Executive control of cognition, emotion and behavior in children with Tourette's syndrome

A two-year follow-up study

Kjell Tore Hovik

Submitted for the PhD degree at the Department of Psychology,
Faculty of Social Sciences, University of Oslo.

The research was conducted at Innlandet Hospital Trust Lillehammer, Division of Mental Health Care, and the Department of Psychology, University of Oslo.

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SUMMARY

The ability to exert executive control over aspects of cognition, emotion and behaviour in children and adolescents with Tourette's syndrome (TS) deviates from typically developing children (TDC), and represents a potential threat to their health and well-being. Knowledge about these processes and their development over time in young persons with TS is scarce, and is essential for understanding and treating this group of vulnerable children.

In the first study, we found that children with TS were superior in inhibiting a prepotent response compared with children with Attention-deficit/Hyperactivity Disorder (ADHD) and TDC, and that co-occurring ADHD in the children with TS negatively influenced performance. This finding provided evidence in support of the hypothesis that levels of inhibitory control can distinguish children with TS, ADHD and TDC, and that some children with TS may overly inhibit when responding to certain stimuli.

In the second study, we found that paired scales in the Behavior Rating Inventory of Executive Function (BRIEF) dissociated everyday executive behavior difficulties in children with TS from children with ADHD-Combined type (ADHD-C), ADHD-Inattentive type (ADHD-I) or high-functioning Autism Spectrum Disorder (ASD). The parents of the children with TS reported more emotional control difficulties in their children relative to other executive behavior problems compared with the children in the other groups. This finding provided evidence in support of the hypothesis that having TS involves significant difficulties controlling emotional behaviour in their everyday lives.

In the third study, we found that an improvement in executive functioning (working memory, inhibition and mental flexibility) over a two-year period was not closely associated with fewer symptoms of anxiety or depression or increased control over emotional behavior in the children with TS or ADHD-C. Although there was a significant decrease in depression symptoms after two years in the children with TS, the self-reported level of depression and anxiety symptoms in these children remained significantly higher compared with the TDC at follow-up. Important clinical implications of the results from the third study include the importance of assessing and treating emotional symptoms in children and adolescents with TS or ADHD-C during a critical time in their maturational development. The third study also provided evidence that children with TS preferred the more cautious choice compared with the children with ADHD-C when faced with making decisions with uncertain outcomes. Varying sensitivity to reinforcement contingencies is an important consideration in treating children and adolescents with behavior difficulties.

LIST OF PAPERS

I. Hovik, K.T., Plessen, K. J., Skogli, E. W., Andersen, P. N., & Øie, M. (2013). **Dissociable Response Inhibition in Children and Adolescents with Tourette's Syndrome Compared with Children with ADHD.** *Journal of Attention Disorders,* 2013 Nov 25, DOI: 10.1177/1087054713512371

II. Hovik, K. T., Egeland, J., Isquith, P. K., Gioia, G., Skogli, E. W., Andersen, P. N., & Øie, M. (2014). **Distinct Patterns of Everyday Executive Function Problems Distinguish Children With Tourette Syndrome From Children With ADHD or Autism Spectrum Disorders**. *Journal of Attention Disorders,* 2014 Sep 24, DOI: 10.1177/1087054714550336

III. Hovik, K. T., Plessen, K. J., Cavanna, A., Skogli, E. W., Andersen, P. N., & Øie, M. (2015). **Cognition, Emotion and Behavior in Children with Tourette's Syndrome and Children with ADHD-Combined subtype – A Two-Year Follow-Up Study.** *PLOS ONE,* 2015 Dec 16, DOI: 10.1371/journal.pone.0144874

ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ADHD-C	Attention Deficit Hyperactivity Disorder combined subtype
ADHD-I	Attention Deficit Hyperactivity Disorder inattentive subtype
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ASD	Autism Spectrum Disorder
BRIEF	Behavior Rating Inventory of Executive Function
CBT	Cognitive-Behavioral Therapy
CPT	Continuous Performance Test
CW 3	Color-Word Interference Test, Condition 3
CW 4	Color-Word Interference Test, Condition 4
D-KEFS	Delis-Kaplan Executive Function System
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - fourth revision
EF	Executive Function
HDT	Hungry Donkey Task
HRT	Habit Reversal Training
IGT	Iowa Gambling Task
IQ	Intelligence quotient
KSADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime version
LN	Letter-Number Sequencing Test
PFC	Prefrontal Cortex
RCMAS-2	Revised Children's Manifest Anxiety Scale, second edition
SD	Standard Deviation
SMFQ	Short Mood and Feelings Questionnaire
STROOP	Color-Word Interference Test
TDC	Typically Developing Children
TS	Tourette's Syndrome
WASI	Wechsler Abbreviated Scale of Intelligence
WISC-IV	Wechsler Intelligence Scale for Children – fourth revision

1. INTRODUCTION

1.1 Tourette's Syndrome (TS) - diagnostic criteria, aetiology and prevalence

Tourette's Syndrome (TS) is a childhood-onset, neurodevelopmental disorder characterized by the presence of chronic motor and phonic tics (Plessen, 2013). Tics are rapid, repetitive movements and vocalizations that usually occur in bouts of waxing and waning intensity (Leckman, 2003). The unwanted movements are often a source of distraction and distress for the child, and are transiently suggestible and suppressible (Leckman, Bloch, Scahill, & King, 2006).

Diagnostic criteria currently in use are the Diagnostic and Statistical Manual, 5th edition (DSM-V) (American Psychiatric Association, 2013) and the International Classification of Disease and Related Health Problems, 10th revision (ICD-10) (WHO, 1998). The forthcoming revision of ICD-10 (ICD-11 is scheduled for publication in 2017) is expected to be harmonized with the DSM-5 criteria (Baird, 2013; Reed, 2010). The DSM and ICD criteria are broadly congruent with each other in the diagnosis of TS and require the presence of multiple motor tics and one or more vocal tics persisting for more than one year and the absence of another medical reason that might cause tics (Woods & Thomsen, 2014). Even though no other symptoms are required for diagnosis of TS, the disorder has long been associated with a variety of social, emotional and behavioral problems that are often considered more troublesome for the child than the tics themselves (Singer, 2005).

Evidence supports TS being an inherited, biological disorder of the brain, yet the precise aetiology and underlying neurobiological mechanisms remain enigmatic (Ganos, Roessner, & Munchau, 2013; Leckman, 2003). The heredity and genetic basis of TS are under active investigation (Abelson et al., 2005). Multiple studies suggest that the heritability of TS is as high as 60% (Davis et al., 2013). Research into possible causes of tics ranges from investigating the role of the dopaminergic system and autoimmune responses and infections, to pre-natal and perinatal factors, as well as genetic factors (Ali, Morrison, & Cavanna, 2013).

TS is estimated to affect approximately 1% of schoolchildren across all nationalities and socio-economic classes (Robertson, Eapen, & Cavanna, 2009; J. S. Stern, Burza, & Robertson, 2005). The prevalence of all tic disorders is even higher than 1%. An epidemiological study conducted in Sweden indicated that up to 6.6% of 7-15-year-old youth had experienced some kind of tic disorder during the previous 12 months (Khalifa & Von Knorring, 2003). The lifetime prevalence of some form of tic disorder is as high as 20% (Bloch & Leckman, 2009).

1.2 Commonly co-occurring disorders in TS

A number of disorders commonly co-occur in children with TS, and the lifetime prevalence of any psychiatric comorbidity in individuals with TS is 85.7% (Hirschtritt et al., 2015). In a large clinic-based multicenter study encompassing 3500 patients with TS worldwide, the most commonly reported comorbidities were attention deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), depression, anger control problems and self-injurious behaviors (Freeman et al., 2000). ADHD is the most common co-occurring disorder in TS with the rate of co-occurrence at approximately 60% (Freeman & Tourette Syndrome International Database, 2007). TS plus ADHD is considered a more severe condition than TS alone (Freeman & Tourette Syndrome International Database, 2007; Spencer et al., 1998), and some research suggests that distinguishing the approximately 40% of children with TS without ADHD from the 60% of children with TS plus ADHD is important for predicting short- and long-term prognoses and treatment (Denckla, 2006).

The genetic component in TS is highly associated with both ADHD and OCD (Mathews & Grados, 2011). A total of 72.1% of participants in a major study involving 1,374 participants with TS were found to fulfil criteria for either ADHD or OCD (Hirschtritt et al., 2015). Despite genetic overlap, however, TS, ADHD and OCD have distinct genetic architectures (Davis et al., 2013; Hirschtritt et al., 2015). Whereas ADHD and OCD are highly heritable in families with TS, the genetic relationship is closer between TS and OCD and between OCD and ADHD, than between TS and ADHD (Mathews & Grados, 2011). Chronic tics and OCD have been proposed to be manifestations of the same underlying genetic susceptibility as TS (Eapen, Pauls, & Robertson, 1993).

Emerging evidence suggests a pathogenetic overlap between TS and autism spectrum disorder (ASD) (State, 2010). TS and ASD are both conditions with symptoms that begin to appear during childhood and mostly affect males. Clinical symptoms such as obsessions, compulsive behaviors, involuntary movements (tics in persons with TS and stereotypies in persons with ASD), poor speech control and echolalia are common in both conditions (Clarke, Lee, & Eapen, 2012). ASD is over-represented in children with TS, occurring in about 4 to 5% of the TS population (Burd, Li, Kerbeshian, Klug, & Freeman, 2009). One study found that while 5% of individuals with TS also had a diagnosis of Asperger's syndrome, 17% showed three or more autistic symptoms, and 65% had deficits relating to ASD (Kadesjo & Gillberg, 2000). A considerable overlap of symptom profiles among commonly occurring

disorders in children with TS represents a challenge for the clinician working with these children.

Other comorbid conditions common in persons with TS include anxiety, oppositional defiant disorder, conduct disorders, and personality disorders (Robertson, 2008). A high prevalence rate of comorbid learning disabilities is also found in persons with TS (Burd, Freeman, Klug, & Kerbeshian, 2005). TS is more common in boys than in girls (ratio of approx. 5:1), and the syndrome in males is associated with higher rates of comorbidities than in females (Freeman et al., 2000; Hirtz et al., 2007; State, 2011).

1.3 Executive function (EF) in TS

Cognitive deficits are common in individuals with TS (Rasmussen, Soleimani, Carroll, & Hodlevskyy, 2009) and can cause considerable suffering for those afflicted and their families (Leckman et al., 2006). Mental processes involved in the monitoring and regulation of cognition, emotion and behavior develop throughout childhood and adolescence and are referred to as *executive function, cognitive control or executive control* (Anderson, 2002; Elliott, 2003; Miller & Cohen, 2001; Vohs & Baumeister, 2004). Although there is a lack of agreement on a standard definition for these various terms, the term *executive function* (EF) is often used as an umbrella term for the management of cognitive processes (Elliott, 2003). Although there is general consensus that core components of EF include inhibition, working memory and mental flexibility (Best & Miller, 2010; Diamond, 2013), EF is also used in an even broader context to encompass brain processes involved in monitoring and regulating emotion and behaviour (Diamond, 2013; Eisenberg & Spinrad, 2004; Jurado & Rosselli, 2007).

The prefrontal cortex and basal ganglia (e.g. striatum) are central in the mediation of brain processes involved in EF and regulate both voluntary movement, but also higher mental processes that control cognition, decision-making, the planning of complex behavior and neuropsychiatric symptoms (Bonelli & Cummings, 2007; Elliott, 2003; Koechlin, Ody, & Kouneiher, 2003). Importantly, the functioning of the prefrontal cortex and the basal ganglia is closely related to tic generation and tic severity experienced by young individuals with TS (Baym, Corbett, Wright, & Bunge, 2008).

EF plays a central role in mediating between competing top-down and bottom-up influences in the prefrontal cortex (PFC) (Hanif et al., 2012; Hofmann, Schmeichel, & Baddeley, 2012; Koechlin et al., 2003). Bottom-up influences refer to lower-level processes (e.g. automatic processes, sensory and emotional activation), whereas top-down influences

refer to higher-level goals (e.g. adhering to cultural norms, delaying gratification, etc.) (Aron, 2007; Pashler, Johnston, & Ruthruff, 2001). EF are key components of self-control and self-regulation, with broad and significant implications in our everyday lives (Miyake & Friedman, 2012). Converging evidence from several research fields suggest a model whereby the frontal cortex is involved in representing relevant thoughts and guiding appropriate behaviors, and the basal ganglia are involved in the management of competing action alternatives (Casey, Tottenham, & Fossella, 2002). As most human behavior reflects the joint impact of higher-level goals (top-down influences) and recent stimuli (bottom-up influences) (Pashler et al., 2001), gaining a better understanding of EF and executive control in children with TS is relevant for the early treatment, follow-up and well-being of these youth. The top-down/bottom-up framework provides a flexible approach to understanding impaired executive control of behavior and self-regulatory failure in both psychiatric and normal populations of young people (Banich, 2009; Heatherton & Wagner, 2011).

1.3.1 Hot and cold aspects of EF in TS

Traditionally, most neurocognitive tests assessing EF engage cognitive processes with little emotional salience and are therefore referred to as cold EF (Chan, Shum, Toulopoulou, & Chen, 2008). A relative consensus has emerged that cold EF processes include inhibition, working memory (updating), and mental flexibility (Miyake & Friedman, 2012). Whereas individuals with TS typically have normal intellectual functioning (Singer, 2005), they commonly display a variety of neuropsychological deficits relating to EF (Rasmussen et al., 2009). In a study involving children with TS aged 7 to 14, there was a trend for the children with TS without co-occurring ADHD or OCD to have difficulties on measures of response inhibition, divided attention and mental flexibility compared with typically developing children (TDC) (Chang, McCracken, & Piacentini, 2007). One frequently cited study concluded that inhibition is a significant area of impairment in individuals with TS without co-occurring ADHD, whereas the effect of ADHD in children with TS is impairment on multiple measures of cold EF (inhibition, working memory, and mental flexibility) (Channon, Pratt, & Robertson, 2003). In a review comparing measures of cold EF in children with TS, ADHD, high-functioning ASD and TDC concluded that each clinical disorder is distinct in terms of consistency, severity and profile of EF impairment (Pennington & Ozonoff, 1996). The last-mentioned review found that deficits in inhibition were prominent in children with ADHD but not in children with ASD, in which there were marked differences in cognitive flexibility compared with children with ADHD. Regarding children with TS, the authors suggest that

there is a puzzling inconsistency in results on EF tasks by children with TS due either to a failure to control for comorbid conditions, or because EF deficits may not be as central a part of the cognitive phenotype of TS as they are for ADHD or ASD.

