Yale Global Tic severity scale

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1. Introduction

1.1 Tourette syndrome

1.1.1 Overview

Tourette Syndrome (TS) is a neurodevelopmental disorder with a typical onset in early childhood around 3 to 8 years (Leckman, 2002), and approximately 0.8 - 1 % of school-aged children are affected (Knight et al., 2012; Robertson, 2003). TS is characterized by the combination of multiple motor tics and at least one vocal tic for more than 1 year, although not necessarily concurrent, in the absence of secondary causes and with onset before 18 years (American Psychiatric Association, 2013). Tics are sudden, rapid, repetitive and non-rhythmic movements or vocalizations that resemble voluntary actions (Ganos, 2016). Usually, tics appear in form of bouts with tic-free intervals, are waxing and waning in intensity, frequency, and severity over weeks and months (Peterson & Leckman, 1998); they can change character and may persist during sleep. Tics can be present as simple tics that involve a single muscle/muscle-group and complex tics that resemble goal-directed behaviour without the obvious purpose. They can also be categorized as clonic (duration shorter than 100 ms) or tonic/dystonic tics (duration more than 300 ms) (Cath et al., 2011). Further, tics can be divided in motor tics if they lead to a movement or vocal (phonic) tics if they generate a sound. Motor tics usually precede the onset of vocal tics by several years (Leckman, 2002) and often involve muscles in the head, face or neck in form of simple tics like eye blinking, facial grimacing, head jerks. The manifestation of tics typically follows a rostrocaudal gradient (Ganos & Martino, 2015) and as childhood progresses, motor tics can also involve other regions of the body, as well as show an increase in complexity, frequency and severity. Vocal tics commonly start as simple tics including coughing, throat clearing, humming, sniffing and often worsen over time into more complex vocalizations, such as words and phrases, repetition of vocalization made by others (echolalia) or by themselves (palilalia). About 14-20% of TS patients experience vocal tics of involuntary uttering socially inappropriate words

or sounds (coprolalia), or motor tics of involuntary performance of obscene gestures (copropraxia) (Freeman et al., 2009), the symptoms for which the condition seems to have become predominantly known. Tic severity for both motor and vocal tics is often exacerbated by stress, fatigue, anger and changes in temperature (Bloch, 2008).

Tics are often described as semi-voluntary and self-directed as they may be suppressed for a certain amount of time at the cost of increasing discomfort for the patient (Cath et al., 2011). However, tic suppression is strenuous, and allowing the tic to unfold, reduces the unpleasant bodily sensation, which is preceding a tic, the so-called “premonitory urge” (Leckman, 2002). Awareness of these sensory phenomena seems to appear with a lag of three years after tic onset (Leckman, Walker, & Cohen, 1993), is tic-dependent (Leckman, Bloch, King, & Scahill, 2006) and age-dependent (Banaschewski, Woerner, & Rothenberger, 2003). The reduction of the unpleasant feeling that follows a tic performance may contribute to a negative reinforcement of performing the tic habit (Plessen, 2013).

The natural course of TS is characterized by an increase of tic severity until the age of 10-12 years, following an attenuation of tic symptoms during or after puberty such that about 80% of patients no longer experience impairments from tics by the age of 18 (Cath et al., 2011). The reduction of tic symptom severity with age happens at the same time as brain systems for self-regulatory control develop during adolescence (Davidson, Amso, Anderson, & Diamond, 2006; Tau & Peterson, 2010), particularly the maturation of the frontal cortex (Gogtay et al., 2004). This may thus suggest that the basis of the condition is a developmental diversification rather than a progressive disorder (Singer & Minzer, 2003). Which developmental factors and neural mechanisms are responsible for modulation of tics during adolescence is an important question, because research leading to the identification of these factors may improve existing treatment options, or lead to the development of new strategies (Spessot, Plessen, & Peterson, 2004). Mapping the neurophysiological underpinnings of these mechanisms and how these factors specifically act on brain development in individuals with TS is crucial. Furthermore, a better understanding of the alterations

of neural development of individuals with TS may also lend insight into general mechanisms of brain development in adolescents.

The topics of this dissertation include measures of brain electrophysiology, as well as an overview of adaptive and plastic processes seen in structural and functional neuroanatomy in young people with TS.

1.1.2 Aetiology

A number of risk factors are frequently considered to account for the variable expression of tic disorders. Genetic factors are thought to be responsible for familial vulnerability to TS and related disorders (Pauls, 2003). Heritability of TS was initially assumed to be autosomal dominant (Pauls & Leckman, 1986), recently however the putative genetic mechanisms have been considered heterogeneous and based on a polygenetic aetiology (Robertson, Althoff, Hafez, & Pauls, 2008). Twin studies have pointed to both genetic and non-genetic factors, and finally genetic association studies have initially reported findings from most chromosomes (2, 3, 4, 5, 8, 9, 10, 11, 13, 17, and 19) (as cited in (Robertson et al., 2008)). However, replication studies with larger samples are thus far missing. In one study (Abelson et al., 2005) a frameshift mutation and sequence variants in *Slit* and *Trk-like 1* (*SLITRK1*) gene on chromosome 13q311 was found in three of 174 unrelated TS patients, but not in 3600 controls. However, several studies (Deng, Le, Xie, & Jankovic, 2006; Verkerk et al., 2006; Wendland, Kruse, & Murphy, 2006) reported a lack of specificity, or failed to replicate this finding. Therefore, while there seems to be an association to TS (Miranda et al., 2009), these two particular DNA changes are unlikely causal in Tourette syndrome (Keen-Kim et al., 2006; Scharf et al., 2008). Recently, association between the histamine decarboxylase (*HDC*) gene and TS onset has been found in Canadian, German, and Italian samples, providing support for the histaminergic hypothesis in TS aetiology and point to a possible role of histamine pathways in neuronal development (Karagiannidis et al., 2013). With the increasing accessibility and reduced cost of powerful genetic analysis techniques, such as genome/exome sequencing, more work is needed to explore the genetic and epigenetic mechanisms that cause the variable TS phenotype (Robertson, 2012).

A set of epi-genetic factors is thought to play a role 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 it is well known that tic symptoms exacerbate following a stressful life-event (Leckman, 2002). Stress-related neurotransmitters and hormones, such as corticotropin-releasing factor, have also been found in higher concentrations in cerebrospinal fluid of patients with Tourette syndrome (Chappell et al., 1996). While this not specific to TS, as similar associations have been described for other neuropsychiatric conditions during childhood, these findings suggest that stress-related neurobiological mechanisms may confer a vulnerability to TS. Additionally, children with low birthweight, perinatal hypoxic events, maternal stress and also extreme maternal 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 also increase risk of the manifestation of TS (Leckman, 2002).

The male-to-female ratio of TS is 4.3:1 (Bruun & Budman, 1997; Freeman et al., 2000), and the increased male preponderance 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). Some clinical traits of TS may support this notion: 1. tic severity typically increases in pubescence, when gonadal androgen production increases in both males and females, 2. androgen drug administration in adults exacerbates tic symptoms and severity (Leckman & Scahill, 1990), and 3. blocking of androgen receptors can attenuate tic severity in some individuals (Peterson et al., 1994). Of note, girls with TS tend to show increased masculine play preferences, while boys with TS showed a heightened masculine play pattern, which correlated positively with symptom severity (G. M. Alexander & Peterson, 2004). Frequent male-to-male transmissions within families seem to rule out the presence of an X-linked vulnerability gene (Leckman, 2002).

A post-infectious aetiology has been suggested for some cases of TS, but the literature is not clear to date. An autoimmune response after β -haemolytic streptococcal infections was reported to trigger onset and exacerbation of tics and associated behaviour (Swedo et al., 1998). However, the link between autoantibodies and the specific neurochemical changes described involving dopaminergic and possible serotonergic abnormalities remains a topic of debate (A. J. Church, Dale, Lees, Giovannoni, & Robertson, 2003; K. Harris & Singer, 2006; Wolf & Singer, 2008).

1.1.3 Clinical Assessment and Diagnosis

The diagnostic criteria for TS currently in use are described in *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (World Health Organization, 1992) and in the *Diagnostic and Statistical Manual of Mental Disorders: DSM-5* (American Psychiatric Association, 2013).

Initially, the clinical diagnosis is based on both of the child's report, and the observations of caregivers and clinicians. Typically, clinician, family and child together work to reconstruct the child's history and present level of function to determine appropriate treatment approaches (Leckman, 2002). During consultations, assessment and quantification of tics can be difficult due to variation of tics over time or due to the patients' suppression of tics. Therefore, it can be helpful to include other information from teachers, direct observations at home/school or videotape tic monitoring (Cath et al., 2011). To complete the picture, it is useful to map comorbidities and how tics interfere with the child's emotional, social, familial and school experiences to get an impression of the global functioning of the child (Leckman, 2002). Both motor and vocal tics can persist during all stages of sleep, although much attenuated, and can cause sleep disturbances (Rothenberger et al., 2001). Tics can also be misread as akathisia, tardive dyskinesia, stereotypes or other hyperkinetic or psychogenic movement disorders (Swain, Scahill, Lombroso, King, & Leckman, 2007), but can be differentiated from other hyperkinetic movement

disorders (with exception of akathisia and psychogenic movement disorder), if patients are able to suppress the movements (Jankovic, 2001) and if patients experience tics as a voluntary movement to relieve an inner tension (Cath et al., 2011). A physical examination is important for distinguishing TS from other movement disorders, such as myoclonic dystonia, epilepsy, or stereotypies. The evaluation should include an Electroencephalogram (EEG) and structural neuroimaging in cases where the presentation of symptoms or age is not typical (Cath et al., 2011).

Patient and parent education helps to recognize recurrent behaviours as tic symptoms (Leckman, 2002). To ascertain all important symptoms and conditions of patients with tics, a standardized clinical psychiatric interview should be used, such as the *Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present/Lifetime* (K-SADS; Kaufman et al., 1997) or other structured interviews (Cath et al., 2011). Additionally, an instrument measuring likelihood of having Tourette syndrome can be used, such as the *Diagnostic Confidence Index* (Robertson et al., 1999) together with checklists on tic characteristics and severity with information from both the patient and the parents, as e.g. the *Yale Global Tic Severity Scale* (YGTSS; Leckman et al., 1989). Tic severity and tic symptoms may also be assessed 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). Premonitory urge symptoms can be registered with the help of the *Premonitory Urge for Tics Scale* (PUTS; D. W. Woods, Piacentini, Himle, & Chang, 2005).

Another important aspect of the initial evaluation is to check for the presence and severity of co-occurring disorders with Attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) being the most common ones. Those associated disorders often cause disturbing symptoms and the standard work-up of patients with TS should therefore also include a standardized diagnostic procedure and dimensional specific questionnaires, such as e.g. the *Children's Yale-Brown*

Obsessive Compulsive Scale for OCD symptoms (Goodman et al., 1989) or the *Conners' Parent rating scales* (Conners, 1997) for ADHD symptoms. It is also important to map symptoms of depression and anxiety (Burd, Freeman, Klug, & Kerbeshian, 2005).

1.1.4 Comorbidity

Comorbid disorders are rather the rule than the exception in children with TS. Approximately 90% of TS patients have a co-occurring condition, with ADHD and OCD being the most common (Robertson, 2012). However, other conditions like sleep disorders, anxiety, depression or learning difficulties are frequent as well and can influence the patient's neuropsychological profile with psychosocial, educational, and neuropsychological consequences (Como, 2001).

ADHD, characterized by hyperactivity, inattention and impulsivity is observed in about 60% of children with TS syndrome (Robertson, Banerjee, Eapen, & Fox-Hiley, 2002). Problems with externalizing symptoms and psychosocial functioning occur more frequently in children with comorbid ADHD (A. S. Carter et al., 2000; Gorman et al., 2010; Sukhodolsky et al., 2003), while children with pure TS showed internalizing symptoms (A. S. Carter et al., 2000). Problems with academic skills, especially concerning writing (Como, 2001) and other learning disabilities (Burd et al., 2005) have been found to be primarily related to co-existing ADHD. Problems with executive functions are thought to primarily stem from the ADHD symptoms (Roessner, Becker, Banaschewski, & Rothenberger, 2007) due to distractibility and impulsivity, and early reports suggesting executive function deficits to be specific to TS may not have controlled sufficiently for comorbid ADHD condition (Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2005).

Up to 50% of all TS patients have obsessive compulsive symptoms (Bloch & Leckman, 2009; Swain et al., 2007) with an onset around puberty when tics reach the worst-ever level, but also later in adulthood (Bloch & Leckman, 2009). OCD and TS are thought to share a similar underlying genetic vulnerability (Pauls, 2003; State et al., 2003). However, some clinical features of OCD appear quite differently in

patients with TS from those seen in patients with primary OCD (Cath et al., 2001; Como, LaMarsh, & O'Brien, 2005; Eapen, Robertson, Alsobrook, & Pauls, 1997). Generally, the consensus is that individuals with TS tend to have more forced touching, counting, repeating, ordering and self-harm compulsions and violent, miscellaneous, sexual and symmetrical obsessions whereas contamination obsessions and cleaning compulsions are more common in OCD patients without comorbid TS (Cath et al., 2000; Miguel et al., 1997). However, a recent study suggests an alternative pattern where patients with tics and OCD show generally more OCD symptoms than OCD patients without tics (Hojgaard et al., 2016). Interestingly, obsessive-compulsive symptoms in individuals with TS correlate positively with intelligence quotient (IQ) measures (Bloch et al., 2006).

Although many patients with TS experience obsessive compulsive symptoms, severity of those symptoms may not be sufficient to meet the diagnostic criteria for OCD (Como et al., 2005). Further, it can be difficult to distinguish between complex tics and obsessive compulsive symptoms. Therefore, it has been suggested to refer to *obsessive compulsive behaviour* (OCB) which also includes the “just right” feeling that patients with TS frequently experience (Leckman, Walker, Goodman, Pauls, & Cohen, 1994). However, OCD/OCB often remains undetected in patients with TS and may impact family interactions and self-esteem of the child over years. Education of parents and children thus is an important aspect of TS and should comprise follow-up consultations, especially with regard to the later onset of OCD symptoms (Bloch et al., 2006).

Other comorbid conditions include self-injurious behaviour, personality disorders, oppositional defiant disorder, conduct disorder, and autism spectrum disorder and can significantly affect patient's overall quality of life (A. S. Carter et al., 2000; Eddy et al., 2011; Robertson, 2000). The exact relationship between TS and symptoms of depression or anxiety is still unclear and may be a biological condition either accompanying TS, or manifesting independently of TS, but could also be a result of psychosocial complications that children with TS may experience in academic or peer settings, or a complication of OCD, or other comorbidities

(Robertson, 2006). Notably, depressive symptoms are also seen as side effects of neuroleptic medication used in tic treatment.

1.1.5 Treatment

Since the focus of this thesis is on TS in childhood and adolescence, the following paragraph deals with treatment options suitable for children and adolescents, excluding therapy options not recommended for this age group. Children with TS typically experience social, educational and emotional impairments, which can impair their quality of life. This is exacerbated by comorbid conditions that affect the majority of children with TS in their everyday life. In mild cases, reassurance along with a “watch and wait strategy” (Roessner, Plessen, et al., 2011) and psychoeducation to the child, the parents and the teachers regarding accommodations in school settings can be sufficient to calm the situation and to reduce the tics. Psychoeducation provides relevant information about the condition and helps promoting coping strategies and self-efficacy, which goes in line with an increased tolerance for symptoms and stress reduction. In Norway, such information is available from the National Competence Centre for Neurodevelopmental Disorders and Hypersomnia (NevSom: <http://www.nevsom.no/>), and from the National Tourette Association patient support group (Norsk Tourette Forening: <http://touretteforeningen.no/>).

Although varied therapeutic strategies are available for TS, no intervention has been proven singularly effective for the multiple symptoms associated with TS. The goal of the treatment for children with TS should thus not be the complete elimination of tics, but to maximize social functioning and to ameliorate emotional burden. In addition to psychoeducation, behavioural interventions should be considered for persons with a clear impairment associated with the tic behaviour. Many behavioural treatment options are available including habit reversal training (HRT), comprehensive behavioural intervention for tics (CBIT), mass negative practice, awareness training and exposure and response prevention. HRT and exposure and response prevention are recommended as first line behavioural treatments in the

European guidelines (C. Verdellen, van de Griendt, Hartmann, Murphy, & Group, 2011).

HRT is a cognitive-behavioural intervention that has been shown to reduce tic severity in both adults and children with TS, e.g. (Deckersbach, Rauch, Buhlmann, & Wilhelm, 2006; Himle, Woods, Piacentini, & Walkup, 2006; Piacentini et al., 2010; Wilhelm et al., 2003; Wilhelm et al., 2012). HRT addresses one tic at a time and the core components of HRT are the awareness training of a tic occurrence followed by competing response practice, which the patient learns to initiate for a certain amount of time or until the urge goes away and social support. In summary, HRT is shown to be effective for both vocal and motor tics, for tic severity as well as tic frequency and without any symptom substitution. HRT is indicated for both children as well as adults independent of medication status in systematic studies of effect (D. W. Woods, Conelea, & Walther, 2007; D. W. Woods et al., 2011). CBIT utilizes relaxation training and behavioural rewards additionally to the core HRT components (D.W. Woods et al., 2008).

Exposure and response prevention is based on the assumption of a negative reinforcement circuit. The unpleasant feeling of a premonitory urge that is relieved by the performance of a tic acts as an impulse to complete a tic. Exposure and response prevention addresses all tics at the same time and aims at interrupting this vicious cycle of stimulus-response sequences through habituation to the premonitory experiences, thus resulting in tic reduction, without rebound-effect (C. W. Verdellen, Hoogduin, & Keijsers, 2007).

An earlier randomized-controlled study comparing HRT and Exposure and response prevention training sessions revealed no differences between treatment conditions, and concludes that tic symptoms can be treated effectively with both methods (C. W. Verdellen, Keijsers, Cath, & Hoogduin, 2004), however, only HRT and CBIT have consistently demonstrated efficacy (McGuire et al., 2014). HRT, CBIT and exposure and response prevention are good treatment options for patient with premonitory urges, however, the awareness of sensory phenomena seems not be

necessary for the ability of tic suppression (Banaschewski et al., 2003). Additionally, second line behavioural interventions, such as contingency management or function-based interventions should be considered when first line interventions do not show sufficient effects. Unfortunately, behavioural treatment options are less often used due to limited availability, access or lack of treatment response (C. Verdellen et al., 2011). Pharmacological treatment should be considered either additionally, or as first line intervention, if the tics are so disturbing that the child is experiencing functional impairment socially or emotionally, or if tics cause physical pain (Roessner, Plessen, et al., 2011).

Unfortunately, while several classes of antipsychotic medications are used, pharmacological therapy in TS is lacking evidence-based guidance. Haloperidol is still the only drug being formally licensed in Europe for the indication of TS or tics while all other medications are prescribed off-label based on limited study data. A recent systematic overview from United Kingdom comparing efficacy of pharmacological treatments (Whittington et al., 2016), concluded with a recommendation to start pharmacological treatment with α -2 adrenergic agonists (clonidine, guanfacine) due to their medium-sized effect on tic reduction and the relatively benign side effect profile. If α -2 adrenergic medications are ineffective or poorly tolerated, atypical antipsychotic drugs as risperidone and aripiprazole should be considered. This class of medication blocks both dopamine and serotonin receptors with less severe side effects than older antipsychotics (haloperidol, pimozide). In particular, aripiprazole shows promising effects in treatment-refractory patients with lower probability to induce weight gain (Roessner, Plessen, et al., 2011). The selective norepinephrine reuptake inhibitor atomoxetine also showed a positive influence on tics in patients with co-occurring ADHD, but with more severe side effects like cardiovascular adverse effects, liver injury, and increased risk of suicidal behaviour. Benzamides (Tiapride, Sulpiride) are considered beneficial due to their tolerability-efficacy-balance (Roessner, Plessen, et al., 2011), but their clinical efficacy and pharmacological properties are not sufficiently investigated in larger studies. Generally, due to the side-effect profile and the dynamic symptom patterns in

TS, pharmacotherapy should be monitored closely and drug holidays for patients receiving medication is a good way to re-evaluate the indication of the drug (Roessner, Plessen, et al., 2011).

Children with TS and 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 or OCB in children with TS, cognitive behavioural therapy (CBT) should be considered as a first-line intervention (Hojgaard et al., 2016; C. Verdellen et al., 2011) and pharmacological treatment with a selective serotonin reuptake inhibitor (SSRI), if CBT does not show the expected effect (Pediatric O. C. D. Treatment Study Team, 2004). A recent study found that continued CBT in children with OCD may be a viable option in CBT-non-responders and without the potential adverse effects of a pharmacological treatment (Skarphedinsson, Weidle, et al., 2015), however children and adolescents with TS and comorbid OCD, who are not responding to an initial CBT treatment, may profit more from SSRI treatment (Skarphedinsson, Compton, et al., 2015), or a combination of CBT and SSRI (Pediatric O. C. D. Treatment Study Team, 2004) than continued CBT alone. A meta-analysis of the dose-response relationship of SSRI suggested that 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, 2010).

The Tourette Syndrome Medical Advisory Board Practice Committee currently recommends α -2 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). This recommendation is supported by findings of a systematic review (Whittington et al., 2016) and the *European Society for the Study of Tourette syndrome* group (Roessner, Plessen, et al.,

2011). The combination of an α -2 agonist and a stimulant may improve treatment results (Debes, Hjalgrim, & Skov, 2009).

1.1.6 Pathophysiology: Generation and Suppression of Tics

The precise pathophysiological mechanisms underlying TS remain unknown, but the fact that both tics and voluntary actions can be suppressed leads to the assumption that tics are generated by the same pathways that are involved in the generation of voluntary actions (Ganos & Martino, 2015; G. M. Jackson, Draper, Dyke, Pepes, & Jackson, 2015), including the prefrontal cortex, thalamus, and basal ganglia (Leckman, Bloch, Smith, Larabi, & Hampson, 2010). These regions are connected by multiple parallel and 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, 1999). It is likely that dysfunctions of these circuits, especially within the cortical-striato-thalamo-cortical (CSTC) circuits which mediate the integration of movement, sensation, emotion and attention, and self-regulatory control (Marsh, Zhu, Wang, Skudlarski, & Peterson, 2007), are involved in the pathophysiology of TS (Albin & Mink, 2006; J. A. Church et al., 2009; Leckman, Vaccarino, Kalanithi, & Rothenberger, 2006; Raz et al., 2009; Robertson et al., 2017; Singer, 2005; Sowell et al., 2003; Spessot & Peterson, 2006), and especially in the suppression of tics (Gerard & Peterson, 2003; G. M. Jackson et al., 2015; Jung, Jackson, Parkinson, & Jackson, 2013). While the exact number of CSTC circuits still remains controversial, four seem to be important in the pathophysiology of TS: 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; Robertson et al., 2017). The CSTC circuits contain a wide spectrum of neurotransmitters. Although changes in the dopaminergic neurotransmission have been considered to be most likely through clinical treatment studies, research and post-mortem findings, variability in the tic phenomenology and in co-occurring disorders suggests that more than one neurotransmitter system may be involved, and affection in noradrenergic, glutamatergic, opioid, cholinergic, γ -

amino butyric acid-ergic, and serotonergic systems have also been implicated (Swain et al., 2007), especially the calibration of the excitatory–inhibitory balance through glutamate and γ -amino butyric acid has been pointed out (Draper et al., 2014; G. M. Jackson et al., 2015; Robertson et al., 2017). The basal ganglia mediate action selection, action gating, reward based learning, motor preparation, and timing of movements. Based on the neurophysiologic properties of the basal ganglia neurons, and it appears most likely that specific movement patterns result primarily from striatal activity, however other parts of the basal ganglia also seem to be involved (Albin & Mink, 2006). A simplified model of the CSTC circuit includes two different striato-thalamic pathways: a direct pathway with an overall excitatory effect that passes striatal information via the Globus pallidus internus and the Substantia nigra pars reticularis to the Thalamus, and an indirect pathway with an overall inhibitory effect that transports information from the striatum via the Globus pallidus externus and the subthalamic nuclei to Globus pallidus internus and the Substantia nigra pars reticularis to the Thalamus (Mink, 2003, 2006).

1.1.7 Observations from Neuroimaging

Over the last decades, neuroimaging studies of children with Tourette syndrome have shown a wide spectrum of both anatomical and functional brain alterations, including changes in: volume of grey and white matter structures, cortical thickness, diffusivity and connectivity between white matter structures as well as changes in functional connectivity and activity.

In anatomical magnetic resonance imaging (MRI) studies, cortical thinning of the sensorimotor, primary motor, and premotor cortices has been described in several studies in children with Tourette syndrome (Fahim et al., 2010; Sowell et al., 2008) as well as in adults (Draganski et al., 2010; Muller-Vahl et al., 2009; Worbe et al., 2010). 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), larger hippocampus and

amygdala (Peterson et al. 2008), thalami (Miller et al., 2010), putamen and corpus callosum (Roessner, Overlack, et al., 2011).

Diffusion tensor imaging (DTI) showed altered interhemispheric connectivity in children (Plessen, 2006) and adults with TS (Neuner et al., 2010). Changes in diffusivity have among others been described in the subcortical nuclei (Makki, Behen, Bhatt, Wilson, & Chugani, 2008), in corticostriatal pathways and fronto-striatal circuits (Govindan, Makki, Wilson, Behen, & Chugani, 2010), and in somatosensory pathways in children with TS (Thomalla et al., 2009).

Functional magnetic resonance imaging (fMRI) studies have reported that children with TS show changes in activation of fronto-striatal circuits during a Stroop task (Marsh et al., 2007), a Simon task (Raz et al., 2009), or during eye blinking inhibition (Mazzone et al., 2010). Other findings include activity alterations in the medial and lateral prefrontal cortex (S. R. Jackson et al., 2011; Marsh et al., 2007; Roessner et al., 2012), precentral gyrus and caudate nuclei (Roessner et al., 2012) and subcortical nuclei (Baym, Corbett, Wright, & Bunge, 2008).

In conclusion, neuroimaging studies in children with TS have shown somewhat diverse findings and certain identification of an endophenotype has not been possible so far, probably due to inherent differences in sample sizes and heterogeneous study populations. Analytical differences may also play a role (Ganos, Roessner, & Munchau, 2013; Robertson et al., 2017).

1.2 Performance Monitoring

1.2.1 Overview

Performance monitoring is a broad area that includes conflict and error processing, and adaptive effects necessary for optimal task performance as e.g. attentional control, response selection, action facilitation and inhibition, as well as prevention of undesirable actions/outcomes (Ullsperger, Danielmeier, & Jochem,

2014; Wiersema, van der Meere, & Roeyers, 2007). While mechanisms underlying performance monitoring still are not fully understood, five psychological and neurobiological informed models have been suggested so far: mismatch theory, response conflict monitoring, reinforcement learning theory, action outcome prediction, and action value updating, in our work we primarily draw from the conflict monitoring literature (Ullsperger et al., 2014).

Our current understanding is that the performance monitoring system provides signals for adaptive optimization of goal-directed behaviour and signals the need for adjustments required in responses after errors and, more generally, whenever the action outcome is at risk (Botvinick, Cohen, & Carter, 2004; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007). These adjustments range from immediate compensatory mechanisms to long-term changes in behaviour and learning.

Action goals are tracked continuously and behaviour optimized to adjust action outcomes (C. S. Carter & van Veen, 2007; Ullsperger, 2006). In particular, brain responses to unfavourable outcomes and signals for subsequent adaptation have been studied (Ridderinkhof et al., 2004; Rushworth et al., 2007). Such adjustments are initiated by enhancing and updating context and rule representations, thereby optimizing goal-directed behaviour (Botvinick et al., 2004; Holroyd et al., 2004). Brain activation studies using event-related potentials (ERP), neuroimaging with functional magnetic resonance imaging, single- and multiunit 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 cortex including Brodmann area 8 produce error-related signals and thus play key roles for momentary adaptations such as post-error slowing and post-error reduction of interference (Ullsperger, 2006), whereas inferior frontal and midline parietal regions can be associated with more tonic maintenance of effort (T. Eichele et al., 2008) as e.g. increase in attention (Sarter, Gehring, & Kozak, 2006).

The existing work on neuropharmacology of performance monitoring suggests a dominant role of dopaminergic circuits (Ullsperger et al., 2014). However, it has been considered to be most likely that also other neurotransmitter as serotonin, norepinephrine, adenosine and γ -amino butyric acid are involved (Jocham & Ullsperger, 2009). A recent model suggests that also acetylcholine plays a key role in cortical excitability and attentional performance (Sarter et al., 2006). This draws interesting parallels to pathways that are affected in TS.

Outside of the narrow parameters of laboratory settings, we assume that a tic intrusion into other ongoing behaviour constitutes a violation of expected outcomes of a motor plan. Therefore, we can ask if, and to which degree the performance monitoring system is altered in persons with TS, and if inter-individual differences in clinical symptoms are related to EEG/ERP indices of performance monitoring.

1.2.2 Performance Monitoring in Tourette Syndrome

The presence and degree of impairment in performance monitoring in patients with TS is a matter of ongoing research, and discussion due to 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 (H. Eichele, Eichele, et al., 2010; 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 (G. M. Jackson, Mueller, Hambleton, & Hollis, 2007; Mueller, Jackson, Dhalla, 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 negative correlation to tic-severity in children with TS (Peterson et al., 2001) suggests that parallel processes may be involved in performance monitoring and in tic-suppression. Behavioural 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 ADHD and OCD and it thus remains unclear if those findings reflect deficits specific to TS or are 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).

1.2.3 The Flanker Task

Flanker tasks are choice response time tasks that demonstrate response priming and are used in psychological research to measure a participant's capacity for response inhibition. In the original design described by Eriksen and Eriksen (B. A. Eriksen & Eriksen, 1974), a participant had to respond to a certain target letter placed in the central position which was flanked by distracting letters. The target letter was either flanked by congruent letters that indicated the same response as the target letter, by neutral letters that did not require a response or by incongruent letters that required withholding the response initiated by the flanking letters and then to give the opposite response. The incompatible flankers induced interference between the incongruent target- and flanker-responses, resulting in slower RTs to incompatible

trials than to compatible trials. Several modifications of this experiment have been presented since its inception, for example the size and contrast of the letters, the use of forward or backward masking (C. W. Eriksen & Schultz, 1979), as well as changes in the spatial orientation (e.g., Kopp, Rist, & Mattler, 1996) or placement above and below the target (e.g., Danielmeier, Wessel, Steinhauser, & Ullsperger, 2009). Other experiments have used numbers, colour patches, arrows, or symbols as fishes, (e.g., McDermott, Perez-Edgar, & Fox, 2007).

RTs in incongruent trials following congruent trials are typically longer than RTs in incongruent trials following incongruent trials and “the greater this competition, the longer the latency of the correct response” (Coles, Gratton, Bashore, Eriksen, & Donchin, 1985). This so called Gratton effect represents a conflict adaptation mechanism (G. Gratton, Coles, & Donchin, 1992), and adjusts the level of cognitive control according to the previous trial with higher cognitive response conflict leading to higher cognitive control in the subsequent trial (Ullsperger, Bylsma, & Botvinick, 2005). Trial-to-trial adjustments can not only be measured after errors and correctly solved high-conflict trials, but also over longer time-spans when expectancy and sequence are manipulated (H. Eichele, Juvodden, Ullsperger, & Eichele, 2010; Steinhauser et al., 2012).

1.3 Electrophysiology

1.3.1 Electroencephalography

Electrical brain activity was originally measured by Richard Caton in 1875. After the first publication about electrical activity recordings from the human brain by Berger (Berger, 1929), it has become one of the most common methods to study brain activity non-invasively and at low cost. The EEG measures mostly summed electrical activity from cortical populations of neurons (but also some glia cells). While not detecting action potentials per se, EEG picks up longer duration potentials that are characterized by either a hyperpolarisation or a depolarisation of the cell

membrane that eventually elicits an action potential in receiving cells. The time-varying inhibitory and excitatory post-synaptic currents that flow during cortical activity produce local electrical fields that can be recorded from electrodes placed on the scalp when amplified. EEG activity is dominated by electrical dipoles formed by cortical pyramidal cells that are often oriented perpendicular to, and close to the surface. Since neural tissue, cerebrospinal fluid, skull and scalp attenuate postsynaptic potentials; these only become measurable on the scalp when larger patches of cortical tissue across spanning several centimetres are synchronously active. Besides the electrical signal from the brain, noise from biological (e.g. eye movement, seating, pulse) and non-biological artefacts (e.g. impedance fluctuation, 50/60 HZ, cable movements) are recorded.

