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## Eye Movement Measures of Cognitive Control in Children with Tourette Syndrome

Cameron B. Jeter

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EYE MOVEMENT MEASURES OF COGNITIVE CONTROL  
IN CHILDREN WITH TOURETTE SYNDROME

by

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EYE MOVEMENT MEASURES OF COGNITIVE CONTROL  
IN CHILDREN WITH TOURETTE SYNDROME

A  
DISSERTATION

Presented to the Faculty of  
The University of Texas  
Health Science Center at Houston  
and  
The University of Texas  
M. D. Anderson Cancer Center  
Graduate School of Biomedical Sciences  
in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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Houston, Texas

May, 2010

You are the Sovereign

Holy One, LORD

Worshipped, Magnified

Honored, Adored.

Intercessor, Advocate

Counselor, Friend

Faithful Emmanuel

On whom I depend.

“Whatever you do, work at it with all your heart,  
as working for the Lord, not for men.”

Colossians 3:23

“Commit your works to the LORD,  
and your thoughts will be established.”

Proverbs 16:3

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# EYE MOVEMENT MEASURES OF COGNITIVE CONTROL IN CHILDREN WITH TOURETTE SYNDROME

Publication No. \_\_\_\_\_

Cameron Beth Jeter, Ph.D.

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Tourette Syndrome begins in childhood and is characterized by uncontrollable repetitive actions like neck craning or hopping and noises such as sniffing or chirping. Worst in early adolescence, these tics wax and wane in severity and occur in bouts unpredictably, often drawing unwanted attention from bystanders. Making matters worse, over half of children with Tourette Syndrome also suffer from comorbid, or concurrent, disorders such as attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). These disorders introduce anxious thoughts, impulsivity, inattention, and mood variability that further disrupt children with Tourette Syndrome from focusing and performing well at school and home. Thus, deficits in the cognitive control functions of response inhibition, response generation, and working memory have long been ascribed to Tourette Syndrome. Yet, without considering the effect of medication, age, and comorbidity, this is a premature attribution. This study used an infrared eye tracking camera and various computer tasks requiring eye movement responses to evaluate response inhibition, response generation, and working memory in Tourette Syndrome. This study, the first to control for medication, age, and comorbidity, enrolled 39 unmedicated children with Tourette Syndrome and 29 typically developing peers aged 10-16 years who completed reflexive and voluntary eye movement tasks and diagnostic rating scales to assess symptom severities of Tourette Syndrome, ADHD, and OCD. Children with Tourette Syndrome and comorbid ADHD and/or OCD, but not children with Tourette Syndrome only, took longer to respond and made more errors and distracted eye movements compared to typically-developing children, displaying cognitive control deficits. However, increasing symptom severities of Tourette Syndrome, ADHD, and OCD correlated with one another. Thus, cognitive control deficits were not specific to Tourette Syndrome patients with comorbid conditions, but rather increase with increasing tic severity, suggesting that a majority of Tourette Syndrome patients, regardless of a clinical diagnosis of ADHD and/or OCD, have symptoms of cognitive control deficits at some level. Therefore, clinicians should evaluate and counsel all families of children with Tourette Syndrome, with or without currently diagnosed ADHD and/or OCD, about the functional ramifications of comorbid symptoms and that they may wax and wane with tic severity.

## Table of Contents

<b>CHAPTER 1</b>	<b>1</b>
INTRODUCTION	1
<i>Diagnosis and Prevalence</i>	2
<i>Natural History</i>	5
<i>Comorbidities</i>	6
<i>Etiology and Genetics</i>	9
<i>Pathophysiology</i>	10
<b>CHAPTER 2</b>	<b>18</b>
ORIENTING IN TS	18
<i>Eye Movements</i>	19
<i>Value of Saccade Research</i>	21
<i>Model of Orienting in TS</i>	23
<i>Previous Eye Movement Studies in TS</i>	24
<i>Current Study</i>	30
<i>Research Plan Part 1: Classic Oculomotor Tasks</i>	31
<i>Research Plan Part 2: Novel Spatial N-back Tasks</i>	32
<i>Research Plan Part 3: Factor Analysis</i>	35
<b>CHAPTER 3</b>	<b>36</b>
METHODS	36
<i>Study Participants</i>	37
<i>Diagnostic Measures</i>	38
<i>General Procedure</i>	39
<i>Eye Movement Tasks</i>	40
<i>Behavioral Testing Procedure</i>	50
<i>Data Analysis</i>	53
<b>CHAPTER 4</b>	<b>54</b>
RESULTS	54
<i>Control and Tourette Syndrome Participants</i>	55
<i>Control and Tourette Syndrome Participants Divided by Comorbid Status</i>	60
<i>Part 1: Classic Oculomotor Tasks – Prosaccade and Antisaccade</i>	63
<i>Part 2: Novel Spatial N-back Tasks – 0-back and 1-back</i>	68
<i>Part 3: Factor Analysis – Eye Movement Variables and Rating Scale Totals/Subscales</i>	75

<b>CHAPTER 5</b>	<b>83</b>
DISCUSSION	83
<i>Collective Results</i>	84
<i>ADHD and OCD in TS: Additional or Integral?</i>	86
<i>TS-only Patients: Tics, but No Cognitive Control Impairments?</i>	88
<i>TS-comorbid Patients: What Pathology Causes Cognitive Control Deficits?</i>	90
<i>Updated Model of Orienting in TS</i>	92
<i>Alternative Model</i>	95
<i>Future Directions</i>	96
<i>Implications for Changed Clinical Care</i>	97
<b>APPENDIX A</b>	<b>99</b>
DIAGNOSTIC RATING SCALES	99
<b>APPENDIX B</b>	<b>109</b>
SAMPLE DATA FILES	109
<b>BIBLIOGRAPHY</b>	<b>114</b>
<b>VITA</b>	<b>136</b>

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## List of Illustrations

<b>Figure 1.1</b> Course of Tourette Syndrome .....	8
<b>Figure 1.2</b> Basal ganglia circuitry .....	12
<b>Figure 1.3</b> Circuitry of the basal ganglia-thalamocortical loops .....	14
<b>Figure 1.4</b> Anatomy of the basal ganglia-thalamocortical loops .....	15
<b>Figure 2.1</b> Model of reflexive and voluntary orienting .....	20
<b>Figure 2.2</b> Model of hypothesized effect of TS on orienting .....	25
<b>Figure 2.3</b> Model of hypothesized effects of comorbidities and TS on orienting .....	33
<b>Figure 3.1</b> Prosaccade task .....	41
<b>Figure 3.2</b> Antisaccade task .....	44
<b>Figure 3.3</b> 0-back task .....	46
<b>Figure 3.4</b> 1-back task .....	49
<b>Figure 3.5</b> Eye tracking set-up .....	51
<b>Figure 4.1</b> TS and Control ADHD and OCD symptom severity .....	57
<b>Figure 4.2</b> TS and Control ADHD and tic symptom severity .....	58
<b>Figure 4.3</b> TS and Control OCD and tic symptom severity .....	59
<b>Figure 4.4</b> Voluntary eye movement performance across age .....	62
<b>Figure 4.5</b> Prosaccade task response time and error rate .....	64
<b>Figure 4.6</b> Antisaccade task response time and error rate .....	66
<b>Figure 4.7</b> Antisaccade task error rate for TS-only patients with lower and higher tic severity .....	67
<b>Figure 4.8</b> 0-back task response time and error rate .....	69
<b>Figure 4.9</b> 1-back task response time and error rate .....	71
<b>Figure 4.10</b> Working Memory Load response time and error rate difference .....	72
<b>Figure 4.11</b> 0-back and 1-back task disinhibitions .....	74
<b>Figure 4.12</b> TS and Control Tic Severity and ADHD/OCD Factors .....	80
<b>Figure 5.1</b> Updated model of orienting in Tourette Syndrome .....	93
<b>Figure 5.2</b> Updated model of orienting in Tourette Syndrome patients with comorbidities .....	94

## List of Tables

<b>Table 1.1</b> Examples of simple and complex motor and vocal tics .....	4
<b>Table 1.2</b> Spectrum of severity of tics .....	7
<b>Table 2.1</b> Confounding factors and results of past eye movement studies in TS (I).....	27
<b>Table 2.2</b> Confounding factors and results of past eye movement studies in TS (II).....	28
<b>Table 4.1</b> TS and Control demographics and diagnostic rating scale scores .....	56
<b>Table 4.2</b> TS subtype and Control demographics and diagnostic rating scale scores .....	61
<b>Table 4.3</b> Factor analysis of eye movement variables .....	76
<b>Table 4.4</b> Correlations of eye movement factors with diagnostic rating scales .....	77
<b>Table 4.5</b> Factor analysis of diagnostic rating scale totals and subscales.....	79
<b>Table 4.6</b> Correlations of eye movement factors with diagnostic rating scale factors .....	81

## Abbreviations

1° Motor	Primary motor cortex
ACC	Anterior cingulate cortex
AChE	Acetylcholinesterase
ADHD	Attention Deficit Hyperactivity Disorder
D <sub>1</sub>	Dopamine type 1 receptor
D <sub>2</sub>	Dopamine type 2 receptor
DBS	Deep brain stimulation
DLPFC	Dorsolateral prefrontal cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – Fourth edition
EEG	Electroencephalogram
EMG	Electromyogram
ER	Error rate
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
GABA	Gamma aminobutyric acid
GP <sub>e</sub>	Globus pallidus externa
GP <sub>i</sub>	Globus pallidus internus
LOFC	Lateral orbitofrontal cortex
MRI	Magnetic resonance imaging
N/A	Not applicable
OCD	Obsessive Compulsive Disorder
OFC	Orbitofrontal cortex
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection
RT	Response time
SC	Superior colliculus
SD	Standard deviation
SN <sub>pc</sub>	Substantia nigra pars compacta
SN <sub>pr</sub>	Substantia nigra pars reticulata
STN	Subthalamic nucleus
TMS	Transcranial magnetic stimulation
TS	Tourette Syndrome
y	years

Chapter 1

# Introduction

---

In 1885, Georges Gilles de la Tourette first described nine patients with compulsive tics (Gilles de la Tourette, 1885). Gilles de la Tourette's mentor and the father of modern neurology, Jean-Martin Charcot, chose the eponym Gilles de la Tourette illness, now more commonly known as Tourette Syndrome (TS). While widely documented in the late 1800's, TS was not often detailed again until Arthur Shapiro and others published a monograph in the late twentieth century (Shapiro et al., 1978).

## **Diagnosis and Prevalence**

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Tics are brief, repetitive, stereotyped (i.e., unoriginal, patterned) movements or noises. Intriguingly, tics often appear as segments of familiar motor movements or phonic sounds yet are improper for the situation. Physicians classify tics by their anatomical location, number, frequency, duration, intensity (i.e., exaggerated nature or volume), and complexity (i.e., extent of muscles involved or sounds versus syllables or words produced; Leckman et al., 2006a).

Parents often overlook simple motor and occasional vocal tics. Children suppress or hide tics in the doctor's office, leading many general practitioners to miss tics or mistake those observed as symptoms of allergies or "nervousness," resulting in referrals to ophthalmologists, allergists, or psychologists. This only delays proper diagnosis and treatment, amplifying family distress (Bruun and Budman, 2005; Zinner, 2006).

Further complicating definitive diagnosis, no clinical examination or laboratory test (e.g., blood test or neuroimaging result) exists. Thus, a trained neurologist must base diagnosis on family history, clinical interview, and brief observation. For diagnosis, neurologists widely use the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) from the American Psychiatric Association. Thus, TS is differentiated from transient tic and chronic tic disorders when multiple motor and one or more vocal tics have been present for over a year, with no more than three tic-free consecutive months. Onset must be before the age of 18 and cannot be the result of drugs or other medical condition (APA, 2000).

Although tics occur in up to a quarter of all kids at sometime during childhood (Kurlan et al., 2002; Snider et al., 2002; Robertson, 2003; Khalifa and von Knorring, 2003), only about 1% of children meet diagnostic criteria for TS (Comings and Comings, 1990; Robertson, 2008). Once thought rare, TS may in fact be under diagnosed because of inconsistent diagnostic criteria and a decrease of perceived distress and impairment in some cultures leading to fewer clinic visits (Robertson, 2003). Whether TS is increasing in prevalence, however, is uncertain. There is undoubtedly increased public awareness of TS, but current studies cannot confirm an

actual increase in TS (Robertson et al., 2009). Found four times as often in boys than girls (Freeman et al., 2000), TS affects most all cultures equally, emphasizing the biological, rather than psychiatric, foundation of the disorder (Robertson et al., 2009).

Motor tics are classified as simple or complex. A simple motor tic is a brief, sudden, purposeless movement, typically involving a single muscle. Simple motor tics usually occur in runs, though not always at the same anatomical site. The most common simple motor tics include forceful eye blinking, mouth movements, nostril flares, and shoulder shrugs. An extended, but in no way exhaustive, list appears in **Table 1.1**. Younger patients are often oblivious to their simple motor tics.

As patients mature, simple motor tics are joined by complex motor tics, which are sudden, coordinated, and seemingly purposeful sequential movements of multiple muscle groups over a longer duration. Examples are endless and include head jerks to toss the hair, neck craning followed by a shoulder shrug, and walking interjected with choreographed hops. Patients are often very aware of their complex motor tics, which with increased frequency and intensity often lead to physical pain and fatigue. Further, complex motor tics can be emotionally painful, drawing unwanted stares from bystanders, opening the door for loneliness and low self-esteem. In response, patients will camouflage tics to make them appear purposeful (e.g., arm jerk ending in smoothing the hair). Consequently, a frequent lip-pursing tic may be less impairing than an infrequent obscene gesture.

Moving air through the nose, mouth, or throat produces vocal tics, also called phonic tics (Fahn, 2005). This leads to a nearly endless range of possible vocal tics, some captured in **Table 1.1**. As with motor tics, vocal tics are categorized as simple or complex. A single sound, such as a snort, tongue click, or bird chirp qualifies as a simple vocal tic. These sudden, meaningless noises occur in bouts of repeated succession. Complex vocal tics are comprised of syllables, words, phrases, or variations in speech patterns, such as stuttering or repeating oneself (palilalia) or another (echolalia). Contrary to media portrayal of TS, only around 10% of patients have coprolalia – obscene and socially inappropriate remarks (Goldenberg et al., 1994; Freeman et al., 2000).

One intriguing aspect of tics is their suggestibility. This feature is discernable in multiple settings. During clinical observation and, more specifically, during a structured, systematic interview of current and past symptoms, mentioned tics may appear immediately (often unbeknownst to the child), even if the tic had been absent for months (Leckman et al., 2006b). Suggestibility extends beyond an individual's personal repertoire of tics. Astonishingly, patients in the waiting room of a TS specialty clinic would mimic the tics witnessed in other waiting,

**Table 1.1** Examples of simple and complex motor and vocal tics

<b>Tic Symptom Dimensions</b>	<b>Examples</b>
Simple motor tics: <i>Sudden, brief, meaningless movements</i>	Eye blinking, eye movements, grimacing, nose twitching, mouth movements, lip pouting, head jerks, shoulder shrugs, abdominal tensing, kicks, finger movements, jaw snaps, rapid jerking of any part of the body
Complex motor tics: <i>Slower, longer, more “purposeful” movements</i>	Sustained “looks,” facial gestures, biting, touching objects or self, thrusting arms, throwing, banging, gestures with hands, gyrating and bending, dystonic postures, copropraxia (obscene gestures)
Simple phonic tics: <i>Sudden, meaningless sounds or noises</i>	Throat clearing, coughing, sniffing, spitting, screeching, barking, grunting, gurgling, clacking, hissing, sucking, animal noises, and innumerable other sounds
Complex phonic tics: <i>Sudden, more “meaningful” utterances</i>	Syllables, words, phrases, statements such as “shut up,” “stop that,” “oh, okay,” “I’ve got to,” “honey,” “what makes me do this?” “how about it,” or “now you’ve seen it,” speech atypicalities (usually rhythms, tone, accents, intensity of speech); echo phenomenon (immediate repetition of one’s own [palilalia] or another’s words or phrases [echolalia]); and coprolalia (obscene, inappropriate, and aggressive words and statements)

From Leckman LF, King RA, Cohen DJ. Tics and tic disorders. In: Leckman JF, Cohen DJ with Colleagues from the Yale Child Study Center. *Tourette’s Syndrome – Tics, Obsessions, Compulsions: Developmental Psychopathology and Clinical Care*. New York: John Wiley and Sons; 1998:23-42. Reprinted with permission.

ticcing patients (Ian J. Butler, personal communication). This latter example of suggestibility demonstrates tic response to external, and often unconscious, stimuli (e.g., scratchy shirt tag).

Many children with TS report an urge preceding a tic (Banaschewski et al., 2003). Like an itch before a scratch, this premonitory urge only becomes harder to ignore the longer the tic is resisted. Once the tic is released, children experience fleeting relief until the urge inevitably returns. Indeed, a tic's irresistibility has been cited as its most prominent feature, "The strain in holding back is as great as the relief in letting go" (Wilson, 1940). Of note, it is detection of the urge (often not recognized until preteen years) that alerts kids to attempt to suppress, or hold in, a forthcoming tic. Unfortunately, of the tics TS patients can only hold in, restraint is only temporary (few minutes to an hour; Banaschewski et al., 2003). Despite tics long being classified as entirely involuntary and reflexive (Meige and Feindel, 1907), this ability to suppress tics, albeit momentarily, indicates some voluntary or willful control. Hence, Lang proposed the involuntary label of tics be reevaluated (Lang, 1991). In response, Fahn has offered the term *unvoluntary*, as tics are seemingly a voluntary response to an involuntary sensation (Fahn, 2005).

## Natural History

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Tourette Syndrome has an interesting natural history, or classical pattern of development. Motor tics appear first, around the age of five to seven (Freeman et al., 2000; Leckman et al., 2006a; Zinner, 2006), joined by vocal tics on average two years later, somewhere between 8-15 years of age (Peterson, 1996; Leckman et al., 2006a). Tics progress in a rostral-caudal manner, first affecting the face and head (e.g., eye blinking, head bobbing, and neck craning), then the torso (e.g., abdominal flexing and shoulder shrugging), and finally the limbs (e.g., finger tapping and knee bouncing; Singer and Walkup, 1991; Bruun and Budman, 2005). Furthermore, tics begin as simple and meaningless, involving usually only one muscle group. As the child enters the preteen years, new tics take on a complex nature involving a combination of muscles and sounds that appear almost purposeful. For example, a child with Tourette Syndrome often begins with simple, forceful eye blinks and eye rolls, which later disappear or are joined by a complex tic, such as the combination of a shoulder roll accompanied by a neck crane. As one can imagine, motor and particularly vocal tics draw unwanted attention from bystanders and classmates leading to social stigma, complicating the daily life of a child with Tourette Syndrome.

As implied above, tics change in identity over time and individual tics also change in frequency and severity. Unfortunately, this fluctuation is largely unpredictable. Features of tics



contributing to overall severity are displayed in **Table 1.2**. A given tic may appear for a few weeks or may persist for years. During the presence of one tic, other tics will surface (Bruun and Budman, 2005). Thus, tics naturally wax and wane throughout childhood and adolescence, peaking around age twelve, regrettably at the same time as the natural self-doubts of the teen years. In addition to their long-term variability, tics are further exacerbated by anxiety, stress, and excitement (Findley et al., 2003; Leckman et al., 2006a). This makes a new school year, a timed test, and, ironically, a family vacation to Disney World, prime causes of tic intensification. For unknown reasons, tics mysteriously and overwhelmingly resolve in adulthood (Leckman et al., 1998). By age 18, over 90% of children with TS will experience near resolution of tic symptoms (Goetz et al., 1992; Bloch et al., 2006). **Figure 1.1** illustrates the variable, tiered course of TS into adulthood. While the future extent of TS symptom severity and complexity is unpredictable at diagnosis, one study found caudate brain volume in childhood inversely correlated with tic severity in adulthood (Bloch et al., 2005).

## **Comorbidities**

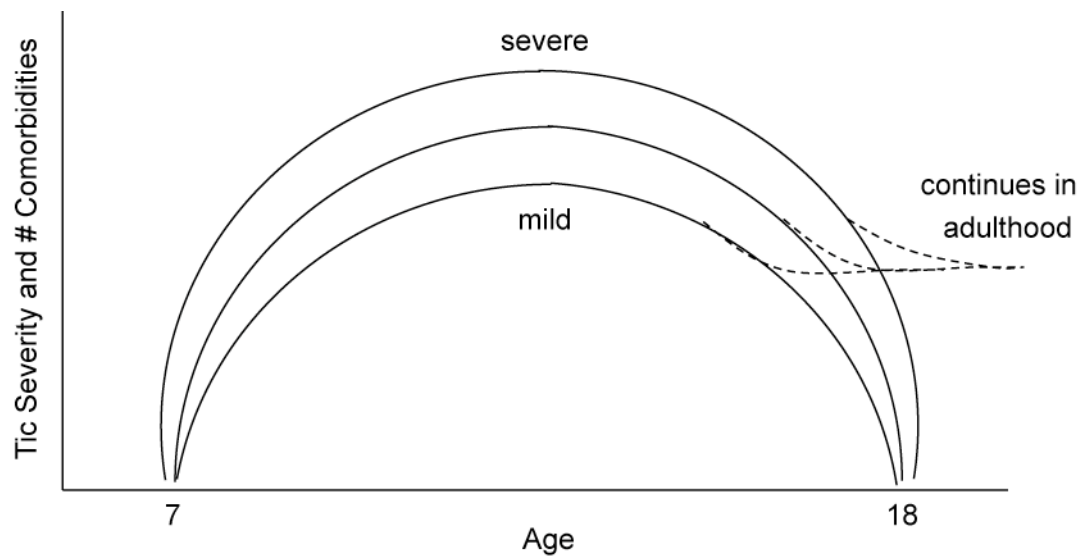
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To make matters worse, many children with Tourette Syndrome also have concurrent, or comorbid, conditions. In fact, one report found only 40% of TS patients do not have a comorbidity (Denckla, 2006). Attention deficit hyperactivity disorder (ADHD) occurs in over 50% of children with TS (Comings and Comings, 1985). As the name denotes, ADHD results in developmental inappropriate hyperactivity, inattention, and impulsivity that may persist into adulthood. As a chief source of dysfunction, ADHD is a major clinical concern (Spencer et al., 2001) and often disrupts social and academic capacity more than tics do (Mostofsky et al., 2001). Another comorbidity, obsessive compulsive disorder (OCD) occurs in about 30% of children with TS (Comings and Comings, 1985). OCD introduces distressing, intrusive, and unwanted thoughts and fears (e.g., worry of an intruder), resulting in ritualized actions or thoughts done to relieve anxiety or distress (e.g., repeatedly checking a locked door). Other less common comorbidities include learning difficulties (e.g., dyslexia), anxiety disorders (e.g., social anxiety), affective disorders (e.g., depression or mania), pervasive developmental disorders (e.g., Asperger's syndrome), and aggressive behavior. Comorbid disorders may develop at any time, but are most likely and numerous in early adolescence, mimicking the progression of tic severity. These comorbidities introduce confusing heterogeneity into the syndrome phenotype and further disable children with TS from focusing and performing well at school and home.