Whereas cold EF tests (e.g. inhibition, working memory, mental flexibility) conducted in the laboratory involve cognitive processes with little emotional salience and activate dorsolateral parts of the prefrontal cortex, EF tasks involving stronger affective salience (e.g. decision-making paradigms) are referred to as hot EF. Hot EF activates areas of the brain that regulate emotions and the brain's reward systems (e.g. orbito-frontal cortex, ventral striatum and the limbic system) (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). Decision-making tasks typically require a choice between competing alternatives involving risk or reward to maximize outcome and thus test sensitivities to reinforcement contingencies (Chan et al., 2008). The relationship between choices and outcomes in these tasks depends on a close interplay between brain regions mediating both cognition and emotion (Bechara, 1997; Bechara, Damasio, Tranel, & Damasio, 2005; Heilman et al., 2010; Maia & McClelland, 2004). The difference between cognitive and more emotional processing in decision-making tasks is often referred to as the difference between hot and cold EF (Prencipe et al., 2011; Zelazo & Carlson, 2012; Zelazo, Qu, & Kesek, 2010).

A clear dissociation between different frontal brain areas involved in cold processing (medial orbitofrontal, rostral anterior cingulated, and posterior cingulated) and hot processing (dorsal anterior cingulated, supplementary motor area, insula, precentral and fusiform gyri) has been shown using functional magnetic resonance imaging, where salience plays a key role in allocating attentional, motivational and computational processes (Litt, Plassmann, Shiv, & Rangel, 2011). Decision-making tasks are common in research involving children with ADHD, as hot EF processes have for some time been thought to constitute a promising endophenotype explaining ADHD symptoms (Castellanos et al., 2006; Sonuga-Barke, 2003). Disadvantageous decision-making is a central problem in childhood and adolescence for all children and is closely associated with risky behavior and poor choices that can prove detrimental later in life (D. G. Smith, Xiao, & Bechara, 2012). Impulse dysregulation is closely associated with risk-taking behavior and self-injurious behavior in children with TS (Mathews et al., 2004), and there is convincing evidence showing risky behavior to be common in children/adolescents with ADHD as well (Groen, Gaastra, Lewis-Evans, & Tucha, 2013).

Early adolescence coincides with asymmetric neural development in which relatively overactive striatal regions create impulsive reward-driven responses that may go "unchecked"

by the slower developing inhibitory mechanisms in the frontal cortex (D. G. Smith et al., 2012). The uneven developmental trajectory emerging during childhood and adolescence in brain regions involved in the top-down control of behavior is in strong contrast with the linear development of memory, speed of processing, and other cognitive abilities (D. G. Smith et al., 2012). An uneven development in the complex balance of top-down and bottom-up executive abilities during this period of childhood and adolescence may permit a larger range of internal and external factors to exert a stronger influence on the course of emerging behavioral characteristics (Casey, Jones, & Hare, 2008).

1.3.2 Emotional control in TS

Even though researchers generally agree that emotion influences cognition and behavior, no consensus on defining emotion exists (Izard, 2010). Some investigators incorporate concepts of drive and motivation when defining emotion (Rolls, 2005); others maintain that emotion is involved in the appraisal of events (Mauro, Sato, & Tucker, 1992). Another approach is to categorize the construct into basic emotions (e.g. anxiety, fear, sadness) (Ekman, 1992), and more complex emotions (e.g. pride, envy, guilt) (Haidt, 2003). Importantly, strong evidence links emotion to bodily sensations and autonomic responses (Damasio, 1999, 2008), which underscores emotion's role as a visceral source of influence on thinking and behavior. A generally accepted description of 'emotion' is that it involves neural circuits, response systems, and a feeling state that motivates and influences thinking, decision-making and behavior (Izard, 2010). The ability to monitor and regulate aspects of emotion is considered part of normal functioning in TDC and adolescents. The aspects of emotion addressed in this thesis are the symptoms of anxiety and depression self-reported by the children and adolescents participating in the study.

There is relative consensus that brain structures linked to emotion generation are subcortical, more 'primitive' and automatic (e.g. processes involving the amygdala, ventral striatum and hypothalamus), and that we are not necessarily aware of a stimulus that might trigger an affective response (Ohman, 2002; Pessoa, 2005). The distinction between processes involved in emotion generation and in emotion regulation, however, is complex and may depend on your research perspective (Gross & Barrett, 2011). Some research on executive control over emotion has focused on interactions between prefrontal and cingulate control systems (top-down systems) and cortical and subcortical emotion-generative systems (bottom-up influence) (Ochsner, Bunge, Gross, & Gabrieli, 2002). Increasing evidence suggests that frontal-subcortical circuitry (e.g. basal ganglia) is intimately involved in regulating

neuropsychiatric symptoms such as anxiety and depression (Bonelli & Cummings, 2007). Evidence of disturbances in the maturational development of the neural systems involved in self-regulatory behavior (frontalstriatal regions and posterior cingulated cortices) has been shown in children with TS (Marsh, Zhu, Wang, Skudlarski, & Peterson, 2007), and could influence their top-down control of behavior. In the latter neuroimaging study, performance on a neuropsychological task was similar between the patients with TS and TDC; however, the magnitude of regional brain activation was significantly higher in the patients with TS, suggesting compensatory activation (possibly in order to maintain task performance). Compensatory cognitive processes in children with TS may thus mask an underlying impairment in executive control when using traditional hot or cold neuropsychological tasks. The disturbances in neural systems involved in self-regulatory control revealed in neuroimaging studies of children with TS are perhaps more easily observed in the form of overt emotional or behavioral problems. Self-report and parent reports of emotional and behavioral difficulties are thus important when assessing the child with TS, as they also are when assessing everyday challenges faced by children with other neurodevelopmental disorders involving disturbances in prefrontal systems such as ADHD and ASD (Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009; Nigg, 2012).

Children with chronic conditions such as TS commonly report more emotional distress in the form of symptoms of anxiety and depression than TDC (Blanchard, Gurka, & Blackman, 2006). A number of studies have shown that children can validly and reliably self-report emotional well-being (Riley, 2004; Varni, Limbers, & Burwinkle, 2007). Anxiety is common in children with TS (Robertson, 2000), and depressive symptomatology is prevalent in children and adolescents with TS (Robertson, Williamson, & Eapen, 2006). A major study involving 802 families found that mood disorders and anxiety disorders are common among TS-affected individuals and tend to begin early in life (Hirschtritt et al., 2015). One study found symptoms of depression to be related to TS alone and not related to the co-occurrence of ADHD (Carter et al., 2000), whereas another study on depressive symptomatology in youth with TS found a complex interrelationship between tic severity, comorbid OCD, comorbid ADHD and depressive symptoms (Robertson et al., 2006). In any event, a disturbingly high occurrence of anxiety and depression symptoms and disorders often continues into adulthood for children with TS (Eapen, Fox-Hiley, Banerjee, & Robertson, 2004). Symptoms of depression are reported by up to 76% of all TS patients attending specialist clinics, and the lifetime risk of major depression in persons with TS is 10 % (Robertson, 2006). Both anxiety and depression result in a lower quality of life and bring with it the potential of hospitalizations and suicide.

Children with ADHD (both ADHD-C and ADHD-I) self-report significant symptoms of both anxiety and depression (Power, Costigan, Eiraldi, & Leff, 2004). Comorbid anxiety disorder exacerbates existing behavior regulation problems in children with ADHD (Sørensen, Plessen, Nicholas, & Lundervold, 2011).

Symptoms of anxiety and depression and impaired cognitive functioning are closely related even in healthy youth (Baumeister, Zell, & Tice, 2007; Eysenck, Derakshan, Santos, & Calvo, 2007; Wagner, Müller, Helmreic, Muss, & Tadic, 2015), and symptoms of depression are associated with enhanced activity in prefrontal structures in TDC (Killgore & Yurgelun-Todd, 2006). Evidence suggests that TS is associated with impaired regulation of both cognition and affect (E. R. Stern, Blair, & Peterson, 2008), and the level of anxiety or depression symptoms is closely associated with severity of functional impairment in children with tics (Lewin et al., 2011). Many problems in TS are attributed to co-occurring conditions, but a study examining the impact of ADHD on TS concluded that TS was associated with significant anxiety and depression symptoms in adolescence regardless of ADHD comorbidity (Roessner et al., 2007). Furthermore, the level of symptoms of depression in young persons with TS commonly increases in line with duration of illness and increasing age (Hoekstra, Lundervold, Lie, Gillberg, & Plessen, 2013; Robertson, 2000).

1.3.3 Behavioral control in TS

Apart from behavior difficulties relating to commonly co-occurring disorders (e.g. ADHD, OCD), problems adaptively regulating everyday behavior is associated with TS and often represents the most debilitating aspect of the condition (Carter et al., 2000; Singer, 2005). As many as 70% of patients with TS in clinical settings experience problems controlling behaviour with emotional salience (e.g. outbursts, rage and aggression) (C. L. Budman, Rockmore, Stokes, & Sossin, 2003), and this type of behavior tends to increase during childhood for children with TS (Hoekstra et al., 2013). The term *emotional behavior* will be used in this thesis to refer to behavior in everyday situations involving high affective salience in which mood, agitation, and excitement must be appropriately adjusted for normal functioning (Gioia, Isquith, Guy, & Kenworthy, 2000b). Difficulty regulating emotions are common reasons for psychiatric referral in children with TS (Cathy L Budman, Bruun, Park, Lesser, & Olson, 2000). An important issue, however, is how best to assess these difficulties. The correspondence between results from neuropsychological tests in the clinic (e.g. inhibitory control tasks) and behavior ratings of EF in everyday situations is typically poor (Toplak, West, & Stanovich, 2013). There is a growing consensus that EF test performance

(e.g. inhibitory control) should not be equated with ratings of EF behavior (e.g. inhibition) (Toplak, Bucciarelli, Jain, & Tannock, 2009). The low correspondence (.15) between psychometric measures and behavioral ratings of EF would seem to indicate separate constructs (Silver, 2014).

Rating scales assessing EF such as the Behavior Rating Inventory of Executive Function (BRIEF) assess the self-regulatory abilities needed for adaptive functioning in everyday situations (Gioia et al., 2000b). Considerable evidence suggests a logical relationship between biological markers of EF and ratings of everyday EF (Isquith, Roth, & Gioia, 2013), and some researchers propose that rating scales assessing EF may be the preferred method of detecting clinical conditions with EF difficulties (Barkley, 2012). One limitation of scales designed to identify behavioral characteristics based on diagnostic categories is that concurrent and sequential comorbidity problems often converge to cause overlapping symptom profiles with little discriminatory power. An influential perspective is that a dimensional approach utilising a so-called *p-factor* to characterizing childhood disorders is preferable to a categorical approach (Caspi et al., 2014). However, assessment scales do allow the clinician to identify specific problem behavior in a child, which then permits more targeted and effective interventions to be implemented (Pelham, 2001).

1.4 Importance of a developmental perspective in TS

Children and adolescents with TS experience varying degrees of severity and intensity of tics concurrently with advances in their executive control abilities. Whereas the typical age of onset for tics is 5-7 years, the condition usually reaches its most severe intensity around the ages of 10–12 years (Felling & Singer, 2011). Tics diminish significantly by the age of 18 years in a majority of cases, and as many as 50% report being virtually tic free by the second decade of life (Robertson et al., 2009). The waxing and waning of tics is thus taking place at the same time as dramatic, cognitive developments are taking place in youth with TS. A study comparing disabling features of the disorder in persons with TS over and under 18 years reported that subjects under age 18 reported more frequent problems with temper control and aggressive behaviors compared with adults with TS (Wand, Matazow, Shady, Furer, & Staley, 1993), suggesting a lessening of some behavior problems with age. A longitudinal study on children with TS, however, reported an increase in emotional problems over a four year period during these important formative years (Hoekstra et al., 2013). Less than 20% of adults diagnosed with TS in childhood report clinically impairing tics, thus these early years for

youth with TS seem to be a period when tics, cognition, emotion and emotional behavior are undergoing rapid developmental change processes simultaneously (Leckman et al., 2006).

A qualitative shift in the nature of thinking takes place in the transition from childhood to adulthood, in which developing children and adolescents progressively enhance their ability to think and act in a more controlled and strategic manner (Blakemore & Choudhury, 2006). Underlying the dramatic cognitive development during these years are significant changes taking place in the structure and synaptic density of the prefrontal cortex, which continues into early adulthood (Petanjek et al., 2011). Cognitive improvements with age in young individuals is thought to be the result of maturation of executive control circuits, in which the frontal cortices become more efficiently connected to the striatum and to the sensorimotor cortices (Eapen & Crncec, 2009; Leckman et al., 2006; Marsh et al., 2007). The implication of research on TDC is that the functional brain circuits necessary for the control and regulation of behavior increase in efficiency throughout childhood and adolescence (Blakemore & Choudhury, 2006), and are not fully developed until late adolescence or early adulthood (Luna, Garver, Urban, Lazar, & Sweeney, 2004). Another important developmental factor in children and adolescents with TS is the effect hormones are having on their brain development. The significant gender imbalance (ratio of 5:1 of boys to girls) in individuals with TS intuitively suggests that sexual hormones are playing a role in the phenomenology of tics. Whereas the influence on brain development from exposure to sex hormones in the prenatal phase is well established, it is now hypothesized that adolescence is a second so-called organizational period in which sex hormones play a crucial role in refining brain functioning (Berenbaum & Beltz, 2011). The effect of this hormonal influence on brain development is taking place precisely during a period of time when most children with TS are experiencing a peak in tic intensity and frequency (ages 10-12) (Felling & Singer, 2011). The precise role of sex hormones in brain development of children with TS, however, is unclear.

Humans in general excel at adapting and adjusting to their environment, and adaption and adjustment is particularly relevant for youth in a development perspective (Povinelli & Bering, 2002). Despite the large literature on EF and executive control in children, no truly developmental account of EF across childhood and adolescence exists (Best & Miller, 2010). Neural, physiological, and behavioral systems are self-organizing and self-regulating and will likely influence each other in the developmental process (E. R. Stern et al., 2008). Stressful conditions (e.g. the persistent urge to tic) can generate responses in the form of thoughts, emotion and behavior, some of which may become habitual and influence the developmental process and course of the individual child. When accounting for the origins of behavior, it is

important to emphasize the increasingly complex self-organization of a developing child (Greenberg, 2014; Overton, 2013). Children with TS have normal levels of intelligence (Singer, 2005), yet struggle with persistent, unwanted tics on a daily basis. Even though the tics are transiently suppressible (Bloch & Leckman, 2009), the repeated suppression of tics may influence their neurobiology (G. M. Jackson, Mueller, Hambleton, & Hollis, 2007; S. R. Jackson et al., 2011; Mueller, Jackson, Dhalla, Datsopoulos, & Hollis, 2006). It is reasonable to assume that youth with TS may develop cognitive, emotional and behavioral characteristics and/or habits related to the persistent suppression of tics (e.g. higher frontal activation to suppress tics, outbursts of emotion, overly cautious response tendencies) (Baym et al., 2008; S. R. Jackson et al., 2011; Mueller et al., 2006; Serrien, Orth, Evans, Lees, & Brown, 2005). Interestingly, the same neural mechanism involved in the generation of tics (cortical-striatal-thalamo-cortical 'CSTC' circuits) underlies habit formation (Leckman & Riddle, 2000). The feedback loops responsible for converting novel actions into automatic actions may thus also be playing a role in the repetitive nature of a tic.