1.3.2 EEG and brain maturation in children

EEG is widely used in clinical settings, as it is the first and most important investigation for the diagnosis and management of epilepsy which is the most common reason for referral to neurology in childhood (Taylor & Baldeweg, 2002). EEG is also a critical tool for intensive care settings including paediatric and neonatal units. Analyses for clinical settings differ from those used for research in the developmental neurosciences, as they are concerned largely with identification and localisation of abnormalities in the EEG. However, dramatic EEG changes with age reflecting major developmental changes in the both grey and white matter can be appreciated (Taylor & Baldeweg, 2002). The EEG in childhood is not comparable with that of adults and is dominated by lower frequency activity; higher frequencies increase in relative power with age. While the relative power of lower frequencies occur in the first year of life, increases in higher frequencies continue to mature until early adolescence (alpha) and even adulthood (beta) (Taylor & Baldeweg, 2002). This varies from brain region to brain region with posterior sites being twice as fast as central sites and anterior sites being slowest allowing estimation of cortical maturity of the various brain regions. The overall amplitude of the EEG signal decreases across childhood due to neuroanatomical maturation and physical skull development. The brain weight increases dramatically from 300-350 g at birth to

1300-1500 g in late adolescence (Picton & Taylor, 2007). Grey matter and white matter develop at different rates. Grey matter first increases during early childhood reflecting synaptogenesis and dendritic arborisation, then grey matter plateaus in mid to late childhood reflecting synaptic proliferations and high connectivity, and then grey matter declines reflecting pruning of synapses as stable and efficient circuits are established (Picton & Taylor, 2007). The decline in grey matter reaches maximal amounts in different ages with different regions (Shaw et al., 2008; Sowell et al., 2004) and in general, maturation follows a posterior-to-anterior and peripheral-to-central pattern (Shaw et al., 2008). White matter on the other hand seems to increase more linearly with age with volume growths until middle age (Giedd, 2004; Giedd et al., 1999; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Tamnes et al., 2010) due to increases in axonal diameter and increasing myelination which contributes to the integration of activity between different brain areas (Giedd, 2004; Giedd et al., 1999; Paus, 2010).

1.3.3 Event-related potentials

When presenting stimuli or tasks while recording EEG, it is possible to analyse the transient responses of the brain by averaging and time-locking to a stimulus or a participant's response. The resulting waveforms are referred to as event-related potentials (ERP), and the ERP provide information about chronometry of processing, can provide localization, and functional information about the process under investigation. ERP components are typically designated by their polarity (P = positive, N = negative) and their order of appearance (e.g. P1, N1, P2, N2, P3 etc.) or their mean latency after stimulus presentation/response (e.g. N170, P300 etc.). ERP components are classically divided by their latency into exogenous and endogenous components. Components with latencies faster than 100ms peak latency are assumed to be primarily determined by the exogenous physical characteristics of the stimulus, while endogenous components occurring later than 100ms after stimulus onset are affected by endogenous aspects of information processing, i.e. changes in attention and cognition based on instruction or context. ERP components are usually quantified in terms of peak latency and maximum amplitude from a pre-stimulus baseline but

also mean amplitude or area under the curve are used for quantification. ERP waveforms have a characteristic shape and are reproducible under similar experimental conditions (S.J. Luck, 2005), but differ depending upon modality (e.g. auditory, visual) and cognitive processes utilized.

1.3.4 Event-related potentials in children

Recordings in children and clinical populations are generally more challenging than those in healthy adults. In terms of signal quality, children tend to have a lower signal-to-noise ratio than adults, in part due to higher amplitude and more variable background EEG activity. Also, head/body and eye movements are more pronounced in children during experimental settings, such that more trials have to be rejected due to associated movement and muscle artefact. Tolerable total time on trial is typically shorter, limiting the number of repetitions and increasing necessity for breaks. The actual ERP waveforms are often more variable from trial to trial and between participants than in adults and this is partly due to increased trial-by-trial variability of the ERP and/or the variability of the background EEG, as well as larger response time variability (when overt responses are made). Also more pronounced changes in the state of arousal or attention due to unstable fluctuations in the developing neural networks that are processing the stimuli may be present (Picton & Taylor, 2007). For recording of the ERPs, guidelines should be followed (Picton et al., 2000) and, especially for developmental studies narrow age ranges should be chosen due to changes in latencies and amplitudes with age (Taylor & Baldeweg, 2002).

1.3.5 ERP correlates of performance monitoring in a modified Flanker task in children

Several studies in adults have identified ERPs in the modified Flanker task that are thought to represent action-monitoring processes (e.g. Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The different experimental approaches allow for a modulation of the sequence of stimulus- and response-locked ERPs, and allow studying the electrophysiological correlates of interference/conflict processing and cognitive control.

The most prominent feature of the stimulus-locked waveform in a flanker task is the N2-P3 complex from about 300ms. The N2 is a fronto-central negativity occurring between 200 and 400 ms after stimulus presentation in children (Folstein & Van Petten, 2008; Johnstone & Galletta, 2013) and reflects early stages of conflict/mismatch detection (Folstein & Van Petten, 2008; Larson, Clayson, & Clawson, 2014). This component is enhanced in incompatible compared to compatible stimuli (Kopp et al., 1996; Yeung, Botvinick, & Cohen, 2004), most likely due to increased activity in the anterior midcingulate cortex or rostral cingulate zone of the medial frontal cortex (Huster et al., 2011; Ridderinkhof et al., 2004). Furthermore, the N2 is responding to changes in stimulus probability/expectancy in a graded fashion (Steinhauser et al., 2012), suggesting a role in the ongoing adaptation of conflict processing, and can also be found in other paradigms involving conflict, e.g. Stroop tasks, Stop-Signal tasks (Folstein & Van Petten, 2008).

The subsequent P3 is a centro-parietal positivity occurring between 300 and 600 ms after stimulus presentation in children (Broyd et al., 2007; Johnstone et al., 2008; Polich, 2007), and has traditionally been associated with a process where the incoming stimulus is compared to the mental representation of the previous stimuli and the stimulus environment is updated (Polich and Kok, 1995). This is closely linked to concepts of orienting/surprise and predictive coding (T. Eichele et al., 2005). In the flanker task, this component is maximal centro-parietally, and is enhanced to incongruent stimuli compared to other stimulus types in both adults (Folstein and Van Petten, 2008; Ridderinkhof and van der Molen, 1995) and children (Johnstone et al., 2009; Rueda et al., 2004). A later aspect of P3, the late positive complex (LPC) is thought to more closely represent working memory and response selection (E. Donchin, 1981; E. Donchin & Coles, 1998; Emanuel Donchin & Coles, 2010; Polich, 2007). Contingent upon this, the P3 is also sensitive to changes in conflict and control (Clayson & Larson, 2011a, 2011b).

In response-locked waveforms, the strongest deflection is the Error-related negativity (ERN) - Error positivity (Pe) after erroneous responses (Falkenstein et al., 1991). The ERN is thought to reflect a signal for the need to adjust performance

generated in the medial frontal cortex (Debener et al., 2005; Larson et al., 2014). The ERN is a negative fronto-centrally distributed deflection with a latency of 50 to 100 ms after response-onset, and when averaged to mastoids, ERN amplitude increases to up to 15 μ V (Ullsperger et al., 2014). The ERN is generated due to increased activity in the posterior medial frontal cortex, especially the anterior midcingulate cortex (Debener et al., 2005). The ERN is preceded and followed by positive deflections with an oscillation frequency in the theta range (5-7 Hz), this suggests a degree of overlap between an event-related transient response and phase-locking of theta oscillations (Ullsperger et al., 2014).

The ERN is followed by the Pe, a P3-like positive deflection, emerging approximately 300 ms after incorrect responses and is thought to be more associated with evaluation and awareness, as well as the salience of errors (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005). Although the Pe is present in children and adolescents, the N2 and ERN seem to be not fully established before late adolescence (Brydges, Anderson, Reid, & Fox, 2013; Davies, Segalowitz, & Gavin, 2004; DuPuis et al., 2015; Ladouceur, Dahl, & Carter, 2004, 2007; Tamnes, Walhovd, Torstveit, Sells, & Fjell, 2013; Wiersema et al., 2007). This might suggest that despite error awareness being established at a young age, that ability of fast/automated detection of errors and conflict, and the modulation of cognitive control, develops later in adolescence (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Ladouceur et al., 2004).

Early deflections as the N1 and P2 are thought to be obligatory, exogenous responses of the primary cortices with heteromodal projections (Steven J Luck & Kappenman, 2011). While the earlier components sensitivity to 'exogenous' stimulus properties is well known, the functions of the P2 are little understood. The N1 amplitude was found to be larger when performing a discrimination task and might reflect a pattern recognition process (Steven J Luck & Kappenman, 2011). The P2 wave was found to be larger in response to stimuli containing targets and it has been suggested that an increase of P2 amplitudes could facilitate the inhibition of other irrelevant stimuli and by that to allow a more efficient processing of the relevant

stimuli (Oades, Dittmann-Balcar, Schepker, Eggers, & Zerbin, 1996). Child/adolescent developmental studies have shown that N1 and P2 amplitudes decrease with age in normal children, concurrent with reductions in reaction time and commission errors (Rueda, Posner, Rothbart, & Davis-Stober, 2004).

1.3.6 EEG/ERP in children with Tourette

EEG/ERP was used here to measure neural correlates of cognitive control and performance monitoring. EEG is a real-time measure of brain activity, with a temporal resolution in the millisecond time-range. Cognitive control and performance monitoring are rather fluid, flexible processes that can best be captured by a technique with such high temporal resolution. EEG is also less susceptible to loss of data due to movement artefacts than MRI which is important to consider when studying participants with tic disorder and hyperactivity. Most importantly, however, only very few ERP studies have included children with TS thus far, mostly using auditory oddball paradigms with variable results (Oades et al., 1996; van Woerkom, Roos, & van Dijk, 1994; Zhu et al., 2006). Only two recent studies using visual task paradigms that included children with TS are available (Shephard, Jackson, & Groom, 2016a, 2016b). While available findings from adult studies (Johannes, Wieringa, Mantey, et al., 2001; Johannes, Wieringa, Nager, et al., 2001; Johannes et al., 2002; Johannes et al., 2003; Serrien, Orth, Evans, Lees, & Brown, 2005; Thibault et al., 2008; Thibault, O'Connor, Stip, & Lavoie, 2009) can be used as a guide, it is important to recognize that results from adults do not readily generalize to young people. This holds especially true for TS continuing into adulthood, where it is assumed that compensatory mechanisms which would be expected for the typical course of the disease have not developed (G. M. Jackson et al., 2015; Peterson, 2001; Plessen et al., 2004).

2. Objective of the thesis

There are several lines of evidence of alterations in the performance monitoring system in children with TS (G. M. Jackson et al., 2015), and we assume that a tic intrusion into other ongoing behaviour constitutes a violation of expected outcomes of a motor plan. Mapping these putative changes in performance monitoring in individuals with TS might aid the development of targeted treatments and increase diagnostic accuracy. The overarching goal of this thesis is thus to better understand the extent of performance monitoring alterations in children and adolescents with TS, and to study both cognitive and brain mechanisms underlying performance monitoring in this group. A complete understanding of performance monitoring in TS involves research from many fields, which is more than can be covered in a single thesis. Thus, the intent here is to narrow the focus of the research to answer specific questions of adaptive changes related to neuroimaging and electrophysiological measurements. In this way, we may add to an increased understanding of performance monitoring and brain functioning in TS, and hopefully contribute to improved diagnostic awareness of performance monitoring alterations in this group.

Deficits in performance monitoring are not readily identifiable in children with TS. Neurobiological evidence suggests that alterations in the efferent/motor branches of cortical-subcortical circuits could predispose to the development of TS and that neuroplastic changes in control systems of the brain could modulate the severity of symptom expression (Plessen, Bansal, & Peterson, 2009). In order to assess the current understanding of adaptive effects in children with TS, we aimed to review and summarize the current research results on neuroplastic changes in functional and anatomical neuroimaging studies. By comparing the correlation of tic severity and adaptive changes from studies of performance monitoring in children with TS, we would map which sub-domains of performance monitoring seem most prominently affected. The review contributes to the delineation of functional compensation in children and adolescents in TS, and improves the understanding of the condition. Hence, in order to gain a more comprehensive insight into the functional

neuroanatomy of TS, with special reference to possible effects of adaptation, we have reviewed the available imaging literature in paper I.

Another approach to understanding brain processes underlying cognition is by studying the brain's functional networks. The interplay between networks with temporally correlated activity has been increasingly implicated as important for normal functioning and has been shown to be dynamically changed by task engagement. One particular network, the cortico-striato-thalamo-cortical circuit, has been described as dysfunctional in children with TS. Activity in this network is also elicited during performance monitoring. However, multiple studies report comparable abilities of cognitive control between children with TS and healthy controls. This has led to suggestions of adaptive effects in this network in children with TS. By employing an electrophysiological approach with high temporal resolution and an experimental setup that is suited to test the dynamics of performance monitoring, we sought to capture different aspects of these networks through studying the intra and inter-individual differences. The convergence of results from these methods could help us to elucidate the extent of network alterations in TS.

Thus, we hypothesized that performance monitoring is an important factor for the clinical impact of tics in children with TS, especially for process of compensation.

To this end, our main questions in **paper I** were -

- 1) Does the current literature support that there are adaptations in the performance monitoring system in children with TS? Which areas emerge as sites of adaptive, compensatory processes in children or adolescents with TS through the use of functional and anatomical MR-neuroimaging and which plastic processes become evident?
- 2) Based on those studies, which factors can we identify that contribute to a more or less successful adaptation to the tics?

In **papers II** and **III** we aimed to explore the following questions -

- 3) Are ERP indices of performance monitoring altered in children with TS?
- 4) Are inter-individual variations in clinical symptoms in children with TS associated with EEG/ERP indices of performance monitoring?

In **paper III** we were in a position to additionally test the question -

- 5) To what extent does brain maturation alter the dynamics of performance monitoring in children with TS?

3. Methods

3.1 Search procedures (paper I)

We limited the review to functional and anatomical MRI studies of children with TS. We performed a structured search in Pubmed (ncbi.nlm.nih.gov/pubmed), with the following search terms and Medical Subject Headings (MeSH): ("Tourette Syndrome"[MeSH] OR "tics"[MeSH] AND ("Magnetic Resonance Imaging"[MeSH] OR "evoked Potentials"[MeSH]) AND (adaptive[All Fields] OR compensatory[All Fields] OR neuroplastic[All Fields] OR plasticity[All Fields] OR reorganization[All Fields] OR ("Changes"[Journal] OR "changes"[All Fields]) OR compensate[All Fields])) NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]) NOT ("deep brain stimulation"[MeSH Terms] OR ("deep"[All Fields] AND "brain"[All Fields] AND "stimulation"[All Fields]) OR "deep brain stimulation"[All Fields]). We also screened ISI Web of Knowledge (apps.isiknowledge.com), and Embase (<http://ovidsp.uk.ovid.com>) databases for additional publications. We limited the search to papers published from January 1997- April 2012 to minimize technical differences in the included studies and assessed differences in study design, image quality and image processing. Thirty-five papers matched the search terms, and we screened the papers for relevance, and selected thirteen for review, including all original studies that used anatomical or functional MRI or DTI and included at least 10 children or adolescents with TS with a mean age younger than 19 years and were written in English, French, Norwegian, Swedish, Danish or German. Findings were categorized by structural MRI, functional MRI or DTI.

3.2 Participants

Participants aged from 8-12 years were initially referred to the study from outpatient clinics of the Department of Child and Adolescent Psychiatry, Haukeland University Hospital in the greater Bergen area in the Hordaland County. Controls

were recruited from local schools in the same geographical area. One hundred and two participants met inclusion criteria, resulting in an overall sample of 41 ADHD, 26 TS, and 35 controls (67 boys).

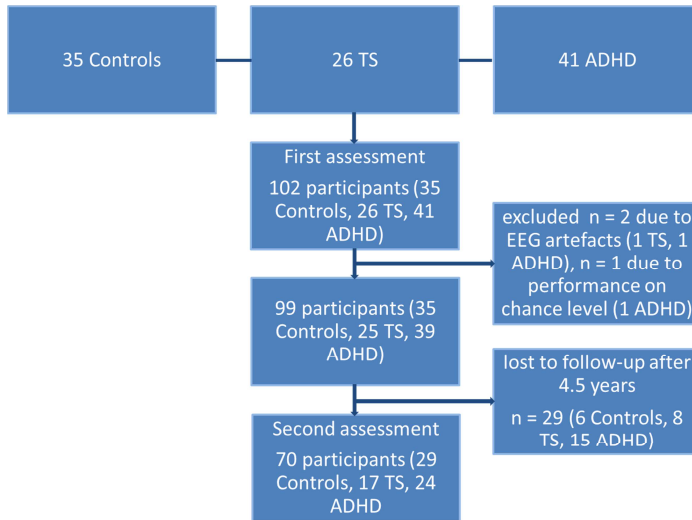


Figure 1: Study design

Participants included in the patient groups met the diagnostic criteria for TS and ADHD, respectively (DSM-IV; American Psychiatric Association, 1994). All children were medication-naïve, had no former treatment for ADHD and the controls were matched for age and gender. Exclusion criteria were IQ below 75, gestational age < 36 weeks, head trauma with loss of consciousness, present or former substance abuse, epilepsy and suspicion of Autism spectrum disorder. Further exclusion criteria for the control group were a lifetime history of TS, ADHD, OCD or a current DSM-IV axis I disorder other than specific phobias.

At the first assessment, all participants were characterized with a clinical-diagnostic semi-structured interview to map psychopathology including comorbid diagnoses, the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997), the DuPaul ADHD-Rating scale (ADHD-RS; DuPaul G.J., Power T.J., & Anastopoulos A.D., 1998) and the Children Global Assessment Scale (CGAS; Shaffer et al., 1983).

Tic severity was estimated by the Yale Global Tic-Severity Scale (YGTSS; Leckman et al., 1989). Full-scale intelligence quotient (FSIQ) was estimated by using the Wechsler Scale for Intelligence (WISC-IV; Wechsler, 2003).

For the second assessment, all participants included at the first assessment were contacted again on average after 4.5 years. Seventy children and adolescents (age range 11-17 years) participated in a follow-up ERP investigation. Use of medication was registered for all participants.

3.3 The modified Flanker paradigm

We employed a modified Eriksen Flanker task that was implemented in the Eprime2 experiment programming platform (Psychology software Tools, <https://www.pstnet.com/eprime.cfm>). Participants were seated in front of a PC screen inside an electromagnetically shielded chamber (Rainford EMC Systems, Wigan, UK). Throughout the experiment, participants were presented a central fixation dot. Trials started with the appearance of 6 flanking arrows below fixation, followed by presentation of a central target arrow after 100 ms resulting in either response-compatible (>>> > >>>, <<<< <<<<) or response-incompatible (>>> <>>>, <<<< <<<<) trials. Trials were presented in two blocks of 200 trials in a random sequence with a short break. Trials were terminated by the motor response and were followed by a fixed 800 ms interval before the onset of the next trial.

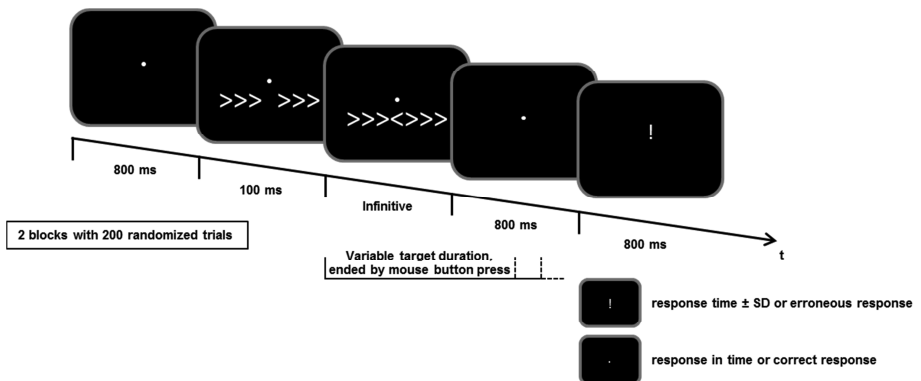


Figure 2: modified Flanker task

After a short training session, participants responded to the task with either a left or right mouse button press of their preferred hand following the direction of the central target arrow. 50% of the flankers were pointing into the same direction as the target (compatible trials), and 50% into the opposite direction (incompatible trials). Overall probability for right/left trials was kept at 0.5. Participants were instructed to respond as quickly and accurately as possible to the target. Feedback was given after erroneous trials or at trials extending an adaptive threshold value (mean response time \pm 1.5 standard deviations).

3.4 EEG recording procedure

EEG data in this thesis were collected in two sessions in the same population administered approximately 4.5 years apart. The core instruments and applied techniques were similar in both data collections and are described jointly.

During EEG recording, a situation as comfortable as possible was created for children and their accompanying caregivers by first showing the EEG recording facilities and briefly explaining EEG equipment before starting the actual recording. In order to optimize increase compliance and optimize signal quality, we showed live EEG traces and explained generation and prevention of biological artefacts. During EEG recording, children were accompanied in the shielded EEG recording chamber by a parent and a member of the staff.

3.5 EEG data acquisition

EEG was recorded from 34 Ag/AgCl electrodes mounted in an elastic cap at Fp1, Fp2, F7, F3, Fz, F4, F8, FT9, FC5, FC1, FC2, FC6, FT10, T7, C3, Cz, C4, T8, TP9, CP5, CP1, CP2, CP6, TP10, P7, P3, Pz, P4, P8, PO9, O1, O2, PO10, Iz, with a ground on FCz, and referenced to Fz. An additional electrode was placed below the left eye to register vertical eye movements, horizontal eye movements were registered between lateral frontal electrodes. Electrocardiographic activity was recorded from an electrode placed on the left chest placed at about the 7th intercostal space in the

mammillary line. Impedances were kept below 10 k Ω . EEG was sampled with Brain Amp MR plus X2 amplifiers (BrainProducts, Munich, Germany) at 1000 Hz with a 10 s time-constant.

3.6 EEG processing

Continuous EEG was preprocessed in the EEGLAB toolbox (Delorme & Makeig, 2004) running in Matlab (Mathworks, Natick, MA, USA). EEG data were re-referenced to a common average reference and filtered using an impulse response filter (Widmann, 2006), followed by visual inspection for EEG abnormalities or non-stereotyped artefacts. Then, automatic artefact rejection was performed to denoise the data where continuous EEG were divided into 1000 ms segments consecutively and detrended. Then, epochs were sorted by a unit variance compound score consisting of normalized root mean square across all channels and time points, spatial standard deviation, skewness, kurtosis and power spectrum ratio between low and high frequencies. Epochs within ± 1 standard deviation were retained and concatenated, and 32 (paper II) or 30 (paper III) components were estimated after principal component analysis compression in a temporal independent component analysis (ICA). Hereafter, we performed automated component selection with the aim of identifying remaining stereotypical artefacts (Viola et al., 2009) as well as event-related components contributing to the stimulus-locked and/or response-locked ERP (Wessel & Ullsperger, 2011) and thus kept 15 components. After a visual cross-check for remaining artefacts and discarding of trials with reaction times < 200 ms or > 2000 ms, 10 to 15 components were back-projected.

3.7 EEG averaging and data extraction

Grand average ERPs for compatible, incompatible and erroneous trials separately from stimulus-locked and response-locked segments were generated and visually inspected. For spatial reduction and to minimize intra-individual variability effects (Handy, 2005) as well as variability seen in different age groups (Brydges et al., 2013; Cycowicz, 2000; Davies et al., 2004), we selected a central region of

interest containing FC1, FC2, Cz, CP1, and CP2, where several components were expressed: N1, P2, P3, LPC (paper II) or P2, early and late P3 (paper III) in stimulus-locked averages, as well as LPC, ERN, early positivity and Pe (paper II) or ERN and Pe (paper III) in response-locked averages. For inference testing, mean amplitudes from 40 ms long time-windows around the grand average peak latency were used to estimate individual amplitudes.

3.8 Statistical analyses

Statistical analyses were performed using Statistica (Statsoft, Tulsa, OK, USA), Matlab (Mathworks, Natick, MA, USA) or R (R Development Core Team, 2008). In general, inference tests were two-tailed, and considered significant at a threshold of $p < .05$.

For the description and for testing possible differences in demographical characteristics between the groups, t-tests or χ^2 -tests were used. Pearson's correlation were computed between behavioural or ERP measurements and tic scores.

In paper II, we used repeated measure analysis of variance to test behavioural and ERP outcome effects with between-subject factor *group*. Further, we conducted univariate Analyses of Covariance with covariates as continuous predictors and post-hoc tests to follow up significant or trend-significant group differences. Additionally, the covariates age and FSIQ were included in analyses of behavioural data, whereas in ERP data age, FSIQ, reaction times/intra-individual variability and response accuracy were included. *Partial eta squared* values were reported for all significant or trend-significant results.

In paper III, we used a mixed-model analysis with repeated measures with an unstructured variance component matrix and RT mean from both assessments as a within-subject factor. In the longitudinal analyses, age at first and second assessment and group were included as between-subject factor whereas age was included as a covariate in cross-sectional analyses.

3.9 Ethical considerations

A written invitation was sent out to the parents or legal guardians of children suitable for inclusion and further information was presented during first telephone contact. In addition, parents and children received further oral and written information when they attended the assessments. Written informed consent from parents and children were obtained before the first interview and experimental situation. Participants and parents who had agreed to be re-contacted were contacted for a second assessment. The study was approved by the Regional Committee for Medical Research Ethics, West-Norway. All EEG recordings were evaluated by a physician in order to check for the presence of EEG abnormalities as far as possible. If abnormalities were detected, findings were reported to referring physicians or psychologists and parents for further follow-up. In case of controls, we reported to their general practitioner. All participants and referring therapists were informed that the EEG recording was part of a research project and did not have optimal sensitivity for clinical assessment.

4. Results

4.1 Paper I

The main findings of paper I, *Neural plasticity in functional and anatomical MRI studies of children with Tourette syndrome* were that existing imaging studies in young persons under the age of 19 years with TS showed differences in brain structure and activation pattern compared to healthy controls during tasks that require overriding of prepotent responses. The typical clinical course of attenuation of tic symptoms during adolescence, in parallel with the emerging capacity to exert self-regulatory control during development, suggests that plastic processes may play an important role in the development and the attenuation of tic symptoms. Along with structural alterations in regions putatively representing sites of tic generation, changes in several other regions most likely represent an activity-dependent neural plasticity that helps to modulate tic severity, such as the prefrontal cortex, but also in the corpus callosum and the limbic system. Factors that potentially influence the development of adaptive changes are age, comorbidity with other developmental disorders, medication use, and IQ. Other factors that influence the results were differences in study-design and MRI techniques for acquisition, and analysis techniques applied to the imaging data. The most prominent limitation of all studies for the study of adaptation was the cross-sectional design.

4.2 Paper II

After the definition of the problem within the context of findings derived from anatomical and functional neuroimaging, we examined *performance monitoring in medication-naïve children with Tourette Syndrome*, and examined compensatory and adaptive processes on an behavioural and electrophysiological level in paper II. The results showed that, overall, participants with TS did not differ from healthy controls and children with ADHD in terms of reaction times, intra-individual variability and accuracy in a modified Eriksen Flanker task when controlling for relevant

comorbidities. However, differences in electrophysiological components existed, because children with TS showed higher amplitudes of an early P3 component of the stimulus-locked ERPs in ensemble averages and in separate trial outcomes compared with healthy controls and with children with ADHD. In response-locked averages, children with TS had a slightly higher positive complex before the motor response, likely also reflecting a late P3 in comparison with controls and children with ADHD. Groups did not differ in post-response components. These findings suggest that children with TS may employ additional resources during overt stimulus processing requiring attention as a compensatory mechanism to maintain equal behavioural performance.

4.3 Paper III

In paper III, *Development of Performance and ERPs in a Flanker task in Children and Adolescents with Tourette Syndrome - a follow-up study*, we aimed to examine developmental behavioural and electrophysiological changes in the same study sample to gain an insight into the change of tics, behaviour and electrophysiology in this age-span. Task performance measured in a modified Eriksen Flanker task improved in all groups with age, and behavioural differences in terms of reaction times, reaction time variability and accuracy between children with TS and controls diminished at second assessment, while differences between controls and children with ADHD largely persisted. In terms of ERP, the early P3 developed earlier in children with TS compared with controls at the first assessment, but trajectories converged with maturation. ERP component amplitudes correlated with total worst-ever tic scores showing that higher worst-ever tic scores were associated with larger ERP amplitudes. When analysing subgroups where TS+ADHD and TS were separated, we found that only developmental trajectories of compatible reaction time variability and incompatible late P3 amplitudes differed between the subgroups, overall indicating no widespread differences between the two subgroups.

5. Discussion

The current work investigates compensation and adaptive effects in performance monitoring in children and adolescents with TS from different angles. In the initial review, we summarized the results from previous anatomical and functional neuroimaging studies in young people with TS with a focus on plasticity. In this paper, we could point to differences in brain regions representing the tic origin along with deviations in other regions that engage in activity-dependent activation that may help to modulate tic severity in TS, as well as in tasks requiring cognitive control/performance monitoring. The conclusion of this review pointed to compensatory effects, in particular alterations of performance monitoring as important aspects of TS that warrant further research. The electrophysiological data in the second paper allowed us to identify differences of ERP measures of attentive processing in a modified Flanker task in children with TS when compared to healthy children. We also reported findings that we interpreted as signs of compensatory modulations of cognitive control and performance monitoring. The follow-up paper with data collected in the same sample on average 4.5 years later provided additional evidence of merging trajectories in electrophysiology and task performance between participants with TS and healthy controls, and illustrated a contrast to the development in children with ADHD. These data are consistent with compensatory mechanism of self-regulatory control during that time period, which probably also facilitate tic suppression. Importantly, comorbid ADHD in children and adolescents with TS was not associated with notable reductions in task performance or specific changes in electrophysiology, as far as we could see from our data. Lastly, we found that ERP components correlated with tic severity and assumed that a higher symptom load earlier in life probably initiated compensatory long-term changes in stimulus and motor processing in order to facilitate optimization of performance.

In the following sections, the findings from the three studies will be briefly discussed, and together with the recent literature, a presentation of *a developmental perspective of electrophysiological correlates of performance monitoring in children with Tourette syndrome* will be presented.

5.1 Compensatory processes in performance monitoring

The topics of neural plasticity and of adaptive processes involved in modulation and suppression of tics in children with TS are still emerging fields. The increasing number of studies pointing to the importance of compensatory processes in the presence of an impaired motor function illustrates the substantial impact of cognitive control and performance monitoring on our current understanding of TS (Baym et al., 2008; Marsh et al., 2007; Raz et al., 2009; Roessner et al., 2012). In fMRI studies, the finding of compensatory processes involved in the activation of prefrontal, cingulate, striatal and thalamic regions are consistent with the assumption that these areas play a major role in guiding the precision of motor movements, but also in processing conflict-evoking trials. Further, reorganization in prefrontal cortex, amygdala, hippocampus and corpus callosum is associated with less severe tic symptoms, and these regions therefore appear to facilitate tic modulation and suppression in children with TS (Peterson et al., 2007; Peterson et al., 2001; Plessen et al., 2004). Moreover, activation in the prefrontal cortex during tic suppression (Peterson, Skudlarski, et al., 1998) highlights the crucial role of self-regulatory functions in TS (Spessot et al., 2004). Finally, indicators of equal or better performance in children with TS when compared to healthy controls imply a stronger influence of cognitive control in TS than previously thought, because prefrontal brain regions involved in tic suppression largely overlap with those typically associated with performance monitoring (Baym et al., 2008; S. R. Jackson et al., 2011; Marsh et al., 2007).

The review in paper I indicated that several aspects may influence the child's capacity of tic modulation. Most studies that were included presented evidence for the hypothesis that underlying plastic processes are correlated with tic-severity. However, the occurrence of many tics per day ultimately may trigger compensatory phenomena, but could also point to a deficit of symptom modulation. Furthermore, variation in tic severity over shorter and longer periods makes an objective measurement of symptoms difficult, especially with correlation of current tic scores. In studies including a broader age range, interactions of age and diagnosis were seen

in most brain regions, which supports the notion that adults with TS are a subsample of all individuals affected with TS and have not undergone the adaptation that leads to an attenuation of tics during adolescence (Peterson et al., 2007; Peterson et al., 2001; Plessen et al., 2004). Further, high comorbidity rates with especially ADHD and OCD in the TS sample may play a role. However, most imaging studies that included both individuals with TS alone and individuals with TS and comorbidity have controlled for comorbid disorders or compared “pure TS” with controls and did not find significant alterations from the main findings (Baym et al., 2008; Marsh et al., 2007; Mazzone et al., 2010; Peterson et al., 2007; Peterson, Skudlarski, et al., 1998; Peterson et al., 2001; Plessen et al., 2006; Plessen, Royal, & Peterson, 2007; Plessen et al., 2004). Moreover, medical treatment for tic suppression may facilitate or inhibit the development of adaptive processes or influence functional and anatomical differences. However, most studies controlled for this confounder and did not find any influence on primary results (Marsh et al., 2007; Mazzone et al., 2010; Peterson et al., 2007; Peterson et al., 2001; Plessen et al., 2006; Plessen et al., 2004), but not all (Miller et al., 2010).