**Table 1.2** Spectrum of severity of tics

<b>Feature</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
Duration	Acute, brief	Intermediate length	Tics status
Motor tics	Simple	Complex	Copropaxia, echopaxia, self-mutilation
Vocal tics	None	Poorly audible noises	Loud noises, coprolalia
Variety of tics	Few	Multiple	Many
Suppressible	Easily	With concentrated volition	No
Interference with life's activities	No disruption	Mildly disruptible	Highly disruptible

From Fahn S. The clinical spectrum of motor tics. In: Friedhoff AJ and Chase TN. *Gilles de la Tourette Syndrome*. Advances in Neurology. Philadelphia: Lippincott Williams & Wilkins; 1982; 35:341-344. Reprinted with permission.



**Figure 1.1** Course of Tourette Syndrome

At diagnosis around age 7, it is unknown whether a given child with Tourette Syndrome will follow a mild or severe trajectory of symptoms. Tic severity and comorbidities (concurrent disorders) increase throughout adolescence but overwhelmingly resolve by age 18 in about 90% of patients. Figure adapted from Ian J. Butler, M.D.

TS is closely intertwined with ADHD and OCD. Symptoms of ADHD often appear between 3-5 years of age, before tic onset at age 6, and are followed by OCD symptoms up to a few years later (Bloch et al., 2005). While Pauls and colleagues proposed there are two types of ADHD, one independent of and another implanted in TS, Towbin and Riddle suggest all TS patients have some degree of ADHD symptomatology – subthreshold in some patients and above threshold for ADHD diagnosis in others (Robertson, 2000). The intimate relationship between TS and OCD is confirmed by historical (e.g., Meige and Feindel, 1907), epidemiological (e.g., Comings and Comings, 1985), phenomenological (e.g., Pitman et al., 1987), genetic (e.g., Pauls et al., 1986a), and neuroanatomical evidence (e.g., Rauch et al., 2001). Specifically, whereas OCD occurs in only 1-3% of the general population, OCD in TS patients is much more prevalent. Also, the symptoms of both TS and OCD patients wax and wane and include compulsive tics like touching, counting, and “evening-up.” Critically, TS, ADHD, and OCD share the common feature of aberrant inhibition of unwelcome thoughts and behaviors, underscoring the related clinical features and likely analogous neural circuitries of each disorder.

## **Etiology and Genetics**

---

Several cited risk factors of TS include prenatal and perinatal adverse events, psychosocial stressors, and post-infectious immune responses. Much controversy surrounds the last (Kurlan and Kaplan, 2004), which proposes that abnormal response to streptococcal infection may lead to onset or exacerbation of neuropsychiatric disorders (Swedo et al., 1998). One type, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), has a similar phenotype as TS and OCD, and is proposed to develop through a process called molecular mimicry. Antibodies in response to streptococcal antigens cross-react with brain targets (e.g., anti-basal ganglia antibodies, Rizzo et al., 2006; but see Singer et al., 2005 and Morris et al., 2009) and lead to neuropsychiatric disorders. Only recently did a large case-control study definitively show no strong association between streptococcal infections and neuropsychiatric syndromes (Schrag et al., 2009).

Many family members of TS patients have transient tics (15-20%) or TS (10-15%) at rates significantly higher than in controls (Pauls et al., 1991; Eapen et al., 1993; Walkup et al., 1996; Hebebrand et al., 1997). Even in Gilles de la Tourette’s original description of TS he noted that three of the nine patients had relatives with tics, and attributed TS to hereditary factors. Over a century later, geneticists are still in agreement with Gilles de la Tourette’s limited data, but still have not yet pinpointed a TS gene(s) or inheritance pattern.

Chromosomal rearrangement studies have reported rearrangement (Donnai, 1987; Brett et al., 1996; Devor and Magee, 1999), translocation (Boghossian-Sell et al., 1996; Cuker et al., 2004), de novo duplication (Kroisel et al., 2001), and inversion (Abelson et al., 2005) on various chromosomes, but without clear association with TS. Candidate gene studies, which identify deviations in genes coding for proteins implicated in the disease of interest, have resulted in negative or equivocal results (Pauls, 2001). Genome-wide linkage studies are used in complex disorders to search for rare mutations in affected families, but such large pedigrees are hard to assemble and have not found strong evidence for linkage in TS (Pauls et al., 1990; Pakstis et al., 1991; Walkup et al., 1996). The most successful studies have been in twins. Monozygotic twins (identical genomes) are 50-70% concordant for TS, whereas dizygotic twins (50% genes shared) are only 9% concordant for TS (Price et al., 1985; Hyde et al., 1992). Thus, monozygotic twins have a many-fold times greater risk to both have TS, indicating multiple genes constitute a risk of TS. Furthermore, because the rate of TS in monozygotic twins is not 100%, environmental factors must have considerable contribution to the disease (Keen-Kim and Freimer, 2006).

The strength of conclusions drawn from genetic studies is severely limited by the heterogeneity of TS. Uncertainty in how to best describe the TS phenotype hampers attempts to link genes to a given trait (Keen-Kim and Freimer, 2006). Consequently, a new method, such as the one presented in the current study, is needed to assist categorization of patients with homogenous symptoms before genetic studies begin.

## **Pathophysiology**

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TS was long thought to be purely a psychiatric disorder, and even as late as the 1960s literature discussed the psychological causation of tics. Margaret Mahler posited that tics developed following a three-stage process triggered by overprotective and restrictive parents and solidified by the child's revolt (Mahler, 1949). In truth, TS is firmly neurologically based, and only a few decades ago the dopamine hypothesis was established after the first reports of pharmacologic response to neuroleptics (dopamine antagonists; Bockner, 1959) and tic exacerbation after high dopamine agonist doses. Neurochemical measurements further substantiated the role of dopamine and serotonin, as abnormal levels of these neurotransmitter metabolites were found in the cerebral spinal fluid (Butler et al., 1979), blood (Leckman et al., 1984; Cath et al., 2001), and urine (Bornstein and Baker, 1988) of TS patients.

While the exact pathophysiology of TS is unknown, loci of dopamine and serotonin interaction are prime candidates. Neurochemical, neuroanatomical, and neurophysiological

evidence points to involvement of the basal ganglia (e.g., Peterson et al., 2003; Cheon et al., 2004; Houeto et al., 2005; Kalanithi et al., 2005), frontal cortex (e.g., Peterson et al., 1998; Moll et al., 1999; Stern et al., 2000; Peterson et al., 2001; Frederickson et al., 2002), and distinct neural circuitry interconnecting the two.

The basal ganglia, comprised of several subcortical nuclei, control and program movements, activating the desired action and inhibiting all inappropriate alternatives (**Figure 1.2**, cf., Hallett, 1993; Mink, 1996). The subthalamic nucleus (STN) and striatum (caudate and putamen nuclei) are the input structures to the basal ganglia. Both receive excitatory, glutamatergic projections from the cortex, although the “hyperdirect” pathway to the STN is exclusively from the frontal cortex (Hartmann-von Monakow et al., 1978), whereas all cortical areas project to the striatum (Kemp and Powell, 1970). This cortical input is topographically organized (parallel), yet broad dendritic trees accept input from multiple cortical areas (convergence) and a given cortical area projects to several striatal zones (divergence; Selemon and Goldman-Rakic, 1985). Further, each cortical projection synapses onto a dendritic spine head of medium spiny neurons in the striatum (Bouyer et al., 1984; Cherubini et al., 1988), while the dopamine-containing substantia nigra pars compacta (SN<sub>pc</sub>) phasically projects onto the shaft of the same spine (Carpenter, 1981). This anatomic framework allows the striatum to transform and integrate incoming signals for action selection.

Ultimate basal ganglia output depends on the class of dopamine receptor activated in the striatum. Two classes of dopamine receptors have been described – the D<sub>1</sub> class (D<sub>1</sub> and D<sub>5</sub> receptors) and the D<sub>2</sub> class (D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> receptors; Sibley et al., 1993) – and each class produces an opposite effect. D<sub>1</sub> receptors in the striatum send focused inhibitory GABA projections to the basal ganglia output structures, the globus pallidus internus (GP<sub>i</sub>) and substantia nigra pars reticulata (SN<sub>pr</sub>; Gerfen and Young, 1988; Gerfen et al., 1990). This “direct/go” pathway serves to inhibit the basal ganglia’s tonic inhibitory output, releasing distinct thalamic regions to activate their cortical targets and thus generate discrete desired action(s). In parallel with the “direct/go” pathway, activated striatal D<sub>2</sub> receptors phasically send GABA-ergic inhibitory signals to the globus pallidus externa (GP<sub>e</sub>; Gerfen and Young, 1988; Gerfen et al., 1990), which in turn disinhibits the subthalamic nucleus (STN) through GABA-ergic inhibitory projections (Kita et al., 1983). The STN tonically sends quick, divergent glutamatergic excitation to the GP<sub>i</sub>/SN<sub>pr</sub> (Brochie and Crossman, 1991; Rinvik and Ottersen, 1993). This “indirect/stop” pathway, together with the “hyperdirect” pathway, serves to provide widespread excitation to the basal ganglia’s tonic inhibitory output, further clamping down the thalamus and preventing cortical initiation of diverse, undesired actions. Taken together, the “direct/go” and “indirect/stop”/“hyperdirect” pathways work in delicate “push-pull” concert to

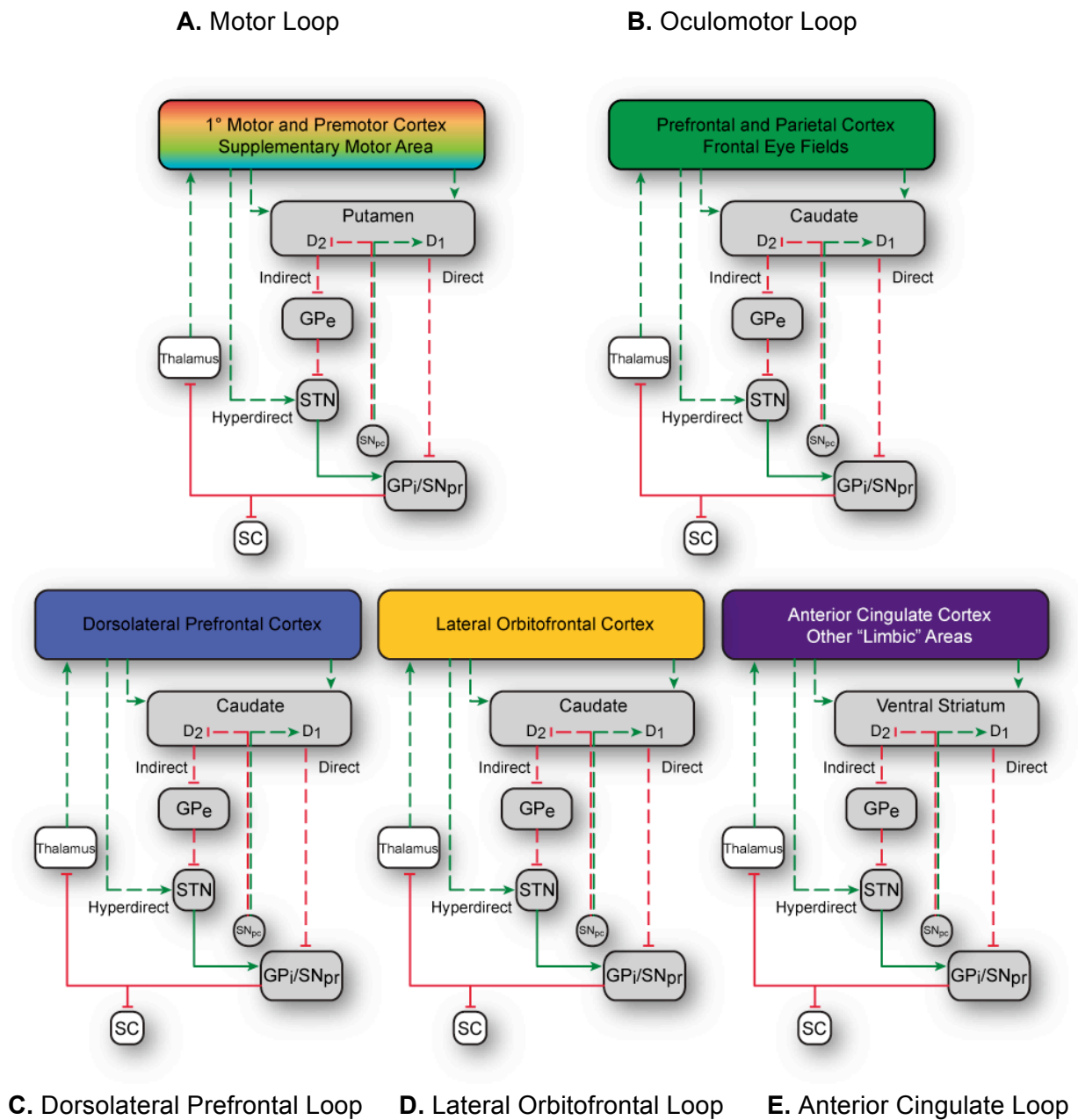


disinhibit (and thereby select) the precise suitable response and maintain inhibition on (and thus prevent) the myriad, undesired alternatives, respectively.

In addition to motor control, the basal ganglia are involved in the control of a variety of functions including cognition, emotions, and learning. The basal ganglia control these functions through five parallel basal ganglia-thalamocortical loops (Alexander et al., 1986). In each loop, discrete areas of the cerebral cortex project to certain basal ganglia nuclei, which send information to specific thalamic nuclei and terminate on originating cerebral structures unique to that loop. The information in each circuit is topographically organized. While the loops are structurally and functionally segregated, the operations processed at each level of one circuit are analogous to that of the others. Hence, an abnormality measured at one level in a basal ganglia-thalamocortical circuit may indicate dysfunction at the same level of other loops (Alexander et al., 1986).

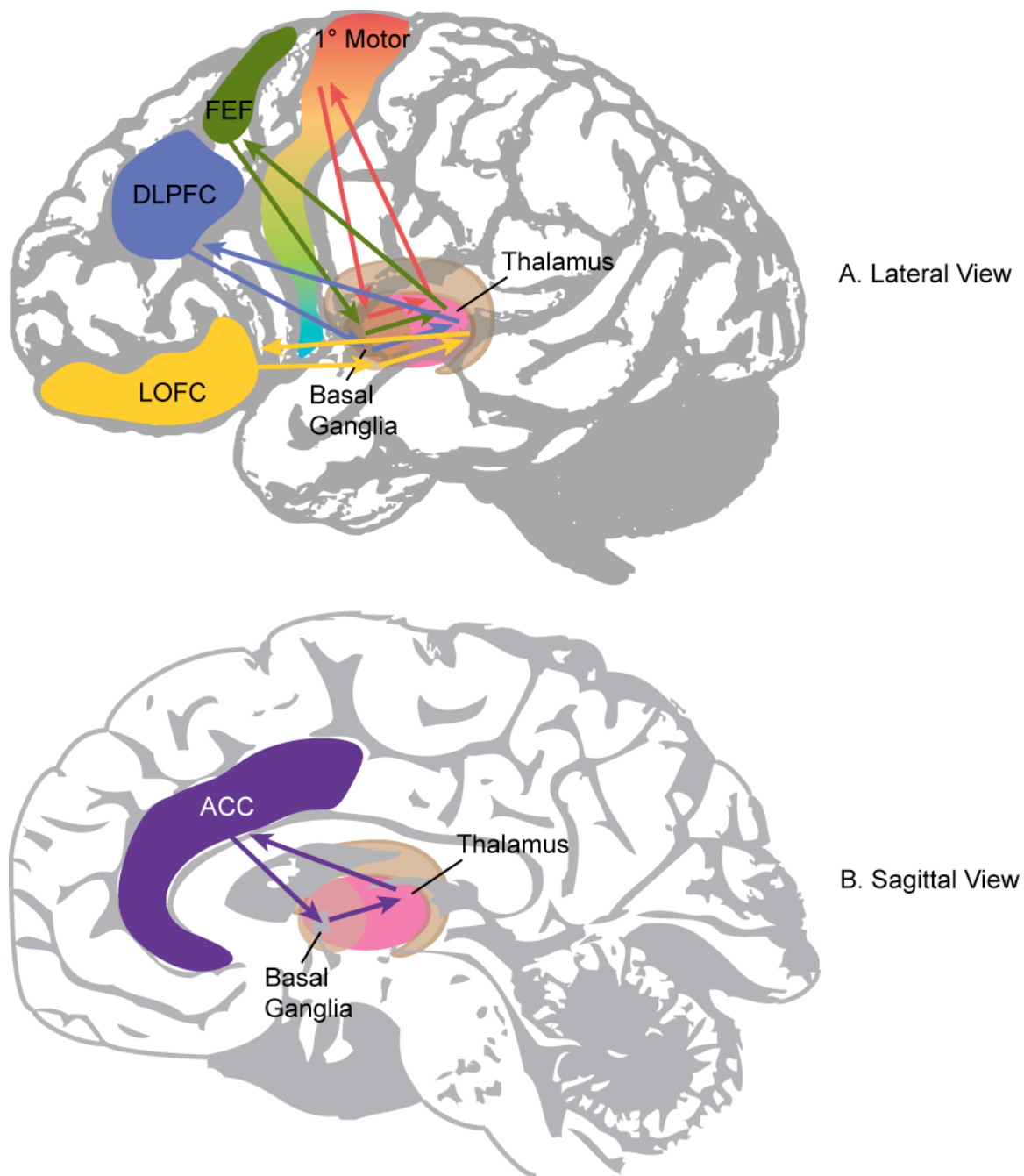
Specifically, the five basal ganglia-thalamocortical loops include the Motor, Oculomotor, Dorsolateral Prefrontal, Lateral Orbitofrontal, and Anterior Cingulate circuits (see **Figure 1.3** and **Figure 1.4**). The Motor Loop, which provides motor control, begins in motor cortices, projects to the putamen, onto ventrolateral pallidal segments and caudolateral SN<sub>pr</sub>, through the ventrolateral thalamic nucleus, and back to motor cortices. The Oculomotor Loop controls externally and internally generated eye movements via frontal cortices, caudate, dorsomedial GP<sub>i</sub> and ventrolateral SN<sub>pr</sub>, and ventral anterior and mediodorsal thalamic nuclei. The Dorsolateral Prefrontal Loop subserves spatial memory, executive function, and attention. It is comprised of dorsolateral prefrontal cortex (DLPFC), dorsolateral caudate, dorsomedial GP<sub>i</sub> and rostromedial SN<sub>pr</sub>, and ventral anterior and mediodorsal thalamic nuclei. The Lateral Orbitofrontal Loop originates in lateral orbitofrontal cortex (LOFC) and includes ventromedial caudate, dorsomedial GP<sub>i</sub> and rostromedial SN<sub>pr</sub>, and ventral anterior and medial dorsal thalamic nuclei. This Loop supplies inhibitory control and flexibility of response, as ablation of LOFC in monkeys results in perseveration and reduced capacity for switching between behavioral sets (Iversen and Mishkin, 1970; Butters et al., 1973). Finally, the Anterior Cingulate Loop, which is responsible for limbic (i.e., emotional and motivational) processes, involves the anterior cingulate cortex (ACC), ventral striatum, rostromedial GP<sub>i</sub> and rostromedial SN<sub>pr</sub>, and mediodorsal thalamic nucleus.





**Figure 1.3** Circuitry of the basal ganglia-thalamocortical loops

Each loop entails distinct subpopulations of cells in cortical, striatal, pallidal, nigral, and thalamic regions. **A.** The Motor Loop includes specific motor cortices and the putamen. **B.** The Oculomotor Loop involves frontal cortices and the caudate. **C.** The Dorsolateral Prefrontal Loop involves the DLPFC and the caudate. **D.** The Lateral Orbitofrontal Loop includes the LOFC and caudate. **E.** The Anterior Cingulate Loop involves the ACC and ventral striatum. Shaded boxes comprise the basal ganglia, green projections are excitatory, red are inhibitory, dotted lines are phasic, solid lines are tonically active. See text for abbreviation details.