In general, the many developmental influences on brain function in children and adolescents with TS are critical to the course of their condition and future well-being (E. R. Stern et al., 2008). One aspect complicating the effort to gain an understanding of these many influences is differing maturational trajectories among various brain functions. In a study involving TDC aged 8 to 15 years, improvements in cold EF tasks occurred earlier in the age range and improvements in hot EF tasks occurred later (Prencipe et al., 2011). The authors of the latter study maintain that although similar abilities may underlie both hot and cold EF tasks, their study shows that hot EF abilities develop more slowly, which may have implications for the risky behavior often observed during adolescence. It is likely that experiences and influences during these childhood and adolescent years affect an individual differently depending on the maturation and balance of hot and cold EF abilities. Children with impaired top-down control over bottom-up influences may be more vulnerable to the negative effects of adverse events and less resilient than children with a higher level of top-down control (Maier, 2015). The spectacular increase in physical strength and struggle for independence during adolescence, in combination with immature cognitive, emotional and behavioral control, represents a tremendous potential for serious consequences for the health and well-being of developing youth (Boyer, 2006).

1.5 Bio-psycho-social and dual-process approaches

The complexity of TS requires an approach to understanding the condition that accounts for many factors influencing the development, course and prognosis of persons suffering from TS (Robertson, 2000). The bio-psycho-social approach emphasises multiple factors influencing tics and cognitive, emotional and behavioral development in children with TS (Suls & Rothman, 2004). Three central factors in the bio-psycho-social view will be described in the following: the biological, the psychological, and the social. This will be followed by a description of how a dual-process view may conceptualize the daily challenges facing children with TS.

A neurobiological model of the disorder conceptualizes tics as a difficulty inhibiting sensory urges and behavior (O'Connor, 2002). Paralimbic and sensory association areas are implicated in the generation of a tic, which is thought to be similar to movements triggered internally by unpleasant sensations (e.g. an itch or a blink) (Bohlhalter et al., 2006). Tic symptoms may thus be fragments of innate behavior, and the sensory urges preceding tics may be internal cues involved in the assembly of behavioral sequences. There is no consensus, however, on the primary site of neurobiological dysfunction, which may lie in the failure to regulate impulses rather than the generation of impulses.

Several lines of evidence suggest that abnormal basal ganglia functioning is the main reason for the involuntary tic movements experienced in subjects with TS (Albin & Mink, 2006; Ganos et al., 2013; G. M. Jackson et al., 2007). The basal ganglia function as a central switching mechanism, involved in the selection and regulation of goal-directed movements (Mink, 2003; Redgrave, Prescott, & Gurney, 1999) and habit learning (Marsh, Alexander, Packard, Zhu, & Peterson, 2005). Children and adults with TS are often impaired in striatum-based habit learning (Marsh et al., 2004). A considerable amount of research has been devoted to understanding TS as a problem involving the basal ganglia, and may involve structures, neurotransmitters or both. Dopamine and other neurotransmitters regulate messages transmitted along a critical frontostriatal brain circuit (basal ganglia, thalamus, prefrontal and other cortex regions), which influences movement, thought, judgment and behavior sequences (Marsh, Maia, & Peterson, 2009; Swerdlow & Young, 2001). Faulty dopamine regulation at critical points in this circuit could permit unwanted thoughts and behaviors to slip unfiltered through (Mink, 2001; Zinner, 2004). Dopamine neurons also play an important role in mood regulation and decision-making (Ikemoto, Yang, & Tan, 2015; Tye et al., 2013).

Animal studies have shown that stereotyped behaviors arise from the basal ganglia following the application of stimulants (Kelley, Lang, & Gauthier, 1988) or dopamine receptor agonists (Canales & Iversen, 2000). Dopaminergic dysfunction is thus a leading candidate for investigation as a source of tics, as dopamine is among the numerous neurotransmitters known to participate in the transmission of messages through CSTC circuits (Leckman, 2003). Lesions to the basal ganglia in humans produce or exacerbate tic-like behaviors (Dale, 2003; Gomis, Puente, Pont-Sunyer, Oliveras, & Roquer, 2008).

A cognitive psycho-physiological model of the disorder conceptualizes tic habits as a function of cognitive factors such as perfectionist concerns and heightened sensory awareness and self-attention, as well as physiological factors such as high level of motor activation and accompanying elevated muscle tension (O'Connor, 2002). Whereas the onset and generation of tics has a fundamental biological component, severity can be influenced by a variety of psychological factors, as tics may improve with concentration, distraction or physical exercise and may worsen with stress, fatigue, or excitement (Bloch & Leckman, 2009; Nixon, Glazebrook, Hollis, & Jackson, 2014). Co-occurring conditions (e.g. ADHD and OCD) can have a significant impact on lowering the quality of life for children with TS (Bernard et al., 2009), as do anxiety and depression symptoms, which are known to exacerbate existing behavioral problems in youth in general (Eysenck et al., 2007; Wagner et al., 2015). The precise importance and influence of a range of psychological factors that influence tics symptoms, however, remains unclear.

Social and related factors such as family relationships may influence the impact TS may have on a child (Carter et al., 2000). Although the onset of TS does not seem to be related solely to stressful life events (Horesh, Zimmerman, Steinberg, Yagan, & Apter, 2008), evidence suggests that negative life events involving social influences during adolescence influences the course and severity of tics (Steinberg, Shmuel-Baruch, Horesh, & Apter, 2013). A study conducted involving sixty patients aged 7-17 with TS or a chronic tic disorder reported a close association between negative life events involving friends and the severity of vocal tics, and between major life events and the severity of motor tics (Steinberg et al., 2013). Psychosocial stress and social problems interacting with genetic vulnerability are known to influence the development of comorbidities and impact on the long-term outcomes for children with TS (Lin et al., 2002).

A dual-process approach (Grafman & Krueger, 2006) may serve as a useful framework for conceptualizing and understanding the top-down/bottom-up dichotomy of volitional control in children in general and children with TS in particular. This theory is

based on studies reporting that patients with prefrontal lesions perform similarly to TDC in response tasks that measure speed of completion, but do significantly worse when the measure depends on an individual's ability to recruit prefrontal resources to respond accurately (Vendrell et al., 1995). Separate and competing response systems (reflective and explicit versus reflexive and automatic) are presumably involved in responding fast or in responding accurately. Although important criticisms of the dual-process approach are made (Bargh & Ferguson, 2000; Osman, 2004), the view provides a simple dichotomy of executive control in which to understand the conflicting behavioral manifestations of automatic versus controlled behaviors. A prominent dual-process model in the field of cognitive neuroscience that offers a framework for understanding executive control over cognition and emotion is the Iterative Reprocessing Model (Cunningham, Zelazo, Packer, & Van Bavel, 2007; Zelazo & Cunningham, 2007). According to this model, attitudes and evaluations are constructed through the reprocessing (iteration) of information. Fast automatic evaluations involve few iterations, whereas multiple iterations result in more nuanced evaluations that influence and are influenced by more reflective processes (Cunningham et al., 2007). One can imagine that the continuum from quick and automatic evaluations to nuanced and reflective evaluations in volitional control will vary considerably based on a wide range of cognitive, emotional and contextual factors. The model provides a framework for understanding the complex and intertwined web of automatic and control processes influencing behavior in children in general and specifically in children with impaired EF and executive control.

1.6 Treating children and adolescents with TS

No cure for tics is currently available (Leckman, 2003). Behavioral therapy and counselling can improve patients' understanding of the disorder, improve their self-esteem and social functioning, and reduce tics or other maladaptive behaviors (Woods et al., 2011). Habit reversal training has been shown to be effective in reducing tics (Dutta & Cavanna, 2013), and is a recommended one of several first line behavioral treatment for tics in children with TS (Verdellen, van de Griendt, Hartmann, Murphy, & Group, 2011). A major randomized trial involving a Comprehensive Behavioral Intervention for Tics (CBIT) reported results comparable to the success of antipsychotic medication in reducing tics, and the benefit endured for at least six months after the end of the 10-week trial (Piacentini et al., 2010). The two central components in CBIT are tic-awareness training and competing-response training, both of which can be described as interventions aimed at enhancing top-down control over unwanted behavior. Other techniques used to treat children with TS include awareness

training, assertiveness training, cognitive therapy, and acceptance and commitment therapy (Hayes, 2004). If tics severely affect a child's social functioning or self-esteem, or if the tics are painful or self-injurious, medical treatment is warranted. Any medical treatment must take careful consideration of severity, frequency and the existence of co-occurring disorders (Roessner et al., 2011). Threats to the management of TS include inconsistencies in the diagnosis and management plan, and failure to recognize co-occurring conditions, as well as inadequate knowledge and lack of resources to effectively deal with comorbidities (Eapen & Crncec, 2009).

Importantly, parents seem to be more likely to recognize the influence of externalizing symptoms in their children than internalizing symptoms (Storch et al., 2007). Children as young as 5 years old are fully capable of reporting accurately on their health-related quality of life on age-appropriate instruments (Varni et al., 2007). Administering both self-report of internalizing symptoms and parent report of externalizing symptoms is thus advisable to gain a complete overview of the everyday life of a child or adolescent with TS. As greater negative outcomes are associated with externalizing symptoms, children with comorbid tics and externalizing disorders may benefit from undergoing treatment for the externalizing disorder before focusing on the tics, whereas children suffering primarily from tics might likely benefit most from interventions targeted at this source of distress (Storch et al., 2007).

1.7 Unresolved questions regarding TS

Numerous questions regarding TS remain to be investigated, as it is a complex disorder with features overlapping a variety of scientific fields (Robertson, 2000). A central area of research in TS is the individual's control over mental processes. The presence of tics in a child or adolescent suggests an inability to stop or control unwanted movements. This inability to inhibit specific movements such as a tic raises the issue of what cognitive processes underlie the ability to inhibit any impulse to act. Whereas some research has indicated response inhibition difficulties in children with TS (Crawford, Channon, & Robertson, 2005; Muller et al., 2003), recent research has documented enhanced inhibitory abilities in children with TS (G. M. Jackson et al., 2007; Mueller et al., 2006). Increased activation in the direct pathway through the basal ganglia and compensatory activation in the prefrontal cortex and subthalamic nucleus has been shown in children with TS during EF or executive control tasks (Baym et al., 2008). In the latter study, higher tic activity was associated with enhanced activation of dominergic nuclei and stronger engagement of the left prefrontal cortex in the children with TS compared with TDC. Inhibitory mechanisms has been a focus of research in

TS (Eddy, Rizzo, & Cavanna, 2009), but the precise nature of inhibitory control in TS remains one of many unresolved issues surrounding the disorder (Robertson, 2000; Singer, 2005).

Another unresolved issue in TS research is the association with prominent co-occurring disorders in TS. The two most prominent co-occurring disorders in TS are ADHD and OCD, and a pathogenetic model for TS also links the disorder with ASD through neurodevelopmental pathways involving striatal cortical circuitry (Clarke et al., 2012). The issue here is whether the mechanisms or processes underlying behavior symptom profiles similar in TS, ADHD, OCD and ASD are the same or different. Genetics research suggests that the observed relationship between TS and ADHD may be due to a genetic association between OCD and ADHD (Mathews & Grados, 2011), which is an intriguing finding given that these two disorders could be seen as two opposing forces in a dichotomy of 'too much' control versus 'too little' control. Interestingly, the bridge from tics in TS to ADHD and OCD can been described as an urge-relief cycle (Zinner, 2004). The overlapping circuitry generates sensory urges relieved by tics, cognitive-obsessive urges relieved by compulsive behaviors, or a sense of urgency relieved by an impulsive act or inappropriate behavior (Sheppard, Bradshaw, Purcell, & Pantelis, 1999). The analogy could be extended to include children with ASD in their need for predictability relieved by their expectations being met. One model posits that ADHD and ASD are manifestations of the same overarching disorder, with ADHD a milder, less impaired and less severe subtype within the ASD spectrum (Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011; van der Meer et al., 2012). In all the disorders mentioned above, problematic behavior associated with the disorders involves a failure to adapt action appropriately to an external context or situation.

A third important unresolved issue is to what extent anxiety, depression and/or behavioral difficulties are closely associated with TS independent of co-occurring disorders, and to what extent the lack of control over tics is related to the lack of control over emotional and behavioral symptoms. The diagnostic criteria do not require the presence of any internalizing or externalizing symptoms, yet such symptoms are commonly observed in connection with the assessment of individuals with TS in the clinic. Are these symptoms an expression of the same underlying dysfunction causing tics, are they a secondary symptom arising from having a chronic condition, or are they actually co-occurring conditions quite separate from the waxing and waning of tics? Importantly, symptoms of anxiety and depression influence information processing, and thus have an impact on thinking (Beuke, Fischer, & McDowall, 2003). Despite the fact that the relationship between TS and cognitive,

emotional, social and behavioral problems has received increasing attention since the 1990s (Coffey & Park, 1997), the precise nature of these relationships is still unknown.

2. AIMS

As part of the research project "Emotional and cognitive development in children and adolescents with neuropsychiatric disorders" at Innlandet Hospital Trust (IHT), the overall objective of the current study was to investigate executive control of cognition, emotion and behavior in youth with TS based on cross-sectional and longitudinal investigations.

The first research objective (Paper I) was to investigate inhibitory control abilities in children with TS compared with children with ADHD and TDC. Conflicting findings have been published regarding the ability of children with TS and children with ADHD to inhibit responses. By addressing the issue of too much or too little control in these two clinical groups, we hypothesized that this dichotomy may be used to conceptualize how these disorders may differ. We also examined the effect of co-occurring ADHD on the children with TS with regard to inhibitory abilities.

The second research objective (Paper II) was to investigate whether behavior problems could distinguish between children with TS, ADHD-C, ADHD-I or high-functioning Autism Spectrum Disorder (ASD) and TDC. Earlier research has shown considerable overlap of symptoms in these neurodevelopmental disorders. We hypothesized that regardless of overall symptom severity or severity of impairment on individual scales, difficulties controlling behavior involving high emotional salience would be more prominent in the children with TS than in the children with the other disorders.