The general lack of evidence for changes due to medication may either document a real absence of effect, or alternatively represent small effect sizes in small samples, and even smaller subgroups on the different agents. Moreover, IQ plays a crucial role for the capacity of adaptation and cognitive control processes (Shamosh & Gray, 2008). Several studies indicate an IQ lower than the population mean in children with TS (Debes, Lange, Jessen, Hjalgrim, & Skov, 2011; Ozonoff et al., 1994), whereas other studies have not confirmed this result (Mahone et al., 2002; Shucard et al., 1997), potentially due to differences in sample selection and recruitment. In the studies selected for the review, children with TS did not show a significantly lower IQ, although in some instances still a lower IQ than the control sample (see paper I, table 1 and 2). Hence their higher IQ may represent a positive selection for the presence of plastic processes.

Moreover, cross-sectional study-design limits the detection of developmental processes (Kraemer, Yesavage, Taylor, & Kupfer, 2000) as the core characteristic of

adaptive reorganization is the development over time, whereas cross-sectional studies may in the best case enhance the understanding of correlations with age. Further, different methods of acquisition as region-of-interest vs. whole brain exploration, applied imaging sequences, field strength and different analyses methods play a critical role for the interpretation of deviations representing functional or anatomical correlates of compensatory processes. This makes it difficult to combine the findings in a meta-analysis. Despite the wide array of methods used to explore the signs for plastic changes in children with TS, there is a convincing convergence on cortico-striatal pathways.

5.2 Adaptive behavior in performance monitoring

It is well established that dysfunctions of the CSTC circuits lead to an impairment of executive cognitive control over motor behaviour that is characterized by a reduced behavioural inhibition (Albin & Mink, 2006; J. A. Church et al., 2009; Leckman, Bloch, et al., 2006; Marsh et al., 2007). Hence, the study of performance monitoring in children with TS is important as this function is presumably at the core of tic suppression. However, the adaptation of behavioural performance in children with TS is a topic of discussion and existing studies report somewhat inconsistent results in samples with larger age ranges (Baym et al., 2008; Crawford et al., 2005; H. Eichele, Eichele, et al., 2010; E. L. Harris et al., 1995; G. M. Jackson et al., 2007; Mueller et al., 2006; Roessner et al., 2008; Serrien et al., 2005; Shephard et al., 2016a). In order to address some of the possible causes of inconsistent findings, we planned this study in a longitudinal setup in order to better follow behavioural changes over time in children in Tourette syndrome.

The hypotheses for behavioural and electrophysiological analyses were mainly derived from neuroimaging, behavioural literature and current theories of TS and performance monitoring. Based on studies on brain maturation and attenuation of tic symptoms during adolescence, we expected that children with TS would over time show adaptation of performance-monitoring pattern in terms of reaction times, variability of reaction times and response accuracy similar to those of control

children, whereas we expected better performance in TS compared to children with ADHD.

Previous studies of cognitive control over motor outputs have shown comparable or even superior abilities in children with TS (H. Eichele, Eichele, et al., 2010; Greimel et al., 2011; G. M. Jackson et al., 2007; S. R. Jackson et al., 2011; Mueller et al., 2006; Roessner et al., 2008). In our initial assessment, we showed that children with TS performed behaviourally on the same level as control children. We did not find strong group differences between children with ADHD and control children when controlling for relevant covariates, which differs from some previous findings (Albrecht et al., 2008), but not others (Johnstone & Galletta, 2013).

At the second assessment, task performance generally improved in terms of faster reaction times, reduced response variability and higher accuracy in all groups with age. As predicted, the behavioural differences between children with TS and controls diminished at the second assessment. Differences between controls and children with ADHD persisted, and yielded significant group differences. While there were slight differences in behavioural results between paper II and paper III, different steps in data normalization, sample attrition, and statistical model choice can account for this.

The developmental effects on performance for the overall group are consistent with the literature (Posner & Rothbart, 2007; Tamnes et al., 2013). Children with TS improved in most performance measures over time, resulting in converging trajectories between healthy controls and TS following an initial deficit at the first assessment in terms of reaction times, reaction time variability and accuracy. Compared with children with ADHD, children with TS showed larger reductions in their reaction time variability, resulting in significant differences between both groups at the second assessment. When separately analysing children with pure TS and TS with ADHD comorbidity, we found that change of reaction time variability over time was smaller in TS+ADHD, which is in line with the view of increased intra-individual variability as a core feature of ADHD (Klein, Wendling, Huettner,

Ruder, & Peper, 2006). Other behavioural measures showed little discernible differences between TS subgroups in our sample. We interpret these differential trajectories between first and second assessment as an index of adaptation of compensatory self-regulation mechanisms from childhood to adolescence that is brought on by the constant need to suppress tics. Successful tic suppression may lead to increased control over motor outputs and this again may generalize to behavioural measures of cognitive control (G. M. Jackson et al., 2015; Mueller et al., 2006).

5.3 Developmental trajectories in electrophysiology

The data on behavioural performance patterns in children with TS has shown inconsistencies across studies, as outlined above. In contrast to an increasing numbers of fMRI studies of children with TS, only few studies have mapped electrophysiological patterns. The principal advantage of EEG compared to fMRI and behavioural data is that it affords a close examination of the temporal sequence of stimulus/task processing. The few electrophysiological studies available at the outset of the study showed differential P3 modulation, and we therefore focused on P3, also due to its role in performance monitoring. We did separate analyses within the time range of P3 subcomponents to assess differences related to an early P3 component, representing more likely the orienting of attention to stimuli (Polich, 2007), and the later P3b/LPC reflecting response selection and other response-related processing (Falkenstein, Hohnsbein, & Hoormann, 1994). The separation of stimulus- and response-locked LPC allows to study response selection/ orienting and response preparation separately (Verleger, Jaskowski, & Wascher, 2005). We could show higher amplitudes of the stimulus-locked early P3 in unmedicated children with TS compared to children with ADHD and healthy control children across task outcomes. This higher amplitude was sustained through the late positive complex.

Similar to the effect we saw, a recent study using a Go/Nogo-paradigm where TS children showed the largest peak of all groups in the earlier P3 subcomponent around 300-350ms after the flanker (Shephard et al., 2016a) in a cohort with a broader age range, although this was not the focus of the analysis. Also, the authors

assessed changes associated with learning in another study, and a distinct early P3 peak consistently had higher amplitudes in TS (Shephard et al., 2016b), although not separately reported. The earlier discordant findings in the few previous studies of P3 in TS children using auditory paradigms (Oades et al., 1996; van Woerkom et al., 1994; Zhu et al., 2006) may relate to different methods of recruiting the subjects (comorbidities, medication), and to differences in task selection (passive, active, visual, auditory, response mode) (S.J. Luck, 2005), as well as different EEG/ERP post-processing and analysis. In paper II, the use of ICA for artefact reduction, and region of interest averaging allows for a clear representation of a small, but robust ERP difference. We believe that these results can be understood as greater sustained effort and resource allocation in people with TS in processing the stimuli (Isreal, Chesney, Wickens, & Donchin, 1980; S.J. Luck, 2005) that may help children with TS to maintain behavioural performance.

Other research has shown that children with TS have a comparable or in part enhanced control over motor activity (G. M. Jackson et al., 2007; S. R. Jackson et al., 2011; Mueller et al., 2006). Based on our results, we can posit that, in part, these effects already may happen earlier during stimulus evaluation, where an adaptation of the attentional system may result in higher resource allocation toward salient stimuli and an increased ability to suppress distracting information. This would in turn improve response selection, and putatively aid efferent control.

Children with ADHD showed the smallest amplitude across outcomes in our study. Interestingly, the same pattern for this P3 component could be seen in an earlier study using a Flanker paradigm around 300ms after flanker onset, as well as across task conditions (Albrecht et al., 2008, figures 2 and 4, Cz), although not separately reported. A reduced P3 in ADHD is interpreted reflective of diminished evaluative and processing capabilities (Brandeis et al., 2002; Johnstone, Watt, & Dimoska, 2010; Kratz et al., 2011; Lawrence et al., 2005). However, results from children with ADHD appear to be heterogeneous. While a recent study did not find differences on ERP or behavioural measures in children with ADHD compared to a control group when performing a Flanker task (Johnstone & Galletta, 2013), results

from other studies using choice response tasks showed reduced amplitudes and behavioural measures (Johnstone et al., 2010; Kratz et al., 2011). Conflicting findings may be associated to study design or differences in sample population (Johnstone, Barry, & Clarke, 2013). However, when children with ADHD are motivated to perform well, amplitudes resemble those of controls (Groom et al., 2010) and this might have been the case in our study.

As brain maturation is associated with attenuation of tic symptoms during adolescence, we expected converging ERP patterns in children with TS and controls at the second assessment. Indeed, maturation had a considerable effect on several of the ERP components. Younger children displayed smaller ERN, Pe, early P3 and incompatible late P3 amplitudes than older ones, while amplitudes of P2 and compatible late P3 decreased with age. Maturation effects with increased negativity of the ERN are well known (Davies et al., 2004; Ferdinand & Kray, 2014). Similar effects with increased positivity of the Pe were present in the grand average data of an earlier study (Ladouceur et al., 2004), while others could not find these developmental effects (Davies et al., 2004; Wiersema et al., 2007). In our study, children with TS and controls showed an increase in ERN amplitude from the first to the second assessment, while children with ADHD showed a smaller increase in negativity. Developmental changes were not significant in Pe, although maturation effects were most prominent in TS, and flattened for children with ADHD. Indeed, this result is similar to that of a recent meta-analysis, where an overall attenuation of ERN in performance-monitoring tasks were reported for the ADHD group (Geburek, Rist, Gediga, Stroux, & Pedersen, 2013), which implies that these deficits persist with age in ADHD, and may indicate a deficit of immediate detection of an error, whereas the later stages of error processing appear to be less affected.

Developmental trajectories of the early P3 amplitude to compatible trials merged between control children and TS group, whereas at the same time ADHD children remained at lower levels compared to both other groups. Children with TS maintained the largest amplitudes in incompatible trials at the second assessment, with a parallel increase over time compared with controls, while the trajectory for

children with ADHD resulted in an even increased amplitude difference. Despite effects of maturation in all groups the deviant P3 trajectory in ADHD remains into mid-adolescence. Correspondingly, when looking at subgroup analyses between pure TS and TS+ADHD, we observed that children with comorbid ADHD developed slightly lower P3 amplitudes in demanding incompatible trials. Other ERP measures, however, remained without significant differences between subgroups. Together with the relative lack of differences in behaviour across most measures, we could not identify pervasive effects of comorbid ADHD in TS affecting tics, performance or ERP.

The observed correlations between several ERP amplitudes and the worst-ever tic scores are interesting. It has been proposed that the execution of many tics per day may trigger compensatory phenomena over time (S. R. Jackson et al., 2011). Hence, a higher symptom load earlier in life could lead to changes in stimulus and motor processing through mechanisms that involve change of prefrontal control over motor output (G. M. Jackson et al., 2015). In a similar vein, TMS studies have demonstrated that the pre-supplementary motor area may modulate primary motor cortex activity in conflicting situations and thus influence corticospinal excitability (Mars et al., 2009). Extending from a view presented by Jackson (2015) we put forward the idea that tics in TS can trigger adaptation more broadly in the cognitive control network that maintains and optimizes outcomes, rather than just the premotor/motor parts of the loop. Anatomically, adaptive changes outside SMA and precentral regions might therefore be found in the lateral frontal cortex and medial frontal wall including the cingulate gyrus. A mechanism such as the trial-by-trial interplay between cingulate cortex and motor cortex, that optimizes behavioural output after errors and also affects subsequent activity in cortical areas for sensory processing and early attentional function, presumably, might also be at work in tic suppression (Danielmeier, Eichele, Forstmann, Tittgemeyer, & Ullsperger, 2011; Ullsperger et al., 2014). Considering the ERN amplitude effect and correlations we observe, a main cingulate gyrus source of the ERN/Pe is well-documented (Debener et al., 2005), therefore a negative association with tic severity, intuitively, could be an indicator of functional adaptation. This notion is further supported by the fact that some

generators of P3 that are associated with attentional control also are located in medial frontal regions (Gehring & Fencsik, 2001; Huster, Enriquez-Geppert, Lavalée, Falkenstein, & Herrmann, 2013).

5.4 Limitations

In line with previous studies in children with TS, the relatively small sample size is a limitation; this also makes it difficult to provide robust assessments of the impact of comorbid conditions. Within the statistical models employed in papers II and III we tried to estimate the effects of TS, while assuming that confounding effects of comorbid ADHD would be mitigated by adding an ADHD contrast group, and provided additional tests on smaller subgroups where necessary. It is desirable for future studies to acquire larger sample sizes. This is probably best achievable through collaborative efforts across several centres that systematically investigate the role of comorbidities on alterations of cognitive and motor control in the patient groups. The relative lack of effects that would indicate a negative impact of comorbid ADHD on TS in our sample seems at variance with previous work reporting impaired ERPs (Shephard et al., 2016a) and behavioural performance (Greimel et al., 2011; Roessner et al., 2007; Shephard et al., 2016a; Sukhodolsky, Landeros-Weisenberger, Scahill, Leckman, & Schultz, 2010), in participants with TS and ADHD. However, the inclusion of children with ADHD as contrast group as well as analyses with subgroups allowed us to show e.g. higher P3 amplitudes specifically for the TS group. The fact that we did not find significant differences between the TS and TS+ADHD subsamples in the most of the relevant dependent measures reported here justified the inclusion of children with TS only and those with comorbid ADHD in the same group.

Children were medication naïve at the first assessment; however, the numbers of children receiving medication at the second assessment was not sufficient to be considered in the analyses. Although it was not possible to conduct a longitudinal study with multiple assessments over a longer time-span, the measurement of

children at two different time points already contributes important new insight from the follow-up study (paper III).

6. Conclusion and future directions

The work presented herein contributes to the further understanding and establishment of adaptive processes in children and adolescents with TS. The summary in **paper I** identifies compensatory changes in brain structure and function as an important factor in TS. The electrophysiological approach in **paper II** provides evidence for adaptive processes on a behavioural and electrophysiological level in TS, and that comorbid ADHD only marginally affects these changes. By using an electrophysiological approach to measure performance monitoring, we could divide the performance monitoring process into different subprocesses and find an altered sustained attention pattern preceding the response. The follow-up assessment in **paper III** provided evidence for merged developmental trajectories on a behavioural and electrophysiological level in adolescents with TS and controls, and lends support to the assumption that maturation of frontal compensatory self-regulation may facilitate control over tics. The utility of this work lies in the longitudinal approach employed to elucidate adaptive processes of performance monitoring in TS, and illustrates the importance of changes in stimulus and response processing in this patient group.

In the broader perspective, these studies help us to further understand, and to our knowledge for the first time with several timepoints for the measurement of electrophysiological correlates in children with TS at hand, the compensatory adaptive processes in children with TS over time. Their development in terms of cognitive control is similar to healthy control children, though with activations which differ from controls in childhood. During transition to adolescence these neurobiological differences seem to get less prominent in relation to controls. The development in children with TS stands in contrast to children with ADHD, who do not show these underlying compensatory effects but rather display reduced behavioural performance at both timepoints.

The evidence presented herein concerning early compensatory effects may give important clues for understanding early treatment of TS. This detailed knowledge and

heightened clinical awareness concerning underlying neurobiology hopefully will contribute to inform the behavioural treatment options focusing on adaptive and plastic processes of tic suppression and reduction. Evidence for the early presence of compensatory effects already in childhood may indicate that these individuals could already benefit from HRT before the recommended age at around 11 years. Further enhancements in adaptive processes through specific interventions may in the future decrease some of the impairments associated with TS, and thus improve quality of life in this patient group.

There are still many questions regarding the development of cognitive control in children and adolescence with TS that remain unanswered and warrant further study. Additional studies are needed to characterize the functional role of P3 subcomponents, as well as feedback/error-related components in TS in the context of change detection/oddball designs as well as Go/Nogo-type experiments. In the future, we also plan to analyse electrophysiological data other than the ERP in this sample. Data on band-limited power modulation and EEG connectivity in TS is scarce, and we believe the study of non-time/phase-locked oscillatory activity can yield additional insight into tic generation and suppression. Moreover, a combination of several neuroimaging modalities such as magnetic resonance imaging with concurrent EEG recordings in longitudinal settings will supply complementary information regarding localization and timing of the process in question.

Also, considering recent data from theta burst stimulation (C. Gratton, Lee, Nomura, & D'Esposito, 2013; Wu & Gilbert, 2012), we believe that an interventional study approach with transcranial magnetic stimulation together with EEG in people with TS might add significantly to our understanding of the role of control networks. Although untested, it is also conceivable that application of a weak transcranial current in the accessible motor and premotor cortex through transcranial direct current stimulation or transcranial alternating stimulation may also affect TS and controls differentially.

In terms of study design, recruiting larger samples and following children more closely over a longer period of time would not only allow a closer look at the

temporal dynamics of TS symptoms, but also allow addressing the impact of comorbid conditions and medication. This would be particularly informative, as the capacity to modulate tics could be seen in the light of development of self-regulatory abilities in the same population. Furthermore, elucidating development of performance monitoring with computational models that estimate underlying cognitive variables (Forstmann, Wagenmakers, Eichele, Brown, & Serences, 2011) in combination with imaging approaches, may increase our understanding of the origins of adaptive effects in TS.

Source of data

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Neural plasticity in functional and anatomical MRI studies of children with Tourette syndrome

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Abstract.

BACKGROUND: Tourette syndrome (TS) is a neuropsychiatric disorder with childhood onset characterized by chronic motor and vocal tics. The typical clinical course of an attenuation of symptoms during adolescence in parallel with the emerging self-regulatory control during development suggests that plastic processes may play an important role in the development of tic symptoms.

METHODS: We conducted a systematic search to identify existing imaging studies (both anatomical and functional magnetic resonance imaging [fMRI]) in young persons under the age of 19 years with TS.

RESULTS: The final search resulted in 13 original studies, which were reviewed with a focus on findings suggesting adaptive processes (using fMRI) and plasticity (using anatomical MRI). Differences in brain activation compared to healthy controls during tasks that require overriding of prepotent responses help to understand compensatory pathways in children with TS. Along with alterations in regions putatively representing the origin of tics, deviations in several other regions most likely represent an activity-dependent neural plasticity that help to modulate tic severity, such as the prefrontal cortex, but also in the corpus callosum and the limbic system.

DISCUSSION: Factors that potentially influence the development of adaptive changes in the brain of children with TS are age, comorbidity with other developmental disorders, medication use, IQ along with study-design or MRI techniques for acquisition, and analysis of data. The most prominent limitation of all studies is their cross-sectional design. Longitudinal studies extending to younger age groups and to children at risk for developing TS hopefully will confirm findings of neural plasticity in future investigations.

Keywords: Tourette syndrome, children, Magnetic Resonance Imaging, neural plasticity, adaptation

1. Introduction

Tourette syndrome (TS) is a childhood onset neuropsychiatric disorder defined by the presence of mul-

tipl motor tics and at least one vocal tic for more than one year [1] and with a prominent genetic influence [44]. Motor tics usually manifest between the age of 3 and 8 years [31], most commonly as eye blinking, facial grimacing, or nose twitching. Vocal tics typically follow the onset of motor tics by several years [57] and often present themselves initially by coughing, throat clearing or the production of short meaningless sounds. Tic disorders show a typical course in most persons

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affected with the disorder. Tic severity often increases until puberty and subsequently declines such that about 40% of children are tic-free at the age of 18 [33]. This decline in symptoms coincides with the development of self-regulatory control during childhood and adolescence [11,69], which is accompanied by the maturation of the frontal cortex [19].

Motor and vocal tics fluctuate in severity, intensity and frequency [56], and both external and physiological factors influence the expression of tics. Recent evidence thus conceptualizes tics as semi-voluntary habits, rather than involuntary movements [23]. Tics are often preceded by “premonitory urges”, which are unpleasant bodily sensations, acting as internal cues for the execution of a tic [31]. These sensory phenomena consist of a physical experience of tension and prompt a moment of relief after performing the tic. The reduction of this unpleasant sensory experience thus may represent the underlying incentive for the completion of a tic, resulting in a negative reinforcement circuit that supposedly facilitates habit learning. fMRI studies suggest that those urges correlate with increased brain activity within the insula and the cingulate motor areas [5,27] and contribute to tic generation within the cortico-striatal-thalamo-cortical circuits (CSTC) [35,72].

Suppression of tics may be regarded as the repeated overriding of an automatic behavioral response to the premonitory urge. A promising behavioral treatment approach, Habit Reversal Training (HRT), makes use of the fact that in many instances premonitory urges cue the execution of tics [49]. HRT employs the ability of individuals with TS to actively suppress tics while performing a competing motor response. However, the improvement of tic-symptoms during puberty even without the above mentioned intervention suggests that individuals with TS relentlessly and in most instances unconsciously aim to suppress emerging tics to improve their psychosocial function. Multiple studies report superior cognitive control abilities in children with pure TS as compared to controls [25,26,42,62], suggesting a transfer of enhanced behavioral control to other cognitive domains.

Functional and anatomical imaging in TS serve as a window into the developing brain and contribute to the understanding of trajectories of brain development in children with neuropsychiatric disorders. More detailed knowledge concerning underlying neurobiological circuits involved in the disorder will contribute to the development of specific treatment approaches focusing on the facilitation of adaptive and plastic processes with the overall aim to reduce symptoms. Func-

tional imaging of the brain at rest or during tasks relevant to tic suppression can reveal which parts of the brain are involved in the adaptive processes of individuals with TS. A few MR studies in humans have reported direct evidence of plastic changes in anatomic regions as a result of repeated training activity [6,14], setting the framework for mapping neural plasticity in children with TS by means of anatomical MRI. The majority of early imaging studies in TS, however, focused on adult participants, even though the typical course in TS suggests that only a minority of patients retain their tic symptoms through adulthood. Adults with TS thus may represent a selected sample, due to the absence of behavioral adaptation in this group.

Herein, we chose to focus on existing functional and anatomical MRI studies, although other modalities, such as electroencephalography, magnetic encephalography and transcranial magnetic stimulation have in recent years likewise added interesting evidence of the plastic changes in individuals with TS. The existing studies using those modalities, however, have largely examined adults. We will provide a review of findings derived from functional and anatomical imaging studies in children with TS to identify brain areas and processes involved in the development of neural plasticity, along with important sampling characteristics of the studied populations, such as their age, prevalence of comorbid illnesses, and IQ – all factors that are possibly relevant to a more or less successful adaptation to tics.

2. Methods

We limited the scope of this review to functional and anatomical MRI studies and performed the search using Pubmed (ncbi.nlm.nih.gov/pubmed), ISI Web of Knowledge (apps.isiknowledge.com), and Embase (<http://ovidsp.ovid.com>) databases. Combined search terms were (Magnetic Resonance Imaging, MR, MRI, Neuroimaging) AND (Tourette Syndrome, TS, tics, tic disorder) AND (neural plasticity, plasticity, compensatory, neuroplastic, adaptive). Performing this search in April 2012 resulted in 35 original studies that were published or published online ahead of print. The authors screened the abstracts of the initial search results for relevance, and used the reference lists of published articles to identify possible additional studies. The following inclusion criteria were applied: (a) results were published within the last 15 years, due to technical differences in the MRI studies (e.g. resolution

of the MR-images, magnetic field strength) in children with TS before this date (b) language of the publication was English, French, Norwegian, Swedish, Danish or German, (c) included a group of at least 10 participants with the mean age being younger than 19 years. Findings from the 13 studies meeting inclusion criteria were categorized by the different approaches utilized: Structural MRI, functional MRI, and Diffusion Tensor Imaging (DTI) (Table 1).

3. Results

3.1. Functional MRI

3.1.1. Motor activity

Several studies (Table 1) indicate that individuals with TS exhibit an abnormal organization of the motor system, especially in the basal ganglia (for reviews see [18,39,50]). Functional imaging studies of finger tapping tasks can help to identify pathology affecting the motor system. In a recent fMRI study [61], 19 medication-naïve boys with TS and without comorbid conditions showed less activation in the left precentral gyrus in TS compared with the healthy control children in a right index finger tapping paradigm. Boys with TS displayed higher activation in the left caudate nucleus and the right medial frontal gyrus. The authors concluded that alterations in those brain regions could represent signs of early compensation within the functional organization of the motor execution network.

3.1.2. Interference tasks

Interference tasks have been used in several fMRI studies in children with TS because these tasks are similar to the everyday experience of modulating an automatic response (i.e., the tic) to allow for another more appropriate behavior (i.e., the task they are performing). An interference task introduces a response conflict between a correct response based on an abstract, pre-learned mapping rule and an incorrect, but prepotent response triggered, for example, by spatial compatibility between the position of the responding hand and the stimulus as in the Flanker and Simon tasks [55]. Functional imaging allows for the identification of task-related changes in activity and connectivity in brain networks involved in self-regulatory control and the mechanisms that presumably lead to the structural reorganization in the brain of children with TS.

In a Stroop interference task including 32 children with TS and 20 healthy control children (and 34 adults with TS and 50 healthy control adults), participants with TS and healthy controls did not differ in their behavioral performance, but did show different spatial patterns of brain activation [37]. Activations in ventral prefrontal and posterior cingulate cortices showed a prominent interaction between group and age. Post-hoc analyses revealed that individuals with TS, in contrast to controls, showed a tendency to deactivate those regions less and these deactivations further decreased with age. These regions coincided with the default-mode network (DMN). In addition, participants with more severe tics showed increased activation within the dorsolateral prefrontal cortex. The authors concluded that participants with TS overactivated these regions to maintain task performance.

In another fMRI study including 18 unmedicated children with TS compared to 19 controls, tic severity was correlated with slower performance in the most demanding task condition of a cognitive control task involving rule manipulation, task-switching manipulation and interference suppression, indicating that the task was more difficult for individuals with more severe tics [3]. fMRI analyses revealed that greater activation of the dopaminergic substantia nigra/ventral tegmental area and cortical, striatal, subthalamic and thalamic regions in the CSTC circuits correlated with higher tic severity. Finally, participants with TS engaged their prefrontal cortices more while performing the task, compared with the control group, possibly indicating compensatory activation.

A third fMRI study, using the the spatial interference-based Simon task, testing spatial interference, compared brain activation in 22 children with TS with healthy controls in the same age range and with adults in the two groups [54]. Task-relevant activations were more widespread in the younger participants, whereas older individuals showed more specific fronto-striatal activation, indicating a general age-related shift. These age-related differences were more pronounced in the TS group despite comparable performance in the task. In addition, tic severity correlated positively with frontal activation, supporting the authors' suggestion that activation of fronto-striatal circuits supports both efficient performance and regulation of tic severity. Further, the authors suggested that adults with persistent TS may have deficiencies in these circuits due to a failure of prefrontal plasticity and disturbances in striatal function.

Finally, in a manual task-switching paradigm, 10 children with TS showed greater activation in the right

prefrontal cortex at the same level of performance as compared to 15 control children [26]. In addition, the greater activation was strongly related to comparable behavioral performance in children with TS and controls, indicating enhanced cognitive control of motor output during a behavioral task with a high level of intermanual conflict.

3.1.3. *Inhibitory tasks*

The ability to suppress a prepotent response is an important function for executing control. Response inhibition allows appropriate responses to meet complicated task demands and adaptation to changing environments [71]. The most common measures of response inhibition are the go/no-go and stop-signal response time task. In these behavioral tasks, the dominant or more frequent stimulus constitutes a 'go' signal requiring the subjects to respond within a time window and therefore establishes a prepotent response tendency. While there have been no imaging assessments of inhibitory function in childhood TS are available on these canonical response inhibition tasks, a recent fMRI study has examined blink suppression in TS, since premonitory urges in TS are often compared to the feeling of not being allowed to blink [38]. In this study, 22 children with TS were compared with 16 healthy children (along with 16 adults with TS and 17 healthy control adults) while inhibiting their urge to blink. Children with TS showed higher activation in the frontal cortex and striatum during eye blink inhibition. Activation increased more with age in regions of the dorsolateral and inferolateral prefrontal cortex and caudate nucleus in participants with TS. Furthermore, participants with TS showed more activation in the middle frontal gyrus, dorsal anterior cingulate, and temporal cortices. Tic severity correlated inversely with activation in putamen and inferolateral prefrontal cortex.

3.1.4. *Resting state activity*

Resting state networks describe spatially organized and temporally correlated brain activity when participants are at rest and not performing a specific task. Resting state networks include the default mode network, which is often anticorrelated to task-related networks and may therefore represent the systems readiness to engage in interference task [17]. Those networks mature during childhood [16] and may express a factor for the level of maturation of the central nervous system [13]. Resting-state fMRI in 33 adolescents with TS (aged 9–15) revealed immature patterns of functional connectivity, especially in two networks involved in

task cognitive/executive control [8]. The fronto-parietal network is more likely involved in more rapid, adaptive online control, and a cingulo-opercular network that is important for self-maintenance. The developmental transitions seen during maturation in healthy children did not appear in TS, and the brains of children with TS appeared younger than their chronological age. Most differences between groups were present in fronto-parietal networks; individuals with TS showed weaker connectivity between distant areas of the brain, but stronger connectivity between neighboring areas of the brain. On the basis of these results, the authors argued that differences in patterns of connectivity are adaptive effects to support online task-control and to compensate for the inability to suppress tics.

3.2. *Anatomical MRI and Diffusion Tensor Imaging*

Evidence derived from clinical [39], neuropsychological [36] and imaging studies point to the basal ganglia as the region in the brain exhibiting the genetic vulnerability for TS. Several anatomical MRI investigations, and in particular one large study of basal ganglia volumes in children and adults with TS and healthy control subjects [48], revealed smaller volumes of the nucleus caudate bilaterally in children and adults with TS as compared to healthy controls. The presence of significantly smaller caudate nuclei in both age groups suggests that reduced volumes of the caudate nucleus may represent a trait morphological deviation in persons with TS. Moreover, the persistence of decreased volumes of the caudate nucleus into adulthood implies that the caudate nucleus is not a prime target for adaptive changes in response to the presence of tics. The predictive role of the volume of the caudate nucleus was confirmed in a follow-up study of a large sample of children with TS, revealing that the size of the caudate nucleus in childhood correlated inversely with the severity of tics and with Obsessive Compulsive Disorder (OCD) symptoms in early adulthood [4].