**Figure 1.4** Anatomy of the basal ganglia-thalamocortical loops

The five parallel basal ganglia-thalamocortical loops originate and terminate in their own unique cortical areas. Additionally, all loops traverse the same subcortical nuclei, but synapse on distinct subpopulations of cells. **A.** Four loops can be seen on the lateral surface of the brain. The primary (1°) motor cortex is topographically organized (rainbow gradient) and distinct tics correspond to discrete aberrant cells. **B.** One loop is visible only in a sagittal view of the brain. 1° Motor, primary motor cortex; FEF, frontal eye field; DLPFC, dorsolateral prefrontal cortex; LOFC, lateral orbitofrontal cortex; ACC, anterior cingulate cortex

Much evidence supports the dysfunction of the basal ganglia-thalamocortical loops in TS, ADHD, and OCD. Consistent with motor tics originating in the Motor Loop, cortical thinning of sensorimotor areas is reported in TS (Sowell et al., 2008). Emotional disturbances and the occasional obscene nature of gestures and comments (i.e., copropraxia and coprolalia, respectively) in TS give suggestion of Anterior Cingulate Loop involvement as well (Trimble and Robertson, 1987). As the hippocampus projects to the ventral striatum (Krayniak et al., 1981; Kelley and Domesick, 1982), part of the Anterior Cingulate Loop, the involvement of this loop in TS is further supported by reports of an abnormal hippocampus in children with TS (larger volume; Peterson et al., 2007; less gray matter; Ludolph et al., 2006). Cortical thinning (Shaw et al., 2006; Makris et al., 2007) and volumetric abnormalities (Seidman et al., 2006) of DLPFC and ACC have been reported in ADHD, highlighting the involvement of the Dorsolateral Prefrontal and Anterior Cingulate Loops in the disease. Finally, smaller LOFC (Rotge et al., 2009), less activation of LOFC (Chamberlain et al., 2008), and regional cerebral blood flow abnormalities in LOFC and ACC as measured by single photon emission computed tomography (Busatto et al., 2001) implicate the Lateral Orbitofrontal and Anterior Cingulate Loops in the pathophysiology of OCD.

Stated again, the cause of TS is unknown, but likely involves the basal ganglia and frontostriatal circuits. Several anatomic models of TS exist (for review, see Steeves and Fox, 2008), including one based on the above-described modification of Albin and colleagues' classic two-circuit model of the basal ganglia (see **Figure 1.2**; Albin et al., 1989). This early TS model proposed an imbalance between an overactive "direct/go" pathway, which continues to release intended movements, and overactive "indirect/stop" and "hyperdirect" pathways, which fail to inhibit certain involuntary actions (tics). Disparity in other basal ganglia-thalamocortical loops would lead to unwanted thoughts and behaviors. A recent update to the model proposes "centre-surround" activation, stressing the focused inhibition of the "direct/go" pathway, and widespread excitation of the "indirect/stop" and "hyperdirect" pathways on GP<sub>i</sub>/SN<sub>pr</sub> output (Mink, 2001). The "direct/go" pathway serves to create a "centre" of GP<sub>i</sub>/SN<sub>pr</sub> inhibition and consequent excitation of thalamus and cortical motor pattern generators, whereas the "indirect/stop" and "hyperdirect" pathways produce a "surround" of GP<sub>i</sub>/SN<sub>pr</sub> excitation, realized as thalamic inhibition and halt of cortical motor activity. By way of the multiple basal ganglia-thalamocortical circuits, pathologic activity in specific striatal neurons could aberrantly inhibit basal ganglia output topographically, releasing not only distinct, unwanted tics, but also unwelcome thoughts and behaviors. This pathological activation may be isolated to subcompartments of the striatum that in a third model have functional relevance to TS (Canales and Graybiel, 2000). First described by Graybiel and colleagues, striatal regions named

striosomes stain only lightly for acetylcholinesterase (AChE), whereas the surrounding matrix stains heavily for AChE (Holt et al., 1997). Matrix afferents come from many cortical areas and efferents form the “direct/go” and “indirect/stop” pathways to the GP<sub>i</sub>/SN<sub>pr</sub>. Striosomal-based stereotypies observed in stimulant-treated mice lead to the theory that tics may result from metabolic activity imbalance between the matrix and striosome (Mink, 2001; Saka and Graybiel, 2003). In a final model of TS, Leckman and colleagues proposed that asynchronous oscillations of basal ganglia-thalamocortical loops disrupt the tonic inhibitory output of GP<sub>i</sub>, thus repeatedly and momentarily releasing the thalamus to excite cortical areas, producing tics (Leckman et al., 2006c). In support of this, deep brain stimulation (DBS) and lesions of GP<sub>i</sub>, thought to disrupt neural firing, ameliorate tics (Houeto et al., 2005; Zhuang et al., 2009). Intriguingly, single-unit recordings during pallidotomy showed phasic discharge of GP<sub>i</sub> correlating with electromyogram (EMG) recordings of intra-operative tics (Zhuang et al., 2009). The authors proposed GP<sub>i</sub> activity preceding EMG onset up to 2 seconds might represent premonitory urges. In a recent update on basal ganglia models, however, action selection (and therefore improper action release) is proposed to be a function primarily of the cortex, not basal ganglia, as basal ganglia subunits are tightly influenced by their respective cortical inputs (DeLong and Wichmann, 2009). Regardless of the model preferred, a continued search is necessary to clarify the pathophysiology of TS.

TS has baffled and captivated clinicians and researchers for over 125 years. Modern technologies and theories continue to push the field closer to a pathophysiological and etiological consensus. The multifarious dimensions of TS, however, befuddle this effort. Clearer understanding of TS will come after ferreting out the impact comorbidities have on TS phenomenology and pathophysiology.

Chapter 2

# Orienting in TS

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## Eye Movements

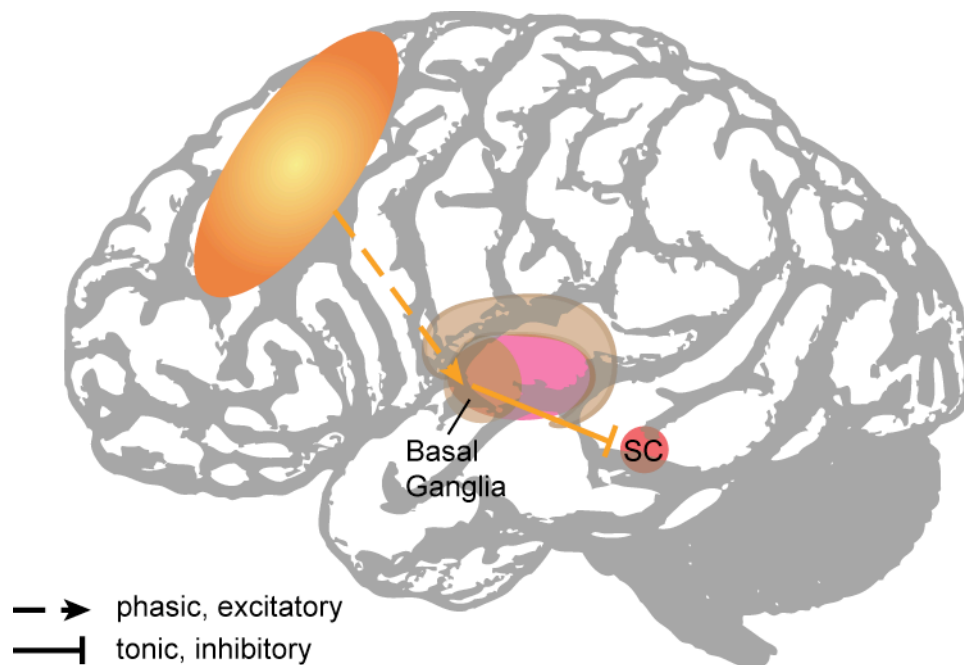
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We make countless eye movements every day, even every minute (three per second!; Rayner, 1998). We execute different classes of eye movements when we read a book, track a buzzing mosquito, or spot out our passenger window the telephone poles whizzing by on a family car trip. These eye movements serve to orient each eye on the same object, effectively centering the object of interest on our fovea, the retinal location of highest acuity. One category of eye movements, saccades, quickly foveate an object or location in space with an abrupt, small, jerky movement. Saccades are further classified as reflexive or voluntary, each controlled by distinct, well-known, and well-studied neurocircuitry.

Reflexive saccades are stimulus driven, as they occur in response to a peripheral stimulus. An instinctive glance to a suddenly appearing light is a reflexive saccade. This type of saccade is generated in a “bottom-up” fashion in that midbrain reflexive control centers detect the external stimulus and automatically orient the eyes to it. Reflexive saccades are driven by the superior colliculus (SC, the midbrain saccade generator) as lesion of it alone results in saccade slowing and a loss of express (fast) saccades (Schiller et al., 1987).

Voluntary saccades are internally driven, dependent on a plan of action informed by prior information. Intentionally looking away from a suddenly appearing light involves a voluntary saccade. This “simple” undertaking demands cognitive control, including inhibition, generation, and working memory. To successfully look away from the light, you must inhibit saccades to the appearing light, generate a saccade to the opposite point in space, and remember what you are trying to accomplish. These components require “top-down” control from the frontal cortex to the SC via the Oculomotor Loop in the basal ganglia (see **Chapter 1**). Explicitly, the dorsolateral prefrontal cortex (DLPFC) inhibits inappropriate reflexive saccades and the frontal eye field (FEF) triggers the generation of planned voluntary saccades (Pierrot-Deseilligny et al., 2004). Further, the “direct/go” pathway releases the SC to produce a saccade and the “indirect/stop” pathway prevents SC execution of an eye movement (refer to **Figure 1.2**; Hikosaka et al., 2000).

The ability to override a reflexive response in preference of a voluntary one is contingent on intact frontal brain regions. Patients with frontal cortex lesions have great difficulty with the antisaccade task in which they must inhibit a reflexive saccade and instead make a voluntary saccade (Guitton et al., 1985). Based on such patient and neurophysiological data, the Tonic Inhibition Model asserts frontal cortical areas, subserving voluntary control, modulate midbrain reflexive control by way of the basal ganglia’s tonic inhibitory output (**Figure 2.1**; Sereno, 1992). Indeed, the basal ganglia perform response



**Figure 2.1** Model of reflexive and voluntary orienting

The Tonic Inhibition Model (Sereno, 1992) maintains that voluntary orienting centers in the frontal lobe (orange oval) activate the basal ganglia to selectively inhibit the midbrain reflexive orienting center. The midbrain is free to automatically respond to external stimuli. For voluntary responses, though, frontal control centers modulate midbrain output by triggering the basal ganglia to select the appropriate response through calculated release of the midbrain from its tonic inhibition. SC, superior colliculus

selection through interconnections with the frontal cortex and brainstem (Hikosaka et al., 2000). Thus, the reflexive control center can respond to external stimuli as needed. To coordinate a voluntary response, however, frontal cortices inhibit brainstem execution of reflexive actions in order to delay the intended response until the appropriate time.

This interplay between reflexive and voluntary systems is evident in everyday examples. When you are walking alone to the parking lot at twilight, a dancing shadow beside some bushes causes you to instinctively jump. In this unnerving situation, your voluntary frontal center only lightly impedes reflexive responses, allowing hypervigilance. Alternatively, when you are rigorously studying in a bustling coffee shop (which, as an aside, I deem counterproductive regardless the strength of your voluntary control), the sea of people and vibrant colors don't even cause you to look up. In this instance, your voluntary center strongly dampens reflexive responding to allow maintained focus.

### **Value of Saccade Research**

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The direct study of saccadic eye movements has great utility. Saccades are a discrete behavioral method with limited output, measureable with extraordinary precision and influenced with slight paradigm and sensory changes (Hutton, 2008). Saccadic eye movements and their neural command have long been studied in non-human primates and lesion patients (Hikosaka and Wurtz, 1983; Bruce and Goldberg, 1985; Guitton et al., 1985; Pierrot-Deseilligny et al., 1991; Everling et al., 1999). Also, cortical neuroanatomy of saccade control has been investigated in healthy adults with intact oculomotor systems by inducing temporary "functional lesions" with transcranial magnetic stimulation (TMS; Muri and Nyffeler, 2008). Consequently, the neural circuitry underlying saccades is intimately known.

Compared to traditional psychological testing, eye movement tests are particularly well suited for evaluating cognitive control and motor processes. First, task instructions are simple and easily understood by all ages. Second, in eye movement tasks, encoding and response processes are in the same modality (visual), whereas in typical tasks translation is required from the stimulus input modality (visual, auditory) to behavior measures (motor, speech), which dilutes the task's ability to directly measure the desired cognitive process. Third, eye movements share brain areas with cognitive control and motor processes (Luna et al., 2004) and different (and experimentally separable) brain areas control reflexive and voluntary saccades. Moreover, saccade tasks have been shown to have greater test-retest reliability than neuropsychological tasks in healthy individuals and patients (Gooding et al., 2004; Hill et



al., 2008) and be more sensitive measures of cognitive control (Broerse et al., 2001) and treatment effects (Hill et al., 2008).

Further, studies of saccades eliminate confounds common to neuropsychological testing. Neurological and psychiatric patient populations (e.g., Parkinson disease and schizophrenia) demonstrate slowing in the initiation and execution of manual responses (e.g., key press) compared with healthy participants (Benson, 1990; Bermanzohn and Siris, 1992; Jogems-Kosterman et al., 2001). Psychomotor slowing is specific to manual response tasks but not eye movement tasks (Gale and Holzman, 2000; Reuter and Kathmann, 2004). Whereas neuropsychological tests tap broad frontal areas, saccade paradigms exploit known, distinct regions. Moreover, saccade tasks do not require additional higher order processing, like for colors, pictures, or words.

Saccade paradigms are particularly effective measures of cognitive control in hard-to-test populations, like patients and children. Eye movement tasks allow careful and easy manipulation of task difficulty and produce robust and sensitive results. Assessment is quick and avoids fatigue common to such participants. Significantly, hypotheses of a disease's neuropathological loci can be appraised by saccade task performance (Farber et al., 1999). Indeed, patients with frontal cortex and basal ganglia neuropathology exhibit saccadic deficits (Guitton et al., 1985; Briand et al., 1999). The utility of saccade tasks in patients and children is demonstrated by successful treatment evaluation (Reilly et al., 2006), prediction of disease outcome (Robert et al., 2009), utility as an endophenotype (Calkins et al., 2008) and biomarker (Blekher et al., 2006), and assessment of cognitive development (Luna et al., 2004). Our lab has extensive experience and success conducting eye movement research in patients and children. We have demonstrated eye movement performance is linked to schizotypy in healthy participants (Larrison et al., 2000), correlates with symptom severity (Briand et al., 2001; Amador et al., 2006; Jeter et al., 2010), evaluates treatment efficacy (Larrison-Faucher et al., 2004; Hood et al., 2007; Babin et al., in preparation 1), differentiates clinically-defined disease subtypes (Jeter et al., 2009), and identifies a cognitively-impaired subtype of schizophrenia (Babin et al., in preparation 2).

In addition to the specific advantages of eye movement studies described above in neurological and psychiatric patient and child populations, saccade tasks are particularly well suited for investigations in TS. As a disease characterized not only by release of situationally unfitting movements and behaviors, but also insufficient generation of pertinent actions, TS dysfunction is synonymous with misdirected cognitive control. Restated, TS patients have a specific lack of response inhibition, response generation, and working memory. These faculties

are also critically employed in voluntary eye movement tasks. Fittingly, common brain areas instruct cognitive control and voluntary eye movements (Luna et al., 2004). Thus, dysfunctional cognitive control, measureable with simple saccade paradigms, can be linked to mutual brain regions. Specifically, the parallel basal ganglia-thalamocortical Motor and Oculomotor Loops underwrite this relationship (see **Chapter 1**), making eye movement experiments useful for understanding how the brain controls movement (Leigh and Zee, 1999). Unlike limb movements, though, eye movements are simple movements not hindered by joints, muscle load restrictions, or large ranges of motion, and so are easily measured. Eye movements are natural, quick, and quantifiable. From decades of non-human primate and lesion patient research, the neural circuitry controlling saccade generation is better understood (Leigh and Zee, 1999). While a few research groups have capitalized on the advantages of oculomotor research in TS, more studies are needed (Rommelse et al., 2008).

Not only are oculomotor tasks poised to effectively evaluate Motor Loop function, but also they are suitable for appraisal of the other three basal ganglia-thalamocortical loops. These parallel loops, namely the Dorsolateral Prefrontal Loop, the Lateral Orbitofrontal Loop, and the Anterior Cingulate Loop, govern spatial working memory and attention, socially appropriate response lability, and mood stability and motivational drive, respectively. Not surprisingly, then, irregularity in these loops leads to ADHD and OCD, the conditions most commonly coexisting with TS. Thus, in conjunction with eye movement investigations of TS cognitive control, saccade tasks can examine the impact of comorbid ADHD and OCD on cognitive control in TS patients. Such an endeavor is imperative to quantify and better understand the specific functional weight TS individuals bear due to comorbid conditions (Gooding and Basso, 2008; Rommelse et al., 2008). Parceling and attributing the impact of comorbid ADHD and OCD will create more homogenous subtypes of TS necessary to advance stymied genetic analyses (Gooding and Basso, 2008).

## **Model of Orienting in TS**

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TS patients are known to have abnormal frontal lobe anatomy and function, perhaps in response to a primary dysfunction of the basal ganglia. As frontal cortices and the basal ganglia are directly involved in the Oculomotor Loop, these disruptions have immediate implications for the control of eye movements. According to the model of reflexive and voluntary orienting in **Figure 2.1**, frontal deficit leads to poor performance on tasks of voluntary orienting. Further, a weak frontal cortex reduces its excitation of the basal ganglia, which, in turn, relents from its tonic inhibitory dominance over the midbrain reflexive control center (SC).

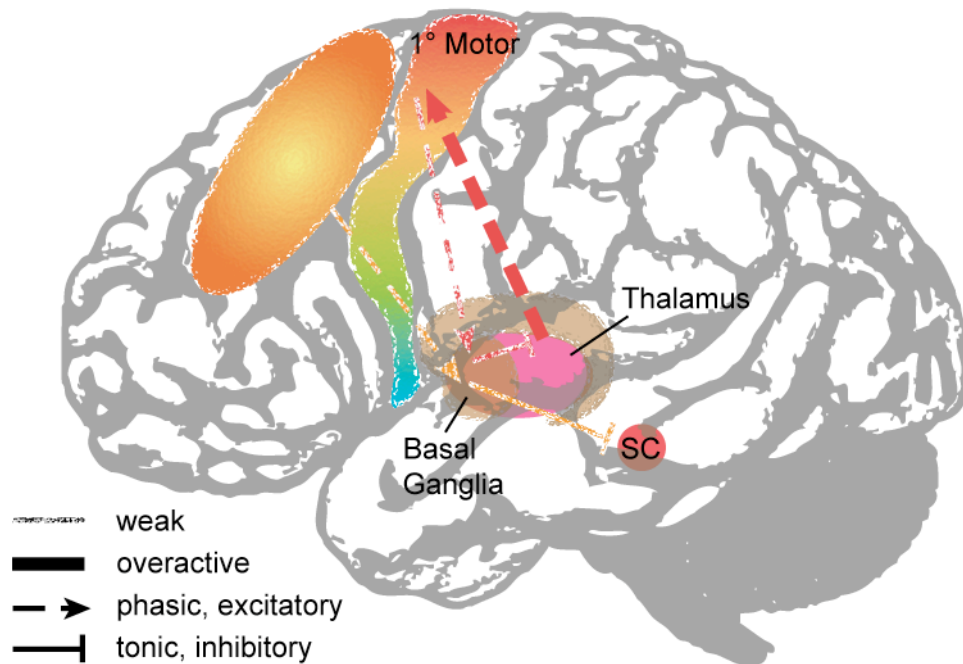
Thus, performance on reflexive eye movement tasks is normal or even hyper-reflexive. **Figure 2.2** details this hypothesized dysfunction in TS. In addition to impacting the SC, reduced basal ganglia output allows the thalamus to excessively activate the cortex, producing tics.

### Previous Eye Movement Studies in TS

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Motivated by all the benefits saccadic research affords, the current study employed behavioral tasks of saccadic response to assay cognitive control in TS. A handful of past investigations have undertaken this endeavor, but taken together, they have emerged in a cacophony of contradiction. Reporting findings from a reflexive saccade task, three groups found normal response times in TS patients (Bollen et al., 1988; Straube et al., 1997; Nomura et al., 2003), while Farber and colleagues (1999) reported faster response times than controls and two teams cited slower response times for TS patients (Mostofsky et al., 2001; Munoz et al., 2002). On eye movement tasks tapping voluntary function, all studies found slower response times (Straube et al., 1997; Farber et al., 1999; Dursun et al., 2000; Mostofsky et al., 2001; Munoz et al., 2002; Nomura et al., 2003). On measures of error rate (percent of responses to an incorrect location), though, two research teams reported increased voluntary antisaccade errors compared to controls (Farber et al., 1999; Dursun et al., 2000), yet three others found no significant increase (Straube et al., 1997; Mostofsky et al., 2001; Munoz et al., 2002).

In only a subset of the oculomotor studies were both reflexive and voluntary tasks administered, enabling consideration of the results in terms of the underlying anatomical and functional relationships between reflexive and voluntary control. While frontal cortices reinforce the basal ganglia's tonic inhibitory output to block midbrain-mediated automatic responses (see **Figure 2.1**), the midbrain reflexive center is allowed to execute automatic responses when momentarily released from basal ganglia domination. This interchange proffers the prediction that a deficit in prefrontal activity can result in both deficits in voluntary orienting as well as decreased inhibition producing normal or hyper-reflexive orienting (see **Figure 2.2**). Evidence from Parkinson's disease patients, as well as other clinical populations across a number of paradigms, supports this assertion (Sereno and Holzman, 1995; Sereno and Holzman, 1996; Briand et al., 1999; Larrison et al., 2000). For response time, three studies (Straube et al., 1997; Farber et al., 1999; Nomura et al., 2003) aligned with the claim that decreased prefrontal activity in TS (demonstrated by increased voluntary eye movement response time) should result in decreased inhibition of reflexive orienting mechanisms (revealed in normal or



**Figure 2.2** Model of hypothesized effect of TS on orienting

Normal orienting is achieved when frontal voluntary control centers modulate the midbrain reflexive center by way of the basal ganglia's tonic inhibitory output. In TS, known abnormalities in the frontal cortex lead to impaired voluntary orienting. Further, weak frontal cortices are lax in properly engaging the basal ganglia to inhibit the reflexive control center. As a result, reflexive orienting is normal or hyper-reflexive. Similar dysfunction in the Motor Loop disinhibits the thalamus, allowing excessive excitation of motor actions (tics). 1° Motor, primary motor cortex; SC, superior colliculus

decreased reflexive eye movement response time) and two did not (Mostofsky et al., 2001; Munoz et al., 2002). For error rate, two supported (Farber et al., 1999; Dursun et al., 2000) and three contradicted the prediction (Straube et al., 1997; Mostofsky et al., 2001; Munoz et al., 2002). The divergence of results prevents a clear understanding of the biological basis of TS.