The third research objective (Paper III) was to investigate the development of EF, levels of anxiety and depression symptoms and behavior problems in children with TS, children with ADHD-C and TDC over a period of two-year period. Based on earlier research, we expected there to be improvements in EF abilities in all the children, and anticipated changes in the level of anxiety and depression symptoms and behavior problems in the children with TS and the children with ADHD-C after two years. Based on our earlier findings regarding dissociable control abilities in the children with TS compared to the children with ADHD, we hypothesized that improved EF abilities would likely be related to changes in levels of anxiety

and depression symptoms and behavior difficulties, suggesting some degree of top-down control over these symptoms.

3. METHOD

3.1 Design

The study applied a naturalistic, cross-sectional approach in papers I and II and a longitudinal approach in Paper III. Combining initial cross-sectional designs with follow-up over time is a recommended approach to studying developmental disorders (Thomas et al., 2009). Even though the follow-up study took place only after two years, childhood and adolescence is a period involving tremendous changes in cognition, emotion and behavior and should present an opportunity to detect important developmental changes. The subjects were recruited from seven Child and Adolescent outpatient Mental Health Centres in Hedmark and Oppland counties. The TDC were recruited from local schools in the same catchment area. Clinical and neurocognitive data were collected from all participants. Participants in the clinical groups received standard psychological treatment and/or medication in the period between inclusion and reassessment.

3.2 Procedure

All participants underwent a comprehensive assessment according to established clinical best-practice guidelines. Neurocognitive testing and clinical evaluations were carried out during the same assessment session. All neurocognitive testing (approximately three hours) included two breaks of 15 minutes each. The interviewers were experienced clinicians, and all were trained in neurocognitive testing and diagnostic assessment prior to inclusion of participants. The project manager (MØ), who is a clinical specialist in neuropsychology, reviewed independently all diagnostic judgments made by the clinicians. Meetings between the clinicians and the project manager were held regularly to arrive at a consensus when the diagnostic assessment was inconclusive. All TDC underwent the same assessment procedures as the clinical participants. Follow-up (T2) assessments were conducted approximately 24 months following baseline assessment. The same procedure was followed in both assessments for all participants.

3.3 Participants

A total of 179 youth ages 8-17 years participated in the overall study at baseline. Participants in the clinical groups were recruited from the Centres for Child and Adolescent Mental Health in Innlandet Health Trust in Norway, where they were referred for diagnostic assessment and treatment of TS, ADHD or high-functioning ASD. The TDC were recruited from local schools in the region and received a small compensation for their participation. There were 19 subjects with TS, 76 with ADHD (33 with ADHD-C and 43 with ADHD-I, 34 subjects with high-functioning ASD, and 50 TDC. At baseline, the mean age was 11.8 (SD = 2.2) in the TS group, 11.7 (SD = 2.0) in the ADHD group, 11.9 (SD 2.3) in the ASD group and 11.6 (*SD* = 2.0) in the TDC. The ratio of boys to girls in the TS group was 5:1, which is the same as that commonly reported in epidemiological studies of children with TS (Freeman et al., 2000; Robertson et al., 2009).

All participants with a history of central nervous system pathology, prematurity (< 36 weeks), a history of stimulant treatment or with an estimated IQ less than 70 were excluded. Participants in the TDC group were screened for mental disorders with the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) in separate interviews for children/adolescents and parents. TDC with a history of psychopathology, head trauma (with a loss of consciousness), or dyslexia were excluded from the study.

In Paper I, the youth with TS, ADHD and the TDC were included. No age difference was detected among the participants. There was a significant difference in gender composition between the youth with TS and the youth with ADHD, with the latter much more evenly balanced between male and female participants. No significant difference in estimated Full Scale IQ was found between the youth with TS and the TDC, but the TDC had a significantly higher Full Scale IQ compared with the youth with ADHD.

In Paper II, the youth with TS, ADHD-C, ADHD-I, high-functioning ASD and TDC were included. No age difference was detected among the groups. For Paper II, the overall ADHD group was divided into the subtypes ADHD-C and ADHD-I. The ADHD-I group was more evenly balanced as to gender, and a significant gender balance difference was identified between the TS and ADHD-I groups; no difference in gender composition was detected between the TS group and any of the other groups. The TDC had a significantly higher estimated Full Scale IQ compared with the ADHD-I group, but no other significant difference among the groups in Full Scale IQ was registered.

In the follow-up study after two years (Paper III), the children with TS were compared with the children with ADHD-C and the TDC. No significant difference in age, gender composition or Full Scale IQ was registered among any of the groups.

At baseline (T1), 11 patients with TS had comorbid disorders: 1xObsessive Compulsive Disorder (OCD), 1xOppositional Defiant Disorder (ODD), 1x ODD & ADHD-C, 2xADHD-I, 2xADHD-C, 3xAsperger's syndrome, 1xADHD-I/Asperger's syndrome. Two children with TS received low doses of an antipsychotic (Quetiapine and Aripiprazole), whereas the remaining fifteen participants with TS were medicine naïve upon inclusion and testing. At T1, only two children with ADHD were on any medication, with low doses of antipsychotics (Risperidone and Quetiapine, respectively). At T1, 28 in the ASD group were diagnosed with Asperger's syndrome and 6 with Pervasive developmental disorder – not otherwise specified. One of the children used a small dose of an antipsychotic (Aripiprazole). Another child with ASD was medicated with stimulants (methylphenidate dosage of 30g). Two other children in the ASD group used stimulant medication (methylphenidate) at T1, but medication was discontinued 24 hours before assessment.

At T2, the two children with TS and either co-occurring OCD or ODD retained this comorbid diagnosis at T2. One child with TS and no comorbid diagnosis at T1 fulfilled criteria for a comorbid general anxiety disorder at T2. Of the children with TS, 32% received a psychostimulant due to comorbid ADHD, 21% received a low dose of an anti-psychotic medication, and one received a low dose of an anti-depressant. Forty-two percent in the TS group received special follow-up at school, and 63% received supervisory counseling by a therapist at their local outpatient clinic. Of the participants with TS taking psychostimulants, all discontinued use at least 24 hours prior to the neurocognitive assessments at T2. In the ADHD group, a majority of the participants with ADHD had completed their clinical treatment, and were no longer patients at the Innlandet Hospital Trust at T2. A total of 42 were prescribed a psychostimulant (Equasym, Concerta, or Ritalin), but were tested after medication was discontinued for at least 24 hours before re-assessment. One female participant forgot to discontinue stimulant medication prior to testing at T2. In the ASD group at T2, one adolescent was prescribed an antipsychotic and an antidepressant medication (quetiapine 75mg, sertraline 100mg), and one was prescribed an antidepressant medication (mianserinhydrokloride 30mg). Three of the youth in the ASD group at T2 were prescribed psychostimulants (methylphenidate). Psychostimulants for all three of these participants were discontinued at least 24 hours prior to neurocognitive re-assessment.

At T2, seven patients in the TS group no longer satisfied formal diagnostic criteria for a tic disorder, while one fulfilled criteria for a Chronic Motor Tic Disorder. Of the 19 children diagnosed with ADHD-C at T2, 11 retained the diagnosis of ADHD-C, 6 fulfilled criteria for ADHD-I and two no longer fulfilled criteria for ADHD. All high-functioning ASD diagnoses determined at T1 were confirmed at T2. There were no dropouts from T1 to T2 among the TS and ASD participants. Three boys with ADHD refused to participate at T2; there were no significant differences in age and Full Scale IQ ($p > .05$) between the children with ADHD available for re-assessment and those three children with ADHD who were lost to follow-up.

3.4 Measures

3.4.1 Clinical assessment

Diagnosis was determined based on semi-structured clinical interviews and standardised rating scales. The K-SADS interview (Kaufman et al., 1997) was conducted separately for children/adolescents and parents to assess psychopathology. The diagnostic evaluation with K-SADS was supplemented with information from the ADHD Rating Scale IV (ARS-IV) (DuPaul, Power, Anastoupolous, & Reid, 1998), the Child Behavior Checklist/6-18 (Achenbach & Rescorla, 2001), and the Autism Spectrum Screening Questionnaire (ASSQ) (Ehlers, Gillberg, & Wing, 1999; Posserud, Lundervold, & Gillberg, 2009). Additional information about school functioning, which is mandatory on referral, was incorporated into the diagnostic evaluation. Diagnoses were considered fulfilled if, based on a comprehensive evaluation of K-SADS, teacher information and standardised rating scales, DSM-IV (American Psychiatric Association., 2000) criteria were met.

3.4.2 Neurocognitive assessment

The psychometric measures included in the neuropsychological battery assessed core EF measures (e.g. working memory, cognitive inhibition and cognitive flexibility), as well as the more specific research measures: focused attention and various decision-making variables. A central tenet in the understanding of EF is that different functions are both correlated (unity) and specific (diversity) (Miyake & Friedman, 2012). Although the administered tests loaded on a range of different functions, we assigned the tests to the following domains:

Working memory: The Letter-Number Sequencing Test (LN) (Wechsler, 2004) was used as a measure of working memory in Paper III. The test consists of ten items. Each item contains three trials with the same number of digits and letters. The test administrator reads

aloud each trial and asks the child to recall the numbers in ascending order and the letters in alphabetical order. In the present study, total correct recalled trials were examined. Lower scaled scores indicated difficulties with the task. Mean reliability for the LN test across all ages is 0.75 (Wechsler, 2004).

Cognitive inhibition: The Colour – Word Interference Test, Condition 3 (CW 3) (D-KEFS; Delis, Kaplan, & Kramer, 2001; Stroop, 1935) was used as a measure of verbal inhibition in papers I and III. In the Inhibition condition, involving the Stroop interference effect, the child names the color of the ink in which a color-name is printed. The Stroop effect refers to the additional response time involved in denoting the name of an incongruent color on the letters of a color-word, compared with simply reading the word. The ability to effectively inhibit the prepotent response tendency of reading the word is reflected in the number of errors. We also determined a contrast measure to control for potential difficulties with more basic skills such as processing speed (Delis et al., 2001). Here, we subtracted the mean sum score of the preceding processing tasks of Color naming and Reading from the time used in the Inhibition condition, [Inhibition – (Color naming + Reading)/2]. This variable was termed Contrast. Response time for the first three conditions, errors on the Inhibition condition and the Contrast score are reported for the verbal response task. For the study in Paper 1, error scores were compared. For the study in Paper III, completion time in seconds was examined. Lower scaled scores indicated difficulties with the task. Mean reliability for the CW 3 test ages 8-19 is 0.90 (Delis et al., 2001).

Cognitive flexibility: The Colour – Word Interference Test, Condition 4 (CW 4) (D-KEFS; Delis et al., 2001) was used as a measure of cognitive flexibility in Paper III. The examinee is asked to switch back and forth between naming the dissonant ink colours and reading the words. For the present study, completion time in seconds was examined. Lower scaled scores indicated difficulties with the task. Mean reliability for the CW 4 test ages 8-19 is 0.80 (Delis et al., 2001).

Motor inhibition: In the Conners' Continuous Performance Test-II (CCPT-II), the child was presented with a repetitive array of visual stimuli on a computer screen for just over 14 minutes (Conners, 2004). The child was instructed to press the space bar every time a letter other than "X" appears, and to not press the space bar when "X" appears. The rate of stimulus presentation varied according to 1, 2 and 4 second intervals throughout the task. Three of the 12 performance scores generated in this test have been empirically shown using principal component analysis to relate in particular to inhibitory dysfunction (Egeland & Kovalik-Gran, 2010): 1) The hit reaction time variable (Hit RT) indicates the average speed of correct

responses for the entire test; 2) The number of commission errors (Commissions) represents the number of times the participant pressed the space bar when the non-target letter "X" is presented; and 3) The Response Style (β) indicator is a ratio indicating a subject's tendency to respond fast or slowly relative to targets and non-targets. A high score on the CPT Response Style Indicator (β) indicates an emphasis on avoiding commission errors. A low score on this measure indicates less concern about mistakenly responding to a non-target (Conners, 2004).

Focused Attention: Variability of Standard Error. In the CCPT-II (described above), the measure Variability of Standard Error is a measure of response speed consistency across 18 separate segments of the test (Conners, 2004). A higher score on this measure is an indication of a greater inconsistency in response speed during the task. In a study using principal component analysis to examine various aspects of attention, the Variability of Standard Error measure related in particular to the ability to focus attention on task (Egeland & Kovalik-Gran, 2010).

Decision-making: The computer-based Hungry Donkey Task (HDT) (Crone & van der Molen, 2004) is a children's version of the Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio, & Anderson, 1994). The basic format of IGT (gambling) is retained, but the HDT (a pro-social game) is considered to be a more appropriate decision-making task for children (Crone & van der Molen, 2004). The HDT was used as a measure of decision-making efficiency in Paper III. Participants are asked to help a hungry donkey collect as many apples as possible by choosing one of four doors (A, B, C, D). The amount of wins and losses varied between choices, and overall gains/losses were displayed with a red/green bar at the bottom of the screen. Doors A and B represent disadvantageous choices (resulting in overall loss), and Doors C and D represent advantageous choices (resulting in overall gain). The selection of Doors A and C involve infrequent, but higher-level losses, whereas the selection of doors B and D involve frequent, but lower-level losses. The task ended after completion of 150 trials. As the risk parameters are uncertain at the start of the task, early choices are considered to be decision-making under ambiguity, whereas later choices are considered to be decision-making under risk (Brand, Recknor, Grabenhorst, & Bechara, 2007). In Paper III, the number of Advantageous choices (Doors C and D) in the last four blocks were summed to represent a measure of "Advantageous choices". "Advantageous choices" was further subdivided. We termed results for Door C a "Safer Choice", based on the logic that by selecting this door the subject ensures a steady gain in outcome by having to endure regularly occurring low-level losses. We termed Door D a "Riskier Choice", because, although it offers the same overall gain as Door C, the subject must endure sudden, large losses. The two advantageous doors

thus offer differing "gain versus pain" schedules and ratios. For a detailed account of the HDT, see Crone & van der Molen (2004).

General cognitive functioning (IQ): The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was administered to estimate IQ in all participants.