Even though these studies shed light on the origin of tic behavior, other circuits are involved in the regulation of tic behavior. It is the interaction of striatal, limbic and cortical portions of the CSTC circuits that largely determines an individual's capacity for self-regulatory control, such as the ability to inhibit unwanted impulses, to monitor ongoing actions or to plan future actions [10]. These circuits are thus of high relevance for successful modulation of tic-behaviors. In line with this notion, a study using high-resolution MRI (Table 2) showed that regional volumes of the

Table 1
Functional MRI studies indicating plasticity in children with TS

Area of interest	Tourette (N); age (SD); age range; gender (male/female)	Controls (N); age (SD)	Comorbidity	The severity	IQ (less), mean (SD)	Medication	Method	Main findings
Motor activity								
Roesner, Whitfoth et al. 2012 [61]	Whole brain /ROI	N = 19; 12.5 years (1.4); age range n.a.; 190	No comorbidity	TSSS score = 1.9, SD = 1.4	IQ (subscales of WISC-Revised), full-scale IQ TS = 106.1 (13.7), controls = 106.3 (10.7)	None	fMRI/finger tapping	TS: ↓ activation in left pre-central gyrus, ↑ activation in caudate nucleus and medial prefrontal cortex
Inference task								
Marsh, Zhu et al. 2007 [37]	Whole brain /ROI	Children N = 32; adults N = 34; children 12.8 years (2.8), adults N = 50; children 35.27 years (11.1); children 8.4-17.5 years, adults 17-52.0 years, children 2/75; adults 20/14 (11.4)	OCD N = 10, ADHD N = 6, OCD+ADHD N = 4	YGTS motor tic present = 18.5, YGTSS lifetime-w.e. children = 28.41, YGTSS phobic tic score present children = 10.2, YGTSS phobic w.e. children = 9.9	IQ (WASI), full-scale IQ TS = 113.9 (13.2), controls = 117.3 (12.3)	Stimulants N = 3, Haloperidol/pimozide N = 6, Risperidone N = 5, α-adrenergic agonists N = 6, SSRI N = 8,	fMRI/ Stroop interference task	TS: failed to ↓ activity in mesial prefrontal cortex, in ventral anterior cingulate cortex, in posterior cingulate cortex, with age, failed to ↑ activity in fronto-striatal circuitry with age
Baym, Corbett et al. 2008 [3]	Whole brain /ROI	N = 18; 10.42 years; 7-13 years; 15/3	OCD N = 8, ADHD N = 59	YGTS mean score = 21, SD = 7	Exclusion IQ (WASI) below 75, estimated IQ TS = 106 (14), controls = 117 (12)	Atomoxetine N = 2, off medication > 40 hours before scanning	fMRI/ cognitive control task	↑ Tic severity correlated to ↓ performance, ↑ tic severity correlated to ↑ activation of dopaminergic nuclei and cortical, striatal and thalamic regions; ↑ tic severity associated with ↑ engagement of subthalamic nucleus
Raz, Zhu et al. 2009 [54]	Whole brain	Children N = 22; adults N = 16; children 13.0 years (2.7), adults 38.1 years (13.5); children 8.9-18.2, adults 23.9-64.6; children 12/10, adults 10/6 (12.4)	OCD+ADHD N = 1	YGTS mean score = 13.0, SD = 2.7	Exclusion IQ (WASI) below 75, full-scale IQ TS = 113.9 (13.2), controls = 117.3 (12.3)	n.a.	fMRI/Simon task	TS; pronounced ↑ specific frontostriatal activation with age, correlation tic severity with ↑ frontal activation
Jackson, Parkinson et al. 2011 [26]*	ROI	N = 10; 13.75 years (1.75 years); 10.8-18.08 years (1 year (N = 13); 8/2)	No comorbidity	YGTS global Yale score present = 31.7, SD = 21.3 for N = 13	IQ (WAS), estimated IQ TS = 106.6 (SD) = 14.7 for N = 13, controls n.a.	Clonidine N = 5, Risperidone N = 1, Fluoxetine N = 1, Melatonin N = 1, Aripiprazole N = 1 for N = 13, 1 TS participant > 1 med.	DTI and fMRI	TS: ↑ BOLD response in right prefrontal cortex during high-conflict trials
Inhibitory task								
Marzzone, Yu et al. 2010 [38]	Whole brain /ROI	Children N = 22; adults N = 29; children 13.1 years (2.6), adults 35.1 years (11.1); age range n.a.; children 19/3, adults 17/12 (11.0)	OCD N = 21, ADHD N = 48; OCD+ADHD N = 4	YGTS mean score present = 18.5, YGTSS lifetime-w.e. score children = 28.9	Exclusion IQ (WAS) below 75, full-scale IQ TS = 116.0 (12.1), controls children = 116.1 (13.4)	Typical neuroleptics N = 5, risperidone N = 4, α-adrenergic agonists N = 2, SSRI N = 2, valproic acid N = 2	fMRI/eye blinking inhibition	TS: fronto-striatal activation ↑ regions during inhibition

Table 1., continued

Area of interest	Tourette (N); age (SD); age range; gender (male/female)	Controls (N); age (SD)	Comorbidity	Tic severity	IQ (Test), mean (SD)	Medication	Method	Main findings
Resting state Church, Fair et al. 2009 [8]	Functional connectivity in 39 previously defined putative regions during resting state N = 33; 12.7 years (SD n.a.); 9:02–15:83 years; 25/8	N = 42; 12.69 years (SD n.a.)	OCD N = 21, ADHD N = 11, OCD+ADHD N = 4	YGTSS mean score = 16.3	Exclusion IQ (WISC-IV) below 80, full-scale IQ TS children = 105.4 (SD n.a.), controls children = 108.5 (SD n.a.)	Alpha2-agonists N = 13, atypical neuroleptics N = 7, stimulants N = 7, SSRI N = 6, benzodiazepines N = 2, antiepileptic meds. N = 2, norepinephrine RI antidepressants N = 2, beta-blockers N = 1, tetracyclic antidepressants N = 1, 13 TS participants > 1 med	fMRI/resting state, functional connectivity	TS: failure to develop age-appropriate networks

*†† = Increased; *† = Decreased; ADHD = Attention-deficit/hyperactivity disorder; BG = Basal ganglia; DLPF = Dorsolateral prefrontal; DTI = Diffusion Tensor Imaging; ROI = Region of interest measurement; SSRI = selective serotonin reuptake inhibitor; TS = Tourette syndrome; TSSS = Tourette Syndrome Severity Scale; YBM = Voxel-based morphometry; VOI = Volume of interest measurement; WASI = Wechsler Abbreviated Scale of Intelligence; WISC = Wechsler Intelligence Scale for Children; WBV = Whole brain volume; YGTSS = Yale Global Tic Severity Scale; YGTSS-we = Yale Global Tic Severity Scale-worst ever score. * Jackson, Parkinson et al. [26] includes a functional and an anatomical study and appears therefore in Table (1) and (2).

Table 2
Anatomical MRI studies indicating plasticity in children with TS

Area of interest	Tourette (N); age range; gender (male/female)	Controls (N); age (SD)	Comorbidity	Tic severity	IQ (ftest), mean (SD)	Medication	Method	Main findings
Cortical regions								
Plessen, Peterson, Staib et al. 2001 [47]	N = 155; 18.7 years (13.4); 6-63 years; 114/41	N = 131; 20.8 years (13.4)	OCD N = 62; ADHD N = 36	YGTSS scores n.a.	Exclusion IQ below 80, IQ scores n.a.	Stimulants N = 3, tridone N = 20, risperidone N = 7, alpha-adrenergic agonists N = 29, SSRI N = 19, tricyclics N = 11	Parcellation of cerebral sub- and divisions	TS: dorsal prefrontal volumes and parieto-occipital regions ↑, inferior occipital volumes ↓
Corpus callosum								
Plessen, Wenzel-Larsen et al. 2004 [53]	N = 158; 18.5 years (13.3); 5-63 years; 117/41	N = 121; 19.7 years (12.6)	OCD N = 39; ADHD N = 32; OCD+ADHD N = 10	YGTSS motor tic present = 11.4, SD = 4.6, Adults mean = 14.9, SD = 4.2, YGTSS lifetime-we-children = 15.0 SD = 4.3, versus adults = 18.8, SD = 2.7, YGTSS phonic we children = 11.6, SD = 4.5, versus adults 14.4, SD = 4.4; YGTSS motor tic present = 11.4, SD = 2.9, YGTSS lifetime-we = 15.5 SD = 5.1, YGTSS phonic tic score present = 9.2, SD = 3.4, YGTSS phonic tic = 10.57 (9.2)	Exclusion IQ below 80, IQ scores n.a.	Traditional neuroleptics N = 12, risperidone N = 4, alpha-adrenergic agonists N = 22, SSRI N = 9, combination of traditional neuroleptics and SSRI N = 4, other N = 1	ROI	Interaction with age: TS children having ↓ CCs and TS adults ↑ CCs
Plessen, Gruner et al. 2006 [51]	N = 20; 13.6 years (1.9); 9-17 years; 20/0	N = 20; 13.4 years (2.4)	OCD N = 4; ADHD N = 5; OCD+ADHD N = 0	YGTSS motor tic present = 15.5 SD = 5.1, YGTSS phonic tic score present = 9.2, SD = 3.4, YGTSS phonic tic = 10.57 (9.2)	Exclusion IQ (WISC-III) below 70, full-scale IQ, TS = 94.5 (10.2), controls = 105.7 (9.2)	Neuroleptics N = 4, alpha-adrenergic agonists N = 2, SSRI N = 1, stimulants N = 2,	DTI analysis of CC subdivisions	TS: ↓ FA values in all subdivisions of the CC
Roessler, Overlack et al. 2011 [60]	N = 49; 12.0 years (1.3); 9-15 years; 49/0	N = 42; 12.1 years (1.3)	No comorbidity	TSSS scores = 2.2, SD = 1.5	IQ (WISC-R), full-scale IQ TS = 109 (13), controls = 110 (11)	None	Volumetric analysis	TS: ↑ left and right putamen, ↑ subregion of the CC
Jackson, Parkinson et al. 2011 [26]*	N = 14; 14.5 years (SD 2.5 years) for white matter N = 13; 10.8-18.08 years for N = 13; 12/2	N = 14; 15.3 years (SD n.a.)	No comorbidity	YGTSS present = 31.7, SD = 21.3 for N = 13	IQ (WASI), estimated IQ TS = 106.6 (SD) = 14.7 for N = 13, controls n.a.	Clonidine N = 5, Risperidone N = 1, Fluoxetine N = 1, Melatonin N = 1, Arripazole N = 1 for N = 13, 1 TS participant > 1 med.	DTI and fMRI	TS: differences in microstructure, including CC and corpus minor, correlation with tic severity
Thalamus								
Miller, Balsas et al. 2010 [40]	N = 149; 18.7 years (13.0); 6-63 years; 112/57	N = 134; 22.9 years (13.7)	ADHD N = 42; OCD+ADHD N = 10	YGTSS scores n.a.	Exclusion IQ (WASI) below full-scale IQ TS = 113.8 (16.8), controls = 120.0 (17.1)	Typical neuroleptics N = 15, atypical neuroleptics N = 7, alpha-adrenergic agonists N = 28, SSRI N = 20, stimulants N = 5, tricyclics N = 12	VOI and surface matching analysis	TS: overall volumes thalamus ↑, locally ↑ over lateral thalamus
Amygdala&Hippocampus								
Peterson, Choi et al. 2007 [45]	N = 154; 18.7 years (13.4); 6-63 years; 115/59	N = 128; 20.2 years (13.2)	OCD N = 48; ADHD N = 42; OCD+ADHD N = 10	YGTSS scores n.a.	Exclusion IQ (Kauffmann Brief Intelligence Test) below 70, full-scale IQ TS = 113 (16.1), Controls = 119.5 (16.9) scores n.a.	Typical neuroleptics N = 19, atypical neuroleptics N = 7, alpha-adrenergic agonists N = 28, SSRI N = 20, stimulants N = 3, tricyclics N = 12	VOI and surface matching analysis	TS: overall volumes amygdala and hippocampus ↓

*↑ = Increased; ↓ = Decreased; ADHD = Attention-deficit/hyperactivity disorder; BG = Basal ganglia; DLPF = Dorsolateral prefrontal; DTI = Diffusion Tensor Imaging; ROI = Region of interest measurement; SSRI = selective serotonin reuptake inhibitor; TS = Tourette syndrome; TSSS = Tourette Syndrome Severity Scale; VBM = Voxel-based morphometry; VOI = Volume of interest measurement; WASI = Wechsler Abbreviated Scale of Intelligence; WISC = Wechsler Intelligence Scale for Children; WBV = Whole brain volume; YGTSS = Yale Global Tic Severity Scale; YGTSS-we = Yale Global Tic Severity Scale-worst ever score. * Jackson, Parkinson et al. [26] includes a functional and an anatomical study and appears therefore in Table (1) and (2).

dorsal prefrontal and parietal cortex were significantly larger and inferior occipital volumes were significantly smaller in 155 children and adults with TS compared to 131 controls (age 6–63 years, 61.9% children). The association of larger cortical volumes in orbitofrontal and parieto-occipital regions with fewer tic symptoms confirmed the clinical significance of these findings, implying that the anatomical deviations represent a plastic reorganization of the prefrontal cortex to facilitate tic suppression [47]. The findings in children, however, differed markedly from those in adults with TS indicated by a strong interaction of Diagnosis x Age x Region, showing that dorsal prefrontal volumes were smaller in adults with TS compared to controls. Activity-dependent plasticity and hypertrophy within prefrontal regions could help to attenuate the severity of tic symptoms due to its capacity to increase the inhibitory reserve in the prefrontal regions and the capacity for self-regulatory control that is noted in the typical development of children and adolescents [11].

The corpus callosum (CC), the largest interhemispheric commissure, connects cortical regions in the brain and thus modulates and influences activity throughout the cortex. A study including 158 individuals ($n = 113 < 19$ years) with TS compared to 121 controls ($n = 66 < 19$ years) revealed that the size of the CC was smaller in children with TS and larger in adults with TS compared with healthy age-matched controls [53]. Furthermore, the size of the midsagittal CC correlated inversely with volumes of the prefrontal cortex in both the TS and control group, but the magnitudes of these inverse correlations was significantly higher in the TS group. Finally, the size of the CC correlated with the severity of motor tics, indicating that a smaller CC may have a protective or compensatory function in subjects with TS. In a region-of-interest Diffusion Tensor Imaging (DTI) study [51], the fractional anisotropy (FA) in the CC was significantly reduced throughout all partitions in 20 boys with TS (9–18 years) compared to 20 control children. FA is a measure of the integrity or the density of white matter, suggesting that its reduction speaks for an impaired interhemispheric connectivity. The authors have argued that a smaller CC, with a reduced interhemispheric connectivity may facilitate prefrontal function and thereby enhance the suppression of tics. This finding was corroborated in a recent study [26] conducting a whole-brain analysis of tract-based spatial statistics in 14 children with TS and 14 controls. Individuals with TS showed several tracts with reduced FA and increased mean diffusivity (MD), especially in the CC

and the forceps minor. FA correlated with tic-severity, in line with the suggestion that the reorganization of the white matter in the CC may be a plastic response to improve prefrontal suppression of tics. Another recent study reported potentially contradictory results: 49 boys with TS showed a larger CC when compared to 42 controls (9–15 years), especially in the motor portion [60], which was considered a result of continuous motor activity due to the execution of tics, however, CC size did not correlate with tic-severity in that study.

The last modulatory station in the cortico-subcortical feedback circuit for self-regulatory control is the thalamus. High-resolution structural MR was used to examine both overall thalamic volume and local volumetric surface differences in a large sample of 149 individuals with TS ($n = 105 < 18$ years) and controls ($n = 58 < 18$ years) [40]. Such fine-grained analyses may help to localize volumetric differences to specific clusters of voxels on a structure's surface with more homogeneous function [2]. Thalamic volume in children and adults with TS was overall enlarged and surface analysis revealed higher local volumes over the lateral thalamus, which is regarded as the anatomical cross-roads of activity-dependent hypertrophy or adaptive response within a larger compensatory system [21]. However, an interaction of Diagnosis x Sex indicated that female participants with TS showed a proportionally larger outward deformation. Finally, the inverse correlation of outward subregion with symptom severity was valid only for the female participants with TS.

Limbic portions of the cortical-subcortical circuits have been implicated in TS in one major study [45]. Using anatomical MRI, the authors reported that children with TS have an overall enlargement of hippocampus and amygdala in a large sample including 154 TS ($n = 109 < 18$ years) and 128 control subjects ($n = 72 < 18$ years). Moreover, detailed morphometric analyses of the surface of both regions localized the volumetric differences mainly to the head and the distal tail bilaterally and left medial border of the hippocampus and the dorsal and ventral surfaces of the amygdala. The local volumes of these subregions on the surface of the structures declined with age in the TS group resulting in larger subregions in children, but smaller subregions in adults with TS, compared with the controls, where these strong correlations with age were absent. Finally, inverse correlations of those local volumes with tic severity suggested the adaptive and compensatory nature of the hypertrophy, in line with the hippocampal involvement in the extended networks of neural compensation and finally the intimate interaction of the hippocampus and the amygdala with prefrontal regions [7].

4. Discussion

We reviewed original studies using functional and anatomical MRI to improve the understanding of neuroplastic changes the brain of children with TS. This resulted in the identification of several complementary processes of neural plasticity involved in the execution and the modulation of tics.

First, most fMRI studies indicate the presence of adaptive compensatory processes at a functional level that help to maintain performance in the presence of an impaired motor function [3,37,54,61]. Evidence for underlying disturbances in motor circuits is consistent with reduced inhibitory interneurons in the striatum [28] and with the notion that individuals with TS show reduced inhibition of their motor cortices [73]. Moreover, motor activity is postulated as excessive within the basal ganglia's direct output pathway, which would in turn disinhibit thalamocortical projections and produce excess synaptic activity within the motor portion of the CSTC loops [41]. These compensatory processes involve the activation of the prefrontal, cingulate, striatal, and thalamic regions and are consistent with the role that these regions play in guiding the precision of motor movements, but also in conflict-evoking interference tasks.

Second, activity-dependent hypertrophy in motor areas has been shown to result in a plastic reorganization of parts of the brain that are directly involved in the performance of tics, such as excessive tic-related activity in motor circuits [60].

Third, compensatory reorganization appears to develop in brain regions involved in facilitating the successful modulation and suppression of tics. This continuous activity presumably results in an enlargement of the prefrontal cortex [47], the amygdala, and hippocampus [45], but a smaller CC [53], all of which were associated with less severe symptoms. These findings suggest a compensatory response that helps to attenuate symptoms by increasing the inhibitory reserve, consistent with the role of the dorsal prefrontal region in subserving self-regulatory functions of fronto-striatal circuits [67]. The importance of the prefrontal cortex for the suppression of tics has been documented in the first fMRI study in adults with TS, revealing significant activations in prefrontal and fronto-temporal regions and the caudate nucleus during periods of voluntary tic suppression compared with a rest condition, where participants were not suppressing their tics [46].

Finally, several studies imply that children with TS are superior to controls in cognitive control tasks, with

enhanced self-regulatory control in a compensatory manner, which is, however, difficult to disentangle from the transfer seen in the brain e.g. as the result of cognitive training. Although the anatomical MRI studies in children with TS discussed here have not measured the capacity of self-regulatory control, several of the fMRI studies have used paradigms that involve cognitive control, where children with TS showed comparable [3,37] or better performance than controls [26]. The capacity for cognitive control in patients with TS is a topic of discussion and existing reports suggest conflicting results [9,15,43,59,65]. Several behavioral investigations also suggest that children with TS even may exert enhanced inhibitory control in situations that require cognitive control. Children with TS out-perform controls in directing their eye-movements [25,42]. In addition, because tic suppression activates the same prefrontal brain regions as tasks requiring cognitive control, parallel processes may be involved in performance monitoring and in tic-suppression [46].

4.1. Clinical characterization

Several intra-individual variables may determine the capacity of a child to unconsciously learn to modulate tics, which in the long run, may lead to a plastic reorganization of the brain. The present studies, which have been selected for their focus on adaptive control and plasticity, may illuminate the significance of a few of these factors.

4.1.1. Tic severity

The evidence pointing toward underlying plastic processes is mostly based on correlations with tic-severity in the presented studies. The execution of many tics per day may trigger compensatory phenomena, but on the other hand, it may also represent the inherent lack of capacity to modulate the symptoms. Furthermore, the fact that tics wax and wane in their frequency and characteristics over hours, days, and months, makes the objective measurement of symptoms difficult. The studies selected in this review almost exclusively reported tic severity by using the Yale Global Tic Severity Scale (YGTSS) [32], with the exception of [61] who used the Tourette Syndrome Severity Scale (TSSS) [63]. Although the reported measurements differ with respect to reporting motor or vocal scores, either as "present" or "worst-ever" scores (see Tables 1 and 2), all selected studies demonstrated inverse correlations of anatomic or functional deviations with tic-severity, that is, participants with the least severe tics also had largest devi-

ations, and the authors thus interpreted their findings as compensatory phenomena. Although the YGTSS has good psychometric properties [32], and one study has demonstrated consistency between two YGTSS administrations separated by time and completed by different interviewers [68], it is a mere clinical measure and none of the studies report any reliability ratings, which must be regarded a general limitation.

4.1.2. Age

Although the search was limited to studies that mainly included children and adolescents with TS, some included individuals with TS throughout lifetime and most show that correlations with age play an important role. Large samples that included children and adults with TS and age-matched controls deriving from a general population show prominent interactions of diagnosis with age in most regions of the brain [45,47,53] with the exception of the basal ganglia [48]. Neuroimaging studies to date support findings from clinical studies suggesting that adults with TS are a subsample of all individuals affected with TS, who have not undergone the adaptive processes that lead to an attenuation of tics in the majority of cases. However, this evidence is merely based on cross-sectional studies, in the absence of longitudinal studies.

4.1.3. Comorbidity

Rates of comorbidity with OCD in TS patients exceed 40% in clinical samples of adults [29,70]. Comorbidity with ADHD is observed in 60% of children with TS in clinical samples [58]. Evidence from neuroimaging studies that included both individuals with TS alone and individuals with TS and comorbid ADHD suggest that comorbid ADHD does not significantly alter the primary findings in samples of individuals with TS, thus providing support for the hypothesis of a shared genetic vulnerability as expressed in deviations of brain morphology in these comorbid conditions [52]. The extant literature suggests that comorbid OCD does not have an explicit influence on brain activation or morphology, though most studies have controlled for the presence of comorbid disorders in their statistical models. Moreover, analyses restricted to all individuals with “pure” TS and the control group, as performed in [3,37,38,45–47,51,53], have helped to confirm that primary findings were not driven by comorbid conditions.

4.1.4. Medication

Most of the selected studies have included children on tic-suppression medication, with the potential that

these pharmacological agents may facilitate or inhibit the development of adaptive processes or influence functional and anatomical differences. Although several of the agents may have unwanted side effects along with alleviating tics, it is unlikely that the medication status of children with TS has influenced the primary findings, as most authors consider medication as a potentially confounding variable [37,38,45,47,51,53] (though see [40], where effects of medications were apparent). This is in contrast to other neuropsychiatric disorders, such as ADHD, where subgroups of patients on or off medication have showed differences in brain morphology [24,66] and in longitudinal development [64]. The general lack of evidence for changes due to medication may either be a real absence of effect, or alternatively represent small effect sizes in small samples and even smaller subgroups on the different agents. Larger studies should thus attempt to map the effects of medication on brain anatomy and function in parallel to running psychopharmacological studies testing the effectiveness of the agents used to treat tics.

4.1.5. Intelligence

IQ plays a crucial role for the capacity of adaptation and the general psychosocial outcome in children with neuropsychiatric disorders. Several studies indicate an IQ lower than the population mean in children with TS [12,43], whereas other studies have not confirmed this notion [34,65], potentially due to differences in sample selection and recruitment. In the studies selected for the review, children with TS did not show a lower IQ than the mean, although in some instances still a lower IQ than the control sample (see Tables 1 and 2). Hence their higher IQ may represent a positive selection for the presence of plastic processes.

4.2. Study characteristics

4.2.1. Study-design

All studies are cross-sectional in their design, which limits their ability to infer to developmental processes [30]. The core characteristic of compensatory processes is the development over time, whereas cross-sectional studies may in best case enhance the understanding of correlations with age.

4.2.2. MRI methodology

The techniques used to collect and analyze data play an important role for identifying deviations that may represent functional or anatomical correlates of compensatory processes. The studies presented here include anatomical and functional MRI studies, yet

they use different methods of acquisition and analyses, which makes it difficult to combine the findings in a meta-analysis. Despite the wide array of methods used to explore the signs for plastic changes in children with TS, there is impressive convergence on cortico-striatal pathways, and it is possible to pinpoint processes and areas involved in neural plasticity.

5. Future directions

The presented studies provide evidence for the existence of ubiquitous compensatory phenomena in children with TS. All findings, however, are of correlational nature and consist most typically of deviations in brain activation or morphology that correlated with a clinical measure – tic-severity. The interpretations concerning the compensatory changes put forward by the authors lack causal relation in the absence of underlying ultrastructural components. In future studies it will be crucial to measure a child's capacity of self-regulatory control in TS, both in terms of understanding whether the capacity of self-regulatory control may be a protective factor for developing symptoms or for the ability to modulate tics.

Longitudinal imaging of representative samples of children at high risk or of younger children with TS will in the future hopefully provide clues to understanding differences in the trajectories of brain development in children with TS and provide a valid approach for disentangling causes from compensatory effects. Imaging of children who are at risk for developing TS with a combination of several MRI modalities, including anatomical MRI, functional MRI, DTI, spectroscopy, and possibly concurrent EEG recordings, will aid the pathophysiological interpretation of imaging findings in TS, supplying complementary views of brain structure and function that together will be more helpful in identifying endophenotypes for disease vulnerability that are independent of the compensatory effects of having TS with the typical symptoms of the illness [20]. A prospective longitudinal follow-up of children at high-risk that would permit scanning the sample at multiple time points would help to distinguish the trait vulnerabilities to changes related to symptom exertion and to compensatory changes that emerge early in the course of the disorder. Moreover, combining longitudinal studies with randomized clinical trials, such as trials of cognitive or behavioral exercises that are designed to encourage tic modulation, may provide the experimental control to determine whether ev-

idence from cross-sectional studies is validated in rigorous experimental settings. In consideration of future developments, the technical advances in imaging and image processing will likely begin to bridge the gap from research to clinical applications. MRI scans may become sensitive at the level of the individual, permitting comparisons of brain activation and anatomy that may confirm or oppose a given clinical diagnosis [22].

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Performance Monitoring in Medication-Naïve Children with Tourette Syndrome

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Background: Tourette syndrome (TS) is a childhood-onset neurodevelopmental disorder and its impact on cognitive development needs further study. Evidence from neuropsychological, neuroimaging and electrophysiological studies suggests that the decline in tic severity and the ability to suppress tics relate to the development of self-regulatory functions in late childhood and adolescence. Hence, tasks measuring performance monitoring might provide insight into the regulation of tics in children with TS.

Method: Twenty-five children with TS, including 14 with comorbid Attention-deficit/hyperactivity disorder (ADHD), 39 children with ADHD and 35 typically developing children aged 8–12 years were tested with a modified Eriksen-Flanker task during a 34-channel electroencephalography (EEG) recording. Task performance, as well as stimulus-locked and response-locked event-related potentials (ERP) were analyzed and compared across groups.

Results: Participants did not differ in their behavioral performance. Children with TS showed higher amplitudes of an early P3 component of the stimulus-locked ERPs in ensemble averages and in separate trial outcomes, suggesting heightened orienting and/or attention during stimulus evaluation. In response-locked averages, children with TS had a slightly higher positive complex before the motor response, likely also reflecting a late P3. Groups did not differ in post-response components, particularly in the error-related negativity (ERN) and error-related positivity (Pe).

Conclusions: These findings suggest that children with TS may employ additional attentional resources as a compensatory mechanism to maintain equal behavioral performance.

Keywords: Tourette syndrome, ADHD, children, P3, event-related potentials, performance monitoring

INTRODUCTION

Tourette Syndrome (TS) is a childhood onset neuropsychiatric disorder with multiple motor tics and at least one vocal tic for more than 1 year (American Psychiatric Association, 1994). Tics are often described as semi-voluntary, because children with TS can suppress their tics for a certain amount of time at the cost of increasing discomfort for the patient (Spessot et al., 2004). However, tic suppression is tiring and effortful, and may contribute to an increased feeling of “premonitory urge,” which is an unpleasant bodily sensation preceding a tic and relieved by tic expression (Leckman, 2002). This reduction of unpleasant bodily sensation may contribute to a negative reinforcement of tic performance habit (Plessen, 2013).

Tic symptoms often attenuate in adolescence and about 40% of children are tic-free at the age of 18 (Leckman et al., 1998; Burd et al., 2001; Bloch and Leckman, 2009). This typical course of symptoms suggests that individuals with TS constantly, and often unconsciously, aim to suppress emerging tics to improve their psychosocial function (Eichele and Plessen, 2013). This process coincides with the development of self-regulatory control during childhood and adolescence (Davidson et al., 2006; Tau and Peterson, 2010) and maturation of the frontal cortex (Gogtay et al., 2004).

The ability to dynamically adapt the behavior to situational demands is a crucial part of adequate daily functioning (Ullsperger, 2006; Ullsperger et al., 2014). This requires a set of processing functions that localize to a broad network of brain areas encompassing frontal cortices, basal ganglia and thalamic nuclei, the cortico-striato-thalamo-cortical (CSTC) circuits. Activity in this network is elicited during performance monitoring and can be tested with the Eriksen-Flanker task (Eriksen and Eriksen, 1974).

Attention networks contribute to the perception of environmental cues that is essential for regulating behavior (Posner et al., 2014), and thus underlie the capacity of self-regulation (Rothbart et al., 2011). Different tasks of performance monitoring have been widely used to study this form of control (Fan et al., 2002). Recent work indicates that inhibitory control networks involving CSTC circuits are engaged during conflict trials to prevent attentional capture and interference (Tau and Peterson, 2010). Finally, imaging studies of individuals with TS indicate that inhibitory cognitive control processes might be altered (Worbe et al., 2015).

Due to the assumption that persons with TS show impairment of the CSTC circuits and the overlap of these networks with those involved in performance monitoring, the latter may also show impaired function. However, multiple studies report comparable, or even superior abilities of motor and cognitive control in children with TS compared with controls (Ozonoff and Jensen, 1999; Serrien et al., 2005; Mueller et al., 2006; Jackson et al., 2007, 2011; Eichele et al., 2010a). It is therefore of interest to investigate possible adaptive effects in this network. Many persons with TS are co-diagnosed with at least one further psychiatric disorder, with attention-deficit/hyperactivity disorder (ADHD) being the most common comorbid condition with 50–60% of all Tourette syndrome patients (Robertson, 2012; Hirschtritt et al., 2015). The

reasons for the high co-occurrence have been widely discussed in the last decades but exact mechanisms still remain unclear. Evidence suggests that deficits in the basal portions of CSTC circuits represent shared neurobiological substrates for both disorders (Vloet et al., 2006; Sobel et al., 2010). Studies comparing children with TS with and without comorbid ADHD implied that children with comorbid ADHD showed impaired performance in tasks demanding cognitive control (Roessner et al., 2007; Greimel et al., 2008, 2011; Sukhodolsky et al., 2010). This is in line with findings suggesting altered behavioral and electrophysiological measures of performance monitoring tasks in persons with ADHD (Barry et al., 2003; Liotti et al., 2005; Johnstone and Galletta, 2013; Johnstone et al., 2013).

Different trial types modulate the sequence of stimulus- and response-locked event-related potentials (ERP) in the electroencephalogram (EEG) and outcomes indicate modulations of interference/conflict and control. The stimulus-locked N2 reflects early stages of conflict/mismatch detection (Folstein and Van Petten, 2008; Larson et al., 2014). This component is also reduced in children with ADHD (Albrecht et al., 2008). We decided to focus on the subsequent P3 that is thought to reflect a neural representation of a sensory process where the incoming stimulus is compared to the mental representation of the previous stimuli and the stimulus environment is updated. This is closely linked to concepts of orienting/surprise and predictive coding (Eichele et al., 2005). A later aspect of P3, the late positive complex (LPC) is thought to more closely represent working memory and response selection (Donchin, 1981; Donchin and Coles, 1998, 2010; Polich, 2007). Contingent upon this, the P3 is also sensitive to changes in conflict and control (Clayson and Larson, 2011a,b). Due to the ability of children with TS to react to the presence of internal cues (premonitory urges) we expected a superior function of this electrophysiological correlate for performance monitoring.

After errors, the error-related negativity (ERN) and error positivity (Pe) are detectable. The ERN arises immediately after error commission (Debener et al., 2005; Larson et al., 2014) and reflects automatic error detection in the mesial frontal cortex. Individuals with several neuropsychiatric disorders, including adolescents with ADHD (Albrecht et al., 2008) show a reduction of this early negativity. Finally, the ERN is followed by the Pe, a P3-like positive deflection, emerging approximately 300 ms after incorrect responses and is associated with evaluation and awareness, as well as the salience of errors. It is important to note here that the ERN is not fully established before adolescence and was therefore not focus in our study, whereas the Pe amplitude does not appear to change much with age (Davies et al., 2004; Ladouceur et al., 2007; Wiersma et al., 2007; Brydges et al., 2013; Tammes et al., 2013; Dupuis et al., 2015).

To our knowledge, no prior ERP study has used this type of Flanker task in children with TS. However, one behavioral study reported that children with TS performed slightly less accurately on incompatible trials (Crawford et al., 2005). Only few ERP studies overall have included children with TS, mainly auditory oddball paradigms have been used with variable results (Van Woerkom et al., 1994; Oades et al., 1996; Zhu et al., 2006). A recent study using a Go/Nogo paradigm (Shephard et al., 2015)

did not report significant differences in the ERP in children with TS compared with controls. However, here two distinct subcomponents of a P3 can be appreciated, which each show a differential amplitude modulation between the groups, where indeed the TS group grand average has highest amplitudes during an earlier subcomponent (Shephard et al., 2015) and thus add to motivate further study of this component in children with TS. Interestingly, this component seems reduced in children with ADHD (Albrecht et al., 2008). These independent observations motivate the focus on P3 in the current analysis.

A larger amount of data exists from children with ADHD, indicating either non-different or reduced N2, P3, ERN, and Pe amplitudes compared with controls (for an overview, see Barry et al., 2003; Johnstone et al., 2013). We aimed at investigating electrophysiological measures in the Flanker task related to attention, stimulus evaluation, conflict and control in medication-naïve children with TS, compared with medication-naïve children with ADHD and controls, primarily in the N2-P3 latency range and the post-response ERN-Pe. We hypothesized that participants with TS would show a typical or enhanced performance and ERP amplitudes similar to control participants, whereas participants with ADHD would show impaired performance (Willcutt et al., 2005; Mazaheri et al., 2014) and reduced ERP amplitudes. Due to the limited ERP-literature on children with TS we do not only present hypothesized effects but all components involved in the Flanker task for reference and discovery of knowledge in the field of child psychopathology (Loo et al., 2015). Comparisons between groups should not be limited to measurement of one component to ensure that significant differences between groups are not ceiling effects transporting smaller differences from one component to the next until adding up to a significant difference (Picton et al., 2000).