How could the findings from these studies be so different? On closer inspection of the study designs, three aspects emerge as confounding factors. When sufficient regard is not given to the influence of these factors on oculomotor performance, the conclusions drawn from a study will be attributed solely to disease effects, when in reality other obstructing factors are at play (Reilly et al., 2008). Regrettably, most studies did not even consider culprit confounds; only a few groups performed underpowered post hoc analyses. In the following paragraphs I will enumerate the complicating factors of medication status, age, and comorbidity in prior eye movement studies in TS and address why these aspects must be constrained to provide clear ascertainment of cognitive control in pure TS. **Table 2.1** and **Table 2.2** catalog each study, reviewing how study design features obfuscated results.

Medication status is the first confound frequently present in eye movement studies in TS. Psychiatric medications are known to alter eye movement performance (for review, Reilly et al., 2008). TS participants were commonly tested while actively taking pharmacological treatments for their symptoms. Risperidone (dopamine [D<sub>2</sub>] and serotonin [5HT<sub>2A</sub>] antagonist) is a common pharmacotherapy in TS and has been shown to slow reflexive saccade response time (Sweeney et al., 1997; Nieman et al., 2000). Hence, it is possible TS studies that do not control for medication may show saccadic response time increases due to medication differences. For example, one previous study examined performance in risperidone-treated TS patients and found increased reflexive eye movement response times (Munoz et al., 2002). Interestingly, risperidone has been shown to decrease antisaccade errors (Burke and Reveley, 2002; Harris et al., 2006). Studies in risperidone-treated TS patients that do not control for medication may show normal antisaccade error rate (Munoz et al., 2002) that may be due to medication normalizing an antisaccade deficit in TS. While some groups did attempt to probe for a drug effect and argued for its absence, such post hoc analyses are known to be underpowered (Reilly et al., 2008).

A second confound of previous saccade work in TS is age. Not only is controlling for age important because TS severity changes drastically throughout development and neurobiological differences exist between children and adults with TS, but also many studies have documented development of oculomotor function during childhood (Munoz et al., 1998; Fukushima et al., 2000; Klein and Foerster, 2001; Luna et al., 2004). Reflexive saccade

**Table 2.1** Confounding factors and results of past eye movement studies in TS (I)

Study	Was confound controlled?			Tasks	Dependent Measures		
	Medication	Age	Comorbidity		RT	Direction ER	Timing ER
<b>Bollen et al., 1988</b>	No	Yes, Children	No	Prosaccade	0		N/A
	Post hoc claims no difference	11.2 y (8-15 y)		N/A			
<b>Narita et al., 1997</b>	Yes	Yes, Child	Case Study	Prosaccade			N/A
		13 y	ADHD/OCD	Antisaccade		+	N/A
<b>Straube et al., 1997</b>	No	Yes, Adults	No	Prosaccade	0		N/A
				Antisaccade	+	0; + SD	N/A
	Post hoc claims no difference	26±3.7 y (17-32 y)		Memory Guided	0		
				Sequential Mem	0	+	
<b>Farber et al., 1999</b>	No	Yes, Adults	No	Prosaccade	–		+ (gap)
	Post hoc claims no difference	40.6 y (18-58 y)	Yet known ADHD/OCD	Antisaccade	+	+; in 19%	N/A

ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder; y, years; RT, response time; ER, error rate; + slower or greater than controls; – faster or less than controls; 0 no difference from controls; SD, standard deviation; N/A, not applicable

**Table 2.2** Confounding factors and results of past eye movement studies in TS (II)

Study	Was confound controlled?			Tasks	Dependent Measures		
	Medication	Age	Comorbidity		RT	Direction ER	Timing ER
<b>Dursun et al., 2000</b>	No	No	No	N/A			
		Mixed					
<b>Mostofsky et al., 2001</b>		31.3 y (14-51 y)		Antisaccade	+	+	N/A
	Yes	Yes	Yes	Prosaccade	+, + CV TS+ADHD		N/A
		Children		Antisaccade	+	+	N/A
		Split below and above 10	Excluded OCD; split TS w/ADHD	Memory Guided	TS+ADHD	TS+ADHD	+
<b>Munoz et al., 2002</b>	No	No	No	Prosaccade	+		N/A
		Mixed					
	Post hoc claims no difference	27.2 y (10-55 y)	Post hoc claims no difference	Antisaccade	+	0	N/A
<b>Nomura et al., 2003</b>	Yes	Yes	No	Prosaccade	0		N/A
	Exclude medicated results	Children		Memory Guided	+		- 6-8 y + 9-11 y

ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder; y, years; RT, response time; ER, error rate; + slower or greater than controls; – faster or less than controls; 0 no difference from controls; CV, coefficient of variation; N/A, not applicable

response time is greatly prolonged in 6-7 year olds, but decreases to adult levels by the age of 10-11 years. Studies that do not consider developmental differences in saccade parameters may report response time increases due to age effects. Most previous studies enrolled adults or a broad range of ages rather than only children (Straube et al., 1997; Farber et al., 1999; Dursun et al., 2000; Munoz et al., 2002). Only two studies have considered oculomotor development (Mostofsky et al., 2001; Nomura et al., 2003); one found increased reflexive response time in participants less than 10 years old. Again, there are also important developmental changes in antisaccade error rates. Antisaccade error rate decreases to near adult levels around age 16 (Munoz et al., 1998; Fukushima et al., 2000; Klein and Foerster, 2001). Only one prior study considered an age effect on antisaccade errors and found more errors in those less than 10 years old than those older than 10 years (Mostofsky et al., 2001).

Comorbid status is the final confound present in past oculomotor studies in TS. Most TS patients have a concurrent pathology, or comorbidity, such as ADHD or OCD, which may impact eye movement findings. In point of fact, multiple eye movement studies in children with ADHD alone report increased reflexive response time variability (Mostofsky et al., 2001; Munoz et al., 2003) and increased antisaccade response time and errors compared to controls (Klein et al., 2003; Munoz et al., 2003; Karatekin, 2006). Only one study has been conducted in children with OCD alone and compared to controls found increased antisaccade errors and anticipatory errors in a memory-guided task (Rosenberg et al., 1997). Four prior studies in TS did not consider the impact of concomitant conditions (Bollen et al., 1988; Straube et al., 1997; Dursun et al., 2000; Nomura et al., 2003). Of the three studies that did, Farber and colleagues (1999) hinted at differing performance in TS subpopulations. This study reported that while TS antisaccade errors were significantly increased compared to controls, the increased errors were from a subset comprising 19% of the patients. Straube and colleagues (1997) also reported increased antisaccade errors, but the large error rate variability suggests subpopulations. Only Mostofsky and colleagues (2001) controlled for ADHD and found TS patients with ADHD had greater prosaccade response time and response time variability, more antisaccade errors, and more anticipatory saccades during the delay period of a memory saccade task compared to patients with only TS. This pattern of results suggests TS patients with a comorbidity display unique, separable results (and underlying pathophysiology) from patients with only TS. Also to be considered, age effects may occur in comorbid populations. Only one study considered this in TS patients with ADHD and found a significant interaction between age and diagnosis (Mostofsky et al., 2001).



## Current Study

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The goal of my study was to obtain an accurate saccadic measure of cognitive control in unmedicated children with TS and assess the influence of comorbid conditions. Further, this study improved upon prior work in this field by controlling for medication status, age, and comorbid conditions known to have produced conflicting results. These precautions ensured my observed outcomes were a direct reflection of TS pathology, not study confounds. First, to avoid diverse impacts of medications on eye movement performance, I included only unmedicated TS patients. Such patients are not rare. Family members are often more troubled by TS than the patient and because symptoms wax and wane in severity, initiating educational interventions and lifestyle adjustments before jumping to medications is best (Swain et al., 2007). Second, this study limited enrollment to children 10-16 years old. The age of peak tic severity occurs in this age range (Leckman et al., 1998; Bloch et al., 2006). At ten years old most visual functions stabilize and become adult like (Klein and Foerster, 2001), cerebral blood flow to frontal lobe grey matter reaches adult patterns (Ogawa et al., 1989), and right hemisphere fronto-temporal/occipital EEG coupling becomes evident (left coupling occurs earlier; Thatcher et al., 1987). Around age 16, antisaccade error rate decreases to near adult levels (Munoz et al., 1998; Fukushima et al., 2000; Klein and Foerster, 2001). Therefore, I restricted enrollment to this smaller age range and carefully selected each control participant to be within six months of age of one or more TS patients. Thirdly, this study compared two subsets of TS patients, individuals with TS only and those with TS and comorbid ADHD and/or OCD. Thus, largely unhindered by medication, age, or comorbidity, this unique, carefully controlled study directly measured aspects of cognitive control.

I used traditional reflexive and voluntary saccade tasks to evaluate orienting in TS. These tasks included the reflexive Prosaccade task (automatically look to a peripheral target when it appears), and the voluntary Antisaccade task (deliberately look opposite the suddenly illuminated target). I also created variants of the spatial N-back task – the 0-back task (look to the last stimulus in a variable series of flashes) and 1-back task (look to the next-to-last stimulus in a variable series of flashes). Versions of these N-back tasks were extensively pilot tested in healthy adults and children (Jeter et al., submitted). The design is scalable for difficulty, producing robust results regardless of the number of stimuli or possible stimulus locations. Whereas the Prosaccade is a control task, the Antisaccade, 0-back, and 1-back tasks are powerful measures of response inhibition, response generation, and working memory. These tasks require the same processes that allow proper execution of body movements and are thought to be dysfunctional in TS. In addition to suppression of automatic and early responses (like withholding tics), these tasks require remembering and generating

voluntary eye movements at the proper time to a specific non-illuminated location (voluntarily generating a proper non-tic action). Performance of TS patients, broken down by TS children with or without comorbid ADHD and/or OCD, was compared to typically developing children. The research plan and hypotheses for these comparisons are detailed in the next sections.

In addition to evaluating cognitive control in TS, my study will verify a couple cognitive theories. First, are reflexive and voluntary functions really inversely related in TS as current models hold (i.e., inadequate volitional control produces normal or hyper-reflexive responses; see **Figure 2.2**)? Independent or positively related, rather than inversely related, results from reflexive and voluntary eye movement tasks would necessitate revision of this cognitive model. Second, do multiple aberrant basal ganglia-thalamocortical loops coincident with TS and implicated in the cause of comorbid ADHD and OCD (see **Chapter 1**) induce worse eye movement performance? If TS patients with comorbid conditions perform poorly compared to individuals with TS only, such a contention is upheld.

### **Research Plan Part 1: Classic Oculomotor Tasks**

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The goal of the current study, to obtain an accurate saccadic measure of cognitive control in children with TS and assess the influence of comorbid conditions, was completed in two parts. First, basic reflexive and voluntary orienting in TS patients was assessed with classic oculomotor tasks. As detailed above, past evaluations of reflexive and voluntary eye movement performance in TS has produced mixed results. When tested with reflexive, Prosaccade tasks, TS patients have demonstrated slow reflexive responses (Mostofsky et al., 2001; Munoz et al., 2002) and normal reflexive responses (Bollen et al., 1988; Straube et al., 1997; Farber et al., 1999; Nomura et al., 2003). So, too, on Antisaccade tasks of voluntary function, TS patients have shown increased errors (Farber et al., 1999; Dursun et al., 2000) and normal error rates (Straube et al., 1997; Mostofsky et al., 2001; Munoz et al., 2002). Any attempt at deducing the biological truth from these disparate results, although valiant, is grasping at straws. Even if a composite view is proposed, such a model of TS is undeniably influenced by medication, age, and/or comorbid status and thus is not representative of the pure disease. Critically, then, this study probes TS reflexive and voluntary eye movement performance while controlling for confounding factors.

I expected unmedicated TS patients without concomitant ADHD or OCD to exhibit impaired voluntary orienting and normal or heightened reflexive orienting (i.e., prolonged response time and increased errors on an Antisaccade task and normal or faster Prosaccade response times). This hypothesis follows from the model of orienting in TS depicted in **Figure**

**2.2.** Because of involvement of additional basal ganglia-thalamocortical loops, I expected those TS patients with comorbid ADHD and/or OCD to display even more exaggerated voluntary orienting yet largely normal reflexive orienting (i.e., slower response times and more errors on an Antisaccade task than healthy control children or patients with TS only). Indeed, children with only ADHD have slower response times and increased errors on Antisaccade tasks compared to healthy control children (Klein et al., 2003; Munoz et al., 2003; Karatekin, 2006). Children with OCD also have more Antisaccade errors than typically developing children (Rosenberg et al., 1997). Increasingly impaired voluntary function in TS patients with comorbid conditions points to pathophysiology additional to that of individuals with TS only. Thus, in an extended model of orienting in TS (see **Figure 2.3**), overlay of defective basal ganglia-thalamocortical circuits representing TS, ADHD, and OCD results in progressively weaker frontal voluntary control and diminished basal ganglia output.

## **Research Plan Part 2: Novel Spatial N-back Tasks**

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The second part of the current study was to evaluate childhood cognitive control in TS and its comorbidities using a variant of the spatial N-back task (Callicott et al., 1998). The N-back task is a working memory task in which participants must continually revise and update their mental set with each subsequent stimulus in order to properly respond to a specific previously presented stimulus. N-back tasks allow working memory load to be adjusted for difficulty, as higher N requires more stimuli to be held in mind (e.g., the 0-back task requires response to the current stimulus, the 1-back task requires response to the previous stimulus, etc.). While most spatial and non-spatial N-back tasks are runs of continually appearing stimuli, my novel version was designed in blocks of discrete trials. This enabled all stimuli to be identical squares (rather than numbers, for example) differentiable only by location, duplicating the Prosaccade and Antisaccade task stimuli. Participants completed N-back tasks of two levels of difficulty, 0-back and 1-back, suitable for a child patient population (Jeter et al., submitted).



While no group has tested TS patients on saccadic spatial N-back tasks, a select few have administered saccadic working memory tasks. Unfortunately, research groups did not report the same dependent variables, preventing complete comparison of results. In the Memory Guided task, participants must look to a remembered location at the appropriate time. Straube and colleagues (1997) found normal response time, whereas Nomura and colleagues (2003) found slower response time. Nomura and colleagues (2003) also reported fewer distracted saccades in children with TS, and Mostofsky and colleagues (2001) were able to identify this increase specifically in TS patients with ADHD compared to those with TS alone. More similar to spatial N-back tasks, the Sequential Memory task requires participants to maintain fixation on a central light during a sequence of peripheral flashes. Munoz and colleagues (2002) reported increased anticipatory errors in TS patients.

As with the Antisaccade task, which also tested voluntary function, I expected unmedicated patients with TS alone to exhibit impaired cognitive control on these voluntary tasks (i.e., prolonged response time and increased errors on both N-back tasks). Furthermore, compared to healthy age-matched peers, I expected children with TS only to perform even more poorly on the 1-back task than the 0-back task, as the former entails greater working memory load. Because of involvement of additional basal ganglia-thalamocortical loops, I expected the voluntary performance of TS patients with comorbid ADHD and/or OCD to be even more lacking (i.e., slower response times and more errors on both N-back tasks than healthy controls or patients with TS only).

Highlighting deficits on tasks demanding working memory, children with only ADHD have slower response times (Mostofsky et al., 2001) and increased anticipatory errors (Ross et al., 1994; Castellanos et al., 2000; Mostofsky et al., 2001; Rommelse et al., 2008) on Memory Guided tasks, which, like N-back tasks, require a delayed response to a remembered target. Compared to normal controls, children with OCD tend to have more anticipatory errors on Memory Guided tasks (Rosenberg et al., 1997). One study of children with TS and concomitant ADHD reported increased anticipatory errors compared to children with TS only (Mostofsky et al., 2001). This result supports the model of orienting for TS patients with comorbidities (**Figure 2.3**), contending that the additional impaired basal ganglia-thalamocortical circuits representing TS, ADHD, and OCD result in progressively weaker frontal voluntary control.

### Research Plan Part 3: Factor Analysis

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As a third focus, I undertook an endeavor to reduce this study's many variables into meaningful factors, each comprised of related dependent variables. Two factor analyses were completed. The first created factors explaining the variance in the eye movement response time and error rate variables. The second divided the variance in the totals and subscales of three diagnostic rating scales administered to assess symptoms of TS, ADHD, and OCD.

Both factor analyses are novel to the literature. Very few studies have analyzed eye movement variables by factor analysis, and then only Prosaccade and Antisaccade tasks (Fischer et al., 1997; Klein and Foerster, 2001; Fischer et al., 2000). Factor analyses of clinical symptoms are much more common, often in the creation or validation of a diagnostic rating scale (Conners et al., 1998; Storch et al., 2005; Storch et al., 2006). These factor analyses of symptoms, however, have not assessed multiple diagnostic rating scales at once. Such a test would provide insight into the interrelatedness of frequently co-occurring disorders.

I expected the eye movement variables to divide into factors representing reflexive and voluntary processes (i.e., a Prosaccade factor and an Antisaccade, 0-back, and 1-back factor). In previous factor analyses of eye movement tasks, variables from the reflexive Prosaccade task loaded a different factor than variables from a voluntary Antisaccade task in both healthy participants (Fischer et al., 1997; Fischer et al., 2000; Klein and Foerster, 2001) and those with dyslexia (Fischer et al., 2000). As each disorder is comprised of a common constellation of symptoms, I expected some diagnostic rating scale factors to represent a single scale, with the possibility of other factors representing a potpourri of mixed subscales.

## Chapter 3

# Methods

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## Study Participants

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Before testing, each participant's parent or guardian gave informed consent and as children, each participant gave assent. The University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects approved the study consistent with the Declaration of Helsinki.

### Patients

TS patients were recruited through The University of Texas Child and Adolescent Neurology Clinic without bias for gender or ethnicity. Patients were diagnosed with TS based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV). Dr. Ian J. Butler, a pediatric neurologist and TS expert, performed independent evaluations of each TS patient, including clinical history and neurological examination to ensure each patient met the study inclusion criteria.

- **Inclusion Criteria for TS Group**

1. Diagnosis of TS based on DSM-IV diagnostic criteria
2. Aged 10-16 years
3. Normal (or corrected-to-normal) vision

- **Exclusion Criteria for TS Group**

1. Tic disorder (did not meet TS diagnostic criteria) or psychogenic tics
2. Unable or unwilling to wean off neurological or psychiatric medications in order to be medication-free one week prior to testing
3. (a) Other active medical or major psychiatric disorders except ADHD or OCD, (b) substance abuse, (c) history of electroconvulsive therapy, (d) neurosurgery, (e) history of head injury, or (f) brain tumor or infection

### Controls

Control participants were recruited from the community by Institutional Review Board-approved flyers and a listing on The University of Texas Health Science Center at Houston Clinical Trials website. The control group was not case-matched to TS patients, but rather each control participant was matched by gender and within 6 months of age to 2 or 3 TS patients. Thus, the control group had an equivalent gender ratio and similar age mean and standard deviation as TS patients (see **Results, Table 4.1**).

- **Inclusion Criteria for Control Group**



1. Aged 10-16 years
  2. Normal (or corrected-to-normal) vision
- **Exclusion Criteria for Control Group**
    1. Diagnosis of a neurological or psychiatric condition
    2. Currently using neurological or psychiatric medications
    3. Sibling or parent with an active neurological or psychiatric disorder
    4. (a) Substance abuse, (b) history of electroconvulsive therapy, (c) neurosurgery, (d) history of head injury, or (e) brain tumor or infection

## Diagnostic Measures

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Dr. Butler assessed TS patients in the clinic as described above. In the experimental session, diagnostic rating scales were administered to assess disease state and symptom severity of each child. All participants (TS patients and Controls) and their parent(s) or guardian independently completed the diagnostic rating scales. As an expert rater, I also evaluated each participant. My ratings of each child only differed from the participant's self-report value when the rating was obviously contrary to behavior I observed during the two-hour testing session. Thus, for two diagnostic scales, each participant had three scores, one each from the participant, parent(s) or guardian, and me. On the scale assessing OCD symptoms, only the participant and parent(s) or guardian values were used, as I did not know each child well enough to accurately evaluate his or her internal obsessions and daily compulsions, and these would not fully be evident in a two-hour testing session. The diagnostic rating scales are available in **Appendix A** and the group means for these measures are in the **Results, Table 4.1**. Scales always were administered in the same order and after eye movement tasks.

- Attention Deficit Hyperactivity Disorder Rating Scale – IV (ADHD-IV; DuPaul et al., 1998): This self-report scale is a reliable measure to assess childhood and adolescent attention and behavior deficits. ADHD-IV subscales include inattention and hyperactivity.
- Obsessive Compulsive Inventory – Child Version (OCI-CV; Foa et al., 2010): All participants completed this self-report inventory as a measure of obsessive-compulsive characteristics. Derived from the adult OCI, the OCI-CV authors revised and simplified the inventory to be well suited for a child population. OCI-CV subscales addressed obsessing, washing, hoarding, doubting/checking, neutralizing, and ordering.

- Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989): This self-report version of the YGTSS rated number, frequency, intensity, complexity, and interference of motor and phonic tics separately and impairment combined. The correlation between the self-report and clinician versions of the YGTSS is  $r = 0.86$ ,  $p < 0.0001$  (Leckman et al., 1994b).

## General Procedure

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All aspects of experimental design were optimized for use in a child patient population. Testing sessions were scheduled at each family's convenience, usually on a Saturday. Under the guidance of Dr. Ian Butler, their pediatric neurologist, willing TS patients on neurological or psychiatric medications (12 of 39 patients) were placed on an individualized weaning schedule. This ensured each patient had a proper washout period of at least one week prior to testing.