3.4.3 Symptom and behavior assessments

3.4.3.1 Parent-rated scales

The *Behavior Rating Inventory of Executive Function* (BRIEF) for children and adolescents aged 5-18 is an 86-item parent and teacher form that allows professionals to assess everyday executive functions in the home and school environments (Gioia et al., 2000b). The parent-rating form was used in the current study. The rating instrument is composed of eight clinical scales, two broad indices and one overall score. The Behavior Regulation Index (BRI) consists of the clinical scales Inhibit, Shift and Emotional Control, and the Metacognition Index (MCI) consists of the clinical scales Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor. An overall measure of behavior problems is given in the Global Executive Composite (GEC) (Gioia et al., 2000b). The current study used the Norwegian version of the parent-rating form, which has shown high internal consistency (Chronbachs α = .76-.92) (Fallmyr & Egeland, 2011), and similar levels to that reported for the English version (.80-.98) (Gioia, Isquith, Guy, & Kenworthy, 2000a). Evidence of construct validity for the instrument has been demonstrated by convergent and discriminant analyses with several established behavior and attention scales (Isquith et al., 2013). Elevated T-scores on the BRIEF indicate a higher degree of impairment. A short description of the eight clinical scales are as follows: *Inhibit:* The ability to control his or her impulses, to stop own behavior at the proper time, and to be able to continue in the right direction and solve the task. *Shift:* The ability to move freely from one situation, activity, or aspect of a problem to another in a given situation. *Emotional Control:* The ability to modulate emotional responses appropriately. *Initiate:* The ability to begin a task or activity, and independently generate ideas that are helpful in solving a specific task or problem. *Working memory:* The ability to hold information in mind for the purpose of completing a task. *Plan/Organize:* The ability to manage current tasks and to anticipate future goals. *Organization of Materials:* The ability to organize the world (e.g. workspace, play areas) and keep order of the belongings. *Monitor:* The ability to check work and the effect of own behavior on others (Gioia et al., 2000a). The

BRIEF was used in Paper II to assess the level of everyday executive problems in the subjects.

3.4.3.2 Self-report measures

The Revised Children's Manifest Anxiety Scale, second edition (RCMAS-2) (Reynolds & Richmond, 1985) is a self-report instrument designed to measure anxiety symptoms in children 6 to 19 years of age. Children respond either ''Yes'' or ''No'' to 49-items. Three anxiety factors are assessed: Physiological Anxiety, Worry and Social Anxiety. The three anxiety factors are summed yielding a Total Anxiety score. Elevated raw-scores indicate a higher degree of anxiety symptoms. The RCMAS Total Anxiety Scale has been found to have satisfactory psychometric properties with high test–retest reliability (Pela & Reynolds, 1982; Reynolds, 1981) and consistent construct validity (Reynolds, 1980, 1982; Reynolds & Paget, 1981; Scholwinski & Reynolds, 1985). Satisfactory psychometric properties have been replicated among other cultures as well (Boehnke, Sillbereisen, Reynolds, & Richmond, 1986; Ferrando, 1994; Pela & Reynolds, 1982; Turgeon & Chartrand, 2003). Results from the self-report RCMAS-2 were used in Paper III to investigate level of anxiety symptoms.

The Short Mood and Feelings Questionnaire (SMFQ) is designed to measure symptoms of depression in children 8 to 18 years of age. The short version consisting of 13 items is derived from the original 30-item Mood and Feelings Questionnaire (MFQ) (Costello & Angold, 1988), which has been shown to identify major depressive episodes and other mood disorders in youth diverse in demographic and clinical characteristics (Daviss et al., 2006). Elevated raw scores indicate a higher degree of depression symptoms. The SMFQ has demonstrated high internal consistency (Crohnbach's alpha = .90) (Costello, Benjamin, Angold, & Silver, 1991), and test-retest stability in children (Costello & Angold, 1988). SMFQ has been shown to correlate strongly with the Children's Depression Inventory (CDI) (Kovacs, 1983) and the depression score in the Diagnostic Interview Schedule for Children (DISC-C) (Costello & Angold, 1988) (r = .67 and .51, respectively). Acceptable validity of the Norwegian version of the SMFQ has been reported by Lundervold (1986). Results from the self-report SMFQ were used in Paper III to investigate level of depression symptoms.

3.5 Statistical analyses

Data analyses were conducted using the statistical package SPSS for Windows, versions 18.0 (Paper 1), 19.0 (Paper II) and 21.0 (Paper III) (SPSS, Inc., Chicago, IL). Demographic characteristics were investigated using the Chi-square test for independence (nominal

variables) t-tests and analysis of variance (ANOVA) for continuous variables. Correlational analyses were two-tailed with a significance level of $p \leq 0.05$. Correlations between variables were explored with Pearson's *r*.

In Paper I, the neuropsychological data was analyzed with an ANOVA and post hoc analyses to compare performance by the three groups on the selected measures. All significant group differences were further analyzed in pairwise ANCOVA controlling for the effect of IQ. Additional analyses were conducted to investigate the effect co-occurring conditions had on performance for the children with TS compared with the TDC. The children with ADHD were treated as one group in the main analyses, but were divided into subtypes for subsequent analyses. The children were divided into the following subgroups when reporting results on the main outcome measures: TS-pure (8 children), TS-pure and TS with co-occurring high-functioning ASD (11 children), TS-pure and TS with co-occurring ADHD (12 children), TS without ADHD (13 children), ADHD-Combined Type (33 children), ADHD-Inattentive Type (46 children), and TDC (50 children). Due to the small *n* in the group of children with TS when the children with TS and co-occurring ADHD were excluded, a retrospective two-group Satterthwaite *t* test was conducted using nQuery Advisor software version 6.0 to assess power to detect significant differences in some of the follow-up analyses.

In Paper 2, ratings on the individual scales on the BRIEF were analyzed with ANOVAs and post-hoc analyses with a Bonferroni correction. Repeated measures ANOVAs were performed on each pair of scales to compare the parent rating of the children with TS with each of the other groups. In order to compare the frequencies of the expected scale patterns within each clinical group, a categorical variable was derived for each pair by subtracting the score on the paired scale from the Emotional Control scale. A positive number was labelled "1" indicating a higher level on the scale compared with the paired scale, and a negative number was labelled "2" indicating the opposite. A chi-square test for independence was then performed for each scale classification pair to examine rates of classification into the diagnostic groups.

In Paper 3, mixed between-within subjects ANOVAs (mixed ANOVA) were performed for each dependent variable to estimate the effect of time and group on performance scores. Post Hoc comparisons using a Bonferroni adjustment were conducted to examine the relative performance level, as well as symptom load between the groups at T1 and T2. Correlation analyses (Pearson) were then performed to investigate associations between changes in measures assessing focused attention, inhibition, working memory,

mental flexibility and advantageous decision-making variables between T1 and T2, and changes in symptoms of anxiety and depression and emotional behavior difficulties.

3.6 Ethical considerations

The study was approved by the Regional Committee for Medical Research Ethics in Eastern Norway (REK-Øst) and by the Privacy protection ombudsman for research at Innlandet Hospital Trust. It was conducted in accordance with the Helsinki Declaration of the World Medical Association Assembly. In order to ensure a free informed consent, all candidates for the study were duly informed about the research project in an information letter and in the consent form. All parents/caregivers and participants above 12 years gave written informed consent in accordance with the requirements set by the Research Ethics Committee in Eastern Norway. Children under the age of 12 years provided oral consent to participate, and their parents provided written consent for their child. The hospital's research server was used for data storage and only authorized persons had access to the archives in order to ensure the confidentiality of participants. The comprehensive assessment at T1 with neurocognitive testing and diagnostic interviews was clinically relevant and in the interest of participants. All participants and their parents were offered information about the neurocognitive test results, and the diagnostic judgements. Reassessment at T2 was followed up with information to parents and child of the neurocognitive test results.

4. SUMMARY OF PAPERS

Paper I:

Dissociable Response Inhibition in Children with Tourette's Syndrome Compared With Children With ADHD

Objective: The aim of this study was to investigate whether performance in a verbal response task (Color-Word Interference Test) and a motor response task (Conners' Continuous Performance Test) discriminates children with TS, ADHD and TDC.

Method: Nineteen children with TS, 79 with ADHD, and 50 TDC participated (8-17 years).

Results: Children with TS committed significantly fewer errors in the verbal response task than those with ADHD. Moreover, children with TS, but without ADHD performed better than TDC. Errors in motor task and speed of response did not distinguish between groups. A cautious tendency of response correlated positively with rates of tics in children with TS.

Conclusion: Children with TS were superior in inhibiting a prepotent verbal response; however, comorbidity with ADHD in those children negatively influenced performance**.** Results support the hypothesis that levels of inhibitory control distinguish children with TS, ADHD and TDC.

Paper II:

Distinct Patterns of Everyday Executive Function Problems Distinguish Children With Tourette Syndrome From Children With ADHD or Autism Spectrum Disorders

Objective: Everyday executive function was investigated in children with TS, Inattentive or Combined presentations of Attention-Deficit/ Hyperactivity Disorder (ADHD-I/ADHD-C), high-functioning Autism Spectrum Disorder (ASD) and TDC.

Method: Nineteen children with TS, 33 ADHD-C, 43 ADHD-I, 34 high-functioning ASD, and 50 TDC participated (8-17 years). Parents completed the Behavior Rating Inventory of Executive Function (BRIEF). **Results:** Children with TS, ADHD-C, ADHD-I or high-functioning ASD were rated with significantly more regulation problems on all scales compared with TDC. Considerable overlap of symptoms between clinical groups makes differentiation difficult on individual scales. Scale configurations showed children with TS to have more problems with emotional control than cognitive flexibility in relation to children with high-functioning ASD, more problems with emotional control than inhibitory control in relation to children with ADHD-C and more problems with emotional control than planning/organizing in relation to children with ADHD-I.

Conclusion: Paired BRIEF scales dissociated executive function problems in children with TS from children with ADHD-C, ADHD-I or high-functioning ASD. Clinical relevance is discussed.

Paper III:

Cognition, Emotion and Behavior in Children with Tourette's Syndrome and Children with ADHD-Combined Subtype – A Two-Year Follow-Up Study.

Background: This two-year follow-up study investigates whether changes in executive function (EF), focused attention and decision-making in children and adolescents with TS or ADHD are associated with changes in anxiety and depression symptoms and/or emotional behavior difficulties. **Method:** Nineteen children with TS, 33 with ADHD-C, and 50 TDC were examined with a battery of psychometric measures and rating forms at baseline and two-

years later. A standardized battery of psychometric measures and rating forms were administered at baseline and two-years later.

Results: All three groups improved in measures of core EF over time, whereas only the TDC improved in focused attention. In the decision-making task, none of the groups improved in overall advantageous decision-making; however, the children with TS preferred a safer strategy in selecting advantageous choices than the children with ADHD-C and the TDC at T2. Children with ADHD-C and with TS showed higher symptoms of anxiety and depression and more emotional behavior difficulties compared with TDC at both time points. Finally, children with ADHD-C self-reported more depression symptoms than those with TS at both assessments. For the TS group, safer decision-making was related to more control over emotional behavior difficulties.

Conclusion: More efficient control over core cognitive processes was not associated with fewer symptoms of anxiety or depression or increased control over emotional behavior in children with TS or ADHD-C. This study emphasizes the importance of addressing symptoms of anxiety and depression in children with TS or ADHD-C, and that children with TS or ADHD-C likely differ in their sensitivity to reinforcement contingencies.

5. DISCUSSION

5.1 Main findings

5.1.1 Summary of main findings relating to the children with TS

- Children with TS performed more accurately in a response inhibition task compared with children with ADHD (Paper I).
- Parents of children with TS reported significant behavioral problems relating to a range of everyday executive control difficulties compared with TDC (Paper II). Emotional behavior difficulties (e.g. regulating emotional outbursts) is the most serious difficulty relative to other executive control difficulties for children with TS compared with children with ADHD or high-functioning ASD (Paper II).
- Children with TS self-reported a significantly higher level of anxiety and depression symptoms than TDC at baseline and after two years (Paper III). The children with TS self-reported a significantly lower level of depression symptoms compared to the ADHD-C at baseline and follow-up (Paper III).

- More efficient cold EF (inhibition, working memory, mental flexibility) in children with TS over time was not related to a reduction in anxiety or depression symptoms, nor fewer emotional behavior difficulties (Paper III).
- Children with TS preferred a more cautious choice in a decision-making task (hot EF) compared with children with ADHD-C and TDC (Paper III).
- A preference for safer choices (hot EF task) in children with TS over time was related to a reduction in emotional behavior difficulties (Paper III).

5.1.2 Executive control in children and adolescents with TS

The complex behavioral spectrum of TS is daunting (Cavanna, Servo, Monaco, & Robertson, 2009), and no single approach is sufficient to grasp the complexity of challenges faced by children with TS (Robertson, 2000). Our approach to studying this complex condition has been to investigate specific cognitive, emotional and behavioral difficulties experienced by children and adolescents with TS and to reflect on the children's ability to exert executive control in dealing with these difficulties. The bio-psycho-social paradigm is used to draw on several perspectives to better understand the complexity of factors underlying and influencing the course of TS, and a top-down, bottom-up view of executive control is used to provide a simple framework in which to try to understand potential factors influencing executive control over thoughts, emotion and behavior (Banich, 2009; Heatherton & Wagner, 2011). A priori we know that youth diagnosed with TS suffer from persistent, disturbing tics that they can delay, but cannot fully stop or control (Leckman et al., 2006). What does this say about their ability to control other overt behavior, what does this say about their ability to regulate aspects of their emotional well-being, and how might maturing cognitive abilities and other emerging factors influence their development? In three studies, we addressed topics relating to these top-down control issues by comparing youth with TS not only with TDC (Papers I, II and III), but also with children with ADHD (Papers I & II) or ADHD-C (Paper III) and children with high-functioning ASD (Paper II). Both ADHD and ASD are disorders related genetically to TS and in many aspects present overlapping symptom profiles. A central issue in all three disorders (TS, ADHD and ASD) is the balance between top-down and bottom-up control of behavior, as all of these disorders are associated with abnormal frontal-striatal functioning and deficient self-regulatory control of behavior compared with TDC. Despite overlap in symptoms, however, each disorder is unique. For example, impaired inhibitory control is the focus of research in both ADHD (Castellanos et al., 2006) and TS (Eddy et al., 2009); but whereas

children with ADHD do not necessarily have tics, children with TS are not necessarily impulsive. Difficulties regulating behavior adaptively in social situations is a focus of research in both ASD (Gilotty, Kenworthy, Sirian, Black, & Wagner, 2002) and TS (Hoekstra et al., 2013), yet the nature of their ability to adapt their behavior appropriately in various contexts differs in significant respects. There is a consensus among researchers that children with all three of these neurodevelopmental disorders display executive control difficulties, but the precise nature of these difficulties is in dispute and currently under active investigation. The focus in this thesis is on executive control issues relevant to children and adolescents with TS in particular, as contrasted with the comparison groups (TDC, ADHD and high-functioning ASD) in the respective studies. Our findings regarding executive control will now be discussed in terms of executive control of cognition, emotion (anxiety and depression symptoms), and behavior.