We focus on performance monitoring in children with TS, and, due to ADHD being a frequent comorbidity, we also included participants with TS and comorbid ADHD. This group is compared with children with ADHD, and a group of typically developing children. This allows to leverage the impact of comorbid ADHD in combination with TS, as well as to measure the specific contribution of TS on our main outcome variables. The recent attempt to collect data across the boundaries of diagnostic entities calls for the inclusion of contrastgroups to allow differentiating characteristics found in individuals with a specific disorder from more general markers present across conditions (Cuthbert, 2014).

MATERIALS AND METHODS

Participants

One hundred and two participants were recruited for a prospective longitudinal study of children with ADHD, Tourette syndrome, and control children aged 8–12 years. Participants with ADHD and 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 from local schools in the same geographic regions. The Regional Ethics Committee approved the study, and written

consent in accordance with the Declaration of Helsinki was obtained from all parents. The diagnostic procedure consisted of a semi-structured interview, the K-SADS (Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children; Kaufman et al., 1997); the Children Global Assessment Scale (CGAS; Shaffer et al., 1983), and the DuPaul ADHD-Rating Scale (ADHD-RS; Dupaul et al., 1998), along with a best estimate consensus procedure that considered all available study material (Leckman, 2002). TS and ADHD diagnoses, respectively, met the criteria set in Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association, 1994). Tic symptoms were measured with the Yale Global Tic Severity scale (YGTSS; Leckman et al., 1989). All children were native Norwegian speakers of Caucasian origin, were medication-naïve and had no prior treatment for ADHD. Exclusion criteria for the control group were a lifetime history of Tic disorder, Obsessive compulsive disorder (OCD), ADHD, or a current DSM-IV axis I disorder. Additional exclusion criteria for all groups were epilepsy, head trauma with loss of consciousness, autism spectrum disorder, prematurity (gestational age <36 weeks), or a full scale intelligence quotient (FSIQ) below 75, measured by the Wechsler Intelligence Scale for Children-IV (Wechsler, 2003). Children with ADHD had a diagnosis of ADHD, combined type ($n = 25$), inattentive type ($n = 11$) or hyperactive type ($n = 3$). Within the study groups, the following comorbid disorders were present: oppositional defiant disorder (ODD; ADHD $n = 17$, TS $n = 7$), and three children with ADHD also had conduct disorder (CD), chronic and transient tics (ADHD $n = 3$), OCD (TS $n = 2$), and elimination disorder (ADHD $n = 4$, TS $n = 3$, controls $n = 2$). Moreover, several children fulfilled criteria for phobia (ADHD $n = 7$, TS $n = 3$, control $n = 1$), separation anxiety (ADHD $n = 6$, TS $n = 1$) and general anxiety (ADHD $n = 3$, TS $n = 1$). Thirteen children with TS had an additional ADHD diagnosis (ADHD combined type $n = 7$, ADHD inattentive type $n = 6$), 1 of these had an additional OCD diagnosis.

Experimental Design

After instruction and training, participants performed a modified visual Eriksen-Flanker task implemented in E-prime 2 (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Participants were instructed to fixate a dot presented in the center of a PC screen. Trials began with the presentation of 6 horizontal flanker arrows appearing below fixation. Participants should respond as fast as possible, and as accurate as possible with either a left or a right mouse button press following the direction of a central target arrow that appeared after 100 ms, pointing either into the same direction as the flanker arrows in compatible trials (<<<< < <<<<, >>>> > >>>>) or in the opposite direction in incompatible trials (<<<< > <<<<, >>>> < >>>>). The target- and flanker-arrows remained on screen until a response was registered. Trials were terminated by the motor response and followed by an 800-ms interval before onset of the next trial. Stimuli were presented in two blocks with 200 trials that were pseudorandomized separately for each participant. The overall probability of compatible and incompatible trials, as well as left and right responses

were kept at 0.5. Performance feedback was given during the experiment when responses were erroneous or slower than an adaptive individual threshold value (mean response time plus 1.5 standard deviations (SD)).

EEG Acquisition

EEG was recorded continuously in an electromagnetically shielded chamber. Data were sampled at 1000 Hz frequency with a time-constant of 10 s and a high cutoff at 250 Hz with Brain Amp amplifiers (BrainProducts, Munich, Germany). An elastic cap containing 34 Ag/AgCl electrodes placed at Fp1, Fp2, F7, F3, Fz, F4, F8, FT9, FC5, FC1, FC2, FC6, FT10, T7, C3, Cz, C4, T8, TP9, CP5, CP1, CP2, CP6, TP10, P7, P3, Pz, P4, P8, PO9, O1, O2, PO10, Iz was used. Channels were referenced to Fz. Vertical eye movements were recorded with a bipolar derivation between Fp1 and an additional electrode placed below the left eye, horizontal eye movement were recorded with a bipolar derivation between F7 and F8. Additionally, electrocardiogram was monitored. Impedances were kept below 10 k Ω .

EEG Processing

We preprocessed the EEG in Matlab (Mathworks, Natick, MA, USA) using the EEGLAB toolbox (Delorme and Makeig, 2004) and in-house scripts.

The continuous EEG data were resampled to 500 Hz. The data were then re-referenced to common average reference, and filtered from 0.5 to 45 Hz using a finite impulse response filter generated with the firfilt plugin (Widmann, 2006).

For artifact removal/reduction, the data were segmented into stimulus-locked (-0.5 to $+1$ s), and response-locked epochs (-1 to 0.5 s). The prestimulus period was used as baseline for both epochs. Epochs were excluded when exceeding a ± 300 μ V amplitude criterion. The remaining epochs were sorted using a summary score of root mean square amplitude across all channels and time points, spatial SD, power spectrum ratio between low and high frequencies, skewness and kurtosis, normalized to unit variance across epochs. Only epochs within ± 1 SD were retained for further analysis. These epochs were concatenated and subjected to temporal independent component analysis (ICA) using the infomax algorithm (Bell and Sejnowski, 1995), and 32 components were estimated. We used spatial templates to identify horizontal and vertical eye movements and ECG artifacts, and removed these automatically (Viola et al., 2009). Following the rationale presented in COMPASS (Wessel and Ullsperger, 2011), we assumed that components of interest were broad, dipolar topographies with time-locked event-related responses, and we therefore generated scores based on the spatial smoothness of the component scalp maps and the root mean square of the event related average, and retained the top 15 components. These were then visually cross-checked, and components reminiscent of artifacts were marked. Between 10 and 15 components were kept and back-projected in this manner.

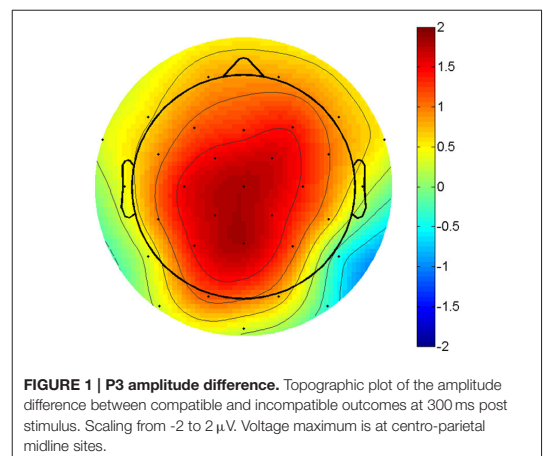
Averaging and Data Extraction

We sorted compatible, incompatible and erroneous trials and visually inspected the grand averaged data across all participants to generate ERP for further testing. Upon inspection of grand

average ERP data and difference waves, we found that conditional effects on several components were consistently expressed around Cz/Vertex, which is in line with other work in this age group (Cycowicz, 2000; Stige et al., 2007). We therefore used regional averaging, for spatial data reduction, and controlling for inter-individual variability (Handy, 2005). This provides a better fit to the statistical models by collapsing together electrodes that commonly covary, in the same way that adding a spatial factor would do, however without complicating the analysis by additional terms of interaction. Moreover, it helps to control for variability (as seen in different age groups e.g., Cycowicz, 2000; Davies et al., 2004; Brydges et al., 2013) over locations by averaging across locations. This method addresses the objection to the large degrees of freedom that multiple electrode readings afford (Handy, 2005). We selected a central region of interest containing FC1, FC2, Cz, CP1, and CP2 with clear N1 (108 ms), P2 (196 ms), P3 (320 ms), and LPC (598 ms) waveforms in the stimulus-locked average, as well as LPC (-82 ms) in the response-locked average, and a clear modulation between outcomes (see **Figure 1**). ERN was identified as the first post-response negativity maximal on erroneous trials. The early positivity is defined as the first positive wave post-response—this common post-response component is labeled P2 or P90 elsewhere (Brunia and Van Boxtel, 2000). Error response generated an additional broad positivity Pe with peak latency at 268 ms post-response. Because latency jitter in ERP components between trials, especially in children, and peak amplitudes can be influenced by group differences in signal-noise-ratio, analyses of mean amplitudes were chosen (Luck, 2005). Amplitudes were extracted from 40 ms long windows centered on the grand average peak latency and were used for testing of group differences.

Statistics

Statistics were performed in Matlab and Statistica (Statsoft, Tulsa, OK, USA). Repeated measure analyses were conducted to test outcome effects in the behavioral and the ERP data



(congruent vs. incongruent vs. error trials) and “group.” Additional univariate Analysis of Covariance (ANCOVA) were conducted for behavioral measures and ERP components as dependent variable, group as categorical factor and covariates as continuous predictors to test group differences. Significant or trend-significant effects were followed-up with additional *post-hoc* tests. All statistics were considered significant at $p < 0.05$. The effect size indicator partial eta squared (η_p^2) is reported for each significant/trend-significant statistical comparison as a measure of the strength of the effect, with of 0.01 representing a small effect, 0.06 a medium effect, and 0.14 a large effect (Cohen, 1988). To demonstrate the adequacy of pooling children with TS with and without comorbid ADHD, we also performed ANCOVAs with four groups, separating TS only and TS+ADHD, control group, ADHD, with the main behavioral and ERP result.

Response times (RT) and response accuracy (RACC) averages were generated for all possible outcomes. Premature responses faster than 200 ms and slow responses >2000 ms were not considered in the averages. RTs were analyzed with covariates:

Age: Because of substantial speeding of RT, and improvement of accuracy with age across the entire sample regardless of group, all analyses included age as a covariate.

FSIQ: We decided to analyze the behavioral data with FSIQ as covariate for the sake of consistency across behavioral- and ERP analyses. This appears to be the most sound practice in our case, however see relevant publications for a discussion on this issue (Willcutt et al., 2005; Dennis et al., 2009).

ERP components were analyzed with covariates:

Age: Groups did not differ in mean age. However, to control within group variation of electrophysiological measures we followed current guidelines (Picton et al., 2000). Age in particular influences many features in the EEG, resulting also in prominent maturational changes of ERP amplitudes and latencies (Davies et al., 2004; Wiersema et al., 2007; Brydges et al., 2013; Rojas-Benjumeda et al., 2015).

FSIQ: Earlier research has also shown that IQ differences account for variability of ERP measures. We therefore decided to include IQ as a covariate in line with other studies in the field (Pelosi et al., 1992; Deary and Caryl, 1997; Jausovec and Jausovec, 2000; Ramchurn et al., 2014).

RT/ IIV: Response times and their variability substantially affect ERP features (Eichele et al., 2010b). This is partly due to task-induced amplitude modulation, and partly nuisance variability due to spatio-temporal overlap of stimulus and response-related components, see also (Ramchurn et al., 2014).

RACC: Average accuracy provides a gross measure of the effort that an individual invests in a task, therefore adjusting for ACC is useful to account for state and trait factors not specifically related to diagnosis/group.

ADHD symptom scores were included initially as a covariate in the statistical models for the behavioral and the ERP correlates, but proved non-significant and were subsequently removed from both models. Pairwise correlations were used to further investigate significant effects of the group factor and covariates. To test for post-error slowing (PES) and to compensate for confounders, we conducted a pairwise comparison of post-error

and pre-error trials around each error (Dutilh et al., 2012) followed by an ANCOVA, including the covariates age and FSIQ.

Behavioral Characteristics

Data from two participants (with ADHD and with TS/ADHD, respectively) were discarded due to excessive EEG artifact, data from another participant (ADHD) were discarded due to performance on chance level, data from 99 participants thus were included, 39 children with a diagnosis of ADHD, 25 children with TS (11 TS “only” and 14 TS+ADHD), and 35 typically developing children. Children’s age ranged from 8 to 12 years ($M = 10.05$; $SD \pm 1.21$), 64 participants were boys and groups did not differ for age or sex. 15 participants were left-handed. Groups differed in FSIQ, similar to findings reported in other studies (Bornstein, 1991; Ozonoff et al., 1998; Baym et al., 2008; Debes et al., 2011), and FSIQ was employed as a covariate. Groups also differed in ADHD-RS total values. Current tic severity in the TS group was 11.3 ± 3.34 for motor and 8.00 ± 4.83 for vocal tics, and lifetime worst ever score 15.68 ± 3.44 for motor and 11.95 ± 5.0 for vocal tics (Table 1).

RESULTS

Behavioral Performance

We observed no significant differences between groups for premature responses, but a significant effect of FSIQ, with a weak correlation where lower FSIQ correlated with more premature responses ($r = -0.29$). Slow responses were more frequent in all groups compared with fast responses, also with a significant FSIQ effect, with correlations for lower FSIQ predicting more frequent slower responses ($r = -0.34$) and age ($r = -0.38$). (Table 2).

Reaction Times

A Repeated Measure Analysis revealed a typical RT pattern for the Flanker task with fast RT in compatible (CC) responses, slower incompatible (IC) responses and faster RT in erroneous trials in all three groups, and trend-significant group differences across all three outcomes [$F_{(2, 96)} = 2.85$, $p = 0.06$, $\eta_p^2 = 0.06$], without significant interactions of outcome-by-group. *Post-hoc* assessment revealed trend-significant differences for CC responses ($p = 0.07$) and erroneous responses ($p = 0.08$) between controls and ADHD and a significant difference in IC

TABLE 1 | Sample characteristics.

	Controls Mean \pm SD	ADHD Mean \pm SD	TS Mean \pm SD	Statistics
FSIQ	105.82 \pm 1.68	91.71 \pm 1.59	97.96 \pm 1.99	$F_{(2, 96)} = 18.51$, $p < 0.001$, $\eta_p^2 = 0.28$
Age (years)	10.04 \pm 0.21	10.18 \pm 0.19	9.87 \pm 0.24	$F_{(2, 96)} = 0.49$, n.s.
Sex (% male)	57.14	69.23	68	$\chi^2 = 1.34$, n.s.
Handedness (% right handed)	91.43	84.62	76	$\chi^2 = 2.7$, n.s.
ADHD-RS total score	2.91 \pm 1.33	30.73 \pm 1.26	22.12 \pm 1.57	$F_{(2, 96)} = 117.09$, $p < 0.001$, $\eta_p^2 = 0.62$

ADHD, attention-deficit/hyperactivity disorder; TS, Tourette syndrome; FSIQ, full scale intelligence quotient; ADHD-RS, attention-deficit/hyperactivity disorder rating scale; SD, standard deviation.

TABLE 2 | Behavioral performance.

	Controls		ADHD		TS		Repeated Measure ANOVA		ANCOVA	
	Mean ± SD		Mean ± SD		Mean ± SD		Outcome	Group	Outcome × group	Covariates
RT CC (ms)	646.44 ± 19.69	677.37 ± 18.43	652.99 ± 21.26	$F_{(2, 96)} = 136.9$, $p < 0.001$, $\eta^2 = 0.59$	652.99 ± 21.26	$F_{(2, 96)} = 2.85$, $p = 0.06$, $\eta^2 = 0.06$	$F_{(4, 192)} = 1.14$, n.s.	$F_{(2, 94)} = 0.65$, n.s.	FSIQ $F_{(1, 94)} = 11.77$, $p < 0.001$, $\eta^2 = 0.11$; Age $F_{(1, 94)} = 64.68$, $p < 0.001$, $\eta^2 = 0.41$	
RT IC (ms)	773.11 ± 25.73	840.70 ± 24.01	789.58 ± 27.77					$F_{(2, 94)} = 1.77$, n.s.	FSIQ $F_{(1, 94)} = 10.19$, $p < 0.01$, $\eta^2 = 0.09$; Age $F_{(1, 94)} = 61.04$, $p < 0.001$, $\eta^2 = 0.39$	
RT error (ms)	624.42 ± 29.70	644.70 ± 27.79	627.28 ± 32.06					$F_{(2, 94)} = 0.13$, n.s.	FSIQ $F_{(1, 94)} = 7.5$, $p < 0.01$, $\eta^2 = 0.07$; Age $F_{(1, 94)} = 34.06$, $p < 0.001$, $\eta^2 = 0.27$	
IIV CC (ms)	209.48 ± 10.98	245.21 ± 10.27	231.66 ± 11.85	$F_{(2, 92)} = 25.46$, $p < 0.001$, $\eta^2 = 0.21$	$F_{(2, 92)} = 5.68$, $p < 0.01$, $\eta^2 = 0.11$	$F_{(4, 192)} = 0.71$, n.s.	$F_{(2, 94)} = 2.46$, n.s.	$F_{(2, 94)} = 0.13$, n.s.	FSIQ $F_{(1, 94)} = 14.43$, $p < 0.001$, $\eta^2 = 0.13$; Age $F_{(1, 94)} = 32.72$, $p < 0.001$, $\eta^2 = 0.26$	
IIV IC (ms)	245.13 ± 12.95	261.21 ± 12.12	266.46 ± 13.98				$F_{(2, 94)} = 0.66$, n.s.	$F_{(2, 94)} = 0.83$, n.s.	FSIQ $F_{(1, 94)} = 12.66$, $p < 0.001$, $\eta^2 = 0.12$; Age $F_{(1, 94)} = 22.48$, $p < 0.001$, $\eta^2 = 0.19$	
IIV error (ms)	271.01 ± 20.41	309.89 ± 19.09	290.70 ± 22.03						FSIQ $F_{(1, 94)} = 7.75$, $p < 0.01$, $\eta^2 = 0.08$; Age $F_{(1, 94)} = 26.73$, $p < 0.001$, $\eta^2 = 0.22$	
Compatible errors(%)	6.57 ± 1.07	7.85 ± 1.01	9.32 ± 1.26	$F_{(1, 96)} = 142.14$, $p < 0.001$, $\eta^2 = 0.6$	$F_{(2, 96)} = 2.46$, $p = 0.09$, $\eta^2 = 0.05$	$F_{(2, 96)} = 3.01$, $p = 0.06$, $\eta^2 = 0.06$	$F_{(2, 92)} = 1.47$, n.s.	$F_{(2, 92)} = 0.32$, n.s.	FSIQ $F_{(1, 94)} = 7.12$, $p < 0.01$, $\eta^2 = 0.07$	
Incompatible errors (%)	18.96 ± 2.37	20.65 ± 2.21	21.78 ± 2.56					$F_{(2, 92)} = 0.32$, n.s.	FSIQ $F_{(1, 92)} = 9.53$, $p < 0.01$, $\eta^2 = 0.003$	
Responses <200ms (n)	6.79 ± 2.64	4.77 ± 2.47	9.01 ± 2.85				$F_{(2, 94)} = 0.63$, n.s.	$F_{(2, 94)} = 0.63$, n.s.	FSIQ $F_{(1, 94)} = 8.35$, $p < 0.01$, $\eta^2 = 0.08$	
Responses >2000ms (n)	12.49 ± 3.59	21.65 ± 3.36	11.73 ± 3.87				$F_{(2, 94)} = 2.29$, n.s.	$F_{(2, 94)} = 2.29$, n.s.	FSIQ $F_{(1, 94)} = 7.22$, $p < 0.01$, $\eta^2 = 0.07$; Age $F_{(1, 94)} = 23.22$, $p < 0.001$, $\eta^2 = 0.19$	
PES (ms)	79.47 ± 20.71	87.11 ± 19.38	36.73 ± 22.36				$F_{(2, 94)} = 1.67$, n.s.	$F_{(2, 94)} = 1.67$, n.s.	FSIQ $F_{(1, 94)} = 8.01$, $p < 0.01$, $\eta^2 = 0.08$; Age $F_{(1, 94)} = 56.71$, $p < 0.001$, $\eta^2 = 0.38$	
Overall RT (ms)	695.49 ± 22.16	735.80 ± 20.73	690.72 ± 23.92					$F_{(2, 94)} = 1.8$, n.s.	FSIQ $F_{(1, 94)} = 17.21$, $p < 0.001$, $\eta^2 = 0.15$; Age $F_{(1, 94)} = 38.29$, $p < 0.001$, $\eta^2 = 0.29$	
Overall IIIV (ms)	255.11 ± 11.26	286.59 ± 10.53	270.25 ± 12.15					$F_{(2, 92)} = 0.25$, n.s.	FSIQ $F_{(1, 92)} = 10.05$, $p < 0.01$, $\eta^2 = 0.10$	
Overall RAOC (%)	86.68 ± 1.63	86.54 ± 1.52	84.64 ± 1.75							

CC, compatible correct; IC, incompatible correct; PES, post-error slowing; RT, reaction time; IIIV, intraindividual variability; RAOC, response accuracy; ANCOVA, analysis of covariance; ANOVA, analysis of variance; ADHD, attention-deficit/hyperactivity disorder; TS, Tourette syndrome; SD, standard deviation; n.s., not significant; Responses >2000ms are considered equivalent to omissions, Responses <200ms are considered false alarms.

trials ($p < 0.01$) between controls and ADHD. No differences between children with TS and controls.

When controlling for covariates in a follow-up ANCOVA, the CC, IC or erroneous RTs did not differ between groups (Table 2).

Response Accuracy

Errors were defined as incorrect key presses to compatible and incompatible trials. As expected, significantly more errors occurred to incompatible than compatible trials [$F_{(1, 96)} = 142.14, p < 0.001, \eta_p^2 = 0.6$]. A repeated measure analysis revealed a trend-significant group difference [$F_{(2, 96)} = 2.46, p = 0.09, \eta_p^2 = 0.05$] and a trend-significant outcome-by-group difference [$F_{(2, 96)} = 3.01, p = 0.06, \eta_p^2 = 0.06$] which was due to higher incompatible error rates in children with ADHD ($p < 0.01$) and TS ($p < 0.05$) than controls.

After controlling for covariates (ANCOVA), groups did not differ in error rates for either CC or IC responses, or for overall RACC with a significant effect of FSIQ (Table 2).

Post Error Slowing

ANCOVA for PES yielded no significant group differences (Table 2).

Intraindividual Variability

A repeated measure analysis of IIV showed smaller IIV for compatible trials, larger IIV in incompatible trials and largest IIV in erroneous trials, and significant group differences across

all three outcomes [$F_{(2, 96)} = 5.68, p < 0.01, \eta_p^2 = 0.11$]. No significant interaction for outcome-by-group was found.

When controlling for covariates in the follow-up ANCOVA groups did not differ with respect to IIV, but the relevant covariates FSIQ and age reached significance in the overall IIV, as well as in the separate CC, IC and error trials (Table 2).

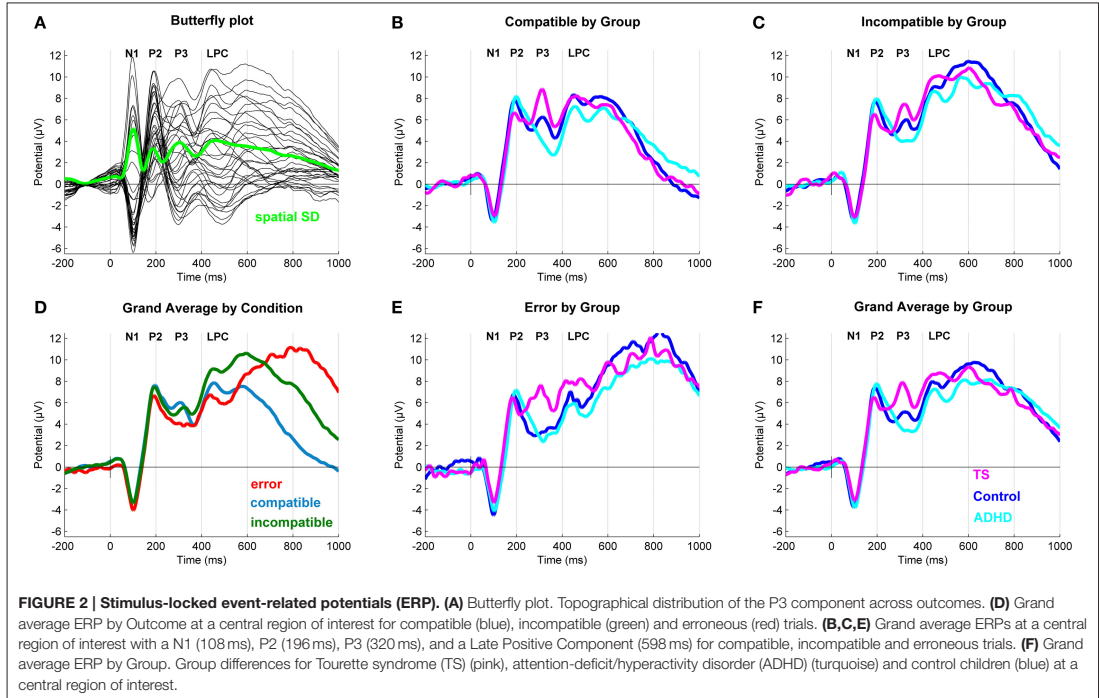
Electrophysiological Results

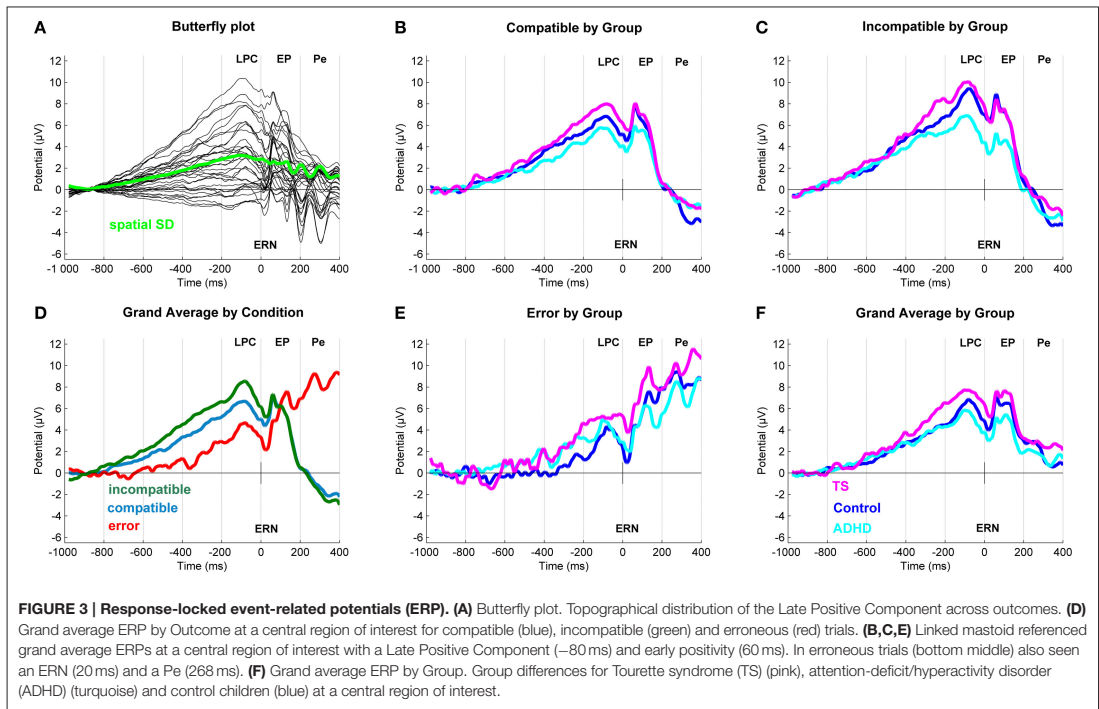
After inspection of the grand averages of the stimulus-locked (Figure 2) and response-locked (Figure 3) ERP data, we conducted repeated measure analyses for the components separately to test the presence of the typical compatibility/conflict effects considering the factors “outcome,” “group” and the “outcome x group” interaction. We observed significant “outcome” effects for the stimulus-locked P3 and LPC and the response-locked LPC, ERN and Pe. Trend-significant effects of “outcome” were seen in the P2, no significant effects of outcomes were seen for N1 and response-locked early positivity. We also did observe “group” and “outcome x group” effects, which were followed-up by appropriate ANCOVA designs controlling for confounds (Tables 3, 4).

Stimulus-Locked ERPs (Table 3)

N1 (108 ms)

ANCOVA showed no group differences in compatible, incompatible, and error outcomes. A significant effect of RT and IIV was present in incompatible correct outcomes.





P2 (196 ms)

No group effects were found in ANCOVA for compatible, incompatible, and erroneous P2 amplitudes.

P3 (320 ms)

ANCOVA yielded a significant group effect for compatible correct [$F_{(2, 91)} = 4.62, p = 0.01, \eta_p^2 = 0.09$] and erroneous responses [$F_{(2, 91)} = 5.17, p < 0.01, \eta_p^2 = 0.10$]. Incompatible correct outcomes also approached significance [$F_{(2, 91)} = 2.82, p = 0.06, \eta_p^2 = 0.06$], and a significant effect of RACC and IIV was observed. A *post-hoc* assessment revealed that, P3 amplitudes across outcomes were higher in children with TS compared to both controls ($p < 0.05$), and those with ADHD ($p < 0.05$). No significant differences were found between participants with ADHD and controls.

LPC (600 ms)

ANCOVA showed no significant group difference in compatible correct outcomes, there was a significant effect of RACC. Similarly, no differences were present in incompatible correct outcomes, while a significant covariate-effect of IIV was present. No differences were found in erroneous LPC amplitudes.

Response-Locked ERPs (Table 4)

LPC (−80 ms)

ANCOVA showed no significant group differences in compatible and erroneous amplitudes. Incompatible amplitudes showed a

trend-significant group effect [$F_{(2, 91)} = 2.5, p = 0.08, \eta_p^2 = 0.05$], with a significant effect of RACC and RT. *Post-hoc* tests showed higher amplitudes in TS vs. controls ($p = 0.04$), and a similar trend between TS and ADHD ($p = 0.09$), but no difference between controls and ADHD.

ERN (20 ms)

In this sample, we did not observe a distinct negative ERN in this age group, consistent with Davies (Davies et al., 2004). However, the most negative amplitudes during the post-response period were seen for erroneous trials, and a trend-significant outcome-by-group effect [$F_{(4, 192)} = 2.09, p = 0.08, \eta_p^2 = 0.04$]. However, this was due to higher incompatible amplitudes for controls than ADHD ($p = 0.03$) and similarly for TS compared to ADHD ($p = 0.06$), whereas no differences were seen between TS and controls. Note though that there is a substantial carry-over of the amplitude modulation from the preceding LPC into this time-window, especially for correct responses.

When controlling for covariates, ANCOVA showed no group differences in any trial outcome, whereas clear effects of age and RT were present for incompatible correct.

Early positivity (60 ms)

ANCOVA showed no significant group differences across outcomes. Significant effect of RT and age were present only for incompatible outcomes.

TABLE 3 | Stimulus-locked ERP amplitudes.