Behavioral testing (eye movement tasks) and diagnostic rating scales were completed in The University of Texas Medical School at Houston. All participants (except one very wiggly 10-year-old boy) were tested on one day. The wiggly boy completed three of the four eye movement tasks and all diagnostic rating scales during our first testing session. At the second testing session three and a half weeks later, he completed the one remaining eye movement task and repeated the diagnostic rating scales. For analysis, the self-report, parent, and expert diagnostic rating scale scores from his two testing sessions were averaged.

During each testing session, consent was obtained from the parent(s) or guardian and assent from child participants. A background questionnaire (see **Appendix A**) was completed to gather information on first-degree relatives with schizophrenia, bipolar disorder, or other psychiatric, neurological, or developmental disorders. Further questions inquired about previous diagnoses (including streptococcus, implicated as a risk factor), medications, and nicotine or caffeine intake, as these substances are known to possibly affect eye movements. Patients and parent(s) or guardian also reported age at first tic onset, age of diagnosis, types of motor and vocal tics from childhood to the present, when tics most likely occur, how patients knew a tic was about to happen, and whether and for how long patients could suppress tics.

Following informed consent, assent, and background questionnaire completion, parent(s) or guardian waited in an adjacent room and completed three diagnostic rating scales to assess the child participant on symptom severity. Child participants completed the behavioral testing followed by the diagnostic rating scales. All participants also agreed to give a saliva sample for proteomic analysis, in collaboration with Pramod Dash, Ph.D., and future correlation with behavioral measures.

## Eye Movement Tasks

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### Overview

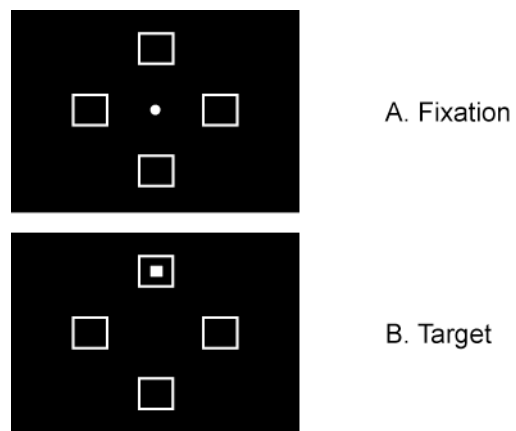
Extensive pilot testing guaranteed the eye movement tasks were simplified as much as possible (Jeter et al., submitted). Each task took between 5 and 15 minutes to complete, with all tasks completed within one hour, including breaks. The brevity of the tasks and ample breaks ensured that even the youngest and most inattentive child was not fatigued. I used white stimuli on a black screen so potential color vision deficiencies would not be a factor (Melun et al., 2001). Each task was devised to test specific cognitive processes. An important element of task design was that each task required the same response (a vertical or horizontal saccade). Thus, any performance differences among groups could be ascribed to an aspect of cognitive control, not to a change in sensory or motor control. One task was designed as a control to verify equivalent sensorimotor control in TS and control children.

### Prosaccade

In this task (**Figure 3.1**), participants simply looked to a stimulus that appeared randomly in one of four peripheral locations. The Prosaccade task served as a control task, verifying that sensory-input (stimulus) and motor-output (an eye movement of a specified amplitude) processes were intact.

The computer screen was black ( $25.3^\circ \times 19.5^\circ$  of visual field;  $0.32 \text{ cd/m}^2$ ) with a central grey fixation circle ( $0.2^\circ$  diameter;  $28.04 \text{ cd/m}^2$ ) surrounded by four open boxes ( $1.1^\circ \times 1.1^\circ$ ;  $28.04 \text{ cd/m}^2$ ) placed in cardinal directions (north, south, east, and west),  $7^\circ$  eccentric to the central fixation point. The open boxes at potential target locations served as landmarks to increase the spatial accuracy of participant saccades (Briand et al., 2001; Karatekin, 2006). Stimuli were filled white boxes ( $0.2 \times 0.2^\circ$ ;  $156.61 \text{ cd/m}^2$ ), which could appear in one of the four landmark boxes. An eye movement was recorded when both areal and velocity criteria were met:

- Fixation Window: A region  $5.8^\circ$  in diameter was centered over the fixation point. Fixation was maintained if the participant's current eye position was determined to be within in this window.
- Target Window: A region  $4.2^\circ$  in diameter was centered over each landmark (target location). Saccades to the target were considered correct if they terminated in this region.
- Velocity Criteria: Initiation of an eye movement was indicated by velocity above  $18.0^\circ/\text{s}$  and the end was indicated by velocity below  $4.6^\circ/\text{s}$ .



**Figure 3.1** Prosaccade task

See text for task procedure details. Correct response is an upward saccade.

Specifically, participants were instructed to fixate on a central fixation point and make a speeded, accurate saccade to the peripheral target when it appeared. To initiate each trial, participants had to first fixate the central fixation point for 400 ms (**Figure 3.1A**). Next, a peripheral target appeared simultaneously with the offset of the central fixation point (**Figure 3.1B**); this is called a step paradigm, as the target appears to step outward from the fixation point. Finally, the participant made a saccade to the peripheral target. The Prosaccade task comprised of 8 practice trials and 48 task trials with equal target presentation in each of the four landmarks. Each trial was classified and recorded based on the participant's eye movement response and saved in a file.

- Break in Fixation: If an eye movement was made before target presentation, the trial was aborted, recorded as a discarded trial, and added to the trial pool to be re-presented in random order.
- Correct: If an eye movement was initiated after target presentation and ended in the correct Target Window, it was recorded as a correct trial. Trial details (response time, duration, gain [i.e., spatial accuracy], and eye position coordinates sampled every 4 ms) were recorded.
- Error: If an eye movement was made after target presentation and it ended anywhere but inside the correct Target Window, it was recorded as an error trial. Trial details (response time, duration, gain, and eye position coordinates sampled every 4 ms) were recorded. Visual feedback ("wrong place"; 24 point font, 28.04 cd/m<sup>2</sup>) was presented just below the fixation point.
- Timeout: For the first 28 patients and 8 controls, if an eye movement was not made within 1492 ms of target presentation, the trial was aborted, recorded as a timeout, and added to the trial pool to be re-presented in a random order. Once I discovered the timeout parameter was mistakenly this long, I reduced the setting such that subsequent participants had 906 ms after target presentation to complete an eye movement. This change was made to reduce the number of discarded trials, as trials with response times longer than 900 ms were trimmed from analysis. Visual feedback ("too slow"; 24 point font, 28.04 cd/m<sup>2</sup>) was presented just below the fixation point and auditory feedback (double tone, 45 then 44 Hz) was presented.

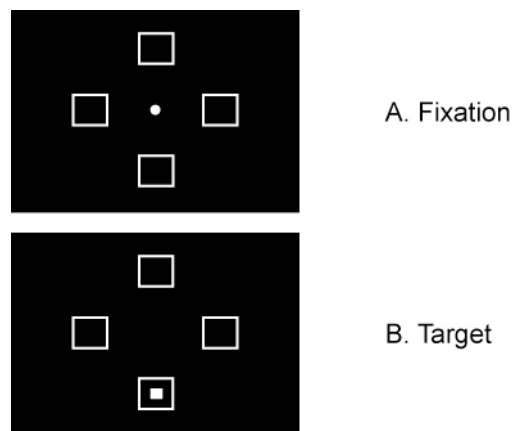
## **Antisaccade**

In this task (**Figure 3.2**), participants inhibited the reflexive impulse to look to the peripheral stimulus and instead voluntarily generated an eye movement to the opposite landmark. This task tested the participants' cognitive control.

The computer screen, "Fixation Window," "Target Window," and "Velocity Criteria" settings were identical to those for the Prosaccade task.

Specifically, participants were directed to fixate on the central fixation point and make a speeded, accurate saccade directly opposite a peripheral stimulus when it appeared. Participants fixated the central fixation point for 400 ms to initiate each trial (**Figure 3.2A**). Next, a peripheral target appeared simultaneously with the offset of the central fixation point (**Figure 3.2B**); again, this is called a step paradigm, as the target appears to step outward from the fixation point. Lastly, the participant completed an eye movement to the stimulus's mirror location on the opposite side of the screen. The Antisaccade task comprised of 8 practice trials and 48 task trials with equal target presentation in each of the four landmarks.

The "Break in Fixation," "Correct," "Error," and "Timeout" parameters were identical to those in the Prosaccade task.



**Figure 3.2** Antisaccade task

See text for task procedure details. Correct response is an upward saccade.

## 0-back

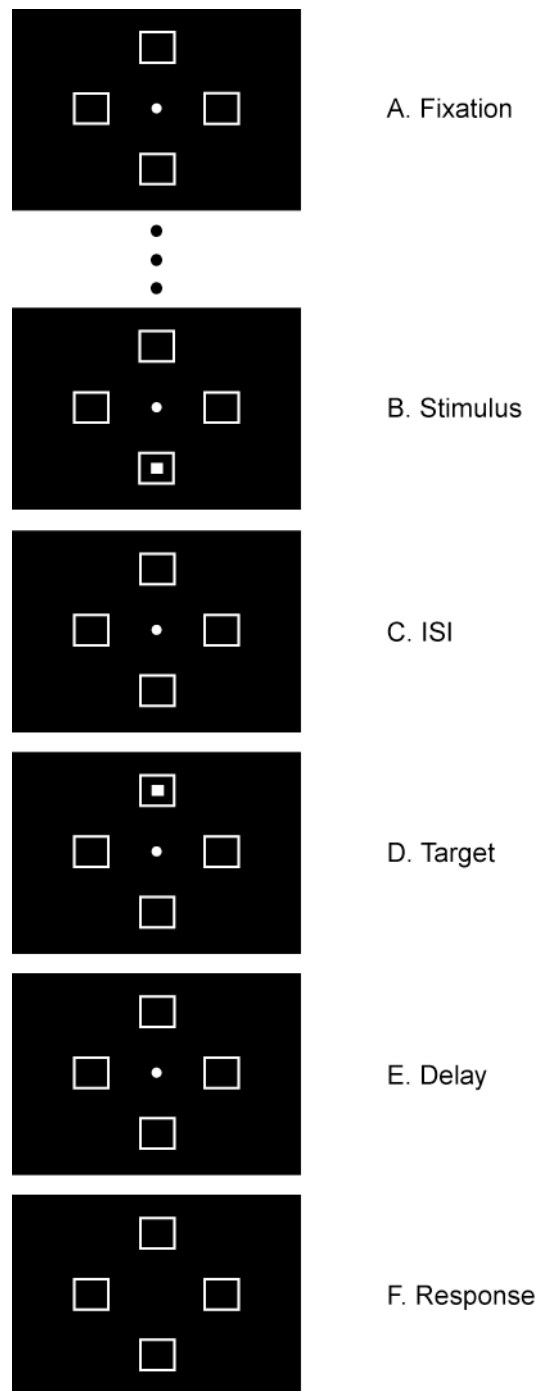
In this task (**Figure 3.3**), participants observed a series of sequential stimulus flashes, each in a different location and made a saccade to the remembered location of the last, or 0-back, stimulus. This task was a classic test of working memory.

The computer screen, “Fixation Window,” “Target Window,” and “Velocity Criteria” settings were identical to those for the Prosaccade task.

Specifically, participants were told to fixate on the central fixation point throughout a succession of flashes occurring (without location repeat) in the four peripheral landmarks. Once the fixation point disappeared, participants were to make a quick and accurate saccade to the last flash of the remembered sequence. To initiate a trial, participants first had to fixate the central fixation point for 750 ms (**Figure 3.3A**). While participants kept their eyes on the fixation point, 2 or 3 white, square stimuli appeared in sequence, each in a unique landmark. Stimuli appeared for 80 ms with a 350 ms interstimulus interval (ISI) between each stimulus (**Figure 3.3B-D**). The participants continued to fixate during a 500 ms delay until the central fixation point was extinguished (**Figure 3.3E**). This served as the “go signal,” at which the participants made a saccade to the remembered location of the last, or 0-back, stimulus, be it the second of two or third of three flashes in the sequence (**Figure 3.3F**). The random presentation of two or three stimuli per trial (each in 50% of the trials) prevented participants from using predictive strategies to time the initiation and direction of the saccade. The 0-back task comprised of 8 practice trials and 96 task trials with equal final stimulus presentation in each of the four landmarks. Every participant saw the same 96 trials of stimulus sequences, as the trials were run from a file of pre-generated random sequences.

Inherently, an N-back task first requires the subject to remember N+1 locations at once, and second to update those locations – dropping the old one and remember the new – while retaining the presentation order of each. This second demand to actively manipulate the information in mind crucially differentiates the N-back task as a measure of working memory rather than short-term memory, as the latter only requires memory on a short time-scale. Such delayed response task measures of working memory critically rely on the prefrontal cortex (Barch et al., 1997).





**Figure 3.3** 0-back task

See text for task procedure details. Correct response is an upward saccade. The ellipsis after the fixation screen denotes the omission of an additional stimulus and ISI occurring on 50% of the trials. The possibility of an additional stimulus prevented participants from predicting the timing and direction of their saccades. ISI, interstimulus interval

Each trial was classified based on the participant's eye movement response and saved in a file.

- Discarded: If an eye movement was made at an improper time, such as before offset of the fixation point, the trial was aborted, recorded as a discarded trial, and added to the trial pool to be re-run in a random order. Trial details (locations of sequence stimuli, final eye position, type of discard, time point in trial of discard, and eye position coordinates sampled every 4 ms) were recorded. Discarded trials were further classified based on when the saccade was made.
  1. Break in Fixation: If an eye movement was made before stimulus presentation, the trial was aborted, recorded as a fixation break, and added to the trial pool to be re-run in random order.
  2. Disinhibition: If an eye movement was made after the first stimulus, but before the offset of the fixation point, the trial was aborted, recorded as a discarded trial, and added to the trial pool to be re-run in a random order. Trial details (time point in trial of eye movement and 10 eye position coordinates sampled every 4 ms) were recorded.
  3. Timeout: For 28 patients and 8 control participants, if an eye movement was not made within 1492 ms of target presentation, the trial was aborted, recorded as a timeout, and added to the trial pool to be re-run in a random order. However, once this long timeout parameter was discovered, the setting was changed such that subsequent participants had 906 ms after target presentation in which to make an eye movement. This change was made to reduce the number of discarded trials after trimming trials with latencies longer than 900 ms. Visual feedback ("too slow"; 24 point font, 28.04 cd/m<sup>2</sup>) was presented just below the fixation point and auditory feedback (double tone, 45 then 44 Hz) was presented.
- Correct: If an eye movement was made after offset of the fixation point and it ended in the correct Target Window, it was recorded as a correct trial. Trial details (response time, duration, gain, and eye position coordinates sampled every 4 ms) were recorded.
- Error: If an eye movement was made after offset of the fixation point and it ended anywhere but inside the correct Target Window, it was recorded as an error trial. Trial details (response time, duration, gain, and eye position coordinates sampled every 4 ms) were recorded. Visual feedback ("wrong place"; 24 point font, 28.04 cd/m<sup>2</sup>) was presented just below the fixation point.

## 1-back

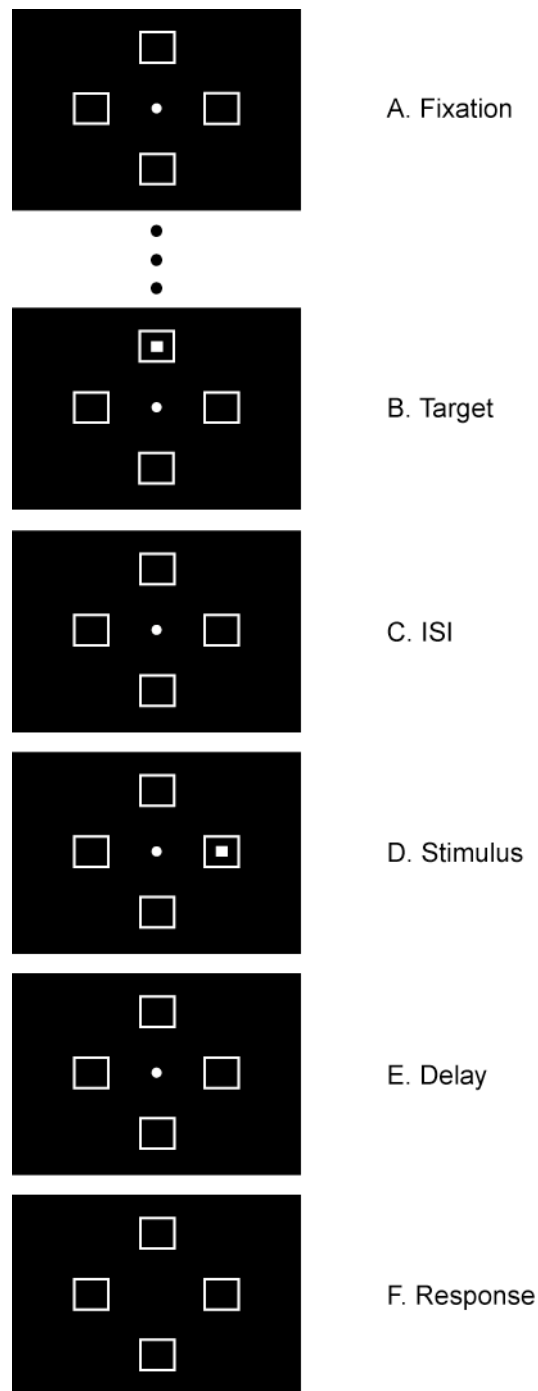
In this task (**Figure 3.4**), participants observed a series of sequential stimulus flashes, each in a different location, and made a saccade to the remembered location of the next-to-last, or 1-back, stimulus. This task was a classic test of working memory.

The computer screen, “Fixation Window,” “Target Window,” and “Velocity Criteria” were identical to those for the Prosaccade task.

Specifically, participants were told to fixate on the central fixation point throughout a succession of flashes occurring (without location repeat) in the four peripheral landmarks. Once the fixation point disappeared, participants were to make a quick and accurate saccade to the next-to-last flash of the remembered sequence. Trial events and timing proceeded identically to those in the 0-back task, with the exception that when the central fixation point disappeared, participants made a saccade to the remembered location of the next-to-last, or 1-back, stimulus, be it the first of two or second of three flashes in the sequence (**Figure 3.4F**). Again, the random presentation of two or three stimuli per trial (each in 50% of the trials) prevented participants from using predictive strategies to time the initiation and direction of the saccade. The 1-back task comprised of 8 practice trials and 96 task trials with equal next-to-last stimulus presentation in each of the four landmarks. Every participant saw the same 96 trials of stimulus sequences, as the trials were run from a file of pre-generated random sequences.

Critically, the 1-back task required participants to continually update their mental set by holding the two most recent locations in mind – exchanging the earliest presented for the most recent stimulus – all while remembering presentation order. In comparison to the 0-back task, which required memory of and response to only the most recent stimulus, the 1-back task demanded greater working memory load as correct response necessitated maintaining two locations and presentation orders in active memory storage.

The “Discarded,” “Correct,” and “Error” parameters were identical to those in the 0-back task.



**Figure 3.4** 1-back task

See text for task procedure details. Correct response is an upward saccade. The ellipsis after the fixation screen denotes the omission of an additional stimulus and ISI occurring on 50% of the trials. The possibility of an additional stimulus prevented participants from predicting the timing and direction of their saccades. ISI, interstimulus interval

## Task Counterbalance

The four eye movement tasks described above were semi-counterbalanced. The N-back working memory tasks were always completed first, and the basic orienting tasks were completed second. This ensured the children completed the lengthy tasks (in trial duration and number of trials) first, leaving the shorter tasks (again, in trials and trial duration) as a fresh surprise and motivator to maintain cooperation and attention. Both TS and healthy control children were assigned a counterbalance order in this rotation, respectively:

- 0-back, 1-back, Prosaccade, Antisaccade
- 0-back, 1-back, Antisaccade, Prosaccade
- 1-back, 0-back, Prosaccade, Antisaccade
- 1-back, 0-back, Antisaccade, Prosaccade

## Behavioral Testing Procedure

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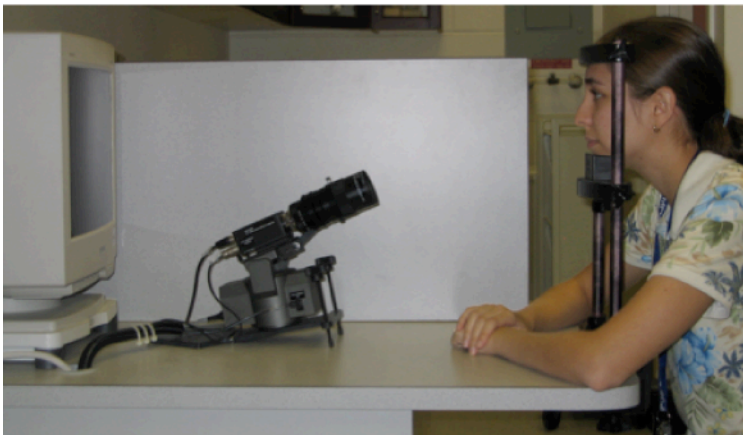
Following parental/guardian informed consent, child participant assent, and completion of the background questionnaire, families were introduced to the entire experimental set-up (**Figure 3.5A**) and procedures. Then, families departed to rest in the adjacent waiting room (**Figure 3.5B**), which was filled with kid-friendly décor and toys, perfect for accompanying siblings and participant breaks. Testing room lights were turned off and participants were allowed to dark-adapt as they were seated in a (non-rolling, non-swiveling!) chair and fitted in the chin rest (**Figure 3.5C**). Each task (“games,” as called for the kids’ benefit) began with an explanation of rules and example trials acted out on a printed page of the basic task screen. Participants could ask questions both before and after a set of practice trials, which could be repeated, to ensure each child understood the rules before continuing with the experimental trial block. Because trials were self-paced, participants were encouraged to rest their eyes or sit back from the chin rest, as trials only continued when the eye tracking camera detected the participant’s gaze at the fixation point on the monitor.