5.1.3 Executive control of cognition in TS

Conceptualizing TS as a difficulty inhibiting sensory urges or behavior as in the neurobiological model implies impairment in essential top-down regulatory processes (O'Connor, 2002). Some studies addressing inhibition in children with TS have reported impaired inhibitory abilities in children with TS using traditional neuropsychological tasks (Crawford et al., 2005; Muller et al., 2003), yet others have not found differences in inhibitory function in children with TS compared to TDC (Roessner, Albrecht, Dechent, Baudewig, & Rothenberger, 2008). Studies on behavioral inhibition in children with TS are thus equivocal. Interestingly, a number of recent studies using neuroimaging techniques have described enhanced inhibitory activity in brain regions involved in inhibiting responses in children with TS compared with TDC (Baym et al., 2008; G. M. Jackson et al., 2007; Mueller et al., 2006). One approach to resolving these somewhat inconsistent findings is to consider that enhanced brain activity may be activated in order to compensate for a deficit, i.e. a compensatory strategy to maintain task performance (S. R. Jackson et al., 2011). Enhanced activation in order to maintain task performance would require a greater application of cognitive resources to the brain region responsible for coordinating the task. Repeated activation in the same brain region will likely result in a strengthening of capacity, which may then have a generalizable effect to other areas. This explanation would support a hypothesis of stronger top-down executive control in children who repeatedly practice inhibiting unwanted impulses to act (e.g. children with TS).

In Paper I, the inhibitory control abilities of children with TS were examined using neuropsychological tests commonly used in research on children and adolescents. We compared a group of children with TS with a group of children with ADHD, who are generally associated with inhibitory control difficulties (Fillmore, Milich, & Lorch, 2009). We also tested a group of TDC as controls. Children with TS are known to have motor control deficits (Roessner et al., 2012), and so we included measures of inhibition covering both motor (CPT) and verbal (Stroop) domains. The executive control required in response inhibition tasks can be thought of as a conflict between the prepotent response and a nonhabitual response involving multiple levels of control (Bugg & Hutchison, 2012). A crucial aspect of executive control is the ability to stop or inhibit a prepotent response (Jha et al., 2015). We thus had a particular interest in the number of errors made in the motor and verbal tasks administered in the study, which could be interpreted as a concrete behavioral manifestation of a failure to stop a prepotent response. Only a few studies administering the Stroop task to children and adolescents with TS have been published (Chang et al., 2007; Channon et al., 2003; Sukhodolsky, Landeros-Weisenberger, Scahill, Leckman, & Schultz, 2010); however, all of these studies reported only the speed of completion on the task and not the number of errors performed during the task. To our knowledge, no previous studies involving children or adolescents with TS have reported results on the number of errors on the verbal response measure used in our study (Stroop).

The children with TS in our study were more effective than the children with ADHD in inhibiting a prepotent response in the verbal task (Stroop), but no different in the motor task (CPT). The effect size was much higher for the verbal task (Eta^2 = .07) compared with the motor task (Eta^2 = .03). Lower cognitive load on the motor response task might have reduced power to detect a difference on this task, and some research indicates that a heavy load on response inhibition tasks is essential for discriminating between impaired and normal inhibitory functioning. Two important differences in the tasks may explain the differing results. First of all, the verbal response task (Stroop) allowed the child to himself or herself determine the pace of stimulus presentation, whereas this was not possible for the child in the computerized motor response task (CPT). If executive control is viewed as a cascade of nested levels of processing in distinct frontal regions (Koechlin et al., 2003), then a self-determined pace would allow for more complex processing compared with responding to a preset pace set by a computer. Second, the prepotent effect of a word (Stroop task) naturally involves more activation due to more associative context than an alphabetic letter (CPT), which would make the prepotent effect of reading a word more difficult to override than reading a letter in the

alphabet. In activating prefrontal resources to override a prepotent verbal response, a task that permits control over the rate of response would allow for more flexibility in selecting accurately compared with a task that does not permit control over the rate of response.

One measure of how the groups of children in the first study (Paper I) were responding to prepotent congruent or incongruent stimulus prompts in the response inhibition task is the Response Style Indicator (also known as β) in the motor response task (CPT). On this measure, a higher ratio indicates an emphasis on avoiding errors (i.e. hesitating when presented with incongruent stimulus) (Conners, 2004). Whereas a higher value indicates that caution is a priority, a lower value suggests a riskier response style (Conners, Epstein, Angold, & Klaric, 2003). Recent research has shown that the processing involved in emphasizing accuracy versus speed takes place in frontal regions (striatum) intricately involved in executive control (Forstmann et al., 2010; Forstmann et al., 2008). We expected here that the children with TS would have a higher ratio indicating an emphasis on responding accurately and committing fewer errors, and that the children with ADHD would have a lower ratio indicating less concern about responding accurately and consequently committing more errors. Unexpectedly, both the children with TS and the children with ADHD had significantly higher ratios compared with the TDC. Both the children with TS and the children with ADHD were hesitating before responding to an incongruent stimulus compared with a congruent stimulus. A reasonable interpretation of this response tendency shared by the two clinical groups is that both children with TS and children with ADHD were not able to process a response requiring additional frontal activation as efficiently as the TDC; both groups needed more time to decide on an appropriate response.

In the motor task (CPT), the children with ADHD performed more errors on average compared with the children with TS, but the result was not significant. If we assume that the style of responding to congruent and incongruent stimuli was similar across tasks (CPT and Stroop), then we can use the results in the verbal response task (Stroop) to inform the interpretation of response style in the motor response task (CPT) and more easily suggest a reason for the hesitation in responding. The children with TS were likely using the relative delay when responding to incongruent stimuli to activate more frontal resources and to respond more accurately; the children with ADHD, on the other hand, were less able to activate more frontal resources and thus performed more errors. Importantly, the TDC had the lowest ratio in Response Style compared with both the children with TS and the children with ADHD, indicating a more balanced rate of processing of congruent and incongruent stimuli compared with the two clinical groups. Although this result was unexpected, there is evidence to support

this finding and interpretation. A study involving children with ADHD-C found deficits in efficient performance in incongruent trials compared with the TDC on the same type of response selection tasks used in our study (Randall, Brocki, & Kerns, 2009), and another study reported inefficient responding to conflicting stimulus in adults with TS on a computerized task involving the Simon effect (the inhibition of inappropriate responses) (Georgiou, Bradshaw, Phillips, Bradshaw, & Chiu, 1995).

The uneven response style exhibited by the children with TS and the children with ADHD compared with the TDC is also relevant in relation to results in Paper III regarding the decision-making task, as it involves an emerging response pattern unique for the children with TS (i.e. enhanced control, overly accurate). The decision-making paradigm used in the follow-up study (Paper III) involves selecting between competing alternatives involving uncertain risk and reward contingencies, and the outcome in these tasks depends on a close interplay between brain regions mediating both cognition and emotion (Bechara et al., 2005; Heilman et al., 2010). We are not aware of any prior studies investigating the decision-making skills of youth with TS. One study examining decision-making skills in adults with TS and adults with OCD reported deficient decision-making skills in the adult subjects with TS compared with TDC (Watkins et al., 2005). This study used a different decision-making task that the one used in our study, however, and only reported overall proportion of choices with the most likely outcome; the study did not investigate the possibility of subjects showing a preference for cautious or riskier choices. Studies investigating the decision-making skills in children with ADHD have reported contradictory findings (DeVito et al., 2008; Skogli, Egeland, Andersen, Hovik, & Oie, 2014; Toplak, Jain, & Tannock, 2005). Because of the lack of literature for children with TS and conflicting results in studies for children with ADHD, we were not able to confidently predict the likely outcome on this task. We were also unsure any pattern of decision-making would emerge, as decision-making skills are not thought to reach adult levels until late adolescence (Crone & van der Molen, 2004).

Although we did not ask the subjects in a methodical way whether they had a strategy in their choices on the decision making task (HDT), we assumed that they would subconsciously learn which doors gave favorable outcomes over time. Interestingly, we found that the rate of selecting overall advantageous choices was the same in the children with TS, the children with ADHD and the TDC at both baseline and follow-up. When we examined the tendency to prefer the cautious or riskier advantageous choice, however, a distinct pattern of decision-making emerged in the analyses for the children with TS compared with the children with ADHD-C. Whereas no difference in cautious or riskier decision-making was registered

between the any of the groups at T1, the children with TS clearly preferred the more cautious choice compared with the children with ADHD-C at T2. In other words, the children with TS overwhelmingly preferred the advantageous choice that involved lower, but more frequent losses, compared to the alternative equally advantageous choice that involved much higher, but less frequent losses. This change in decision-making preference by the children with TS suggests a developmental shift in preference to more cautious choices during their adolescent years. It can be argued that the preference by the children with TS for the cautious alternative in the decision-making task is consistent with the more accurate response style shown in the verbal and motor response tasks described earlier. Cautious and accurate responding versus an emphasis on speed is a process mediated in frontostriatal networks (van Maanen et al., 2011). Selecting accurately and selecting cautiously both reflect enhanced top-down executive control. The children with TS seem to be exerting a distinct top-down control over their responses compared to the children with ADHD on these widely differing tasks. Importantly, the difference in inhibitory control was registered at baseline for the children with TS compared to the other groups, whereas the preference for cautious choices emerged only after two years at the follow-up testing.

Regarding the verbal response task (Stroop) in Paper I, the original analyses with the entire group of TS children did not reveal a difference in the number of errors compared with the TDC. Knowing the effect ADHD has on response inhibition, however, we conducted further analyses in which we excluded the six children in the TS group with co-occurring TS+ADHD. The results indicate that the group of children with TS without ADHD performed significantly less errors on the verbal response task compared with the children with TDC. The resulting pure TS group was small and so the results are in need of replication; however, our findings do provide evidence that ADHD has a negative effect on accurate responding. The mean value for riskier choices in the decision-making task for the children with ADHD also indicated that they seemed to prefer the riskier choice, however, this result did not reach statistical significance. The finding regarding the tendency of children with ADHD to commit more errors in tasks compared with TDC is consistent with another study concluding that abnormal error processing characterizes young persons with ADHD compared to TDC (van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007).

Interestingly, the results of a study involving children with ADHD with or without tics provide evidence to support our findings regarding the effect of tics or ADHD on performance in cognitive tasks. The study examined attention and inhibition in children with ADHD and found that the effect of tics in children with ADHD was to improve performance

on these measures compared with the children with ADHD but without tics (Greimel, Herpertz-Dahlmann, Gunther, Vitt, & Konrad, 2008). Greimel and her colleagues posited that the consequence of inhibiting tics over time in the children with ADHD may be the emergence of compensatory neural mechanisms that improved neuropsychological performance compared with the children without tics. A basic property of the living brain – neuroplasticity - is the ability to adjust and adapt to internal and external influences (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Based on this basic property of brain change over time due to internal or external influences, it is not unreasonable to consider the likelihood that having tics over time may enhance top-down control of behavior.

It is important to emphasize that the findings do not apply to individual responses in isolation, but rather relatively enhanced inhibitory control over time in relation to prepotent responses in a laboratory environment. Although the children with ADHD in our study made almost double the number of errors on the verbal response task (Stroop) after 50 trials (mean = 3.9, SD=3.5) compared with the children with TS (mean = 1.89, SD=1.8), the overwhelming number of responses made by the 'impaired' group with ADHD were actually correct (46 out of 50). Thus, the chance of any one single response being wrong was less than 10% on average for the group of children with ADHD. In other words, in the overwhelming number of trials, both clinical groups responded to a large extent exactly the same. In addition, responding in a controlled environment is quite different than having to respond instantly in a highly charged and stressful situation. For this reason, it is interesting that we also documented enhanced top-down control in children with TS on a more emotionally salient decision-making task, but that this enhanced top-down control emerged at a later time in their development.

In our follow-up study after two years (Paper III), we used core measures of EF to derive a composite EF measure offering more power. The measures were working memory, inhibition and mental flexibility. We narrowed the investigation of EF to compare the children with TS with the children with ADHD-C. Some researchers argue that ADHD-C and ADHD-I represent distinct disorders (Diamond, 2005; Milich, Balentine, & Lynam, 2006). In addition, there is evidence that difficulty controlling behavior is more closely associated with ADHD-C than ADHD-I, and ADHD-C is more commonly co-occurring in children with TS than ADHD-I. (Freeman & Tourette Syndrome International Database, 2007). The children with TS were also compared with a group of TDC. We found that the children with TS, the children with ADHD-C and the TDC developed similarly over two years on core EF measures separately and on the composite score. Thus, we did not find any evidence of a delayed development in any core EF in the two clinical groups. We did, however, detect a developmental delay in the

variability of attention measure in both the children with TS and the children with ADHD compared with the TDC. Performance on the variability of attention measure is considered a measure of focused attention (Egeland & Kovalik-Gran, 2010). Impaired attention has been found in both children with TS (Chang et al., 2007) and children with ADHD (Chhabildas, Pennington, & Willcutt, 2001). Attention strongly mediates goal-oriented behaviors and self-regulatory abilities (Hanif et al., 2012), and thus enhanced control over attention may be an important development advantage of TDC compared with children with TS and ADHD. A study involving TDC revealed a different developmental trajectory for the development of inhibitory functions compared with attention measures for children 3-12 years (Klenberg, Korkman, & Lahti-Nuuttila, 2010). We did not examine the role of attention as an intervening variable in performance on prepotent response tasks, but this is an interesting path to pursue in future investigations of inhibitory abilities in children with TS.

Although we did not have large enough groups of children in the TS and TS+ADHD groups to extensively investigate the role of ADHD in TS, the study in Paper I did provide evidence that co-occurring ADHD in children with TS may reduce the group's inhibitory performance as a whole compared with the TDC. This finding is consistent with other studies finding the co-occurrence of ADHD in children with TS having a detrimental effect on EF in children with TS (Channon et al., 2003).

In summary, the executive control of cognition in children with TS is characterized by more accurate responding in a cold EF task and more cautious responding in a hot EF task compared with children with ADHD. Our findings support a hypothesis of more top-down control over responses in children with TS compared with children with ADHD, and in some contexts compared with TDC as well, during important developmental years in childhood and adolescence.

5.1.4 Executive control of emotion in TS

An important objective in Paper III was to document the level of anxiety and depression symptoms self-reported by children with TS, ADHD-C and TDC at baseline and then after two years. Emotional distress results in a lower quality of life, and children with TS and children with ADHD have been shown to suffer from significant higher rates of symptoms of anxiety and depression than TDC (Hirschtritt et al., 2015; Jensen et al., 2001).

As expected, we found that both the children with TS and the children with ADHD-C self-reported higher levels of anxiety and depression symptoms at baseline and follow-up compared with the TDC. Interestingly, the level of depression symptoms self-reported by the

children with ADHD-C was significantly higher compared with the children with TS at both baseline and follow-up. Depression has been referred to as an "insidious nemesis" plaguing children with ADHD (Lavin, 2008), and our results provide evidence that symptoms of depression in children with ADHD-C are significantly higher compared with the level reported by both children with TS and TDC.