Stimulus-locked	Controls		ADHD		TS		Repeated Measure ANOVA		ANCOVA		
	Mean ± SD (μV)	Mean ± SD (μV)	Mean ± SD (μV)	Mean ± SD (μV)	Mean ± SD (μV)	Mean ± SD (μV)	Outcome	Group	Outcome x Group	Group	Covariates
N1 (108 ms)											
Compatible	-2.72 ± 0.70	-3.04 ± 0.65	-2.42 ± 0.75	-2.42 ± 0.75	$F_{(2, 96)} = 1.89, n.s.$	$F_{(2, 96)} = 0.22, n.s.$	$F_{(4, 192)} = 0.43, n.s.$	$F_{(2, 91)} = 0.19, n.s.$	$F_{(4, 192)} = 0.43, n.s.$	$F_{(2, 91)} = 0.19, n.s.$	$RT F_{(1, 91)} = 5.95, p = 0.02,$ $\eta_p^2 = 0.06; IV F_{(1, 91)} = 7.06, p < 0.01,$ $\eta_p^2 = 0.07$
Incompatible	-2.49 ± 0.68	-3.47 ± 0.63	-2.36 ± 0.73	-2.36 ± 0.73							
Error	-3.07 ± 0.90	-4.03 ± 0.84	-2.79 ± 0.97	-2.79 ± 0.97				$F_{(2, 91)} = 0.74, n.s.$			
Mean	-2.80 ± 0.69	-3.44 ± 0.65	-2.57 ± 0.75	-2.57 ± 0.75				$F_{(2, 91)} = 0.5, n.s.$			
P2 (196 ms)											
Compatible	7.19 ± 0.91	7.05 ± 0.84	6.93 ± 0.96	6.93 ± 0.96	$F_{(2, 192)} = 2.69,$ $p = 0.06, \eta_p^2 = 0.03$	$F_{(2, 96)} = 0.21, n.s.$	$F_{(4, 192)} = 0.35, n.s.$	$F_{(2, 91)} = 0.23, n.s.$			
Incompatible	7.23 ± 0.98	6.73 ± 0.92	6.93 ± 1.05	6.93 ± 1.05							
Error	6.53 ± 1.06	5.82 ± 0.99	5.99 ± 1.13	5.99 ± 1.13				$F_{(2, 91)} = 0.19, n.s.$			
Mean	6.89 ± 0.91	6.64 ± 0.85	6.19 ± 0.97	6.19 ± 0.97				$F_{(2, 91)} = 0.11, n.s.$			
P3 (320 ms)											
Compatible	5.26 ± 1.04	4.70 ± 0.93	8.69 ± 1.07	8.69 ± 1.07	$F_{(2, 192)} = 11.71,$ $p < 0.001, \eta_p^2 = 0.11$	$F_{(2, 96)} = 3.61,$ $p = 0.03, \eta_p^2 = 0.07$	$F_{(4, 192)} = 2.21,$ $p = 0.06, \eta_p^2 = 0.04$	$F_{(2, 91)} = 4.62,$ $p = 0.01, \eta_p^2 = 0.09$	$F_{(4, 192)} = 2.21,$ $p = 0.06, \eta_p^2 = 0.04$	$RACC F_{(1, 91)} = 4.43, p = 0.04,$ $\eta_p^2 = 0.05;$ $IV F_{(1, 91)} = 5.21, p = 0.03, \eta_p^2 = 0.05$	
Incompatible	4.60 ± 1.03	4.46 ± 0.97	7.61 ± 1.12	7.61 ± 1.12				$F_{(2, 91)} = 2.82,$ $p = 0.06, \eta_p^2 = 0.06$			
Error	2.84 ± 1.15	2.89 ± 1.07	7.47 ± 1.23	7.47 ± 1.23				$F_{(2, 91)} = 5.17,$ $p < 0.01, \eta_p^2 = 0.10$			
Mean	4.09 ± 0.99	4.22 ± 0.93	7.81 ± 1.06	7.81 ± 1.06							
LPC (698 ms)											
Compatible	7.12 ± 0.96	7.78 ± 0.89	8.46 ± 1.02	8.46 ± 1.02	$F_{(2, 192)} = 14.35,$ $p < 0.001, \eta_p^2 = 0.13$	$F_{(2, 96)} = 0.61, n.s.$	$F_{(4, 192)} = 0.48, n.s.$	$F_{(2, 91)} = 0.45, n.s.$	$F_{(4, 192)} = 0.48, n.s.$	$RACC F_{(1, 91)} = 3.96, p = 0.05,$ $\eta_p^2 = 0.04$ $IV F_{(1, 91)} = 9.01, p < 0.01, \eta_p^2 = 0.09$	
Incompatible	8.11 ± 1.03	8.89 ± 0.96	10.86 ± 1.11	10.86 ± 1.11							
Error	5.95 ± 1.39	5.73 ± 1.31	8.13 ± 1.50	8.13 ± 1.50				$F_{(2, 91)} = 1.79, n.s.$			
Mean	6.83 ± 1.00	7.72 ± 0.94	9.07 ± 1.08	9.07 ± 1.08				$F_{(2, 91)} = 0.88, n.s.$			

ERP event-related potentials; SD, standard deviation; ANOVA, analysis of variance; ADHD, attention-deficit/hyperactivity disorder; TS, Tourette syndrome; LPC, Late positive component; n.s., not significant.

TABLE 4 | Response-locked ERP amplitudes.

Response-locked	Controls		ADHD		TS		Repeated measure ANOVA		ANCOVA		
	Mean ± SD (μV)	Mean ± SD (μV)	Mean ± SD (μV)	Mean ± SD (μV)	Mean ± SD (μV)	Mean ± SD (μV)	Outcome	Group	Outcome x Group	Group	Covariates
LPC (-82 ms)											
Compatible	6.37 ± 0.88	5.88 ± 0.82	8.14 ± 0.93	8.14 ± 0.93	26.92, $p < 0.001, \eta^2 = 0.22$	8.14 ± 0.93	$F_{(2, 192)} = 26.92, p < 0.001, \eta^2 = 0.22$	$F_{(2, 96)} = 1.21, n.s.$	$F_{(4, 192)} = 2.01, p = 0.09, \eta^2 = 0.04$	$F_{(2, 91)} = 1.84, n.s.$	RACC $F_{(1, 91)} = 8.21, p < 0.01, \eta^2 = 0.08$; RT $F_{(1, 91)} = 16.46, p < 0.001, \eta^2 = 0.15$
Incompatible	7.46 ± 0.87	8.24 ± 0.82	10.23 ± 0.94	10.23 ± 0.94							$F_{(2, 91)} = 2.5, p = 0.08, \eta^2 = 0.05$ $F_{(2, 91)} = 0.17, n.s.$
Error	4.41 ± 1.25	4.34 ± 1.17	5.29 ± 1.34	5.29 ± 1.34							
Mean	6.09 ± 0.86	6.19 ± 0.81	7.79 ± 0.92	7.79 ± 0.92							
ERN (20 ms)											
Compatible	4.55 ± 0.89	4.25 ± 0.84	5.71 ± 0.96	5.71 ± 0.96	13.04, $p < 0.001, \eta^2 = 0.12$	5.71 ± 0.96	$F_{(2, 192)} = 13.04, p < 0.001, \eta^2 = 0.12$	$F_{(2, 96)} = 1.46, n.s.$	$F_{(4, 192)} = 2.09, p = 0.08, \eta^2 = 0.04$	$F_{(2, 91)} = 0.74, n.s.$	RT $F_{(1, 91)} = 16.45, p < 0.001, \eta^2 = 0.15$; Age $F_{(1, 91)} = 6.57, p = 0.01, \eta^2 = 0.07$
Incompatible	4.85 ± 0.90	5.28 ± 0.85	6.52 ± 0.98	6.52 ± 0.98							
Error	1.93 ± 1.50	1.73 ± 1.40	4.24 ± 1.61	4.24 ± 1.61							
Mean	3.77 ± 0.96	3.80 ± 0.80	5.42 ± 1.03	5.42 ± 1.03							
EARLY POSITIVITY (62 ms)											
Compatible	6.47 ± 0.96	6.02 ± 0.89	7.23 ± 1.02	7.23 ± 1.02	1.72, n.s.	7.23 ± 1.02	$F_{(2, 192)} = 1.72, n.s.$	$F_{(2, 96)} = 1.53, n.s.$	$F_{(4, 192)} = 1.69, n.s.$	$F_{(2, 91)} = 0.41, n.s.$	RT $F_{(1, 91)} = 14.17, p < 0.001, \eta^2 = 0.13$; Age $F_{(1, 91)} = 4.35, p = 0.04, \eta^2 = 0.05$
Incompatible	5.80 ± 0.98	6.12 ± 0.93	7.49 ± 1.06	7.49 ± 1.06							
Error	5.12 ± 1.51	4.59 ± 1.41	7.15 ± 1.62	7.15 ± 1.62							
Mean	5.81 ± 1.02	5.61 ± 0.96	7.20 ± 1.09	7.20 ± 1.09							
Pe (268 ms)											
Compatible	-0.07 ± 0.99	-1.45 ± 0.92	-0.88 ± 1.05	-0.88 ± 1.05	115.16, $p < 0.001, \eta^2 = 0.55$	-0.88 ± 1.05	$F_{(2, 192)} = 115.16, p < 0.001, \eta^2 = 0.55$	$F_{(2, 96)} = 0.31, n.s.$	$F_{(4, 192)} = 0.12, n.s.$	$F_{(2, 91)} = 0.44, n.s.$	RT $F_{(1, 91)} = 8.56, p < 0.01, \eta^2 = 0.08$; Age $F_{(1, 91)} = 4.27, p = 0.04, \eta^2 = 0.04$
Incompatible	-1.13 ± 0.94	-1.31 ± 0.88	-0.99 ± 1.01	-0.99 ± 1.01							FSIQ $F_{(1, 91)} = 5.39, p = 0.02, \eta^2 = 0.06$; RACC $F_{(1, 91)} = 8.84, p < 0.01, \eta^2 = 0.09$
Error	9.31 ± 1.68	8.08 ± 1.56	10.42 ± 1.79	10.42 ± 1.79							
Mean	2.58 ± 1.01	1.93 ± 0.94	2.78 ± 1.08	2.78 ± 1.08							

ERP, event-related potentials; SD, standard deviation; ANOVA, analysis of variance; ADHD, attention-deficit/hyperactivity disorder; TS, Tourette syndrome; LPC, Late positive component; ERN, error-related negativity; Pe, error positivity; n.s., not significant.

Pe (268 ms)

ANCOVA showed no group differences throughout. Incompatible ERPs showed a significant effect of RT and age, during erroneous trials with we saw a significant effect of FSIQ and RACC.

Correlation with Symptoms

We found no robust correlations between behavioral or ERP measurements and YGTSS scores.

Grouping of Children with TS Only and with TS and Comorbid ADHD

To demonstrate the adequacy of pooling children with TS with and without ADHD, we performed ANCOVAs with four groups, separating TS only and TS+ADHD, control group, ADHD, with the main behavioral and ERP result.

For RT, this analysis showed no group difference [$F_{(3, 93)} = 1.21$, $p = 0.31$, $\eta_p^2 = 0.03$]. Comorbid ADHD in the TS group resulted in marginally different RTs compared to TS only ($p = 0.99$) and controls ($p = 0.78$). Children with ADHD showed high RTs, but no significant differences to other groups ($p > 0.2$).

Also for the IIV, no group differences were found [$F_{(3, 93)} = 1.21$, $p = 0.31$, $\eta_p^2 = 0.03$] and a *post-hoc* comparison revealed no significant differences between the groups (all $p \geq 0.1$).

For the P3 this analysis repeats a significant group difference [$F_{(3, 90)} = 2.99$, $p = 0.04$, $\eta_p^2 = 0.09$], and showed that comorbid ADHD resulted in marginally lower amplitude values in ERPs compared to participants with TS only without significant differences ($p = 0.63$). Children with TS+ADHD showed trends toward higher amplitudes than controls ($p = 0.06$) and children with ADHD ($p = 0.06$), whereas TS only had significantly larger amplitudes than ADHD ($p = 0.03$), and controls ($p = 0.02$).

Based on these additional analyses, the fact that the sample sizes in analyses of these subsamples are small, and the pattern of results redundant and the high clinical relevance of a comorbid group, we merged all participants with TS into one group.

DISCUSSION

This study investigated electrophysiological differences in a Flanker task in children with TS compared with children with ADHD and with typically developing children. We expected that children with TS would perform comparable or better than controls, whereas children with ADHD would show impairments of behavior and ERP measures.

Our results confirmed that children with TS performed behaviorally on the same level as control children. This finding is consistent with previous studies of behavioral performance (Serrien et al., 2005; Roessner et al., 2008; Eichele et al., 2010a; Greimel et al., 2011). In contrast to our expectations, the present study did not find group behavioral differences between children with ADHD and control children when controlling for relevant covariates, which stands in contrast to some previous findings (Albrecht et al., 2008), but not others (Johnstone and Galletta, 2013).

Children with TS, however, showed higher amplitudes in the stimulus-locked ERPs in the early P3 amplitude compared with children with ADHD and control children across task outcomes, which was sustained through the later positive complex. We speculate therefore, that this increased amplitude might reflect a process that may help children with TS to maintain their behavioral performance. The increase in P3 amplitude might reflect greater sustained effort in the TS group in processing the stimuli (Isreal et al., 1980; Luck, 2005) yielding in turn increased attentional resource allocation during stimulus processing. This is supported by the fact that the P3 in children with TS consistently higher across outcomes. Moreover, the increase in P3 in the TS group might indicate that children with TS displayed enhanced processes to update working memory. Together with the increase in the response-locked LPC amplitude, this might reflect an altered sustained attention/orienting pattern of whether the first decision of stimulus classification has led to appropriate steps of processing (Verleger et al., 2005) in children with TS.

Here, TS children show the largest peak of all groups in the earlier P3 subcomponent around 300–350 ms after flanker onset. A recent study using a Go/Nogo-paradigm (Shephard et al., 2015) in a similar cohort with a broader age range did not report differences in ERP correlates between children with TS and control children. The authors analyzed the P3 complex in a longer time-window from 300 to 650 ms. Interestingly, two distinct subcomponents of the P3 can be appreciated during this period, which each show a differential amplitude pattern between the groups, where indeed the TS group grand average has highest amplitudes during the earlier subcomponent (see Figure 3 in Shephard et al., 2015). Similarly, another experiment from the same group, the authors assessed goal directed learning and showed distinct P3 peaks, where the earlier peak consistently had higher amplitudes in TS (Shephard, 2013, pp. 102–103). With respect to children with ADHD who showed the smallest amplitude across outcomes here, it is interesting to note that the data presented by a prior study had the same pattern for this component at the central site around 300ms after flanker onset, as well as across flanker conditions (see figure 2 and 4 at Cz in Albrecht et al., 2008). Interestingly, in this dataset, the P3 component seemed reduced in children with ADHD (Albrecht et al., 2008, personal communication).

While there are some notable exceptions (Albrecht et al., 2008), many studies using simple choice response tasks in children do not find specific differences in N2 between ADHD and controls (e.g., Banaschewski et al., 2004; Broyd et al., 2005; Wiersma et al., 2006; Spronk et al., 2008). In our data, we saw a small frontal N2 component (not shown), but we did not find any clear negative modulation for incompatible and erroneous trials, or any group differences in the location and latency range of N2 that is typically present in flanker tasks in healthy young adults (e.g., Eichele et al., 2010b). Similarly, in this data we did not see a distinct ERN, or specific group differences therein, which may be explained by the clear developmental effect in this component, in the sense that our sample on average has an immature response (Davies et al., 2004). Due to the close interrelation between the ERN and the midfrontal N2, we can also speculate that frontal

lobe maturation might affect N2 in the same way (Brydges et al., 2012; Tamnes et al., 2013).

We did separate analyses of the P3 subcomponents here to disentangle processing related to an early P3 component, representing more likely the orienting of attention to stimuli (Polich, 2007), and the later P3b/LPC reflecting response selection and other response-related processing (Falkenstein et al., 1994). The separation of stimulus- and response-locked LPC allows to study response selection/ orienting and response preparation separately (Verleger et al., 2005), which gives further insight into motor control in children with TS. It is possible that the greater increase in P3/LPC amplitude in the TS group reflects a stronger consolidation of the Flanker task in children with TS than in children with ADHD and control children (Johnson, 1984) and may suggest that children with TS employ greater resources in this process to maintain performance.

Individuals with TS frequently need to suppress emerging tics to achieve adequate psychosocial function. Other research has shown that children with TS have a generalized increase in cognitive control over motor activity (Mueller et al., 2006; Jackson et al., 2007) and enhanced control over their manual responses on a task-switching paradigm (Jackson et al., 2011), probably as a consequence of tic suppression. Here, we show that these adaptive effects already may happen earlier during stimulus evaluation, where an adaptation of the attentional system may result in higher attentional levels toward salient stimuli and an increased ability to suppress distracting information. This would in turn improve response selection.

The earlier discordant findings in the few previous studies of P3 in TS children may relate to different methods of recruiting the subjects (comorbidities, medication), and to differences in task selection (passive, active, visual, auditory, response mode; Luck, 2005), as well as different EEG/ERP post-processing and analysis. Here, use of ICA for artifact correction, and region of interest averaging allows for a clearer representation of a small, but robust ERP difference that is appreciable already in earlier work (Albrecht et al., 2008; Shephard et al., 2015).

We found smallest P3/LPC component amplitudes in the ADHD group, albeit not reaching significant difference levels compared with controls. This appears generally consistent with existing literature from several choice response tasks in this age group, including the Flanker task (Johnstone et al., 2010; Kratz et al., 2011). A reduced P3 in ADHD is considered reflective of diminished evaluative and processing capabilities (Brandeis et al., 2002; Lawrence et al., 2005; Johnstone et al., 2010; Kratz et al., 2011). Results from this group are heterogeneous however, for example a recent study using a Flanker task did not find differences on ERP or behavioral measures in children with ADHD compared to a control group (Johnstone and Galletta, 2013). Some inconsistencies may be related to study design, i.e., use of different compositions of clinical samples regarding age-range, sample size, medication status/type, gender distribution or comorbid disorders (Johnstone et al., 2013). However, amplitudes of children with ADHD become more like

those of controls when motivated to perform well (Groom et al., 2010) and might have resulted in typical amplitude findings in our study.

We did not find that children with TS used a different strategy in prioritizing either speed or accuracy in compatible or incompatible trials and with respect to symptoms measured with the YGTSS, nor could we find significant correlations for speed or accuracy.

Strengths and Limitations of the Study

All children were medication-naïve. Age and FSIQ differences did not readily explain group differences because groups were matched for age, as well as age and FSIQ were also used as covariates. The inclusion of children with ADHD is a strength of the study, because it allowed to illustrate the specificity of a higher P3 in children with TS, with and without comorbidity.

A limitation here is the relatively small sample size given the incidence, which led us to group TS+ADHD and TS only together. Ideally, the impact of comorbid conditions should be assessed separately, and in more detail, requiring larger sample sizes in future studies, probably best achievable through collaborative multi-site consortia. However, the fact that we did not find any significant differences between these subsamples in the dependent measures reported here justified the inclusion of children with TS only and those with additional ADHD in the same group. The relative lack of negative impact of comorbid ADHD on TS in our sample seems at variance with previous work reporting impaired ERPs (Shephard et al., 2015) and behavior (Roessner et al., 2007; Sukhodolsky et al., 2010; Greimel et al., 2011; Shephard et al., 2015) in participants with TS and ADHD. However, differences in mean age and gender distribution of the samples, as well as use of medication are different. Differences in task design and time on task may also play a role.

Many executive tasks are influenced by global changes in response caution, and motivation and error rates might fluctuate. The skills implemented to solve cognitive challenges may differ considerably in typically developing children from children with ADHD or TS. However, we tried to minimize these influences by keeping the time-on-trial to a minimum, and providing individual feedback after slow and after erroneous trials, respectively. During the experiment and upon debriefing there was no reason to suspect differences in motivation, attention or fatigue across groups and order of tasks was counterbalanced. Also, we used a robust estimate of PES (Dutilleul et al., 2012), that discounts slow drifts.

CONCLUSION

These findings provide further evidence that TS is not associated with widespread executive impairments, but presents robust evidence that adaptive changes, such as a heightened attentional capacity, are a core component of the TS disorder. In particular, we report a differential modulation of a P3-subcomponent that has not received much attention so far.

AUTHOR CONTRIBUTIONS

Conception and design: HE, TE, IB, LS, KH, KP. Acquisition of data: HE, TE, MH, LS, HW, MW, KP. Analysis and interpretation: HE, TE, KP. Writing of article: HE, TE, KP. Critical review of article: HE, TE, IB, MH, LS, HW, MW, KH, KP. Final approval for publication: HE, TE, IB, MH, LS, HW, MW, KH, KP. Agreement to be accountable for all aspects of the work: HE, TE, IB, MH, LS, HW, MW, KH, KP.

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Development of Performance and ERPs in a Flanker Task in Children and Adolescents with Tourette Syndrome—A Follow-Up Study

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Background: Tourette Syndrome (TS) is a neurodevelopmental disorder with childhood-onset, with a typical decline in tic severity, as well as an increasing ability to suppress tics in late childhood and adolescence. These processes develop in parallel with general improvement of self-regulatory abilities, and performance monitoring during this age-span. Hence, changes in performance monitoring over time might provide insight into the regulation of tics in children and adolescents with TS.

Method: We measured reaction time, reaction time variability, accuracy, and event-related potentials (ERP) in 17 children with TS, including 10 children with comorbid Attention-Deficit/Hyperactivity Disorder (ADHD), 24 children with ADHD, and 29 typically developing children, using a modified Eriksen Flanker task in two testing sessions administered on average 4.5 years apart. We then compared task performance, as well as ERP components across groups, and over time using regression models.

Results: Task performance improved in all groups with age, and behavioral differences between children with TS and controls diminished at second assessment, while differences between controls and children with ADHD largely persisted. In terms of ERP, the early P3 developed earlier in children with TS compared with controls at the first assessment, but trajectories converged with maturation. ERP component amplitudes correlated with worst-ever tic scores.

Conclusions: Merging trajectories between children with TS and controls are consistent with the development of compensatory self-regulation mechanisms during early adolescence, probably facilitating tic suppression, in contrast to children with ADHD. Correlations between ERP amplitudes and tic scores also support this notion.

Keywords: Tourette syndrome, ADHD, children, adolescence, event-related potentials, performance monitoring, developmental trajectories, follow-up

INTRODUCTION

Tourette Syndrome (TS) is a neurodevelopmental disorder with childhood onset, defined by the presence of multiple motor tics and at least one vocal tic over the period of 1 year or more (American Psychiatric Association, 1994). Tics typically emerge at around 6 years of age and often follow a developmental time-course in which tics increase in frequency and severity to a worst-ever period around age 8–12 years, and become increasingly controlled during adolescence (Bloch and Leckman, 2009). This typical course coincides with the development of self-regulatory control during childhood and adolescence (Davidson et al., 2006; Tau and Peterson, 2010) and the maturation of the frontal cortex (Gogtay et al., 2004).

Compensatory neuromodulatory alterations in brain function possibly evolve through the constant need to suppress tics (Eichele and Plessen, 2013), resulting in increased sustained attention to emerging tics (or urges) and control over motor output/efferents. This process is thought to involve activity in a functional network that includes the frontal cortices, basal ganglia, and the thalamic nuclei, the so-called cortico-striato-thalamo-cortical circuits (Jackson et al., 2015). Activity in this network is also elicited during tasks requiring cognitive control and performance monitoring such as the Eriksen Flanker task (Eriksen and Eriksen, 1974). A variant of this task is used here in combination with event-related potentials (ERP) to identify underlying electrophysiological markers of attention and inhibitory control, which we assume is employed continuously to suppress tics. While other tasks have previously been used in EEG studies of children with TS, flanker tasks have only been used in behavioral studies in this patient group (Ozonoff et al., 1998; Crawford et al., 2005). We chose this task for our study as it is particularly useful for testing response inhibition and the ability to suppress and overwrite a pre-potent conflicting and opposing response that is prepared but incorrect, while the task is overall balanced for trial probability, and all trials require a motor response.

Several ERP components allow for a more detailed mapping of the performance monitoring process, beyond the importance to measure performance on the task. The P3 component is elicited by salient stimuli around 300 ms, and its dynamics can be described with predictive coding (Eichele et al., 2005). While its earlier subcomponents correspond to orienting and novelty, the later aspect of P3 is thought to more closely represent working memory and response selection (Donchin, 1981; Donchin and Coles, 1998; Polich, 2007), and is also sensitive to changes in cognitive conflict and control (Clayson and Larson, 2011a,b). After errors, the error-related negativity (ERN), as an immediate marker for automatic error detection and the subsequent error positivity (Pe), emerging at 300 ms after incorrect responses, associated with evaluation, awareness, and salience of errors are detectable. Both components show reduced amplitudes in neuropsychiatric disorders, including ADHD (Johnstone et al., 2013). Even though deficits in error processing have been studied extensively in children with ADHD (Johnstone et al., 2013; Plessen et al., 2016), there are to date only few available reports on ERN/Pe to visual tasks in children

with TS (Shephard et al., 2016a,b), thus far showing no clear differences between individuals with uncomplicated/TS only and healthy controls. However, young people with TS and comorbid ADHD showed reduced amplitudes of ERN, Pe, and P3 were seen in a Go/Nogo task, while the presence of comorbidity in TS yielded no differences in the acquisition phase, and marginal differences in the reversal phase of a reinforcement learning experiment.

Most studies measuring performance monitoring in children with neuropsychiatric disorders have used a cross-sectional design. It is, however, difficult to study developmental aspects of behavior with cross-sectional methods, due to cohort effects or possible bias in the selection of different age-groups of participants (Kraemer et al., 2000). Moreover, the interpretation of cross-sectional ERP component amplitudes is challenging in children, due to the uncertainty, whether correlations with age represent physiological changes accompanying maturation or rather increments of cognitive abilities.

The general aim of this study was therefore to track performance monitoring and adaptive effects in children with Tourette syndrome over time. As many children with TS have comorbid ADHD, a contrast group with children with ADHD was included to leverage the impact of comorbid ADHD in combination with TS, as well as a control group. We examined all three groups clinically, behaviorally and with ERPs at two time points, on average 4.5 years apart in a longitudinal design, to avoid the shortcomings of cross-sectional designs. At the first assessment, we found that children with TS showed higher amplitudes of an early P3 component of the stimulus-locked ERPs in the grand average across experimental conditions and in separate trial outcomes. In the corresponding response-locked ERP data, children with TS had a slightly higher positive complex before the motor response, likely reflecting a late P3. Groups did not differ in post-response components. We assumed from those findings that children with TS employ additional attentional resources during stimulus evaluation as a compensatory mechanism to maintain performance (Eichele et al., 2016). We here re-examined the children at a second assessment, and focused on the developmental trajectories of the stimulus-locked attention-related potentials reflected by the early P3 and late P3, as well as on response-locked potentials related to error processing reflected by the ERN and the Pe.

Based on brain maturation and attenuation of tic symptoms during adolescence, as well as previous findings, we expected that children with TS would over time show (i) performance-monitoring pattern in terms of reaction times, variability of reaction times, and response accuracy similar to those of control children, whereas we expected better performance compared to children with ADHD. Further, we expected that children with TS would show (ii) ERP amplitudes similar to those of control children, whereas we expected that children with ADHD would show reduced ERP amplitudes in line with earlier findings. In addition, we explored associations between tic scores and ERP amplitudes under the assumption that tic control during adolescence is related to adaptation in control systems.

MATERIALS AND METHODS

Participants

The original participant group at the first assessment (T1) included 39 children with ADHD, 25 children with Tourette syndrome and 35 control children aged 8–12. The study was approved by the Regional Committee for Medical Research Ethics, West-Norway and written, informed consent was obtained from the legal guardians/parents of all non-adult research participants. Inclusion criteria and results relating only to this cohort are described elsewhere (Eichele et al., 2016). All children that initially participated at T1 were contacted again, and 70 children and adolescents with an age range 11–17 years participated in a follow-up ERP investigation after ~4.5 years [24 ADHD, 17 TS (7 TS “only,” 10 TS+ADHD), 29 controls], hence 70 participants attending both T1 and T2 were included here in the longitudinal design. Dropout rate was 29% for the overall group (17% controls, 38% ADHD, 32%TS). The follow-up investigation at T2 consisted of a semi-structured interview, the K-SADS (Schedule for Affective Disorders and Schizophrenia for School-Aged Children; Kaufman et al., 1997), the Children Global Assessment Scale (CGAS; Shaffer et al., 1983), and the DuPaul ADHD-Rating Scale (ADHD-RS; DuPaul et al., 1998), along with a best estimate consensus procedure that considered all available study material (Leckman et al., 1982). Children met diagnostic criteria for TS and ADHD, respectively (DSM-IV; American Psychiatric Association, 1994). Tic symptoms were assessed using the Yale Global Tic Severity Scale (YGTSS) yielding Total Motor (0–25), Total Phonic (0–25),

and the combined Total Tic Score (0–50) for current and worst-ever tic severity separately in an interview with the child and parents (Leckman et al., 1989). At T1, exclusion criteria for the control group were a lifetime history of Tic disorder, OCD, ADHD, or a current DSM-IV axis I disorder other than specific (simple) phobias. Additional exclusion criteria for all groups were epilepsy, head trauma with loss of consciousness, former, or present substance abuse, suspicion of Autism spectrum disorder, prematurity (gestational age <36 weeks) or a full scale intelligence quotient (FSIQ) below 75, measured by the Wechsler Intelligence Scale for Children-IV (Wechsler, 2003). Among participants the following comorbid conditions were present at T2: oppositional defiant disorder (ADHD; $N = 8$, TS; $N = 2$), conduct disorder (ADHD; $N = 1$), phobia (ADHD; $N = 5$, TS; $N = 3$, control; $N = 2$), anxiety disorder (TS; $N = 1$), transient tics (ADHD; $N = 2$), chronic motor tics (ADHD; $N = 1$), obsessive compulsive disorder (TS; $N = 3$), depression (ADHD; $N = 1$, TS; $N = 1$) and elimination disorder (ADHD; $N = 1$). All children were medication-free and had no prior treatment for ADHD at the first assessment. Participants taking stimulants at the second assessment (21 participants, ADHD; $N = 17$, TS + ADHD = 4) were asked to refrain from taking the medication in the 48 h prior to testing. Other types of medication (antipsychotic 2nd generation + melatonin, TS; $N = 1$, antiepileptic, TS; $N = 1$) were taken as prescribed. Twenty-five children were girls and the groups did not differ for age and sex. Eleven children were left-handed (Table 1). The groups differed in FSIQ scores, similar to findings reported in other studies (Bornstein, 1991; Ozonoff et al., 1998; Baym et al., 2008;

TABLE 1 | Sample characteristics.

	Controls $N = 29$	ADHD $N = 24$	TS $N = 17$	Statistics
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
SAMPLE CHARACTERISTICS				
Sex (% male)	58%	70%	65%	$\chi^2 = 0.85$, n.s.
FSIQ	107.69 \pm 10.82	92.54 \pm 8.09	99.00 \pm 11.57	$F_{(2, 67)} = 14.78$, $p < 0.001$, $\eta_p^2 = 0.31$
AGE (YEARS)				
T1	10.12 \pm 0.99	10.02 \pm 1.28	9.84 \pm 1.28	$F_{(2, 67)} = 0.31$, n.s.
T2	14.68 \pm 1.15	14.49 \pm 1.45	14.17 \pm 1.79	$F_{(2, 67)} = 0.69$, n.s.
Handedness (% right handed)	93%	79%	76%	$\chi^2 = 2.96$, n.s.
ADHD-RS TOTAL SCORE				
T1	3.14 \pm 2.97	30.54 \pm 8.71	20.59 \pm 9.98	$F_{(2, 67)} = 95.18$, $p < 0.001$, $\eta_p^2 = 0.74$
T2	4.81 \pm 5.78	27.36 \pm 10.19	19.39 \pm 10.49	$F_{(2, 67)} = 45.62$, $p < 0.001$, $\eta_p^2 = 0.58$
YGTSS TOTAL SCORE				
T1				
Total current tic severity			19.76 \pm 8.71	
Total worst-ever tic severity			26.82 \pm 8.13	
T2				
Total current tic severity			14.47 \pm 8.18	
Total worst-ever tic severity			31.00 \pm 8.25	

ADHD, Attention-Deficit/Hyperactivity Disorder; TS, Tourette Syndrome; FSIQ, full scale intelligence quotient; ADHD-RS, attention-deficit/hyperactivity disorder rating scale; SD, standard deviation; YGTSS, Yale Global Tic Severity Scale; T1, first assessment; T2, second assessment.

Debes et al., 2011). Groups did also differ in ADHD-RS total values. Total current tic severity in the TS group at T1 was 19.76 ± 8.71 (range 4–38) and decreased significantly over time [T2: 14.47 ± 8.18 , range 4–33, $t_{(1, 16)} = 2.33, p = 0.03$]. Lifetime worst-ever tic severity ranged from 14 to 23 (26.82 ± 8.13) at T1 and from 17 to 48 (31.00 ± 8.25) at T2, indicating a slight increase in the interval, consistent with the expected development (Leckman et al., 1998). The execution of many tics per day may trigger compensatory phenomena, but the fact that tics wax and wane in their frequency and characteristics over hours, days, and months, makes the objective measurement of symptom severity overall difficult. We therefore decided to use worst-ever tic severity for correlation with ERP measures as these might better relate to the accumulated symptom load and may represent a measure for compensatory long-term effects. To control for sampling bias, we compared the baseline characteristics from the first assessment between the dropouts ($N = 29$) and the returning participants ($N = 70$). Age at first examination, gender ratio or handedness did not differ across groups. However, a difference of FSIQ scores for the control group (96.8 at first assessment vs. 107.7 at second assessment) was found. This was not present in the two other groups (Table 1), indicating that the controls participating at T2 were biased toward a higher FSIQ. Sample characteristics, e.g., the ADHD-RS scores and the YGTSS scores did not differ across groups. Thus, despite some attrition, the present sample still was largely representative of the original samples, especially in the two diagnostic groups.