A. Experimenter View of Cart



B. Family Waiting Room



C. Example volunteer on chin rest

**Figure 3.5** Eye tracking set-up

**A.** From left, participant chair and chin rest, eye-tracking monitor/computer, participant flat screen monitor on far side of divider wall, Macintosh computer with custom programs, experimenter seat and monitor. **B.** Comfortable space with fun toys and popular chalkboard. **C.** From left, stimulus screen, ISCAN<sup>®</sup> camera, and example volunteer on chin rest.

## Eye Movement Measurement

Each participant was seated 72 cm from the center of a computer screen in a dark room with his/her head held in place by a chin rest and forehead restraint. Stimuli were presented on a monitor (LCD, 17 inch, 75 Hz refresh rate, 1024 x 768 pixels) connected to a Power G4 Macintosh computer running OS 9 operating system. An infrared eye-tracking camera (ISCAN<sup>®</sup> ETL-200, Burlington, Massachusetts) measured eye movement of the right eye. The eye-tracker, connected to the Macintosh via a USB port, pinpointed the participant's pupil and corneal reflection of infrared rays. Using the spatial difference of these two points, which changed as the participant looked around the screen, the ISCAN<sup>®</sup> equipment could calculate eye position at 240 Hz regardless of small shifts in head or body position. Consequently, further restraint of a participant's head was not needed and childhood squirming or the tics of TS did not affect the measurements. A custom program developed using commercially available software (Vision Shell; Code Warrior) was used to present visual stimuli and record details of eye movements. For each trial in all experiments, the eye position data were analyzed online, automatically canceling trials with invalid eye movements and later re-presenting them in random order.

Before each eye movement task, the participant was instructed to look at nine points on the screen. Corresponding eye position coordinates were recorded. Throughout the task, custom calibration software used these reference points to calculate the x- and y-axis screen coordinates of the participant's pupil (with an error radius about 0.25°).

## Dependent Measures

For each task, two files per participant were saved. The data file recorded specific trial types, timing of precise screen events, and classification of each trial's result (as described above). The x- and y-axis eye position coordinates from every 4 ms sample for each trial were saved in a separate file. Online control of the experiments (e.g., aborting a trial) was enabled by measures calculated from these values. The files were also available for offline analysis (see **Appendix B** for sample outputs). Dependent measures common to each task include:

- Response Time: This was the elapsed time from when the fixation point disappeared until the saccade began, also known as latency. Meeting both areal (gaze outside the Fixation Window) and velocity (movement above 18.0°/s) criteria marked the initiation of a saccade.
- Error Rate: This was the percentage of trials in a task in which the participant made an eye movement at the correct time, but to an incorrect location.

- Working Memory Load: This was a measure of working memory demand on a participant, calculated as the difference in response time or error rate for the 1-back and 0-back tasks. A positive working memory load indicated a greater demand on working memory in the 1-back task. *This measure pertained only to the 0-back and 1-back tasks.*
- Disinhibition: This was a measure of inhibition and was a count of the number of N-back discarded trials in which the participant made an eye movement after the first flash but before the “go signal.” *This measure pertained only to the 0-back and 1-back tasks.*

## Data Analysis

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Customized programming scripts in MATLAB 7.3 for Mac (Mathworks) compiled and averaged each participant's data file from each task. First, trials with a response time less than 100 ms or greater than 900 ms were discarded. From the remaining trials, error rate was calculated as the percentage of trials in which the participant made an eye movement to an incorrect location. Correct trials were further trimmed if response time was 2.5 standard deviations from the participant's mean. Mean response time was calculated from these remaining trials.

The MATLAB output and clinical measures were combined in a PASW Statistics 17.0 for Mac (formerly SPSS) spreadsheet for subsequent analyses. Pearson's correlations (two-tailed) compared the symptom severities of TS, ADHD, and OCD. Those patients with an OCI-CV score greater than 2.33 standard deviations above the mean control participant score and/or an ADHD-IV percentile rank above 85 were classified as TS-comorbid patients. Raw response time and error rate of each behavioral task and working memory load were included in separate multivariate linear models with TS status (Control, TS-only, TS-comorbid) as a main factor, adjusting for age as a covariate, to assess planned contrasts. Because of a non-normal distribution, disinhibitions from the 0-back and 1-back tasks were included in a Poisson loglinear Generalized Linear Model with TS status as the main factor and age as a covariate to evaluate planned contrasts. Response time and error rate of each behavioral task and working memory load were included in a factor analysis and factors with eigenvalues over one extracted. Totals and subscales of the three diagnostic rating scales were included in another factor analysis and again factors with eigenvalues over one extracted. Pearson's partial correlations (controlling for age) compared each of the eye movement factors to each of the diagnostic rating scale raw totals and diagnostic rating scale factors.



## Chapter 4

# Results

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## Control and Tourette Syndrome Participants

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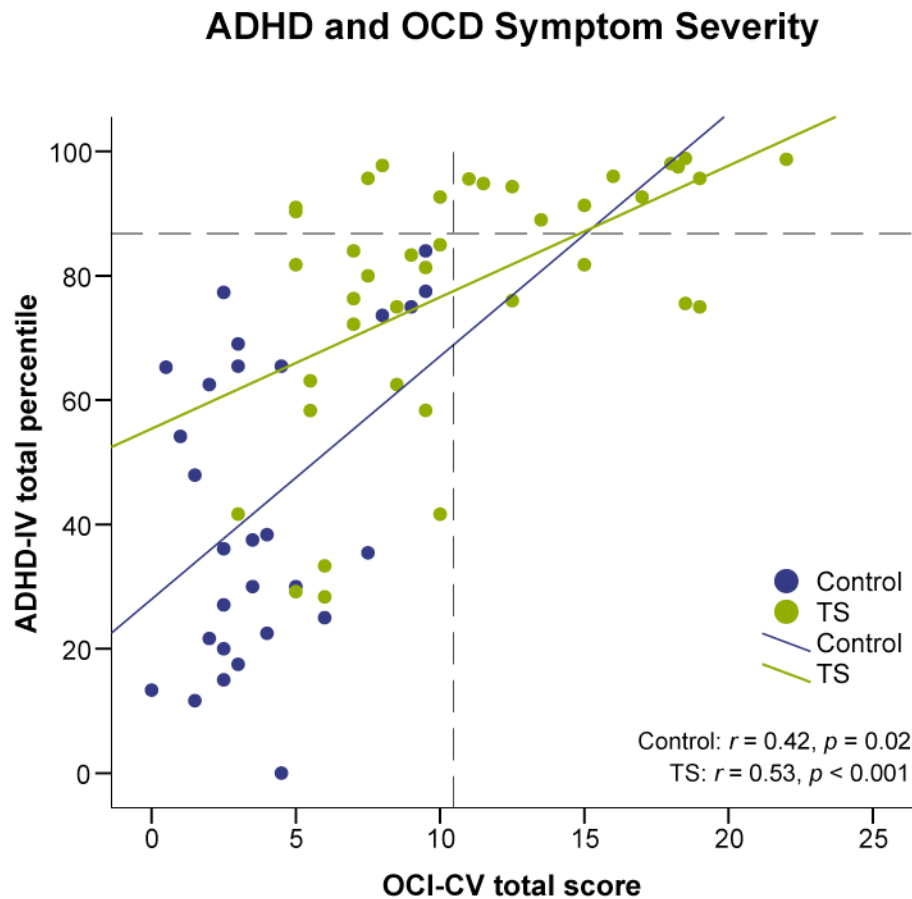
Twenty-nine typically developing children (Controls) and thirty-nine children with TS completed all diagnostic rating scales and eye movement tasks. The age and gender composition of the two participant groups are listed in **Table 4.1** and did not statistically differ from one another (gender:  $t_{66} = 0.55$ ,  $p = 0.59$ ; age:  $t_{66} = 0.29$ ,  $p = 0.77$ ). Three raters per participant independently completed self-report diagnostic rating scales of ADHD (Attention Deficit Hyperactivity Disorder Rating Scale-IV, ADHD-IV), OCD (Obsessive Compulsive Inventory – Child Version, OCI-CV) and TS (Yale Global Tic Severity Scale, YGTSS) to assess symptom severity of the child. For the ADHD and TS scales, every participant had three scores, one each from the participant, parent(s) or guardian, and me. On the scale assessing OCD symptoms, only the participant and parent(s) or guardian values were used, as I did not know each child well enough to accurately evaluate his or her internal obsessions and daily compulsions, whereas I could assess the severity of external hyperactivity, inattention, and tics. Mean scores of these scales are also listed in **Table 4.1**. As expected, Controls and children with TS differed statistically on all scale ratings (ADHD-IV:  $t_{66} = -6.44$ ,  $p < 0.001$ ; OCI-CV:  $t_{60} = -7.24$ ,  $p < 0.001$ ; YGTSS:  $t_{39} = -12.60$ ,  $p < 0.001$ ).

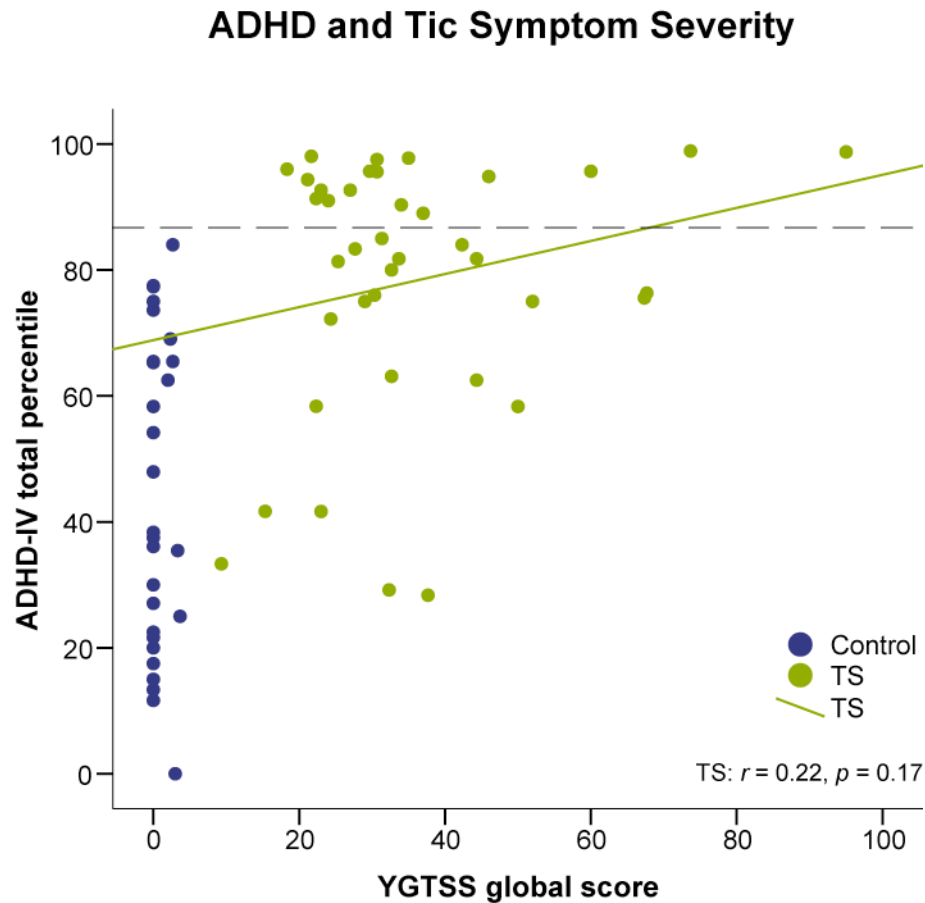
To identify any relationship between symptom severities of TS, ADHD, and/or OCD, individual patient diagnostic rating scale scores were plotted against one another in pairs. Scatter plots of these three comparisons are shown in **Figure 4.1** (ADHD-IV vs. OCI-CV), **Figure 4.2** (ADHD-IV vs. YGTSS), and **Figure 4.3** (OCI-CV vs. YGTSS). Interestingly, patient scores on all three diagnostic rating scales correlated with one another. Patient scores of ADHD symptoms correlated strongly with OCD symptoms (ADHD-IV vs. OCI-CV:  $r(38) = 0.53$ ,  $p < 0.001$ ) and moderately with TS symptoms (ADHD-IV vs. YGTSS:  $r(38) = 0.22$ ,  $p = 0.17$ ). Ratings of patient OCD symptoms significantly correlated with TS symptoms (OCI-CV vs. YGTSS:  $r(38) = 0.35$ ,  $p = 0.03$ ). Thus, as symptoms of one disorder increase, so do symptoms of the other two. This indicates that not only are ADHD and OCD strongly related to one another in TS, but also that these comorbid conditions are inherent in TS, not additional to the disorder as classically thought. Further, this indicates ADHD and OCD symptoms are present at some level in most all TS patients. Only ADHD and OCD diagnostic rating scale scores correlated among Controls; the other scale pairings were not significant (ADHD-IV vs. OCI-CV  $r(28) = 0.42$ ,  $p = 0.02$ ; ADHD-IV vs. YGTSS  $r(28) = 0.05$ ,  $p = 0.80$ ; OCI-CV vs. YGTSS  $r(28) = 0.34$ ,  $p = 0.07$ ).

**Table 4.1** TS and Control demographics and diagnostic rating scale scores

	<b>Gender</b>	<b>Age</b>	<b>ADHD-IV</b>	<b>OCI-CV</b>	<b>YGTSS</b>
Control	19 M, 10 F	13.16 (2.10) [10.19-16.54]	43.3 (24.3) [0-84.0]	3.9 (2.6) [0-9.5]	0.7 (1.3) [0-3.7]
Tourette Syndrome	28 M, 11 F	13.01 (2.11) [10.09-16.95]	78.3 (20.4) [28.4-98.9]	10.8 (5.1) [3.0-22.0]	36.0 (17.5) [9.3-95.0]
	<i>p</i> = 0.59	<i>p</i> = 0.77	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.001

Gender: M = male, F = female. All values are mean (standard deviation) [range]. Age is in years. ADHD-IV, Attention Deficit Hyperactivity Disorder Rating Scale-IV (percentile rank 1-100); OCI-CV, Obsessive Compulsive Inventory – Child Version (score range 0-42); YGTSS, Yale Global Tic Severity Scale (score range 0-100).

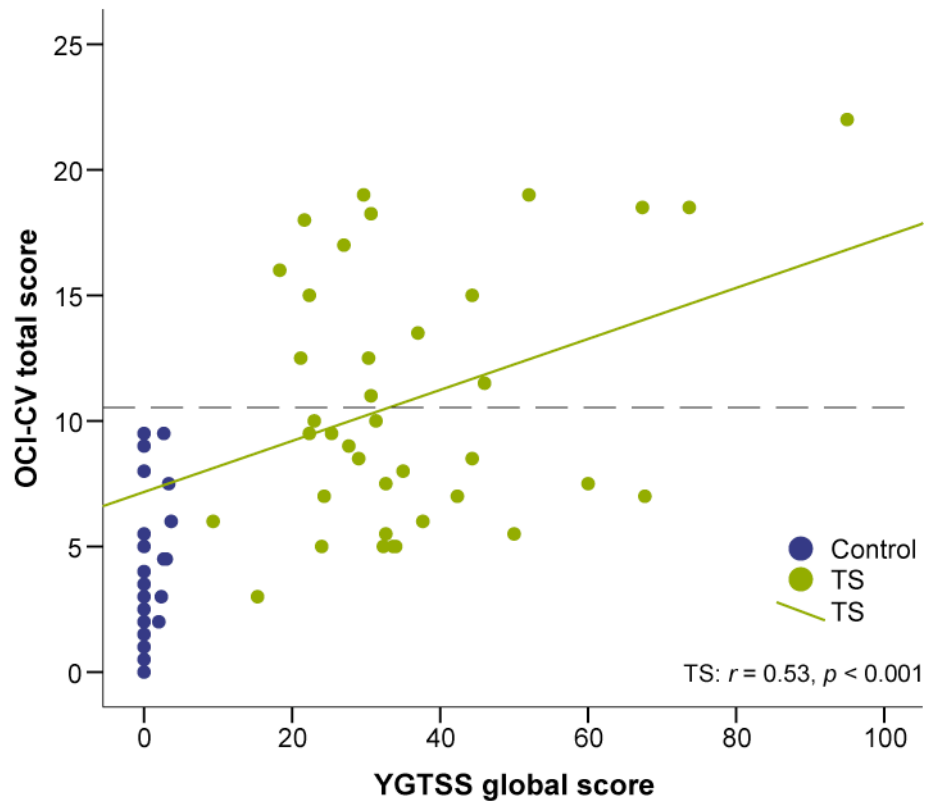




**Figure 4.2** TS and Control ADHD and tic symptom severity

Individual TS patient and Control ADHD-IV percentile ranks are plotted against YGTSS global (total) scores. Dotted line indicates the cutoff score above which participants are classified as having ADHD. ADHD-IV, Attention Deficit Hyperactivity Disorder Rating Scale-IV; YGTSS, Yale Global Tic Severity Scale

### OCD and Tic Symptom Severity



**Figure 4.3** TS and Control OCD and tic symptom severity

Individual TS patient and Control OCI-CV total scores are plotted against YGTSS global (total) scores. Dotted line indicates the cutoff score above which participants are classified as having OCD. OCI-CV, Obsessive Compulsive Inventory – Child Version; YGTSS, Yale Global Tic Severity Scale

## Control and Tourette Syndrome Participants Divided by Comorbid Status

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For a classification of comorbid ADHD, children must have ranked above the 85<sup>th</sup> percentile on the ADHD-IV total score, which is the standard per the ADHD-IV manual. Because I used the OCI-CV while its authors still were determining a cutoff score, I set a value based on the Controls in my study. A classification of OCD was given when a child scored 2.33 standard deviations above the mean of the Controls. This deviance value represents 2% of the population, which is the prevalence of childhood OCD (Zohar, 1999). In the last section, I showed that the symptom severities of TS, ADHD, and OCD correlated with one another. So, all children with TS who scored above the cutoffs for ADHD and/or OCD were assigned to a TS-comorbid group, while those below the cutoffs for ADHD and OCD were considered to have only TS (TS-only). As tic severity correlates with ADHD and OCD symptom severity, the nomenclature of TS-only and TS-comorbid more precisely refers to an overall less and more severe profile, respectively. No control child scored above the ADHD or OCD cutoffs.

**Table 4.2** lists the demographics and diagnostic rating scale scores of the same Controls and TS patients, the latter now divided into eighteen TS-only children and twenty-one TS-comorbid children. These three groups did not differ statistically by gender or age (gender:  $F_{(2,65)} = 1.19, p = 0.31$ ; age:  $F_{(2,65)} = 0.05, p = 0.95$ ), but a higher proportion of females were TS-comorbid patients than males (8/11 girls compared to 13/28 boys). Naturally, the three groups differed on the diagnostic rating scale scores (ADHD-IV:  $F_{(2,65)} = 37.00, p < 0.001$ ; OCI-CV:  $F_{(2,65)} = 53.91, p < 0.001$ ; YGTSS:  $F_{(2,65)} = 61.84, p < 0.001$ ). Controls differed significantly from TS-only patients (ADHD-IV:  $p = 0.001$ ; OCI-CV:  $p = 0.002$ ; YGTSS:  $p < 0.001$ ) and TS-comorbid patients (ADHD-IV:  $p < 0.001$ ; OCI-CV:  $p < 0.001$ ; YGTSS:  $p < 0.001$ ). TS-comorbid children were rated significantly more severe than TS-only children on all but tic severity (ADHD-IV:  $p < 0.001$ ; OCI-CV:  $p < 0.001$ ; YGTSS:  $p = 0.11$ ).

Age is known to affect eye movement performance (Fukushima et al., 2000; Klein and Foerster, 2001; Munoz et al., 1998; Luna et al., 2004), which is why this study not only excluded adults, but also limited the juvenile participant ages to between 10 and 16 years (discussed in **Chpt. 2, Orienting in TS**). Yet, as shown in **Figure 4.4A** and **B**, younger participants, regardless of disease status, had significantly increased response times and more errors (higher error rate) on voluntary eye movement tasks such as the Antisaccade task (response time:  $r(67) = -0.28, p = 0.02$ ; error rate:  $r(67) = -0.61, p < 0.001$ ). Thus, in all analyses of eye movement variables, age was entered as a covariate to eliminate its influence on the behavioral data.

**Table 4.2** TS subtype and Control demographics and diagnostic rating scale scores

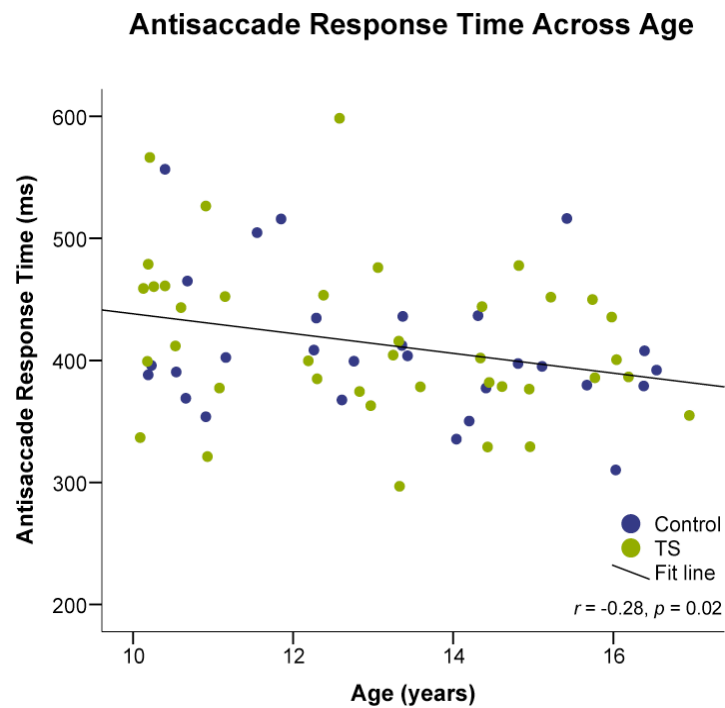
	<b>Gender</b>	<b>Age</b>	<b>ADHD-IV</b>	<b>OCI-CV</b>	<b>YGTSS</b>
Control	19 M, 10 F	13.16 (2.10) [10.19-16.54]	43.3 (24.3) [0-84.0]	3.9 (2.6) [0-9.5]	0.7 (1.3) [0-3.7]
TS-only	15 M, 3 F	12.95 (2.24) [10.18-16.95]	63.1 (20.1) [28.4-84.9]	7.2 (2.0) [3.0-10.0]	32.3 (13.3) [9.3-67.7]
TS-comorbid	13 M, 8 F	13.06 (2.06) [10.09-15.98]	91.5 (7.7) [75.0-98.9]	13.9 (4.9) [5.0-22.0]	39.2 (20.2) [18.3-95.0]
	$p = 0.31$	$p = 0.95$	$p < 0.001$	$p < 0.001$	$p < 0.001$

Gender: M = male, F = female. All values are mean (standard deviation) [range]. Age is in years. See text for planned comparisons between group diagnostic rating scale scores.