Importantly for the children with TS, the levels of anxiety and depression symptoms they self-reported were significantly higher than the TDC and remained significantly higher after a period of two years during adolescence. Analyses with a smaller group of children with TS, in which we excluded the children with co-occurring ADHD, confirmed the same findings of significant higher anxiety and depression symptoms for the group with TS without co-occurring ADHD compared with the TDC. The findings are consistent with results from a study based on parent-reporting of symptoms of anxiety and depression in children with TS with and without co-occurring ADHD that showed the children with TS-only (i.e. without ADHD) had significantly more anxiety and depression symptoms compared with the TDC (Carter et al., 2000).

After documenting levels of anxiety and depression symptoms over time in the groups of children in our study, we investigated whether changes in EF abilities after two years were related to changes in the level of anxiety or depression symptoms. One clinically relevant issue is whether children with TS suffer emotional symptoms due to the same neurophysiologic mechanisms underlying the generation tics, or if these symptoms arise due to distress from having a chronic neuropsychiatric condition or other factors (e.g. comorbidities, difficulties at school, etc.). A relationship between a change in EF (inhibition, working memory, mental flexibility, decision-making or attention) and a change in the level of symptoms of anxiety and depression might indicate that a common underlying mechanism is involved in both symptom expressions.

Although the direction of the relationship is not known and cannot be assumed, anxiety and depression symptoms are closely associated with impaired executive control even in healthy youth (Ng, Chan, & Schlaghecken, 2012). Among the most pronounced deficits in several cognitive domains revealed in a meta-analysis of cognitive functions in children and adolescents with major depressive disorder was impaired inhibitory capacity (Wagner et al., 2015). Neuroimaging studies have revealed that similar regions of the prefrontal cortex are associated with regulating both affect and behavior (Mitchell, 2011; Quirk & Beer, 2006), which is an indication that prefrontal systems are involved in some way in processing both types of information. If the same executive control mechanism is involved in regulating both

tics behavior and emotional distress, then changes in the ability to better regulate one area may be related to changes in better regulating the other. On the other hand, research on the course of symptoms of anxiety and depression in children and adolescents with TS and ADHD indicates that emotional distress tends to worsen in children with TS or children with ADHD over time (Hoekstra et al., 2013; Power et al., 2004; Robertson, 2000), whereas the prevalence of tics in children usually diminishes. A diverging or unrelated trajectory in the maturation of EF and emotional symptoms would suggest that the underlying mechanisms develop independently from each other or that different factors are involved in influencing the two systems.

Each of the groups was analyzed separately in order to uncover any associations among EF measures (e.g. working memory, inhibition, mental flexibility and decision-making) and symptoms of anxiety and depression unique for TS, ADHD or TDC. No correlation was registered between any of the EF measures and a change in levels of anxiety or depression symptoms in any of the groups. We did have a reasonable expectation that some relationship would be detected since top-down frontal structures are involved in EF and regulating levels of anxiety and depression symptoms. These results seem to indicate that better top-down control (i.e. more efficient EF) would not help alleviate the distress caused by symptoms of anxiety or depression. The maturation process of EF abilities does not seem to be closely related to the process of gaining relief from symptoms of anxiety or depression.

In summary, there was no indication that reduction in levels of anxiety or depression symptoms over a period of two years during childhood and adolescence were closely related to improvements in hot or cold EF in children with TS. The results may be interpreted as evidence that levels of anxiety and depression symptoms develop relatively independently from improvements in top-down abilities in children with TS or children with ADHD.

5.1.5 Executive control of behavior in TS

Many children with TS are referred to child health services clinics to address behavior difficulties in their everyday lives that are not directly related to tics. Our findings in the second study (Paper II) revealed that the children with TS were rated by their parents as more impaired on all the scales measuring everyday behavior problems compared with the TDC (Inhibit, Shift, Emotional Control, Working Memory, Initiate, Plan/Organize, Organization of Materials, and Monitor). These findings indicate that children with TS and their parents face a range of behavior challenges in their everyday lives, and are consistent with considerable research showing everyday behavior difficulties are common in youth with TS (Singer, 2005).

Interestingly, all of the children in the clinical groups were rated by their parents as having significantly more behavioral difficulties on most of the scales compared with TDC. This finding might support the use of a p-factor approach in assessing behavior problems in children with the neurodevelopmental disorders included in the study (TS, ADHD-C, ADHD-I, high-functioning ASD). If all of the children with the clinical disorders in the study experience overlapping behavior problem profiles, then it may be more relevant to assess the severity of problems in each area for an individual child rather than to specify the existence of the particular behavior problem. A p-factor is associated with more life impairment, worse developmental histories and more brain function impairments, and researchers who support this dimensional approach believe that patients are better served by describing psychopathological problems dimensionally (a p-factor) (Caspi et al., 2014). One objective in the study on behavior problems in children with TS, however, was not only to register the range and severity of behavior problems in children with TS, but also to identify the relatively most pressing and problematic everyday behavior problem reported by the parents of the children with TS compared with the other clinical groups and TDC.

An important issue to account for when investigating characteristics of children and adolescents with TS is that of co-occurring disorders. Some research suggests that behavior problems in TS are primarily associated with co-occurring ADHD (Carter et al., 2000), and co-occurring conditions in children with TS are known to impair their quality of life more than the tics themselves (Ludolph, Roessner, Munchau, & Muller-Vahl, 2012). We therefore performed the same analyses excluding the children with co-occurring ADHD in the group of children with TS. With the exception of the Organization of Materials scale, the new analyses confirmed the presence of wide-ranging everyday behavior problems in the children with TS after excluding the children with co-occurring ADHD in the TS group from the analyses. In other words, we found that the children with TS were rated as having a broad range of clinically significant behavioral difficulties in their everyday lives regardless of co-occurring ADHD. This result may lead us to suspect that ADHD may be under-diagnosed in the children with TS in our study. First, all of the children in the study underwent rigorous diagnostic evaluations performed by experienced clinicians at two different points in time in which possible ADHD symptoms were carefully assessed, and the level of co-morbid ADHD in the TS group was the same at both baseline and at follow-up. Second, the level of ADHD symptoms in the TS group is significantly lower than the level of symptoms in the ADHD group, despite 6 children in the group with TS having comorbid ADHD. Our finding of behavior problems in the children with TS without ADHD emphasizes the importance of

identifying and treating behavior problems in children with TS regardless of co-occurring conditions. The next issue to be addressed is whether the pattern of behavioral difficulties registered for all the neurodevelopmental disorders compared with the TDC are the same, or whether any distinguishing patterns emerge regarding specific problem areas related to specific disorders.

Applying a technique used in personality psychology to identify specific problem areas in a large number of overlapping scales (Aamodt, 2004), we devised strategic pairs of behavior scales based on literature suggesting the most and least behaviour problems for TS compared with ADHD-C, ADHD-I and high-functioning ASD. The results from the strategic pairs of scales indicated that the Emotional Control (EC) and Inhibit scales successfully distinguished between the TS and ADHD-C groups, the EC and Plan/Organize scales successfully distinguished between the TS and the ADHD-I groups, and the EC and Shift scales successfully differentiated between the TS and ASD groups. In other words, the EC scale that indicates problems controlling behaviour with an emotional salience (e.g. outbursts, agitation, anger) was more problematic for the children with TS relative to other behavioral difficulties compared with the children in the other clinical groups. Interestingly, on the issue of co-occurring ADHD in TS, the results revealed that controlling behaviour involving emotional salience was more difficult for the children with TS than inhibiting behaviour or planning/organising activities. The children with ADHD-C and the children with ADHD-I had other relative dominating behavioral difficulties in relation to children with TS. These results support earlier findings indicating that rage and emotional outbursts are among the most disruptive behaviors in children with TS, and, when present in a child with TS, is often identified as the most impairing problem in their daily lives (C. L. Budman et al., 2003; Dooley, Brna, & Gordon, 1999). Interestingly, the Inhibit scale in BRIEF, which our study found to be relatively more predominant a problem in children with ADHD-C in relation to children with TS, has been found to distinguish children with ADHD-C from children with ADHD-I (Gioia et al., 2000a). We did not directly compare children with ADHD-C and children with ADHD-I in our study, yet our findings do suggest that the predominant behaviour problems in children with ADHD-C and children with ADHD-I may differ. This relative difference in the children with ADHD-C and the children with ADHD-I in dominant problem behaviour compared with the TS also provides evidence to support our decision in the study to divide the children with ADHD into subgroups when examining behavioral differences.

For the children with TS in our study, the study found that about three out of four children with TS have more problems controlling emotional behavior than they do with impulsivity, mental flexibility, or planning/organizing abilities. Previous studies have identified emotional behaviors as a significant problem in children with TS (Cathy L Budman et al., 2000; C. L. Budman et al., 2003), but our study using the strategic pairs technique (Paper II) is the first study to our knowledge to identify emotional behavior difficulties as the comparatively most serious problem for children with TS among a range of other everyday behavior difficulties.

In our study on behavior problems in children with TS (Paper II), we relied on parents to report the everyday behavior of their children. Parents of children and adolescents reliably report problems regulating behavior in real-life situations where their child must regulate their actions on their own (Barkley, 2012; Brown, 2006; Mahone et al., 2002). Problems regulating behavior in everyday settings characterize young persons with TS, ADHD, or high-functioning ASD (Berger, Kofman, Livneh, & Henik, 2007; O'Connor, 2002; Semrud-Clikeman, Walkowiak, Wilkinson, & Christopher, 2010), and assessing such behavior is commonly assessed using rating scales such as the BRIEF (Gioia et al., 2000a). The top-down, frontal dysfunction associated with emotional behavior difficulties (e.g. agitation, outbursts, anger) and impaired decision-making (e.g. impulsivity) is closely associated with negative life outcomes (de Wit, 2009). Specifically, impaired functioning of the orbitofrontal cortex in humans is associated with impulsive or socially inappropriate behavior and difficulties controlling emotional behavior (Berlin, Rolls, & Kischka, 2004). Based on the literature, it appears likely that there is a common vulnerability for children and adolescents with TS and ADHD to develop risky, addictive, and/or emotional behavior difficulties. It may not be as common for children with ASD to exhibit the same risky and addictive behavior problems, but they share with children with ADHD-I, ADHD-C and TS significant difficulties regulating their behavior in everyday situations (Kenworthy, Yerys, Anthony, & Wallace, 2008; Semrud-Clikeman, Walkowiak, Wilkinson, & Butcher, 2010). Research on dopaminergic neurons and genetic studies provide convincing evidence of consistent executive control difficulties involving impulsive, compulsive, and addictive behaviors in children and adolescents with TS, ADHD and ASD (Comings & Blum, 2000). Obtaining an overview of the specific behavior problems in children with any of these disorders will be essential for the proper treatment of these children.

A failure to detect emotional behavior dysregulation could represent a failure to address a potentially serious source of distress for children with TS and their families in their

everyday lives. One influential investigator involved in ADHD research argues that a focus on specific behavior regulation difficulties rather than on a diagnosis may provide a better basis for clinical treatment of children (Pelham, 2001). Unfortunately, the results from our study indicate that no improvement in the self-regulation of emotional behavior (i.e. no decrease in parent-report of behavior problems) took place from baseline to follow-up in any of the groups. We are not able to say whether these children received any treatment to address these problems; however, since no decrease in reported behavior problems were registered, these difficulties were likely not addressed in the clinic during the two years between baseline testing and follow-up.

An important objective of the follow-up study (Paper III) was to investigate a possible relationship between changes in cognitive measures (e.g. working memory, inhibition, mental flexibility and decision-making) and changes in emotional behavior (e.g. emotional control measure on the BRIEF). Such a close association could have clinical relevance in terms of understanding how therapeutic approaches have their effect. In the previous section we reported that we did not find a close relationship between improvement in cognitive performance and changes in anxiety or depression symptoms. Here, we were interested in investigating whether there is a close relationship between psychometric measures and parent-report of changes in emotional behavior in the children with TS.

The results indicated that changes in core EF abilities (working memory, inhibition, and mental flexibility) were not related to changes in emotional behavior problems for the children with TS. One implication of the findings is that the mechanism responsible for mediating processes involved in core EF abilities is separate from the mechanism used to gain control over behavior problems. Otherwise we should have expected that better control over important core EF functions would lead to better control over behavior problems.

The results on the decision-making task may provide a clue to another explanation. The children with TS exhibited a very unique response preference in the decision-making task, i.e. a preference for safer choices, and this preference was highly associated with a reduction in emotional behavior difficulties. Interestingly, a review article examining common ground between decision-making and emotion regulation implicated convergent neurocognitive substrates involving the dorsomedial, dorsolateral, ventrolateral, and ventromedial regions of prefrontal cortex in both processes (Mitchell, 2011). The results in our study may suggest a common underlying mechanism processing the emotional salience involved in EF decision-making and the regulation of emotionally salient behavior in children with TS. These results are based on a correlation study that is not able to confidently predict

the direction of relationship, so we must be careful in drawing conclusions and further investigation may be aimed at replicating the results. Interestingly, the relationship between safer decision-making and less behavior problems was only found in the children with TS. One possible explanation could be that the repeated suppression of tics over some time in children with TS is enhancing their ability to control their behavior and to make careful choices under conditions of uncertainty.

In summary, emotional behavior problems were closely associated with the children and adolescents with TS regardless of ADHD comorbidity, and these difficulties were clinically significant both at baseline and at follow-up. A change in the level of emotional behavior problems reported by the parents of the children with TS was closely related to a change in the children's preference for safer choices in the decision-making task. The results may be interpreted as evidence that better top-down control over emotional behavior problems develops similarly to the top-down control involved in selecting a safer choice in a decision-making task for children with TS.

5.2 Methodological issues

5.2.1 Representativeness and generalizability of results

The clinical participants in this study were recruited as consecutive referrals for assessment from all seven child and adolescent outpatient mental health centers in two neighboring Norwegian counties (Hedmark and Oppland). The clinical subjects in this study may therefore be considered to have a relatively high degree of representativeness for individuals receiving treatment at specialized child psychiatric services in Norway. The sample was drawn from a clinical population, however, and thus represents those who are willing to seek help in a mental health clinic. Our results and conclusions may therefore not be generalizable to the entire TS population, a high percentage of whom may not feel the need for treatment in a mental health facility.

The mothers of TDC children in the project had higher education compared with the mothers of participants in other studies in the field, and may partially support a bias for more high functioning participants in our sample. The education level of the mothers in the TDC group, however, was nearly equal to that of TDC mothers in similar studies in Norway (Heiervang, Mednick, Sundet, & Rund, 2010; Øie, Sundet, & Ueland, 2011).

5.2.2 Possible confounding factors

Prior stimulant medication and other medical problems affecting the central nervous system (i.e. prematurity < 36 weeks) were specified as a priori exclusion criteria in order to control for potential confounders known to influence neurocognition. In a naturalistic study, however, it is difficult to account for all potential confounding variables. When demographic and clinical variables known to influence neurocognition differed between groups, these potential confounders were statistically controlled for whenever possible.