Experimental Design

At both sessions electroencephalogram (EEG) was recorded during performance of a modified Eriksen flanker task implemented in the E-prime 2 experiment programming platform (Psychology Software Tools, <https://www.psnet.com/eprime.cfm>) after verbal and written instruction and a training sequence. At the center of a PC screen, participants were presented a fixation dot. Trials began with the presentation of 6 horizontal flanker arrows appearing below the fixation. Participants were instructed to respond with their preferred hand as fast as possible and as accurate as possible with either a left or a right mouse button press following the direction of a central target arrow that appeared 100 ms after the flankers. The central target arrow pointed either into the same direction as the flanker arrows in compatible trials (<<<< < <<<, >>>> > >>>) or in the opposite direction in incompatible trials (<<<< > <<<, >>>> < >>>). The target and flanker-arrows remained on screen until a response was registered. Trials were terminated by a motor response and were followed by a fixed 800 ms interval before the onset of the next trial. Stimuli were presented in two blocks with 200 trials that were pseudo randomized separately for each participant. The overall probability of compatible and incompatible trials, as well as left and right responses was kept at 0.5, respectively. Performance feedback was given during the experiment when responses were erroneous or slower than the adaptive individual threshold value [mean response time plus 1.5 standard deviation (SD)].

EEG Data Acquisition

EEG was recorded continuously in an electromagnetically shielded chamber (Rainford EMC Systems, Wigan, UK). Data were sampled at a 1,000 Hz-frequency with a 10 s time-constant, with Brain Amp MR plus X2 amplifiers (BrainProducts, Munich, Germany). An elastic cap containing 34 Ag/AgCl electrodes placed at Fp1, Fp2, F7, F3, Fz, F4, F8, FT9, FC5, FC1, FC2, FC6, FT10, T7, C3, Cz, C4, T8, TP9, CP5, CP1, CP2, CP6, TP10, P7, P3, Pz, P4, P8, PO9, O1, O2, PO10, Iz was used. Channels were recorded against Fz with a ground on Fcz. Vertical eye-movements were recorded with a bipolar derivation between Fp1 and an additional electrode placed below the left eye, horizontal eye movement were recorded with a bipolar derivation between Fp1 and Fp2. Additionally, electrocardiographic activity was monitored by an electrode placed on the left chest. Impedances were kept below 10 k Ω .

EEG Processing

Continuous EEG data files were imported into EEGLAB written in Matlab (Delorme and Makeig, 2004) and resampled to 500 Hz. The EEG-data were then re-referenced to a common average reference, and filtered from 0.1 to 40 Hz. After initial visual inspection to rule out focal or generalized EEG abnormalities, and pervasive non-stereotyped signal artifacts we performed automatic artifact rejection in order to denoise the data prior to spatial filtering with independent component analysis (ICA) in an unbiased way. The data were divided into 1000 ms epochs back-to-back. In order to derive a score with high sensitivity for artifacts these epochs were first detrended, and then we computed for each channel the absolute sums of the rectified epoch, as well as its differential. We also computed the standard deviation, skewness, and kurtosis of the time-series. The sum of the power spectrum was estimated, and we derived a dynamic range estimate by dividing the content at high frequencies by the low frequencies. These measures were normalized to unit variance, summed across all channels and normalized. Epochs within ± 1 standard deviation were retained for further analysis, concatenated, and subjected to temporal ICA using infomax (Bell and Sejnowski, 1995). Thirty components were estimated after principal component analysis compression. The resulting component maps and activations were back-projected into the continuous data, and segmented into stimulus-locked (-0.5 to 1 s around flanker) and response-locked (-1 to 0.5 s around button press) sets. Hereafter, we automatically screened the components to retain only task and ERP-relevant sources. Firstly, spatial correlation with templates was used to find components relating to blinks and lateral eye movement (Viola et al., 2009). Then, spatially sparse components, i.e., loading only on single or few electrodes were identified by detecting outliers in the spatial standard deviation. In order to select ERP-relevant components, we first repeated artifact rejection as mentioned above, and, in addition discarded trials with response times < 200 or $> 2,000$ ms, and then generated component timecourses grand average stimulus and response-locked average waveforms; those components contributing variance to the overall ERP were kept (Wessel and Ullsperger, 2011).

Averaging and Data Extraction

We generated ERP-averages from these back-projected data, separately for compatible, incompatible, and erroneous trials from both stimulus- and response-locked segments. We then inspected the grand averaged data across all participants together for both sessions to select regions and timewindows for statistical testing of relevant components. Based on our previous selection and upon inspection of grand average ERP data and difference waves across both age groups, we found that conditional effects on several components were consistently expressed around Cz/Vertex, which is in line with other work (Cycowicz, 2000; Stige et al., 2007). We therefore used a region average from FC1, FC2, Cz, CP1, CP2, for spatial data reduction, and controlling for inter-individual variability (Handy, 2005). Spatial averaging also helps to control for variability as seen in different age groups (e.g., Cycowicz, 2000; Davies et al., 2004; Brydges et al., 2013).

Because latency jitter in event-related potential components between trials, especially in children, and peak amplitudes can be influenced by group differences in signal-noise-ratio, analyses of mean amplitudes were chosen (Luck, 2005). Amplitudes were extracted from 40 ms long windows centered on the grand average peak latency and were used for testing of group differences. The time-windows we focused on for further analyses are the stimulus-locked P2 (170–210 ms), early P3 (310–350 ms), and late P3 (500–600 ms). In the response-locked averages, we extracted the ERN as the difference between -40 to 0 ms and 60 to 100 ms post-response. Pe was estimated as the average between 250 and 290 ms. For reference, we also included the earlier P2 component as a marker of exogenous processing. The stimulus-locked N2, detecting early stages of conflict/mismatch and is often reported in Flanker task studies on adults (Folstein and Van Petten, 2008), however, earlier studies revealed that adult-level N2 amplitudes were not found until the age of 16 (Ladouceur et al., 2007) and we decided therefore not to investigate this latency range further here in this age group.

Statistics

To address our main question, we estimated the differences between groups, as well as effect modification with age and condition. This was done for the behavioral measures Accuracy (ACC), Reaction Time (RT), Reaction Time variability (sdRT), as well as the stimulus-locked ERPs P2, early P3, late P3, and response-locked ERN and Pe. We used a mixed-model analysis with repeated measures with an unstructured variance component matrix. The model included the within-subjects factor flanker outcome with three levels (compatible, incompatible, error) for RTs, with two levels (compatible, incompatible) for ACC, sdRT, and stimulus-locked ERP components, and with one level (error) for response-locked ERPs. In the longitudinal analysis, we included age at first and second assessment, as well as the three groups (Control, ADHD, TS) as between-subject factor. In the cross-sectional analyses, age was included as a covariate. Additionally, RT mean from both assessments was included as a within-subject factor. A random effect variable, assumed normally distributed, accounted for individual responses of the participants. The model was adjusted for all two-way interactions between the variables diagnostic

group, age, and condition. We transformed Accuracy to Arcsine to ensure a normal distribution in the outcome measure. We considered $P < 0.05$ as statistically significant. F -tests were used for hypothesis testing on type three fixed effects and estimates are presented with 95% confidence intervals. All statistical analyses were conducted in R (R Development Core Team, 2008). Further, to investigate associations between neurophysiological data and tic scores, Pearson's correlations were computed in Statistica (Statsoft, Tulsa, OK, USA).

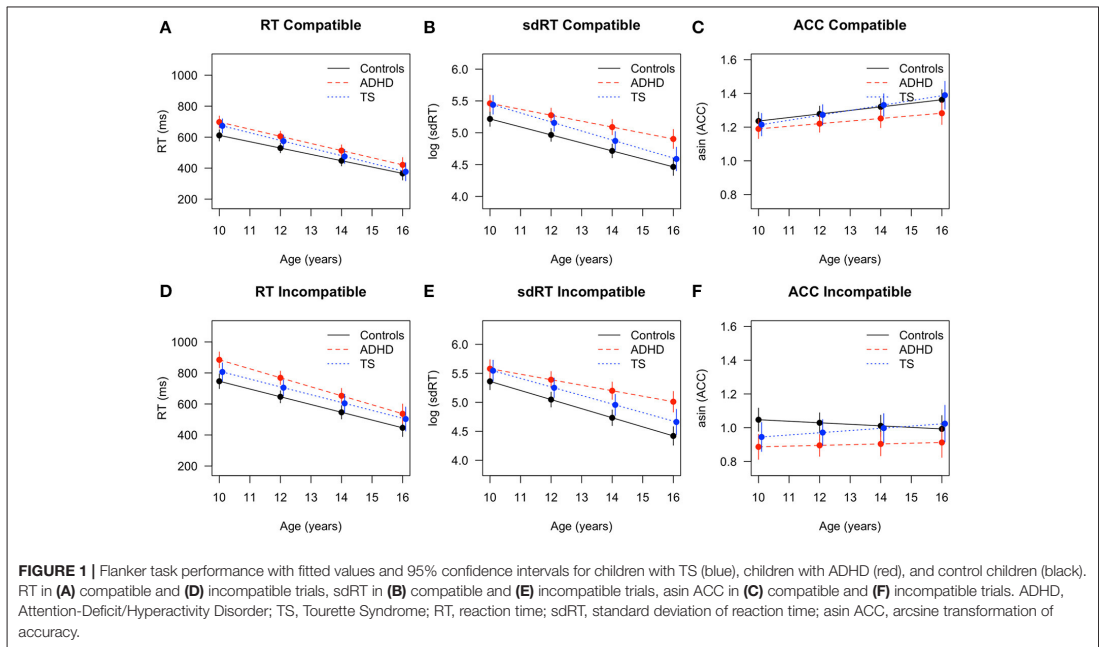
RESULTS

Behavioral Performance

Reaction times decreased with age [$F_{(1, 371)} = 744.06, p < 0.001$] and showed group differences [$F_{(2, 67)} = 6.17, p < 0.004$, ADHD > TS > controls] (Figure 1). A typical Flanker effect (RT error < RT compatible < RT incompatible) was also present [$F_{(2, 335)} = 153.13, p < 0.001$]. An interaction of age by outcome approached significance [$F_{(2, 335)} = 2.75, p = 0.06$]. Directed *post-hoc* tests showed that, controls were faster than children with TS in compatible and incompatible responses at T1 (both RTs $p < 0.05$, erroneous RT $p = 0.06$). Developmental trajectories tended to converge for controls and children with TS during the second assessment where all reaction time differences were minimized (n.s., Figure 1). Controls responded faster than children with ADHD at the first assessment (all RT < 0.05), and those differences persisted in the second assessment (all RTs $p < 0.05$, except erroneous RT $p = 0.06$). Children with ADHD and with TS did not differ in terms of reaction times in either of the assessments.

Reaction time variability decreased with age [$F_{(1, 224)} = 491.97, p < 0.001$], and differed across conditions [$F_{(1, 201)} = 11.67, p < 0.001$, sdRT compatible < sdRT incompatible], without interaction [age \times condition: $F_{(1, 201)} = 2.14, n.s.$]. Both diagnostic groups displayed a higher reaction time variability [$F_{(2, 67)} = 8.67, p < 0.001$, ADHD > TS > controls]. *Post-hoc* tests revealed that controls showed significantly lower variability both in compatible and incompatible trials than children with TS and ADHD at the first assessment (all sdRT $p < 0.05$), whereas children with TS and with ADHD did not differ. At the second assessment, differences between ADHD and controls persisted (all sdRT $p < 0.01$), while differences between children with TS and controls only were present in incompatible trials ($p < 0.05$). When comparing both diagnostic groups at T2, reaction time variability was lower in children with TS compared with ADHD in incompatible trials ($p < 0.05$), and slightly lower in compatible trials ($p = 0.06$). This pointed at diverging trajectories over time in both incompatible (Δ TS vs. Δ ADHD $p < 0.01$) and compatible trials (Δ TS vs. Δ ADHD $p < 0.05$) between these two groups. In addition, differences between children with ADHD and controls increased over time in incompatible trials (Δ controls vs. Δ ADHD $p < 0.01$).

Accuracy increased with age [$F_{(1, 225)} = 14.88, p < 0.001$], and differed across conditions [$F_{(1, 198)} = 436.75, p < 0.001$; ACC compatible > ACC incompatible; age \times condition: $F_{(1, 198)} = 10.33, p < 0.01$]. Groups showed differences in accuracy across both conditions [$F_{(2, 64)} = 3.31, p < 0.04$, controls > TS >



ADHD], without a clear interaction [group \times condition: $F_{(2, 198)} = 2.42, p < 0.09$]. *Post-hoc* tests showed significant differences at the first assessment for incompatible trials between ADHD and controls ($p < 0.01$) and TS and controls ($p < 0.05$), but no group differences between TS and ADHD. Developmental trajectories converged at the second assessment for controls and children with TS and all differences in accuracy were minimized (n.s.). Differences between controls and ADHD persisted ($p = 0.02$), and children with TS were slightly more accurate than children with ADHD ($p = 0.06$, TS > controls > ADHD). In compatible trials, accuracy improved most in children with TS (Δ change $p = 0.03$), followed by controls (Δ change $p = 0.05$), while ADHD showed no relevant improvement. Performance for incompatible trials was more variable, and only children with TS showed a trend toward improved accuracy over time in incompatible trials (Δ change $p = 0.08$), while the other groups remained unchanged overall.

Electrophysiological Results

Response-Locked Components

The ERN amplitude became larger with age [$F_{(1, 90)} = 95.14, p < 0.001$] without an apparent main effect or interaction of other terms [group: $F_{(2, 66)} = 1.54$, n.s.; age \times group: $F_{(2, 91)} = 2.15, p = \text{n.s.}$]. Direct comparison of longitudinal changes showed that ERN amplitudes increased from the first to the second assessment for all groups, however, average ERN amplitude appeared to become larger for controls and children with TS compared to children with ADHD, though without reaching significance (Δ

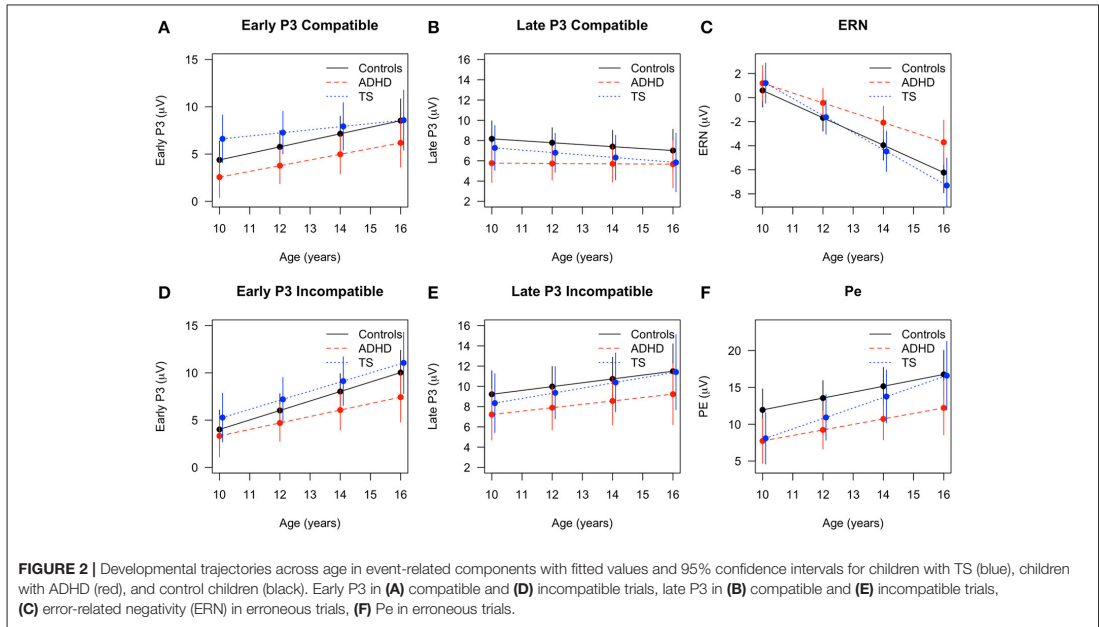
change controls and Δ change TS: $p < 0.01$, Δ change ADHD $p < 0.07$).

Pe amplitude also increased with age [$F_{(1, 84)} = 23.46, p < 0.001$], and simultaneously showed an inverse relation with response time changes [$F_{(1, 131)} = 7.45, p < 0.01$]. Amplitudes differed across groups [$F_{(2, 67)} = 3.16, p < 0.05$] across both assessments with ADHD children showing lowest levels, and no interaction of age with group [$F_{(2, 84)} = 1.18$, n.s.]. Although children with TS appeared on average to show a slightly higher change over time than children with ADHD, no significant *post-hoc* group differences were found (Figures 2, 3).

Stimulus-Locked Components

Younger participants had a higher P2 amplitude than older ones [$F_{(1, 222)} = 17.94, p < 0.001$]. Groups overall displayed similar P2 amplitudes [$F_{(2, 66)} = 0.81$, n.s.], meaningful interactions were not seen, and developmental trajectories showed no relevant differences across groups.

The early P3 showed a significant increase over time [$F_{(1, 223)} = 71.22, p < 0.001$], also showing an inverse relation with response time [$F_{(1, 265)} = 5.70, p < 0.05$]. The overall developmental change did not differ between the groups in the full model [age \times group: $F_{(2, 215)} = 1.16$, n.s.], but *post-hoc* tests showed that children with TS had larger amplitudes in compatible trials than children with ADHD ($p = 0.01$) at the first assessment. Over time, compatible P3 increased for controls and children with ADHD (Δ change controls $p < 0.01$, Δ change ADHD $p = 0.07$, Δ change TS n.s.). In incompatible trials, only



controls increased in amplitude (Δ change control: $p = 0.01$, Δ change TS and ADHD n.s.).

The late P3 differed between conditions [$F_{(1, 200)} = 27.25$, $p < 0.001$], with larger amplitudes in incompatible trials and an inverse relation with response time [$F_{(1, 264)} = 11.78$, $p < 0.001$]. Late P3 amplitudes in compatible trials tended to decrease, whereas incompatible amplitudes marginally increased over time [$F_{(1, 227)} = 3.16$, $p = 0.07$; age \times condition: $F_{(1, 200)} = 9.14$, $p < 0.01$]. Diagnostic groups did not differ in their developmental trajectories [age \times group: $F_{(2, 223)} = 0.10$, $p = \text{n.s.}$] (Figures 2, 4).

Exploratory Analyses

Correlations between ERP Amplitudes and YGTSS Scores

Children with TS showed significant positive correlations between worst-ever total tic scores collected at the first assessment and stimulus-locked amplitudes for the first assessment, compatible P2 ($r = 0.61$, $p < 0.01$), incompatible P2 ($r = 0.67$, $p < 0.01$), compatible early P3 ($r = 0.50$, $p = 0.04$), incompatible early P3 ($r = 0.57$, $p = 0.02$), incompatible late P3 ($r = 0.54$, $p = 0.02$). The ERN, however, correlated inversely with worst-ever total tic scores ($r = -0.49$, $p < 0.05$) for the second assessment, where this component was developed in contrast to the first assessment, where no apparent ERN was present in most participants. A positive correlation was also present with Pe from the second assessment ($r = 0.61$, $p < 0.01$). Worst-ever tic scores from the second assessment correlated positively with stimulus-locked amplitudes from the second assessment, compatible P2 ($r = 0.58$, $p = 0.02$), incompatible P2 ($r = 0.71$, $p < 0.001$), compatible early P3 ($r = 0.52$, $p = 0.03$),

incompatible early P3 ($r = 0.65$, $p < 0.01$), incompatible late P3 ($r = 0.56$, $p = 0.02$). A positive correlation was present for the Pe from the second assessment ($r = 0.53$, $p = 0.04$) (Figure 5). Current total tic severity measures did not significantly correlate with YGTSS measures.

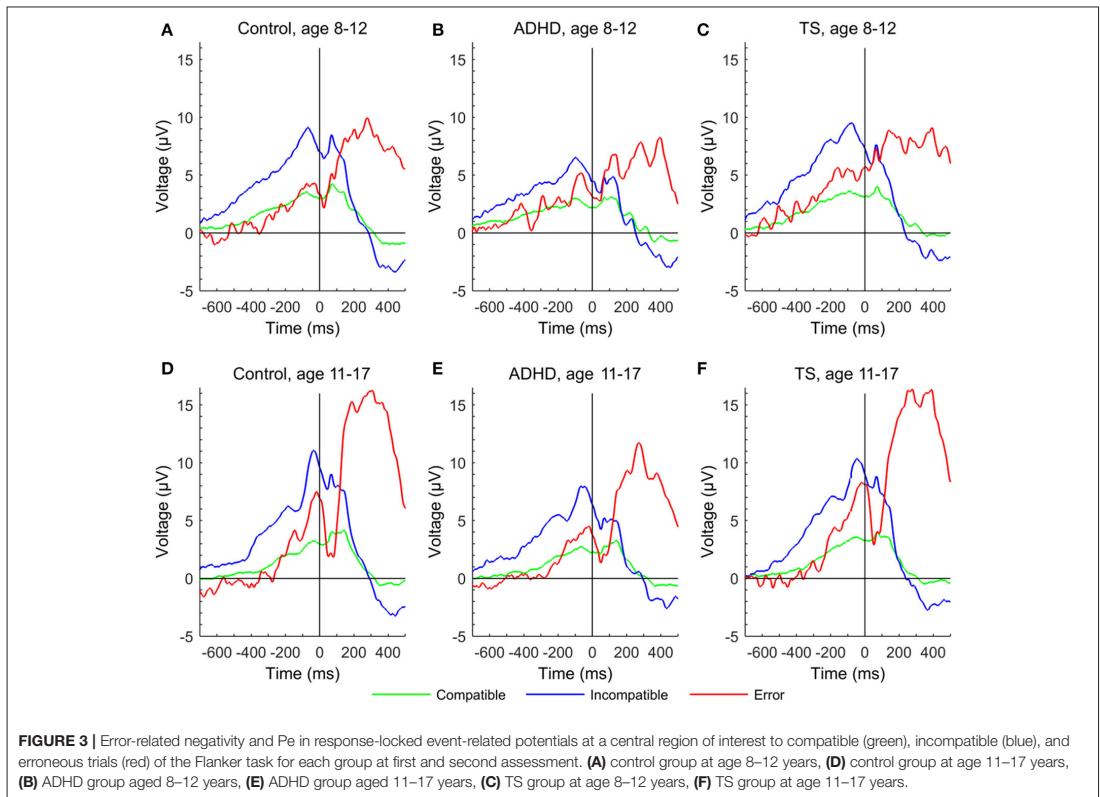
Influence of Comorbid ADHD in Children with TS

To ensure the adequacy of treating children with TS with and without ADHD as one group, we also conducted the mixed-model analysis for the main behavioral and ERP results with four groups (TS only, TS+ADHD, controls, and ADHD), and summarized overall test results here, along with directed *post-hoc* tests between TS only and TS+ADHD.

For RT, the analysis showed group differences as previously [$F_{(3, 65)} = 4.00$, $p = 0.01$]. *Post-hoc* tests between TS only and TS+ADHD were not significant for all RTs at both assessments (all RT $p > 0.32$). Developmental trajectories did not differ between those two subgroups (all Δ change $p > 0.19$).

Reaction time variability yielded a group main effect of similar strength [$F_{(3, 65)} = 5.53$, $p = 0.001$]. All *post-hoc* tests at both assessments between TS only and TS+ADHD were not significant (all sdRT $p > 0.20$). However, trajectories diverged between TS and TS+ADHD in compatible trials (Δ change $p = 0.007$) with lower reaction time variabilities for the TS only group over time, but not in incompatible trials (Δ change $p = 0.08$).

Groups showed differences in accuracy across both conditions [$F_{(3, 63)} = 2.17$, $p = 0.01$]. *Post-hoc* tests for both assessments as well as developmental trajectories did not differ between



TS only and TS+ADHD (all ACC $p > 0.84$, all Δ change $p > 0.79$).

For the response-locked ERN, no significant group differences were found in the analysis with four groups. As noted previously, ERN was not developed in at T1 across groups, and no significant differences between subgroups were seen at T2 ($p > 0.55$), or over time (Δ change $p = 0.32$).

For the Pe, the analysis with four groups repeats a group difference [$F_{(3, 66)} = 2.70$, $p = 0.05$], and shows a trend-significant *post-hoc* test at T1 ($p = 0.07$, TS+ADHD > TS), however trajectories merged between the groups and no differences were found at T2 ($p > 0.82$, Δ change $p = 0.16$).

The stimulus-locked P2 remained without differences between groups overall, component estimates and their changes over time were similar for TS only and TS+ADHD (all $p > 0.13$, all Δ change $p > 0.23$).

Similarly, early P3 results from the main analysis were repeated, no *post-hoc* groups differences between TS only and TS+ADHD were seen (all $p > 0.53$, all Δ change $p > 0.83$).

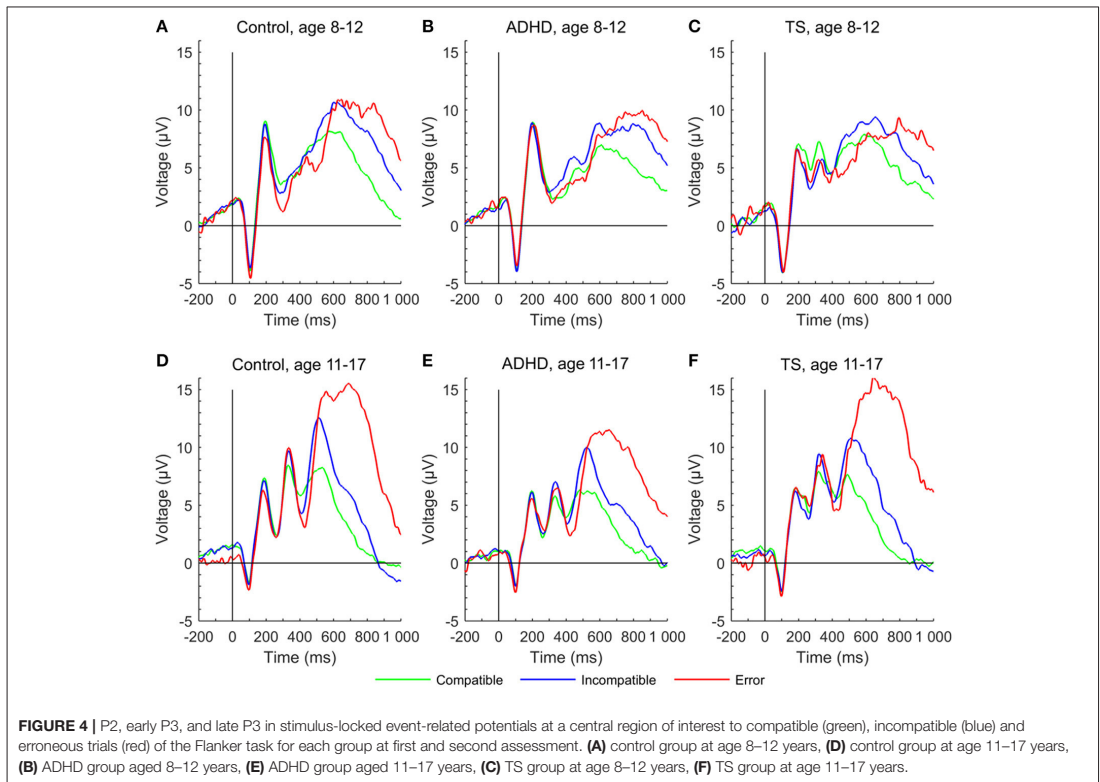
The overall developmental change of the late P3 revealed at trend-significant difference between the groups in the full model [age \times group: $F_{(3, 220)} = 2.57$, $p = 0.06$], but *post-hoc* tests did not show differences between the two subgroups at T1 and

T2 (all $p > 0.12$). However, incompatible late P3 amplitudes increased more over time in the TS only group compared to TS+ADHD, resulting in different trajectories for incompatible trials (Δ change $p = 0.04$), but not for compatible trials (Δ change $p = 0.18$).

While it is noteworthy that some of the measures here showed differences between TS subgroups at T1 or T2, or in terms of change over time, the majority of the data available to us showed no sign of more widespread differences when using two-sample *t*-tests and effect size estimators.

DISCUSSION

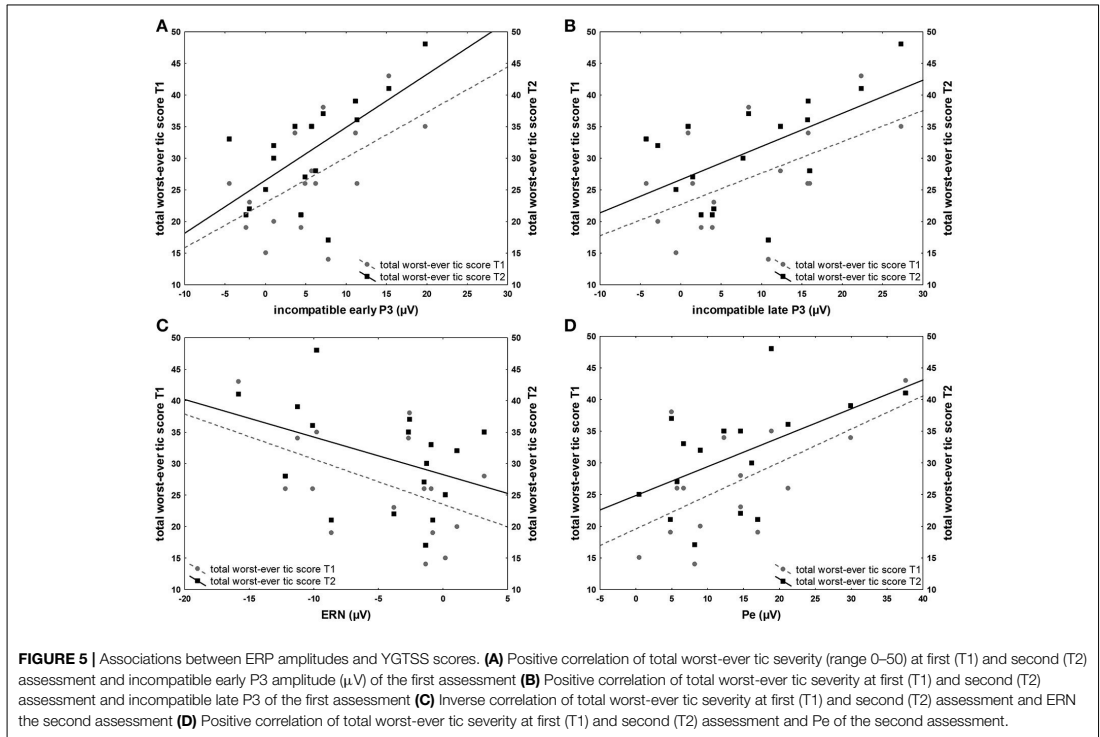
The present examination of attention, cognitive control, and performance monitoring from childhood to adolescence revealed several differences of the developmental trajectories between children with TS, and healthy controls, and in contrast to children with ADHD. Task performance in terms of reaction times, reaction time variability, and accuracy improved in all groups with age, but behavioral differences between children with TS and controls diminished at the second assessment, whereas differences between controls and children with ADHD largely persisted. In terms of ERP, the early P3 developed earlier



in children with TS compared with controls and trajectories converged with maturation. Worst-ever total tic scores correlated positively with stimulus-locked ERP from the first and inversely with response-locked ERP from the second assessment in children with TS.

The developmental effects on performance for the overall group with increased accuracy, faster reaction times, and decreased reaction time variability are consistent with the literature (Posner and Rothbart, 2007; Tamnes et al., 2013). Children with TS improved in most performance measures over time, resulting in converging trajectories between controls and TS following an initial deficit at T1 in children with TS, in terms of reaction times, reaction time variability and accuracy. Compared with children with ADHD, children with TS showed bigger reductions in their reaction time variability, resulting in significant differences between both groups at the second assessment. When additionally separating the two subgroups with and without ADHD comorbidity we saw that reduction of variability was more prominent in the TS only group. The adaptation of behavioral performance in children with TS is a topic of discussion and existing studies report inconsistent results (Harris et al., 1995; Serrien et al., 2005; Mueller et al., 2006; Jackson et al., 2007; Baym et al., 2008; Roessner et al.,

2008; Eichele et al., 2010; Shephard et al., 2016a). Only a few other, behavioral, studies have used variants of flanker tasks in children with TS and found that TS is not associated with widespread executive impairment, however children with comorbid conditions tended to perform less well (Ozonoff et al., 1998; Crawford et al., 2005). While most of our measures show no significant differences between subgroups in this sample, the presence of increased response time variability in comorbid ADHD is not unexpected due to the high penetrance of this feature in ADHD (Klein et al., 2006). However, most studies included participants with a wider age range, or an age range consistent with our first assessment. To our knowledge, no other study assessed behavioral changes over time in children in Tourette syndrome. Differences between first and second assessment in our study may point to adaptation of compensatory self-regulation mechanisms from childhood to adolescence through the constant need to suppress tics. Tic suppression may lead to increased control over motor outputs and by that generalizes to behavioral measures of cognitive control (Mueller et al., 2006; Jackson et al., 2015). On the other hand, our results with differences in the early P3 possibly point at an earlier implementation of adaptive effects already during stimulus evaluation, at least in the context of this task (Eichele



et al., 2016) and our exploratory analyses of ERP amplitudes with tic severity further seem to support this notion.