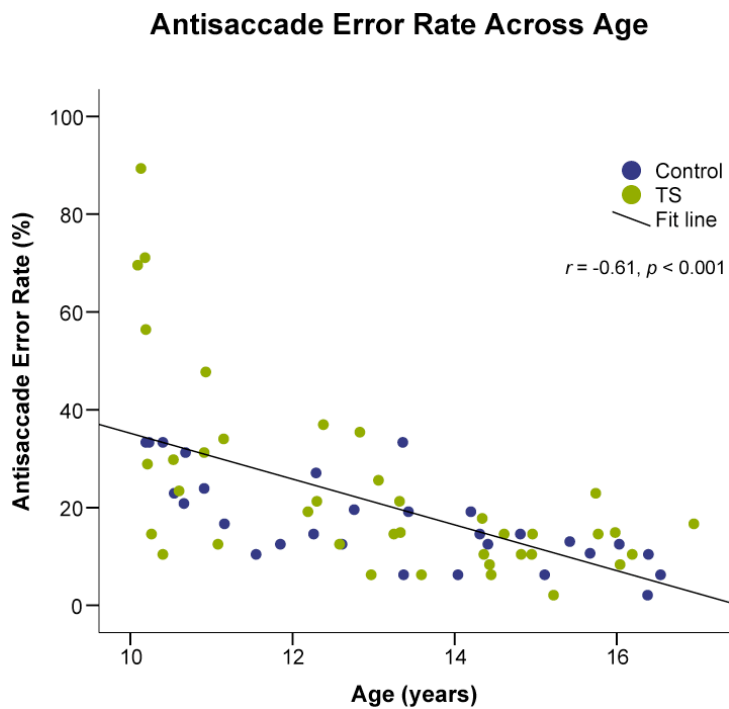
ADHD-IV, Attention Deficit Hyperactivity Disorder Rating Scale-IV (percentile rank 1-100); OCI-CV, Obsessive Compulsive Inventory – Child Version (score range 0-42); YGTSS, Yale Global Tic Severity Scale (score range 0-100).



## A. Response Time



## B. Error Rate



**Figure 4.4** Voluntary eye movement performance across age

**A.** Response times and **B.** errors on a voluntary eye movement task decrease with age.

## Part 1: Classic Oculomotor Tasks – Prosaccade and Antisaccade

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The first part of this study employed the Prosaccade and Antisaccade tasks, two traditional measures of orienting, to assess reflexive and voluntary functioning, respectively.

### Prosaccade Task

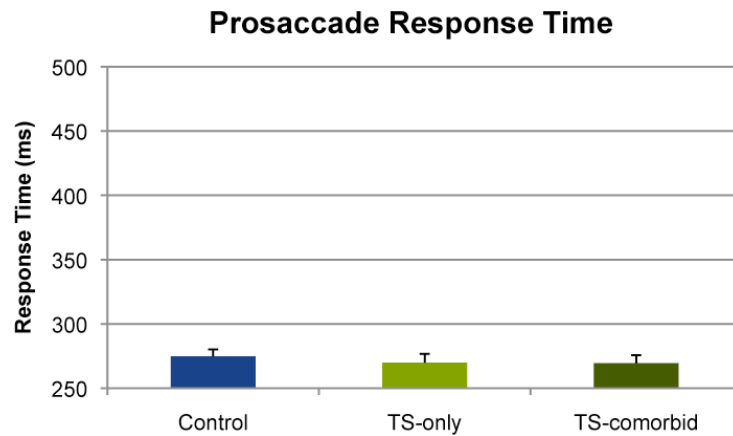
#### Response Time

For each participant, trials with a response time less than 100 ms or greater than 900 ms were discarded. Correct trials were further trimmed if response time was 2.5 standard deviations from the participant's mean. Mostofsky and colleagues used a similar procedure (Within a task, response times  $\leq 115$  ms were trimmed. Additional trials were trimmed if they were 2 standard deviations from the mean response time of the task; Mostofsky et al., 2001). Mean response time was calculated from these remaining correct trials. Controls, TS-only patients, and TS-comorbid patients did not differ from one another on Prosaccade response time ( $F_{(2,64)} = 0.27$ ,  $p = 0.78$ ; **Figure 4.5A**).

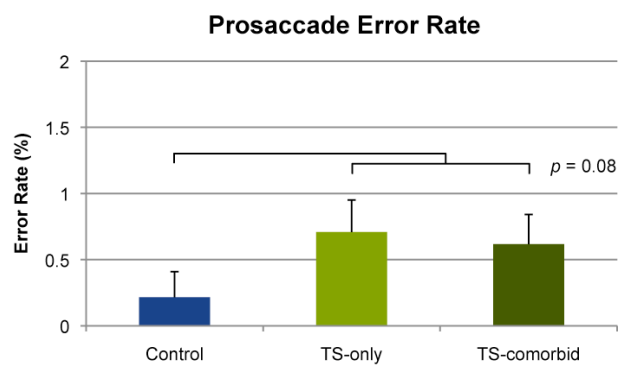
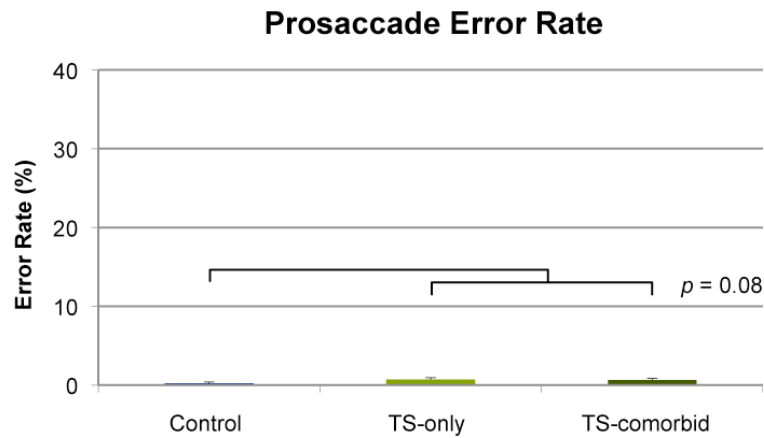
#### Error Rate

From trials remaining after the initial trim (response time less than 100 ms or greater than 900 ms), error rate was calculated as the percentage of trials in which the participant made an eye movement to an incorrect location. Controls, TS-only patients, and TS-comorbid patients had comparable Prosaccade task error rates ( $F_{(2,64)} = 1.56$ ,  $p = 0.22$ ; **Figure 4.5B**). Only when all TS patients were combined did they marginally have more errors than Controls ( $p = 0.08$ ).

## A. Response Time



## B. Error Rate



**Figure 4.5** Prosaccade task response time and error rate

**A.** Response Time. **B.** Error Rate plotted on y-axis for comparison to subsequent tasks. Inset below plotted to visualize group differences. All TS patients combined marginally had more errors than Controls.

## Antisaccade Task

### Response Time

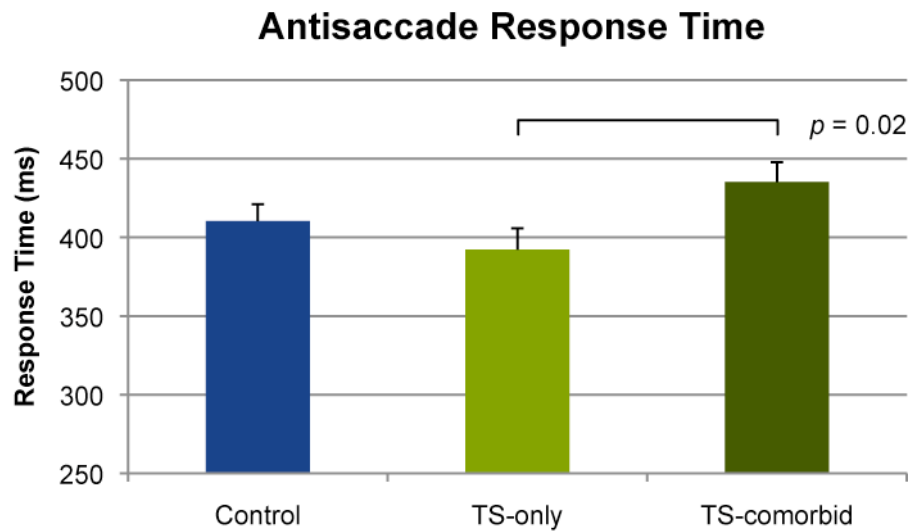
Mean Antisaccade response time for each participant was calculated in the same way as for the Prosaccade task and differed among the groups ( $F_{(2,64)} = 2.83, p = 0.07$ ). TS-comorbid patients took significantly longer to respond than TS-only patients ( $p = 0.02$ ), whose performance was comparable to Controls ( $p = 0.29$ ; **Figure 4.6A**). Controls and TS-comorbid patients did not differ in time to respond ( $p = 0.13$ ).

### Error Rate

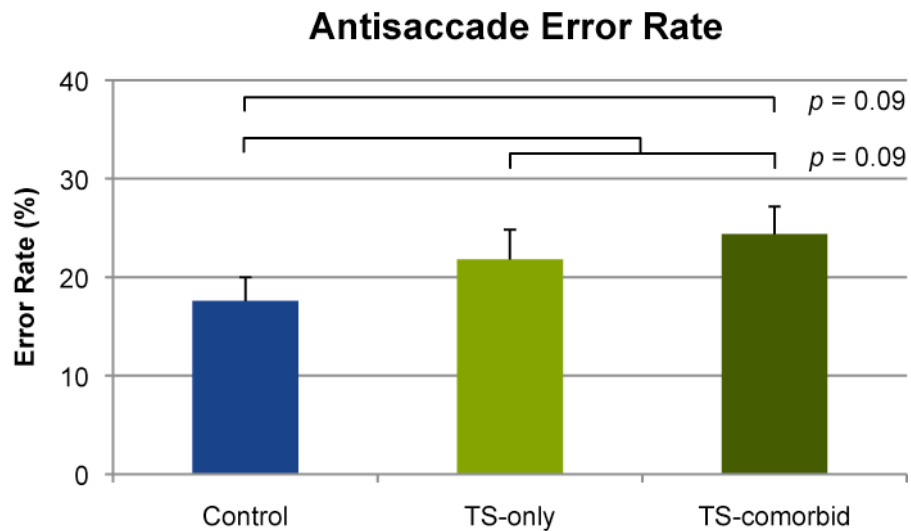
Antisaccade error rate was calculated in the same way as for the Prosaccade task. Antisaccade error rate nearly differed among groups ( $F_{(2,64)} = 1.76, p = 0.18$ ). TS-comorbid patients marginally had more errors on the Antisaccade task than Controls ( $p = 0.07$ ). TS patients combined, regardless of comorbid condition, also showed a statistical trend for more errors than Controls ( $p = 0.09$ ; **Figure 4.6B**). Counter to expected results, Control and TS-only patients had equivalent Antisaccade error rates ( $p = 0.28$ ).

Because increasing tic severity is associated with increasing severities of ADHD and OCD symptoms (**Figure 4.2** and **Figure 4.3**), and TS patients with increased severities of these comorbid conditions tended to have more errors than Controls on the voluntary Antisaccade task (**Figure 4.6B**), I next completed an exploratory analysis to determine whether TS-only patients with high tic severity had increased Antisaccade errors compared to TS-only patients with low tic severity or Controls. Using the median tic severity of the TS-only group (YGTSS = 31.83) as the cutoff, I divided the TS-only patients into higher (TS-only Higher,  $n = 9$ ) and lower (TS-only Lower,  $n = 9$ ) tic severity groups. The groups did differ on Antisaccade error rate ( $F_{(2,43)} = 3.37, p = 0.04$ ). Amazingly, TS-only Higher patients had a significantly greater Antisaccade error rate than TS-only Lower patients ( $p = 0.03$ ) or Controls ( $p = 0.02$ ; **Figure 4.7**). In contrast, TS-only Lower patients had a similar Antisaccade error rate as Controls ( $p = 0.81$ ).

**A. Response Time**

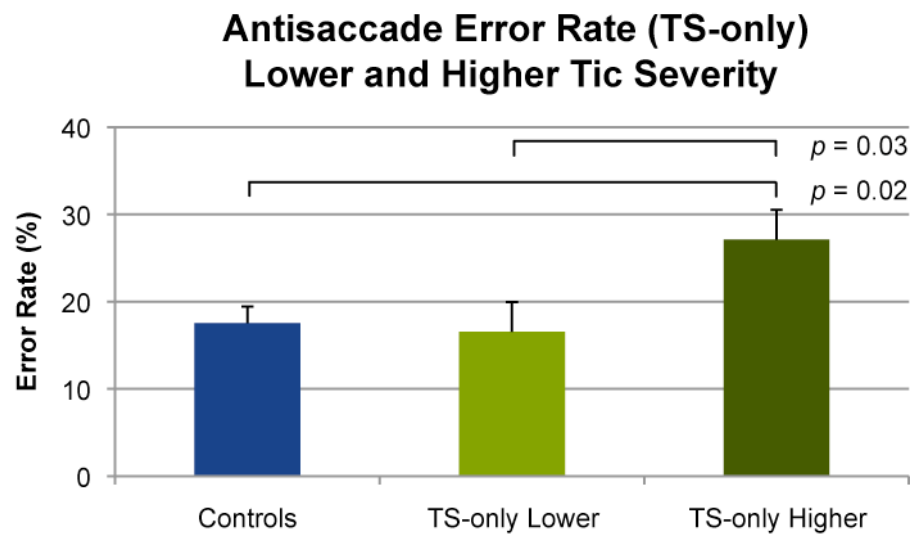


**B. Error Rate**



**Figure 4.6** Antisaccade task response time and error rate

**A. Response Time.** Patients with comorbid conditions were significantly slower to respond than patients without comorbid conditions. **B. Error Rate.** TS-comorbid patients, as well as all TS patients combined, had marginally more errors than Controls.



**Figure 4.7** Antisaccade task error rate for TS-only patients with lower and higher tic severity

While TS-only patients with lower tic severity (TS-only Lower) continued to perform comparably with Controls, TS-only patients with higher tic severity (TS-only Higher) not only had significantly more errors than Controls, but also more errors than TS-only patients with lower tic severity (TS-only Lower).

## Part 1 Summary

These data support the hypothesis that TS patients with comorbid conditions have weak voluntary control in comparison to Controls and patients with TS only. TS-comorbid patients had slowed voluntary responding (Antisaccade response time; **Figure 4.6A**) compared to TS-only patients. Intimating weak voluntary inhibition, TS-comorbid patients tended to have an elevated Antisaccade error rate compared to Controls (**Figure 4.6B**). Unexpectedly, TS-only patients did not show any voluntary deficits compared to Controls.

## Part 2: Novel Spatial N-back Tasks – 0-back and 1-back

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In the second part of this study the 0-back and 1-back tasks, novel measures of spatial working memory, were administered to assess components of voluntary function, specifically response inhibition, response generation, and working memory.

### 0-back Task

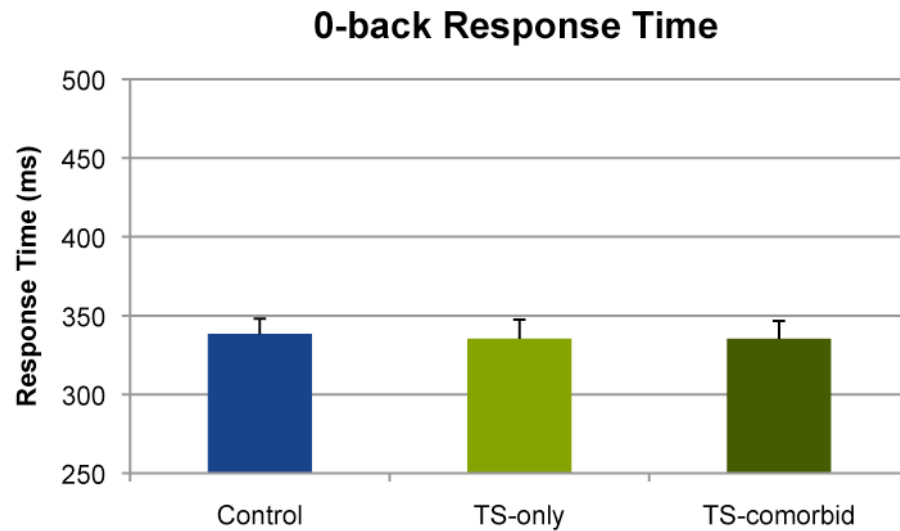
#### Response Time

Each participant's mean 0-back response time was calculated as described in the Prosaccade task response time section. Controls, TS-only patients, and TS-comorbid patients did not differ from one another on 0-back response time ( $F_{(2,64)} = 0.03$ ,  $p = 0.97$ ; **Figure 4.8A**).

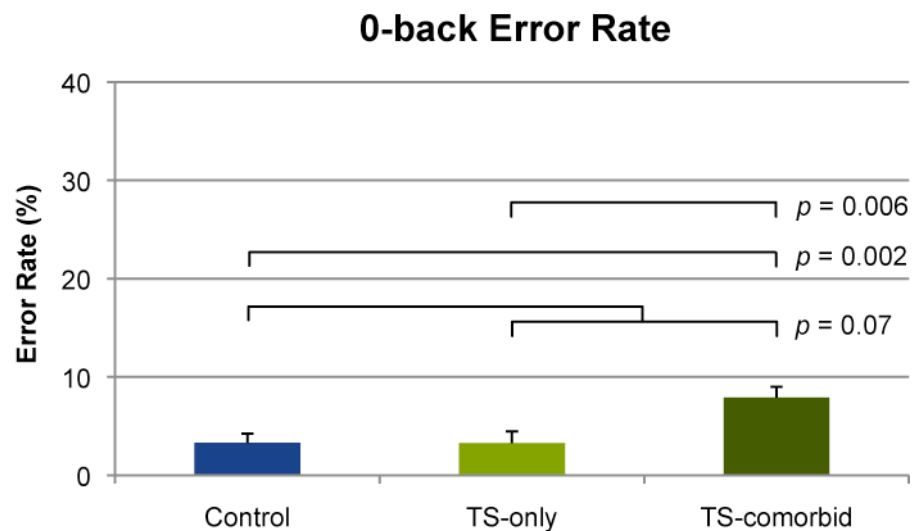
#### Error Rate

Each participant's error rate for the 0-back task was computed as described in the Prosaccade error rate section. 0-back error rate differed across the three groups ( $F_{(2,64)} = 6.08$ ,  $p = 0.004$ ). TS-comorbid patients not only had a significantly higher 0-back error rate than Controls ( $p = 0.002$ ), but they also had a significantly higher 0-back error rate than TS-only patients ( $p = 0.006$ ; **Figure 4.8B**). Again, TS-only patients surprisingly had comparable error rate performance to Controls ( $p = 0.98$ ). When all children with TS were grouped, they showed a marginally greater 0-back error rate than Controls ( $p = 0.07$ ).

## A. Response Time



## B. Error Rate



**Figure 4.8** 0-back task response time and error rate

**A.** Response Time. **B.** Error Rate. TS-comorbid patients not only had significantly more errors than Controls, but also more errors than TS-only patients. Additionally, all TS patients combined had marginally more errors than Controls.



## 1-back Task

### Response Time

Mean 1-back response time for each participant was calculated using the same procedure as for the Prosaccade task. Groups marginally differed on 1-back response time ( $F_{(2,64)} = 1.95, p = 0.15$ ). TS-comorbid patients tended to have increased 1-back response time compared to Controls ( $p = 0.09$ ) and TS-only patients ( $p = 0.09$ ; **Figure 4.9A**). TS-only patients responded in similar time as Controls ( $p = 0.81$ ).

### Error Rate

1-back error rate was calculated in the same way as for the Prosaccade task. Controls, TS-only patients, and TS-comorbid patients had similar 1-back error rate ( $F_{(2,64)} = 1.39, p = 0.26$ ; **Figure 4.9B**).

## Working Memory Load

Working Memory Load is the added demand placed on working memory by the 1-back task compared to the 0-back task. Response time or error rate Working Memory Load is quantified by subtracting the 0-back task performance from that of the 1-back task. A positive value denotes more working memory load in the 1-back task compared to the 0-back task.