General cognitive functioning (IQ) is an important confounding factor when assessing EF, as these variables are highly corrrelated (Ardila, Pineda, & Rosselli, 2000). The study design controlled for IQ below 70, and the influence of IQ on EF performance was investigated by entering it as a covariate in Paper I. The main findings remained significant after controlling for IQ, suggesting that IQ did not confound the main results. There is however a continuing debate in the literature as to whether EF performance should be corrected for overall IQ, because controlling for IQ removes a portion of the variance that may be related to the disorder under investigation (Nigg, 2001). In future studies, a larger group of children with TS could be matched with children similar in age, gender and IQ in order to avoid any of these possible confounding variables.

The beneficial effect of stimulant medication on neurocognition and behavioral problems in children and adolescents with ADHD is well documented (Swanson, Baler, & Volkow, 2011; Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). Since no participants were prescribed stimulants or had previously been medicated with stimulants at baseline, we can rule out this as a confounding variable at T1. After being assessed at T1, participants in the clinical groups received individualized treatment for their disorders at their respective outpatient clinics. Of the children with TS, 32% received a psychostimulant due to comorbid ADHD, and of the children with ADHD, 58% received a stimulant medication. At T2, all of the participants with the exception of one female participant with ADHD discontinued use at least 24 hours prior to the neurocognitive assessment. The reason for the lack of medication use during testing at T2 was to avoid the use of medication confounding the comparison of performance on EF measures at T1 and T2. However, the ratings of anxiety and depression symptoms and everyday behavior problems were based on a period of time in which many of the children were taking medication. The influence of medication could thus be a confounding variable in the comparison of changes in EF measures and changes in levels of anxiety and depression and everyday behavior.

In the interim period, 42% of the children in the TS group received special follow-up at school, and 63% received supervisory counseling by a therapist at their local outpatient clinic. None of the children with TS reported having received any behavioral treatment for their tic condition (e.g. HRT, ERP, Awareness training, etc.). 47% of the children in the ADHD group received special follow-up at school, and 37% received supervisory counseling by a therapist at their local outpatient clinic. The influence of unspecified psychosocial treatments during the interim period could also possibly represent a confounding factor influencing the results.

Neurocognitive performance is expected to improve with increasing age for all of the subjects in the study. Thus, the effect of age is highly relevant. Mean age in the children with TS and the TDC did not differ between groups in Papers I, II or III. Age was thus not believed to confound between group findings in neurocognition. The relatively large age span in our population (9-17 years at T1) may cause some within-group variability in test performance as EF is known to undergo considerable change throughout childhood and adolescence (Anderson, 2002; Best & Miller, 2010).

Another concern is the uneven gender distribution in the children with TS compared with the group with ADHD and TDC. Even though the gender distribution in the group with TS is no different than that commonly reported in epidemiological studies of children with TS (Robertson et al., 2009), gender differences may be influencing some of the findings in the study.

5.2.3 Psychometric properties of tests and scales

Only standardised neurocognitive tests and rating scales demonstrating acceptable psychometric properties were used in the studies included in this thesis. Clinicians were trained in neurocognitive testing and diagnostic assessment prior to inclusion of participants. Frequent supervision meetings were also held in order to maintain reliable assessments between clinicians.

The neurocognitive tests used in this study are commonly used for research purposes and are widely accepted. Measures included from the Delis-Kaplan Executive Function System (D-KEFS) and WISC-IV to assess core EF have all been tested for good psychometric properties (Delis et al., 2001; Groth-Marnat, 2003; Wechsler, 2004; Wodka et al., 2008). Nevertheless low test specificity and a lack of ecological validity have been raised as a concern regarding neurocognitive assessment. Tasks thought to measure EF are typically highly complex and require other skills than those that are the target of the assessment (Miyake,

Emerson, & Friedman, 2000). Thus, cognitive aspects unrelated to EF (e.g reading problems, language deficits, and reduced cognitive tempo) may influence outcome on some EF tasks.

The structured setting with few distractions provided in neurocognitive testing will typically not reflect the natural surroundings of subjects being tested. Thus, performance results attained in most neurocognitive testing will not reflect EF abilities in the real world (Sbordone, 2000). Furthermore, the lack of motivation in a test situation may also influence performance in neurocognitive testing (Sonuga-Barke, 2005). Results from the neuropsychological tests are not generalizable to everyday life; however, they do provide an indication of an individual's performance potential in a structured environment. Concern regarding the ecological validity of assessment of EF was dealt with by including behavior ratings of executive functioning in everyday life (BRIEF), as well as a task assessing decision-making under more emotion salient circumstances in a laboratory setting (Hungry Donkey). The behavior ratings were provided for by the parents of the children in the study. Whereas parents may be good at identifying problems in the daily environment at home, they may not be as good at identifying problems the children experience at school or in other social contexts. For a more complete assessment of a child's executive fuctioning in everyday life, one should also obtain a rating of an external informant such as a teacher.

The assessments of emotional problems were based on widely accepted rating scales demonstrating good psychometric properties. The administration of both self-report and parent-rating scales may be viewed as a strength because child reports may be more informative regarding internalizing problems, while parent ratings seem to be more valuable concerning externalizing problems in paediatric populations (Goodman, Ford, Richards, Gatward, & Meltzer, 2000).

5.3 Implications

The findings in the three studies presented in this thesis may have theoretical and clinical implications for our understanding of TS. First, the relationship between TS and ADHD will be addressed. Second, consequences for the clinical understanding, assessment and treatment of TS will be discussed.

5.3.1 Theoretical implications

One theoretical implication of the findings in this thesis is related to a conceptualization of top-down control in children with TS compared with children with ADHD. In Paper I, the results revealed that the children with TS performed fewer errors on a response inhibition

task, whereas the children with ADHD performed more errors. In Paper II we found that the children with ADHD-C had relatively more behavior problems related to inhibiting behavior compared to the children with TS (i.e. relatively more impulsive). In Paper III we found that the children with TS preferred a more cautious choice on a decision-making task, whereas there was tendency for the children with ADHD-C to prefer the riskier choice. It is reasonable to assume that the more accurate, less impulsive, and more cautious behavior exhibited in children with TS represents more top-down control over behavior than the less accurate, more impulsive, and less cautious behavior in children with ADHD. It is thus possible to conceptualize the effect of TS in children as influencing the child in a 'too much' control direction, whereas the effect of ADHD in children is to influence the child in a 'too little' control direction. The effect of ADHD in children in TS would then be to undermine enhanced top-down control in children with TS.

Another theoretical implication is the effect of continually suppressing tics over time for the children with TS. In Paper III, we found that the preference for cautious choices in the decision-making task developed over a period of two years during adolescence, but was not present at baseline. Consistent with several other studies, this finding can be understood as further evidence to support the hypothesis that the result of continually suppressing tics may have the effect of enhancing top-down control of behavior in children with TS over time (Greimel et al., 2008; G. M. Jackson et al., 2007; Mueller et al., 2006).

5.3.2 Clinical implications

Although we were not able to conduct an intervention study involving the children with TS in connection with this thesis, some of the descriptive data from our findings may have clinical implications, and could be tested out in future intervention studies.

In the the first study, an understanding of the differences in response inhibition could indicate appropriate intervention strategies for children suffering from TS (with or without co-occurring ADHD). Children with differing EF abilities have been found to respond differently to interventions (Semrud-Clikeman, Walkowiak, Wilkinson, & Christopher, 2010). The cognitive-behavioral/psychophysiological model highlights the reciprocal interplay of underlying cognitive (e.g., perfectionist concerns) and physiological factors (e.g. motor activation level) preceding tic onset (O'Connor, 2002). Determining the capacity and style of response inhibition for the individual child could assist in developing a more effect treatment approach for children with TS.

In the second study, the findings identified a more specific characterization of everyday behavior difficulties associated with TS compared with children with ADHD-C, ADHD-I or high functioing ASD. A more accurate characterization of executive behavior difficulties faced by a child or adolescent with TS provides a better basis on which to design a tailored treatment program aimed at alleviating the most pressing and disturbing behavioral difficulties for the child and his or her family.

In the third study, the high self-report of symptoms of anxiety and depression in the children with TS indicates that this should be an important area of focus in treating these children. The finding that after two years of treatment-as-usual, the level of anxiety and depression symptoms is still significantly higher than the TDC may indicate that not enough attention is put to alleviating these subjective symptoms in children with TS. Interestingly, the authors in the Carter study (2000) described earlier found that the internalizing symptoms in the children with TS were primarily related to family functioning. Taken together, the findings from our study and the Carter study indicate the need to assess and treat emotional symptoms (e.g. anxiety and depression symptoms) in children and adolescents with TS regardless of ADHD comorbidity, and that treatment may need to be targeted to improve either internal states in the child with TS, the child's family environment or both.

In addition, the finding in the third study that more efficient control over core cognitive processes did not result in fewer symptoms of anxiety or depression or more control over emotional behavior is important. Instead, we found that the emergence of a more cautious response style in the more emotionally salient decision-making task was related to more control over emotional behavior, which suggests an alternative path for treating these disabling problems in children and adolescents with TS than emphasizing core EF. There is emerging evidence for talking therapies in the treatment of tic disorders having valued outcomes (H. Smith, Fox, Hedderly, Murphy, & Trayner, 2015), and a focus on therapies applying a more generalized approach may have more potential to alleviate the emotional and behavioral difficulties that children with TS face than efforts to enhance neurocognitive functioning.

Another clinically relevant issue is whether there is a close relationship between improvements in EF abilities and a reduction in levels of anxiety or depression symptoms from a therapeutic perspective. A close association might provide evidence to suggest the possibility of training EF functions to address the emotional distress frequently associated with TS. Cognitive-Behavioral Therapy (CBT) is a therapeutic approach in which a patient learns to self-regulate unpleasant emotions, which is essential for mental health (Beauregard, 2007). The ability to regulate one's emotions has been argued to be one of the keys to a

healthy and productive life (Silvers, Buhle, & Ochsner, 2013). CBT targets higher-order executive cognitive functions involving the orbitofrontal cortex (OFC), the medial prefrontal cortex (mPFC), and the ventral and dorsal anterior cingulated cortex (ACC) (Ochsner & Gross, 2007). From a neurobiological perspective, the top-down regulation trained in therapeutic approaches such as CBT leads to reduced emotional response and regulation of negative emotional states (Jokic-Begic, 2010). Frontal areas such as the OFC, mPFC and ACC are all implicated in the top-down processing of emotion (Ochsner et al., 2004; Taylor, Phan, Decker, & Liberzon, 2003; Wright et al., 2008). A review of neurobiology studies of psychotherapeutic changes concluded that CBT leads to reduced fronto-striato-thalamic-activity in anxiety disorder and also possibly, but less certain, for depression (Linden, 2006). Importantly, the fronto-striato-thalamic circuit is the same feedback loop implicated in tic production. Habit Reversal Training (HRT) and Exposure with Response Prevention (ERP) are both recommended as first line behavioral treatments for tics for children in the European Clincal Guidelines for TS (Verdellen et al., 2011), and studies have shown HRT to be as effective in reducing tics as antipsychotic medication, and with long-lasting benefits (Piacentini et al., 2010). If this type of top-down therapy is effective in treating tics which are generated by the same frontal systems as those involved in regulating emotional distress, then the same principles underlying this treatment approach may also be effective in treating the anxiety and depression symptoms reported by children with TS. There is considerable uncertainty with regard to the underlying mechanisms affecting cognitive, emotional and behavior change in young persons with TS, and future research should attempt to disentangle the complex web of processes contributing to positive change and development in these youth.

5.4 Strengths and limitations of study

There are several limitations to this study, all of which have been discussed in the individual papers. Briefly, they include a rather small group of children with TS (19 subjects), a large age span in the groups compared in the study (9-16 years at T1), and the uneven gender distribution (a ratio of 5:1 boys to girls in the TS group).

Although the group of children with TS was rather small, a strength is that the group was recruited from a clinical population with a representative rate of co-occurring conditions (Robertson et al., 2009). The assessment of everyday executive functions with BRIEF and the use of scale classifications (Paper II) provided a more nuanced picture of executive behavior problems in children and adolescents with TS compared with other neurodevelopmental

disorders and the TDC. Additional strengths are the use of both parent ratings (Paper II) and self-report (Paper III). Finally the inclusion of participants never medicated with stimulants prior to assessment at T1 constitutes a major strength of the studies. As stimulant medication may have a beneficial effect on neurocognition, our test results from stimulant-naïve subjects represent a valid picture of performance on core psychometric tasks in children and adolescents with TS. Likewise, all of the TS participants, except one, were tested in a drug free status at T2. A limitation of testing the children without medication at T2, however, is that the descriptions of emotional and behavioral problems are for a period of time when some of the children have been on medication, which could potentially have influenced the correlations with the core psychometric tasks.

5.5 Future research

Factors favorably influencing the maturation of decision-making processes should be an important focus of future TS research aimed at developing more efficient treatment approaches. The approach of using strategic scale classifications to differentiate clinical groups represents a promising first step for the more discriminate use of rating scales in identifying disabling everyday executive behavior difficulties in a child suffering from TS and possibly other co-occurring conditions. An important future area of research is also whether compensatory mechanisms due to the constant suppression of tics is affecting the developmental process and in what way. Future studies should attempt to disentangle the influence of age and other factors by narrowing the age groups investigated, ensuring better control over factors potentially influencing maturational development and including larger groups. There is also a need for longitudinal studies following development over more than a few years. One idea for an upcoming article in our project is to investigate predictors of tic remission in children diagnosed with TS, as 42% of the children with TS in our study no longer fulfilled criteria for a TS diagnosis after two years.

6. CONCLUSION

The interaction of genetic, environmental and emerging factors arising from the combination of many sources of influence in disease expression in TS reflects the complexity of the disorder, which has become a model for understanding developmental psychopathology in a broad sense (Leckman et al., 2006). The overall aim of our study was to gain insight into aspects of executive control in youth with TS, which might provide clues to help better understand and treat these youth. First, we found that children with TS develop similarly to

TDC on a range of psychometric tasks (working memory, inhibition, mental flexibility, decision-making). Despite a similar developmental EF profile compared with TDC, however, the children with TS reported significantly higher levels of anxiety and depression symptoms. The level remained significantly higher in the children with TS compared with the TDC after two years. Emotional behavior is a particular problem in the everyday lives of children with TS, but we found that they struggle with a range of other executive behavior problems in their daily lives as well. When facing choices involving uncertain outcomes on a decision-making task involving higher emotional salience than in the cold EF tasks, the children with TS were less flexible and preferred the more cautious choice than the TDC. Based on earlier research, this tendency could be understood as a behavioral pattern developed as a result of constantly inhibiting tics. Understanding the interplay among cognitive, emotional and behavioral factors influencing development in children with TS is important when treating children with TS and should be a focus of future research.

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