In contradistinction, despite general improvement in performance over time in the ADHD group, most of the ADHD-related performance differences with respect to behavioral performance persisted through development in direct comparison with the controls. The significant group-effect for reaction time variability and error rate in children with ADHD is in line with findings that increased variability and error rate are particularly robust markers of ADHD (for review, see Mullane et al., 2009; Kofler et al., 2013; Michelini et al., 2016). Impairments in those behavioral measures are thought to result from lapses in attention in the flanker congruent condition and as failure in executive control in the incongruent condition (Michelini et al., 2016). This may point to a pattern of performance deficits consistent with the developmental lag model (Doehnert et al., 2010) and probably in relation to reduced activity in the anterior cingulate cortex, and the functional networks in which it is involved (Plessen et al., 2016).

Maturation had a strong effect on the ERP components in the overall group with younger children showing smaller amplitudes in ERN, PE, early P3, and incompatible late P3 while P2 and compatible late P3 amplitudes decreased with older age. The age effects on the error-related components for the overall group with increasing amplitudes of ERN through adolescence are consistent

with prior studies (Davies et al., 2004; Ferdinand and Kray, 2014). We see a similar, but weaker maturation effect for the Pe independent of group. However, this change in amplitude was not present in the respective data reported by Davies et al. (2004) and Wiersma et al. (2007), whereas, a clear difference was present in the grand average waveforms presented by Ladouceur et al. (2004). With respect to the diagnostic groups, children with ADHD showed an attenuated increase in ERN amplitude from the initial to the second assessment in contrast to the children with TS and controls. Groups did not show different developmental trajectories of the Pe. This is in line with a recent meta-analysis comparing ADHD with controls and reporting an overall attenuation of ERN in performance-monitoring tasks while Pe attenuations were not significant in Flanker tasks for the ADHD group (Geburek et al., 2013). This attenuation of the typical increase in ERN amplitude over a period of 4.5 years confirms a deficit of the early detection of an error, whereas the following stage of error processing appears to be less affected in juvenile ADHD. Remarkably, albeit not significant, the gradient of increase in Pe amplitude was steepest in TS (Figure 3F), leading to reduction of group differences between controls and TS while trajectories of children with ADHD was flatter.

Larger amplitudes in early P3 in children with TS compared with controls were seen in the first assessment (Eichele et al., 2016), and interpreted as a reflection of sustained effort in the

TS group to intensify stimulus processing with an increased focused attention to the stimuli, leading to an altered target discrimination pattern. Over time, developmental trajectories of the compatible early P3 amplitude in control children appear to catch up with the TS group, merging in the second assessment on a similar level, whereas at the same time ADHD children trailed both other groups. Remarkably, children with TS maintain the largest amplitudes in incompatible trials at T2, with a very similar increase over time compared with controls, while the trajectory for the children with ADHD flattened, yielding a slightly increased amplitude difference. The deviant P3 trajectory for the children with ADHD thus persisted into mid-adolescence, despite effects of maturation in all groups. Additional studies are needed to characterize the functional role of this P3 subcomponent in TS in the context of change detection/oddball designs as well as Go/Nogo-type experiments.

For the remaining stimulus-locked ERP amplitudes, we observed marginal changes over time. Across trial conditions, ADHD showed smallest amplitudes in the late P3, while TS and controls showed larger amplitudes. There was no appreciable change of compatible amplitudes for the ADHD group, while the TS and control groups showed subtle amplitude reduction over time. On the other hand, the developmental trajectories of the incompatible late P3 increased slightly, and merged in adolescence for TS and controls, but not for the ADHD group. This suggests normal maturation of attention functions and non-significant attenuation in children with TS. For the P2 we expected an amplitude reduction over time based on normative studies (Allison et al., 1983; Mahajan and McArthur, 2012) on visual evoked responses, and this was the case across the entire sample.

The moderate to strong correlations between several ERP amplitudes and the worst-ever tic scores are striking. Positive correlations with stimulus-locked ERP from the first and inversely with response-locked ERP from the second assessment may suggest that the associations provide an indicator for a higher symptom load earlier in life leading to changes in stimulus and motor processing, resulting in an inverse correlation with error-related amplitudes at a later stage. It has been proposed that children with TS gain tic control through compensatory mechanisms that involve alteration of prefrontal control over motor output, experimental support comes specifically from supplementary motor area (Jackson et al., 2015). Consistent with this, transcranial magnetic stimulation studies have demonstrated that the pre-supplementary motor area may modulate primary motor cortex activity in conflicting situations and thus influence corticospinal excitability (Mars et al., 2009). We suggest that such functional adaptations more generally may affect cognitive control feedback loops, i.e., extending to the functional systems in the medial frontal wall including the cingulate gyrus (Ullsperger et al., 2014). In particular, cingulate cortex activity predicts motor cortex activity, and changes in behavior, as well as subsequent activity in sensory cortices on a trial-by-trial basis, presumably in order to provide optimal performance (Danielmeier et al., 2011). It is well-established that the main generator of the ERN/Pe is located in mesial frontal cortex (Debener et al., 2005), therefore

an inverse relation between ERN and tic severity, intuitively, could be an indicator of such a functional adaptation. This impression is further supported by the fact that some generators of P3 sub-processes that represent attentional control are located in the medial frontal cortex (Gehring and Fencsik, 2001; Huster et al., 2013). Surprisingly, correlations were also present with P2. However, we assume that P2 represents primarily sensory processing such that an indirect effect of medial frontal control seems plausible explanation at this point (Danielmeier et al., 2011, 2015). The current analysis was not set up to specifically investigate trial-to-trial connectivity, and concurrent behavior, but ongoing work in our lab further investigates these correlations with time-frequency analysis.

Among the limitations of our study, the relatively small sample size should be mentioned which also required disregarding comorbidities, use of medication, as well as the utilization and efficacy of behavioral treatment options. The latter information was unfortunately not available within the current study setup. Ideally, the impact of comorbid conditions and medication should be assessed separately, and in more detail, however, we performed explorative *t*-tests between these subsamples in the dependent measures and did not find any significant differences between these subsamples. To complement the *t*-statistics, we also estimated Hedges *g* for the total TS sample vs. ADHD, and for the TS-ADHD subgroup vs. ADHD from all relevant dependent measures, and found no robust differences in terms of average effect size. This may justify the inclusion of children with TS only and those with additional ADHD in the same group. The relative lack of negative impact of comorbid ADHD on TS in our sample seems at variance with previous work reporting impaired ERPs (Shephard et al., 2016a) and behavior (Roessner et al., 2007; Sukhodolsky et al., 2010; Greimel et al., 2011; Shephard et al., 2016a) in participants with TS and ADHD. However, differences in mean age and gender distribution of the sample, as well as use of medication are different. Differences in task design and time on task may also play a role. Further, we lost several participants to follow-up yielding sample attrition, which could have altered the sample, especially in the TS group. We conducted *t*-tests of the baseline characteristics between participants lost to follow-up and remaining participants, both for the overall group as well as for the diagnostic groups separately and found no significant differences. We also reviewed the reasons for dropout based on debriefing information for the TS group, only one child did not further participate due to reduction of symptoms, for the remaining seven participants that did not return, other or no reasons were given.

CONCLUSION

Taken together, the present examination of cognitive processes from childhood to adolescence helps us to further broaden our knowledge of electrophysiological correlates in children with TS over time. During development, electrophysiological and behavioral differences between controls and children with TS

decreased and trajectories converged with control children. This may point at compensatory adaptive processes that mitigate symptoms load in children with TS over time. This is in contradistinction to residual deficits in adolescents with ADHD which continued to show reduced performance at both time points. However, some reduction of deficits in absolute terms was also apparent for other measures upon visual inspection, and may have missed significance due to lower statistical power with our overall small sample size.

The developmental changes seen in children with TS support theoretical accounts of the development of cognitive control stating that the ongoing maturation of the prefrontal circuitries, including the ACC, plays a major role in the development of cognitive control (Posner and Rothbart, 2007; van Meel et al., 2012). Further, our findings may support the assumption of the frontal compensatory self-regulation hypothesis linking control over tics with an adaptation of functions in the midfrontal cortex, and its control over motor output already in childhood.

The here presented indications of early compensatory effects may contribute to clinical awareness concerning underlying neurobiology of plastic processes and compensatory effects already in earlier age that may indicate that children with TS could benefit from habit reversal training already before the recommended age. Further, enhancements in adaptive processes through specific interventions may in the future decrease some

of the impairments associated with TS, and thus improve quality of life in this patient group.

AUTHOR CONTRIBUTIONS

Conception and design: HE, TE, LS, KH, and KP. Acquisition of data: HE, TE, LM, SA, and LS. Analysis and interpretation, writing of article: HE, TE, and KP. Critical review of article and agreement to be accountable for all aspects of the work: HE, TE, LM, SA, KH, LS, and KP.

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	Solberg, Ole Asbjørn, PhD	Peacekeeping warriors – A longitudinal study of Norwegian peacekeepers in Kosovo
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H	Svensen, Erling, PhD	WORK & HEALTH. Cognitive Activation Theory of Stress applied in an organisational setting.
	Øverland, Simon Nygaard, PhD	Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries.
	Eichele, Tom, PhD	Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing
	Børhaug, Kjetil, Dr.philos.	Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule.
	Eikeland, Thorleif, Dr.philos.	Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring.
	Wadel, Carl Cato, Dr.philos.	Medarbeidersamhandling og medarbeiderledelse i en lagbasert organisasjon
	Vinje, Hege Forbech, PhD	Thriving despite adversity: Job engagement and self-care among community nurses
	Noort, Maurits van den, PhD	Working memory capacity and foreign language acquisition
2008	Breivik, Kyrre, Dr.psychol.	The Adjustment of Children and Adolescents in Different Post-Divorce Family Structures. A Norwegian Study of Risks and Mechanisms.
V	Johnsen, Grethe E., PhD	Memory impairment in patients with posttraumatic stress disorder
	Sætrevik, Bjørn, PhD	Cognitive Control in Auditory Processing
	Carvalho, Susana Fonseca, PhD	Prevention of bullying in schools: an ecological model
2008	Brønneck, Kolbjørn Selvåg	Attentional dysfunction in dementia associated with Parkinson's disease.
H	Posserud, Maj-Britt Rocio	Epidemiology of autism spectrum disorders
	Haug, Ellen	Multilevel correlates of physical activity in the school setting
	Skjerve, Arvid	Assessing mild dementia – a study of brief cognitive tests.

	Kjønniksen, Lise	The association between adolescent experiences in physical activity and leisure time physical activity in adulthood: a ten year longitudinal study
	Gundersen, Hilde	The effects of alcohol and expectancy on brain function
	Omvik, Siri	Insomnia – a night and day problem
2009 V	Molde, Helge	Pathological gambling: prevalence, mechanisms and treatment outcome.
	Foss, Else	Den omsorgsfulle væremåte. En studie av voksnes væremåte i forhold til barn i barnehagen.
	Westrheim, Kariane	Education in a Political Context: A study of Knowledge Processes and Learning Sites in the PKK.
	Wehling, Eike	Cognitive and olfactory changes in aging
	Wangberg, Silje C.	Internet based interventions to support health behaviours: The role of self-efficacy.
	Nielsen, Morten B.	Methodological issues in research on workplace bullying. Operationalisations, measurements and samples.
	Sandu, Anca Larisa	MRI measures of brain volume and cortical complexity in clinical groups and during development.
	Guribye, Eugene	Refugees and mental health interventions
	Sørensen, Lin	Emotional problems in inattentive children – effects on cognitive control functions.
	Tjomsland, Hege E.	Health promotion with teachers. Evaluation of the Norwegian Network of Health Promoting Schools: Quantitative and qualitative analyses of predisposing, reinforcing and enabling conditions related to teacher participation and program sustainability.
	Helleve, Ingrid	Productive interactions in ICT supported communities of learners
2009 H	Skorpen, Aina Øye, Christine	Dagliglivet i en psykiatrisk institusjon: En analyse av miljøterapeutiske praksiser
	Andreassen, Cecilie Schou	WORKAHOLISM – Antecedents and Outcomes
	Stang, Ingun	Being in the same boat: An empowerment intervention in breast cancer self-help groups
	Sequeira, Sarah Dorothee Dos Santos	The effects of background noise on asymmetrical speech perception
	Kleiven, Jo, dr.philos.	The Lillehammer scales: Measuring common motives for vacation and leisure behavior
	Jónsdóttir, Guðrún	Dubito ergo sum? Ni jenter møter naturfaglig kunnskap.
	Hove, Oddbjørn	Mental health disorders in adults with intellectual disabilities - Methods of assessment and prevalence of mental health disorders and problem behaviour
	Wageningen, Heidi Karin van	The role of glutamate on brain function

	Bjørkvik, Jofrid	God nok? Selvaktelse og interpersonlig fungering hos pasienter innen psykisk helsevern: Forholdet til diagnoser, symptomer og behandlingsutbytte
	Andersson, Martin	A study of attention control in children and elderly using a forced-attention dichotic listening paradigm
	Almås, Aslaug Grov	Teachers in the Digital Network Society: Visions and Realities. A study of teachers' experiences with the use of ICT in teaching and learning.
	Ulvik, Marit	Lærerutdanning som danning? Tre stemmer i diskusjonen
2010	Skår, Randi	Læringsprosesser i sykepleieres profesjonsutøvelse. En studie av sykepleieres læringserfaringer.
V	Roald, Knut	Kvalitetsvurdering som organisasjonslæring mellom skole og skoleeigar
	Lunde, Linn-Heidi	Chronic pain in older adults. Consequences, assessment and treatment.
	Danielsen, Anne Grete	Perceived psychosocial support, students' self-reported academic initiative and perceived life satisfaction
	Hysing, Mari	Mental health in children with chronic illness
	Olsen, Olav Kjellevod	Are good leaders moral leaders? The relationship between effective military operational leadership and morals
	Riese, Hanne	Friendship and learning. Entrepreneurship education through mini-enterprises.
	Holthe, Asle	Evaluating the implementation of the Norwegian guidelines for healthy school meals: A case study involving three secondary schools
H	Hauge, Lars Johan	Environmental antecedents of workplace bullying: A multi-design approach
	Bjørkelo, Brita	Whistleblowing at work: Antecedents and consequences
	Reme, Silje Endresen	Common Complaints – Common Cure? Psychiatric comorbidity and predictors of treatment outcome in low back pain and irritable bowel syndrome
	Helland, Wenche Andersen	Communication difficulties in children identified with psychiatric problems
	Beneventi, Harald	Neuronal correlates of working memory in dyslexia
	Thygesen, Elin	Subjective health and coping in care-dependent old persons living at home
	Aanes, Mette Marthinussen	Poor social relationships as a threat to belongingness needs. Interpersonal stress and subjective health complaints: Mediating and moderating factors.
	Anker, Morten Gustav	Client directed outcome informed couple therapy

	Bull, Torill	Combining employment and child care: The subjective well-being of single women in Scandinavia and in Southern Europe
	Viiig, Nina Grieg	Tilrettelegging for læreres deltakelse i helsefremmende arbeid. En kvalitativ og kvantitativ analyse av sammenhengen mellom organisatoriske forhold og læreres deltakelse i utvikling og implementering av Europeisk Nettverk av Helsefremmende Skoler i Norge
	Wolff, Katharina	To know or not to know? Attitudes towards receiving genetic information among patients and the general public.
	Ogden, Terje, dr.philos.	Familiebasert behandling av alvorlige atferdsproblemer blant barn og ungdom. Evaluering og implementering av evidensbaserte behandlingsprogrammer i Norge.
	Solberg, Mona Elin	Self-reported bullying and victimisation at school: Prevalence, overlap and psychosocial adjustment.
2011	Bye, Hege Høivik	Self-presentation in job interviews. Individual and cultural differences in applicant self-presentation during job interviews and hiring managers' evaluation
V	Notelaers, Guy	Workplace bullying. A risk control perspective.
	Moltu, Christian	Being a therapist in difficult therapeutic impasses. A hermeneutic phenomenological analysis of skilled psychotherapists' experiences, needs, and strategies in difficult therapies ending well.
	Myrseth, Helga	Pathological Gambling - Treatment and Personality Factors
	Schanche, Elisabeth	From self-criticism to self-compassion. An empirical investigation of hypothesized change processes in the Affect Phobia Treatment Model of short-term dynamic psychotherapy for patients with Cluster C personality disorders.
	Våpenstad, Eystein Victor, dr.philos.	Det tempererte nærvær. En teoretisk undersøkelse av psykoterautens subjektivitet i psykoanalyse og psykoanalytisk psykoterapi.
	Haukebø, Kristin	Cognitive, behavioral and neural correlates of dental and intra-oral injection phobia. Results from one treatment and one fMRI study of randomized, controlled design.
	Harris, Anette	Adaptation and health in extreme and isolated environments. From 78°N to 75°S.
	Bjørknes, Ragnhild	Parent Management Training-Oregon Model: intervention effects on maternal practice and child behavior in ethnic minority families
	Mamen, Asgeir	Aspects of using physical training in patients with substance dependence and additional mental distress
	Espevik, Roar	Expert teams: Do shared mental models of team members make a difference
	Haara, Frode Olav	Unveiling teachers' reasons for choosing practical activities in mathematics teaching

2011 H	Hauge, Hans Abraham	How can employee empowerment be made conducive to both employee health and organisation performance? An empirical investigation of a tailor-made approach to organisation learning in a municipal public service organisation.
	Melkevik, Ole Rogstad	Screen-based sedentary behaviours: pastimes for the poor, inactive and overweight? A cross-national survey of children and adolescents in 39 countries.
	Vøllestad, Jon	Mindfulness-based treatment for anxiety disorders. A quantitative review of the evidence, results from a randomized controlled trial, and a qualitative exploration of patient experiences.
	Tolo, Astrid	Hvordan blir lærerkompetanse konstruert? En kvalitativ studie av PPU-studenters kunnskapsutvikling.
	Saus, Evelyn-Rose	Training effectiveness: Situation awareness training in simulators
	Nordgreen, Tine	Internet-based self-help for social anxiety disorder and panic disorder. Factors associated with effect and use of self-help.
	Munkvold, Linda Helen	Oppositional Defiant Disorder: Informant discrepancies, gender differences, co-occurring mental health problems and neurocognitive function.
	Christiansen, Øivin	Når barn plasseres utenfor hjemmet: beslutninger, forløp og relasjoner. Under barnevernets (ved)tak.
	Brunborg, Geir Scott	Conditionability and Reinforcement Sensitivity in Gambling Behaviour
	Hystad, Sigurd William	Measuring Psychological Resiliency: Validation of an Adapted Norwegian Hardiness Scale
2012 V	Roness, Dag	Hvorfor bli lærer? Motivasjon for utdanning og utøving.
	Fjermestad, Krister Westlye	The therapeutic alliance in cognitive behavioural therapy for youth anxiety disorders
	Jenssen, Eirik Sørnes	Tilpasset opplæring i norsk skole: politikeres, skolelederes og læreres handlingsvalg
	Saksvik-Lehouillier, Ingvild	Shift work tolerance and adaptation to shift work among offshore workers and nurses
	Johansen, Venke Frederike	Når det intime blir offentlig. Om kvinners åpenhet om brystkreft og om markedsføring av brystkreftsaken.
	Herheim, Rune	Pupils collaborating in pairs at a computer in mathematics learning: investigating verbal communication patterns and qualities
	Vie, Tina Løkke	Cognitive appraisal, emotions and subjective health complaints among victims of workplace bullying: A stress-theoretical approach
	Jones, Lise Øen	Effects of reading skills, spelling skills and accompanying efficacy beliefs on participation in education. A study in Norwegian prisons.

2012 H	Danielsen, Yngvild Sørebo	Childhood obesity – characteristics and treatment. Psychological perspectives.
	Horverak, Jøri Gytre	Sense or sensibility in hiring processes. Interviewee and interviewer characteristics as antecedents of immigrant applicants' employment probabilities. An experimental approach.
	Jøsendal, Ola	Development and evaluation of BE smokeFREE, a school-based smoking prevention program
	Osnes, Berge	Temporal and Posterior Frontal Involvement in Auditory Speech Perception
	Drageset, Sigrunn	Psychological distress, coping and social support in the diagnostic and preoperative phase of breast cancer
	Aasland, Merethe Schanke	Destructive leadership: Conceptualization, measurement, prevalence and outcomes
	Bakibinga, Pauline	The experience of job engagement and self-care among Ugandan nurses and midwives
	Skogen, Jens Christoffer	Foetal and early origins of old age health. Linkage between birth records and the old age cohort of the Hordaland Health Study (HUSK)
	Leveresen, Ingrid	Adolescents' leisure activity participation and their life satisfaction: The role of demographic characteristics and psychological processes
	Hanss, Daniel	Explaining sustainable consumption: Findings from cross-sectional and intervention approaches
Rød, Per Arne	Barn i klem mellom foreldrekonflikter og samfunnsmessig beskyttelse	
2013 V	Mentzoni, Rune Aune	Structural Characteristics in Gambling
	Knudsen, Ann Kristin	Long-term sickness absence and disability pension award as consequences of common mental disorders. Epidemiological studies using a population-based health survey and official ill health benefit registries.
	Strand, Mari	Emotional information processing in recurrent MDD
	Veseth, Marius	Recovery in bipolar disorder. A reflexive-collaborative exploration of the lived experiences of healing and growth when battling a severe mental illness
	Mæland, Silje	Sick leave for patients with severe subjective health complaints. Challenges in general practice.
	Mjaaland, Thera	At the frontiers of change? Women and girls' pursuit of education in north-western Tigray, Ethiopia
	Odéen, Magnus	Coping at work. The role of knowledge and coping expectancies in health and sick leave.
	Hynninen, Kia Minna Johanna	Anxiety, depression and sleep disturbance in chronic obstructive pulmonary disease (COPD). Associations, prevalence and effect of psychological treatment.

	Flo, Elisabeth	Sleep and health in shift working nurses
	Aasen, Elin Margrethe	From paternalism to patient participation? The older patients undergoing hemodialysis, their next of kin and the nurses: a discursive perspective on perception of patient participation in dialysis units
	Ekornås, Belinda	Emotional and Behavioural Problems in Children: Self-perception, peer relationships, and motor abilities
	Corbin, J. Hope	North-South Partnerships for Health: Key Factors for Partnership Success from the Perspective of the KIWAKKUKI
	Birkeland, Marianne Skogbrott	Development of global self-esteem: The transition from adolescence to adulthood
2013	Gianella-Malca, Camila	Challenges in Implementing the Colombian Constitutional Court's Health-Care System Ruling of 2008
H	Hovland, Anders	Panic disorder – Treatment outcomes and psychophysiological concomitants
	Mortensen, Øystein	The transition to parenthood – Couple relationships put to the test
	Årdal, Guro	Major Depressive Disorder – a Ten Year Follow-up Study. Inhibition, Information Processing and Health Related Quality of Life
	Johansen, Rino Bandlitz	The impact of military identity on performance in the Norwegian armed forces
	Bøe, Tormod	Socioeconomic Status and Mental Health in Children and Adolescents
2014	Nordmo, Ivar	Gjennom nåløyet – studenters læringserfaringer i psykologutdanningen
V	Dovran, Anders	Childhood Trauma and Mental Health Problems in Adult Life
	Hegelstad, Wenche ten Velden	Early Detection and Intervention in Psychosis: A Long-Term Perspective
	Urheim, Ragnar	Forståelse av pasientagresjon og forklaringer på nedgang i voldsrate ved Regional sikkerhetsavdeling, Sandviken sykehus
	Kinn, Liv Grethe	Round-Trips to Work. Qualitative studies of how persons with severe mental illness experience work integration.
	Rød, Anne Marie Kinn	Consequences of social defeat stress for behaviour and sleep. Short-term and long-term assessments in rats.
	Nygård, Merethe	Schizophrenia – Cognitive Function, Brain Abnormalities, and Cannabis Use
	Tjora, Tore	Smoking from adolescence through adulthood: the role of family, friends, depression and socioeconomic status. Predictors of smoking from age 13 to 30 in the "The Norwegian Longitudinal Health Behaviour Study" (NLHB)
	Vangsnes, Vigdis	The Dramaturgy and Didactics of Computer Gaming. A Study of a Medium in the Educational Context of Kindergartens.

	Nordahl, Kristin Berg	Early Father-Child Interaction in a Father-Friendly Context: Gender Differences, Child Outcomes, and Protective Factors related to Fathers' Parenting Behaviors with One-year-olds
2014	Sandvik, Asle Makoto	Psychopathy – the heterogeneity of the construct
H	Skotheim, Siv	Maternal emotional distress and early mother-infant interaction: Psychological, social and nutritional contributions
	Halleland, Helene Barone	Executive Functioning in adult Attention Deficit Hyperactivity Disorder (ADHD). From basic mechanisms to functional outcome.
	Halvorsen, Kirsti Vindal	Partnerskap i lærerutdanning, sett fra et økologisk perspektiv
	Solbue, Vibeke	Dialogen som visker ut kategorier. En studie av hvilke erfaringer innvandrerdømmere og norskfødte med innvandrereforeldre har med videregående skole. Hva forteller ungdommenes erfaringer om videregående skoles håndtering av etniske ulikheter?
	Kvalevaag, Anne Lise	Fathers' mental health and child development. The predictive value of fathers' psychological distress during pregnancy for the social, emotional and behavioural development of their children
	Sandal, Ann Karin	Ungdom og utdanningsval. Om elevar sine opplevingar av val og overgangsprossessar.
	Haug, Thomas	Predictors and moderators of treatment outcome from high- and low-intensity cognitive behavioral therapy for anxiety disorders. Association between patient and process factors, and the outcome from guided self-help, stepped care, and face-to-face cognitive behavioral therapy.
	Sjølie, Hege	Experiences of Members of a Crisis Resolution Home Treatment Team. Personal history, professional role and emotional support in a CRHT team.
	Falkenberg, Liv Eggset	Neuronal underpinnings of healthy and dysfunctional cognitive control
	Mrdalj, Jelena	The early life condition. Importance for sleep, circadian rhythmicity, behaviour and response to later life challenges
	Hesjedal, Elisabeth	Tverrprofesjonelt samarbeid mellom skule og barnevern: Kva kan støtte utsette barn og unge?
2015	Hauken, May Aasebø	« <i>The cancer treatment was only half the work!</i> » A Mixed-Method Study of Rehabilitation among Young Adult Cancer Survivors
V	Ryland, Hilde Katrin	Social functioning and mental health in children: the influence of chronic illness and intellectual function
	Rønsen, Anne Kristin	Vurdering som profesjonskompetanse. Refleksjonsbasert utvikling av læreres kompetanse i formativ vurdering

	Hoff, Helge Andreas	Thinking about Symptoms of Psychopathy in Norway: Content Validation of the Comprehensive Assessment of Psychopathic Personality (CAPP) Model in a Norwegian Setting
	Schmid, Marit Therese	Executive Functioning in recurrent- and first episode Major Depressive Disorder. Longitudinal studies
	Sand, Liv	Body Image Distortion and Eating Disturbances in Children and Adolescents
	Matanda, Dennis Juma	Child physical growth and care practices in Kenya: Evidence from Demographic and Health Surveys
	Amugsi, Dickson Abanimi	Child care practices, resources for care, and nutritional outcomes in Ghana: Findings from Demographic and Health Surveys
	Jakobsen, Hilde	The good beating: Social norms supporting men's partner violence in Tanzania
	Sagoe, Dominic	Nonmedical anabolic-androgenic steroid use: Prevalence, attitudes, and social perception
	Eide, Helene Marie Kjærgård	Narrating the relationship between leadership and learning outcomes. A study of public narratives in the Norwegian educational sector.
2015	Wubs, Annegreet Gera	Intimate partner violence among adolescents in South Africa and Tanzania
H	Hjelmervik, Helene Susanne	Sex and sex-hormonal effects on brain organization of fronto-parietal networks
	Dahl, Berit Misund	The meaning of professional identity in public health nursing
	Røykenes, Kari	Testangst hos sykepleierstudenter: «Alternativ behandling»
	Bless, Josef Johann	The smartphone as a research tool in psychology. Assessment of language lateralization and training of auditory attention.
	Løvvik, Camilla Margrethe Sigvaldsen	Common mental disorders and work participation – the role of return-to-work expectations
	Lehmann, Stine	Mental Disorders in Foster Children: A Study of Prevalence, Comorbidity, and Risk Factors
	Knapstad, Marit	Psychological factors in long-term sickness absence: the role of shame and social support. Epidemiological studies based on the Health Assets Project.
2016	Kvestad, Ingrid	Biological risks and neurodevelopment in young North Indian children
V	Sælør, Knut Tore	Hinderløyper, halmstrå og hengende snører. En kvalitativ studie av håp innenfor psykisk helse- og rusfeltet.
	Mellingen, Sonja	Alkoholbruk, partilfredshet og samlivsstatus. Før, inn i, og etter svangerskapet – korrelerer eller konsekvenser?
	Thun, Eirunn	Shift work: negative consequences and protective factors

	Hilt, Line Torbjørnsen	The borderlands of educational inclusion. Analyses of inclusion and exclusion processes for minority language students
	Havnen, Audun	Treatment of obsessive-compulsive disorder and the importance of assessing clinical effectiveness
	Slåtten, Hilde	Gay-related name-calling among young adolescents. Exploring the importance of the context.
	Ree, Eline	Staying at work. The role of expectancies and beliefs in health and workplace interventions.
	Morken, Frøydis	Reading and writing processing in dyslexia
2016	Løvoll, Helga Synnevåg	Inside the outdoor experience. On the distinction between pleasant and interesting feelings and their implication in the motivational process.
H	Hjeltnes, Aslak	Facing social fears: An investigation of mindfulness-based stress reduction for young adults with social anxiety disorder
	Øyeflaten, Irene Larsen	Long-term sick leave and work rehabilitation. Prognostic factors for return to work.
	Henriksen, Roger Ekeberg	Social relationships, stress and infection risk in mother and child
	Johnsen, Iren	«Only a friend» - The bereavement process of young adults who have lost a friend to a traumatic death. A mixed methods study.
	Helle, Siri	Cannabis use in non-affective psychoses: Relationship to age at onset, cognitive functioning and social cognition
	Glambek, Mats	Workplace bullying and expulsion in working life. A representative study addressing prospective associations and explanatory conditions.
	Oanes, Camilla Jensen	Tilbakemelding i terapi. På hvilke måter opplever terapeuter at tilbakemeldingsprosedyrer kan virke inn på terapeutiske praksiser?
	Reknes, Iselin	Exposure to workplace bullying among nurses: Health outcomes and individual coping
	Chimhutu, Victor	Results-Based Financing (RBF) in the health sector of a low-income country. From agenda setting to implementation: The case of Tanzania
	Ness, Ingunn Johanne	The Room of Opportunity. Understanding how knowledge and ideas are constructed in multidisciplinary groups working with developing innovative ideas.
	Hollekim, Ragnhild	Contemporary discourses on children and parenting in Norway. An empirical study based on two cases.
	Doran, Rouven	Eco-friendly travelling: The relevance of perceived norms and social comparison
2017	Katisi, Masego	The power of context in health partnerships: Exploring synergy and antagonism between external and internal ideologies in implementing Safe Male Circumcision (SMC) for HIV prevention in Botswana
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Jamaludin, Nor Lelawati Binti	The “why” and “how” of International Students’ Ambassadorship Roles in International Education
Berthelsen, Mona	Effects of shift work and psychological and social work factors on mental distress. Studies of onshore/offshore workers and nurses in Norway.
Krane, Vibeke	Lærer-elev-relasjoner, elevers psykiske helse og frafall i videregående skole – en eksplorerende studie om samarbeid og den store betydningen av de små ting
Søvik, Margaret Ljosnes	Evaluating the implementation of the Empowering Coaching™ program in Norway
Tonheim, Milfrid	A troublesome transition: Social reintegration of girl soldiers returning ‘home’
Senneseth, Mette	Improving social network support for partners facing spousal cancer while caring for minors. A randomized controlled trial.
Urke, Helga Bjørnøy	Child health and child care of very young children in Bolivia, Colombia and Peru.
Bakhturidze, George	Public Participation in Tobacco Control Policy-making in Georgia
Fismen, Anne-Siri	Adolescent eating habits. Trends and socio-economic status.