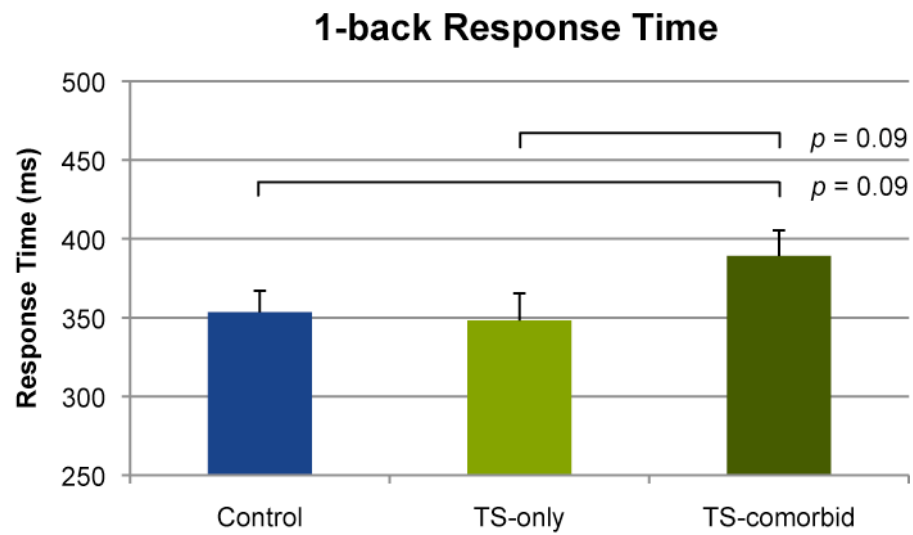
### Response Time

Working Memory Load mean response time was computed by subtracting each participant's mean 0-back response time from mean 1-back response time. There were differences among the groups ( $F_{(2,64)} = 2.71, p = 0.07$ ). TS-comorbid patients not only took significantly longer to respond in the 1-back task than 0-back task compared to Controls ( $p = 0.04$ ), but also longer than TS-only patients ( $p = 0.05$ ; **Figure 4.10A**). As in all other tasks, TS-only patients did not differ from Controls ( $p = 0.91$ ).

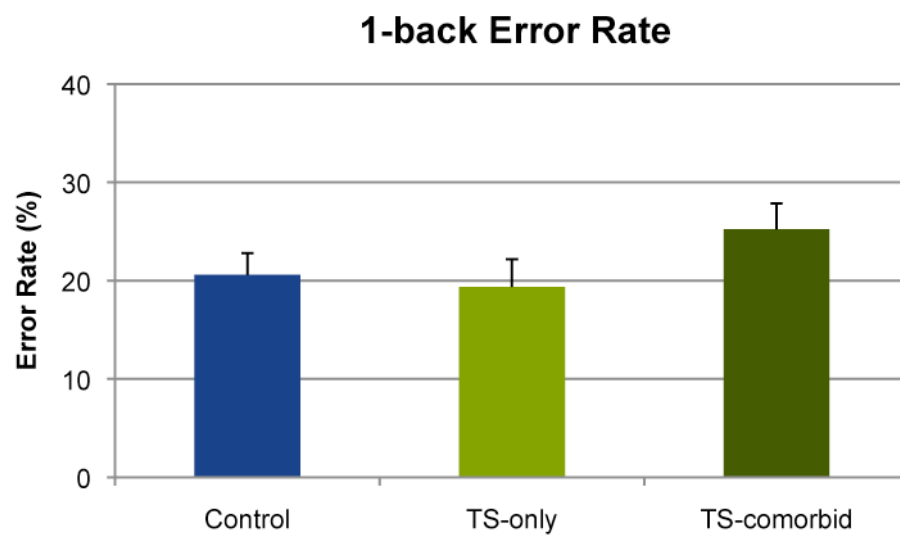
### Error Rate

Working Memory Load error rate was computed by subtracting each participant's 0-back error rate from 1-back error rate. Controls, TS-only patients, and TS-comorbid patients did not differ on Working Memory Load error rate ( $F_{(2,64)} = 0.09, p = 0.92$ ; **Figure 4.10B**).

### A. Response Time



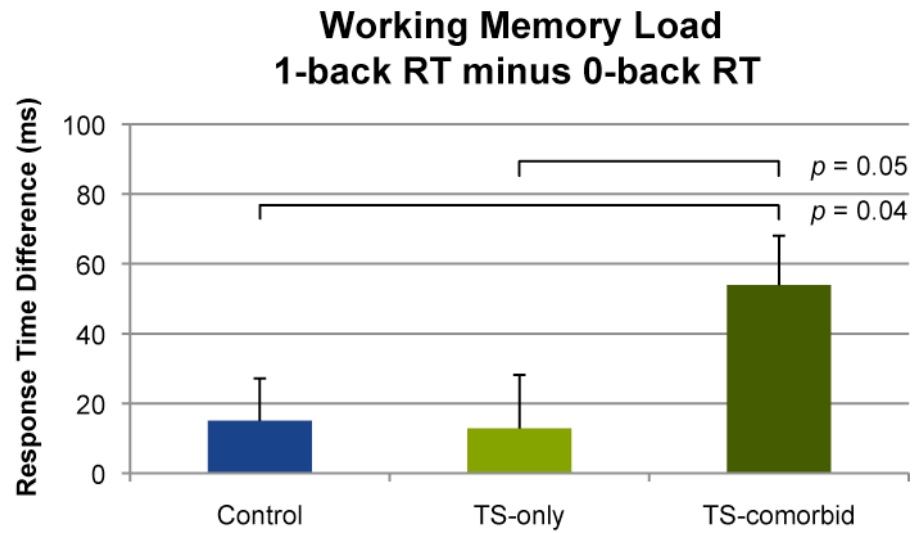
### B. Error Rate



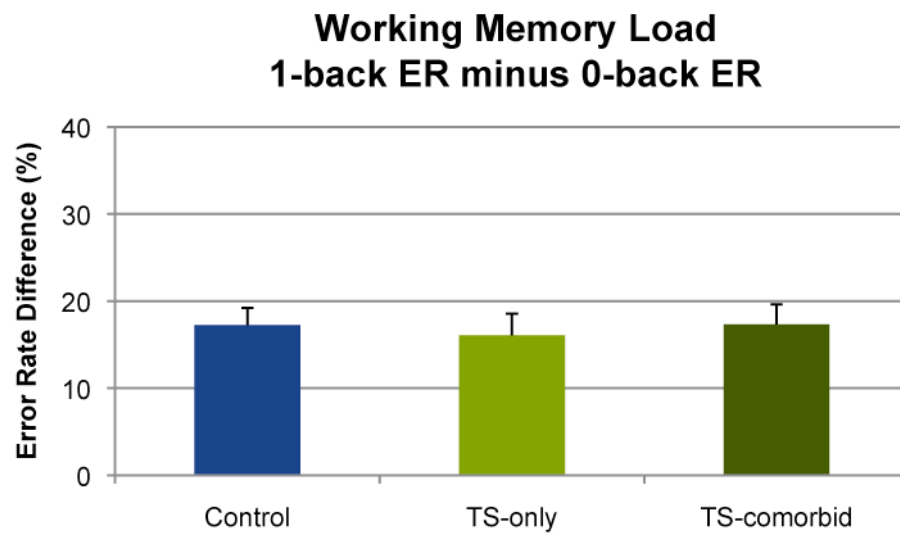
**Figure 4.9** 1-back task response time and error rate

**A.** Response Time. TS-comorbid patients responded in marginally more time than Controls or TS-only patients. **B.** Error Rate.

### A. Response Time Difference



### B. Error Rate Difference



**Figure 4.10** Working Memory Load response time and error rate difference

**A.** Response Time Difference between 1-back and 0-back tasks. Working Memory Load response time difference was significantly greater for TS-comorbid patients than for Controls or TS-only patients. **B.** Error Rate Difference between 1-back and 0-back tasks. RT, response time; ER, error rate

## N-back Task Disinhibitions

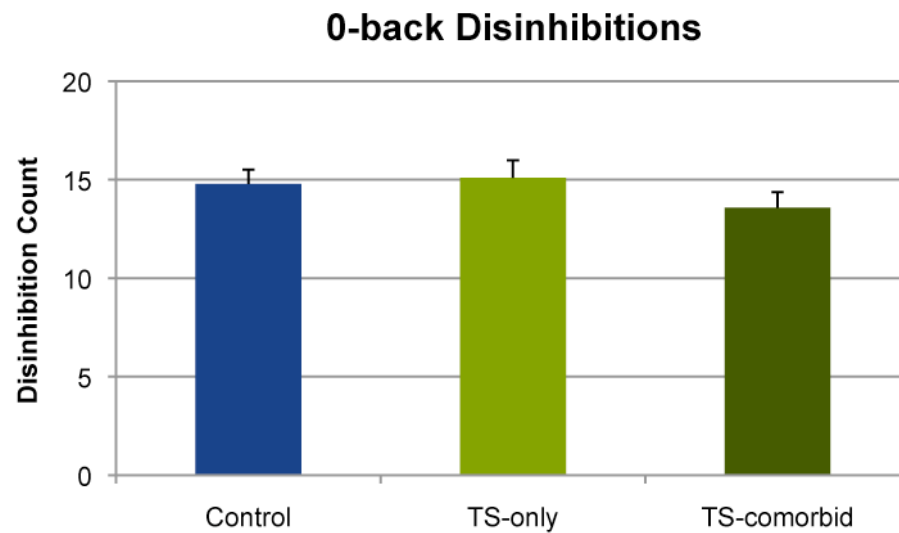
0-back and 1-back response time and error rate were calculated only on trials when participants properly maintained fixation throughout the delay period (see **Methods**, **Figure 3.3** and **Figure 3.4**). Trials in which participants made an early eye movement in response to a mid-trial stimulus flash were considered disinhibitions. While disinhibitions were tallied and saved in a file, these trials were rerun and did not count toward the 96 total trials in a testing block.

The distribution of the number of disinhibitions was non-normal in both N-back tasks for Controls, TS-only patients, and TS-comorbid patients. Thus, the data were analyzed using a Poisson loglinear Generalized Linear Model with age as a covariate. For the 0-back task, all participant groups had equivalent disinhibitions (Wald Chi-Square<sub>(2, 64)</sub> = 1.94,  $p = 0.38$ ; **Figure 4.11A**). For the 1-back task, however, the effect of group was significant (Wald Chi-Square<sub>(2, 64)</sub> = 12.67,  $p = 0.002$ ). Whereas TS-only patients had marginally more disinhibitions than Controls ( $p = 0.08$ ), TS-comorbid patients had significantly more disinhibitions than Controls ( $p < 0.001$ ; **Figure 4.11B**). TS-only and TS-comorbid patients did not differ ( $p = 0.11$ ).

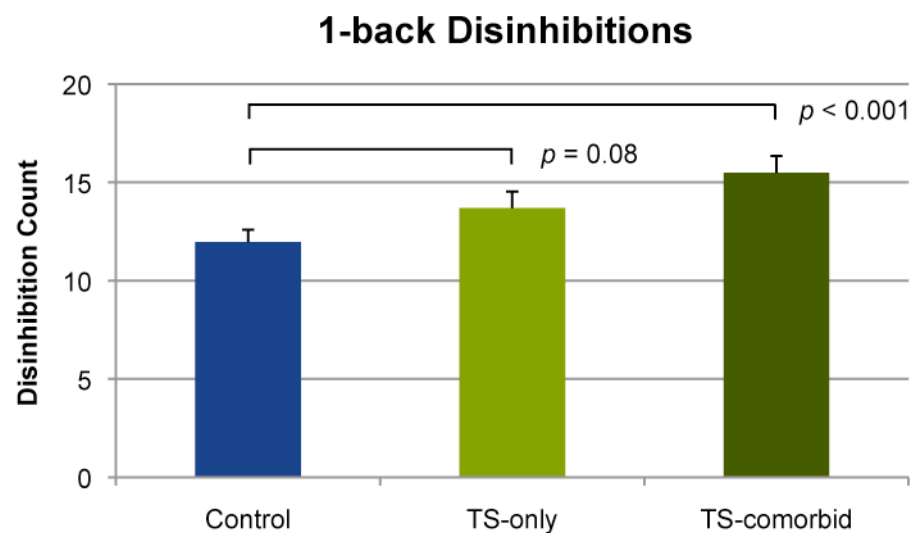
## Part 2 Summary

TS-comorbid patients continued to demonstrate poor voluntary control in comparison to Controls and patients with TS only. Not only did TS patients with comorbid conditions have increased 0-back errors compared to Controls, but also TS-only patients (**Figure 4.8B**). Had TS patients not been subdivided by comorbidity, this significant difference would have been masked as a trend, falsely attributing inhibitory deficits to all TS patients, regardless of comorbid status. As in Part 1, TS-only patients countered my hypothesis and showed no voluntary deficits in comparison to Controls. A tendency for TS-comorbid patients to respond more slowly than Controls or TS-only patients in the 1-back task (**Figure 4.9A**) was significant for Working Memory Load in both cases (**Figure 4.10A**). TS-comorbid patients also made more disinhibitions in the 1-back task than Controls (**Figure 4.11B**).

**A. 0-back**



**B. 1-back**



**Figure 4.11** 0-back and 1-back task disinhibitions

**A.** 0-back task disinhibitions. **B.** 1-back task disinhibitions. TS-comorbid patients had significantly more early eye movements to mid-trial stimuli (disinhibitions) than Controls. TS-only patients tended to have more disinhibitions than Controls.

### Part 3: Factor Analysis – Eye Movement Variables and Rating Scale Totals/Subscales

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In the final part of this study, factor analyses served to 1) reduce my data into fewer, meaningful components that capture the majority of the variance within my original variables and 2) detect structural relationships and explain the pattern of correlations among variables. In a factor analysis, each subject is plotted in an  $n$ -dimensional space where  $n$  represents the number of original variables. A line most closely passing through all data points, and thus accounting for as much variance as possible, is drawn through this space. The extent to which each axis (original variable) correlates with this first factor is its loading strength. Another line (factor) is drawn that accounts for the majority of the remaining variance and is orthogonal to (uncorrelated with) the first factor. This process is reiterated until all variance is accounted for.

#### Eye Movement Variables

To determine if the many eye movement variables could be reduced into meaningful factors that also represent the structural relationships between variables, presumably reflecting brain organization, I conducted a factor analysis of the response time and error rate measures from all four eye movement tasks and working memory load. A variable was considered to have loaded a factor if its correlation (loading) with the factor was greater than  $r = 0.45$ . **Table 4.3** lists the four factors extracted, the amount of variance for which they accounted, and the eye movement variables represented by each factor and at what rotated loading strength.

Fascinatingly, the first two factors seem to represent the respective voluntary functions of inhibition and generation. Inhibition, measured as error rate, is the ability to prevent a response and instead correctly execute another action. Accordingly, the error rate variables from all three voluntary eye movement tasks and measure of working memory strongly loaded on the first, or Inhibition Factor. Generation, measured as response time, activates the appropriate motor action. All voluntary response time variables except 0-back response time loaded the second, or Generation Factor. The last two factors seem to represent different oculomotor functions. 1-back and Working Memory Load error rates loaded the Working Memory factor, whereas Prosaccade response time and error rate and Antisaccade response time loaded the Basic Sensorimotor Performance factor.

Each eye movement factor was independently correlated with each diagnostic rating scale, adjusting for age and the other three factors as covariates. **Table 4.4** shows that the Inhibition Factor correlated significantly with all three clinical measures (ADHD-IV:  $r(62) = 0.27$ ,  $p = 0.03$ ; OCI-CV:  $r(62) = 0.32$ ,  $p = 0.009$ ; YGTSS:  $r(62) = 0.34$ ,  $p = 0.006$ ). The Generation

**Table 4.3** Factor analysis of eye movement variables

Factor Extracted	Variance Explained	Variables	Loadings
Inhibition	21.0%	0-back ER	0.844
		Antisaccade ER	0.746
		1-back ER	0.734
		Working Memory Load ER	0.453
Generation	20.3%	1-back RT	0.906
		Working Memory Load RT	0.904
		Antisaccade RT	0.504
Working Memory	16.9%	Working Memory Load ER	0.671
		1-back ER	0.513
Basic Sensorimotor Performance	16.9%	Prosaccade RT	0.827
		Antisaccade RT	0.622
		Prosaccade ER	0.524

A variable was considered to have loaded a factor if its correlation (loading) with the factor was greater than  $r = 0.450$ . ER, error rate; RT, response time

**Table 4.4** Correlations of eye movement factors with diagnostic rating scales

EM Factor	ADHD-IV	OCI-CV	YGTSS
Inhibition	$r(62) = 0.27$ $p = 0.03$	$r(62) = 0.32$ $p = 0.009$	$r(62) = 0.34$ $p = 0.006$
Generation	$r(62) = 0.16$ $p = 0.20$	$r(62) = 0.30$ $p = 0.02$	$r(62) = 0.24$ $p = 0.05$
Working Memory	$r(62) = -0.14$ $p = 0.26$	$r(62) = -0.10$ $p = 0.44$	$r(62) = 0.02$ $p = 0.88$
Basic Sensorimotor Performance	$r(62) = -0.03$ $p = 0.83$	$r(62) = -0.03$ $p = 0.80$	$r(62) = -0.08$ $p = 0.54$

EM, eye movement; ADHD-IV, Attention Deficit Hyperactivity Disorder Rating Scale-IV; OCI-CV, Obsessive Compulsive Inventory – Child Version; YGTSS, Yale Global Tic Severity Scale; Bold correlations are statistically significant.



Factor correlated significantly with the OCD and tic scales (OCI-CV:  $r(62) = 0.30, p = 0.02$ ; YGTSS:  $r(62) = 0.24, p = 0.05$ ). The Working Memory and Basic Sensorimotor Performance factors did not strongly correlate with any of the three diagnostic rating scales.

### Diagnostic Rating Scale Totals and Subscales

To determine if the aspects of TS captured by each clinical measure overlapped, I also conducted a factor analysis of the diagnostic rating scale totals and subscales. See **Appendix A** for a full list of each diagnostic rating scale's subscales and the questions comprising them. A variable was considered to have loaded a factor if its correlation (loading) with the factor was greater than  $r = 0.45$ . **Table 4.5** lists the four factors extracted, the amount of variance for which they accounted, and the scale totals or subscales represented by each factor and at what rotated loading strength.

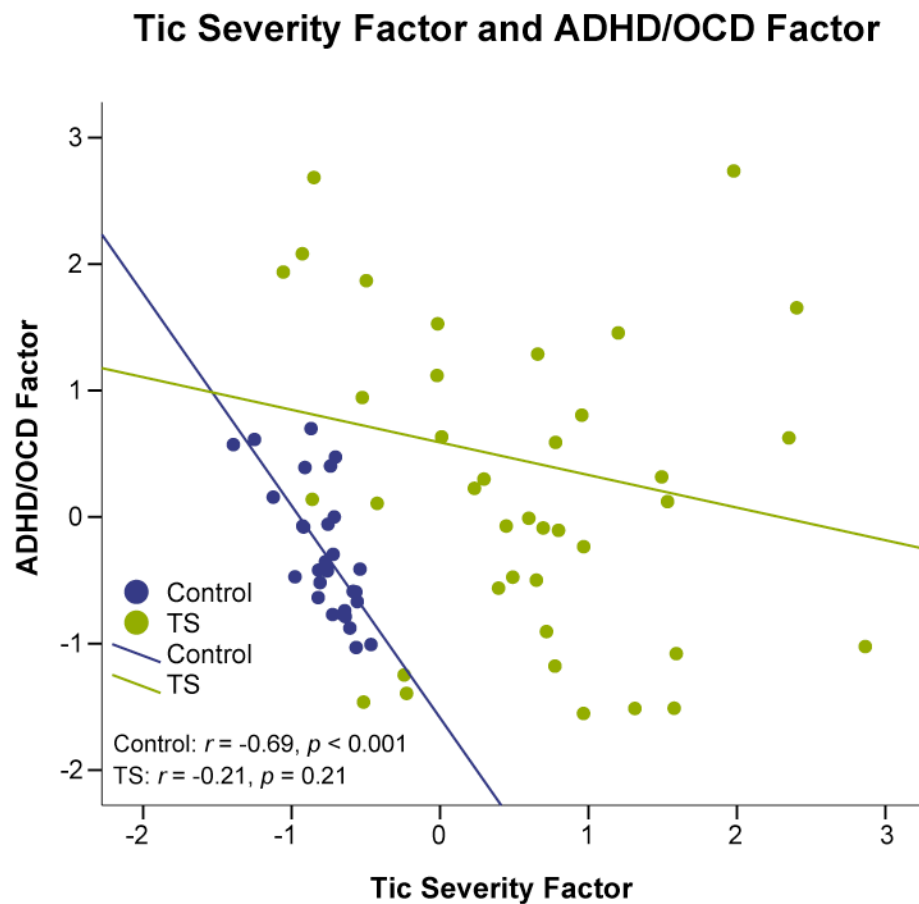
The first factor, or Tic Severity factor, clearly represents the YGTSS, which assesses phonic (vocal) and motor tic severity. Phonic tic subscales loaded more strongly than motor tic subscales. The second factor, or ADHD/OCD factor, primarily represents the ADHD-IV total and its two subscales, but also includes the OCI-CV total and four of its six subscales. The OCI-CV total and a new mix of three of six subscales loaded onto factor three, or the OCD factor. Finally, factor four, or Tic-related OCD factor, captures motor tics and the OCI-CV Washing subscale. **Figure 4.12** is a scatter plot of the ADHD/OCD and Tic Severity Factors. These two factors correlated for Controls ( $r(28) = -0.69, p < 0.001$ ), but not TS patients ( $r(38) = -0.21, p = 0.21$ ).

Lastly, the diagnostic rating scale factors (Tic Severity, ADHD/OCD, OCD, and Tic-related OCD) were correlated with the eye movement factors (Inhibition, Generation, Harder Task, and Easier Task), adjusting for age as a covariate. **Table 4.6** reveals the ADHD/OCD factor significantly correlated with the Inhibition factor ( $r(62) = 0.39, p = 0.001$ ) and Generation factor ( $r(62) = 0.27, p = 0.03$ ).

**Table 4.5** Factor analysis of diagnostic rating scale totals and subscales

Factor Extracted	Variance Explained	Subscales and Totals	Loadings
Tic Severity	39.6%	Phonic Tic Overall	0.929
		Phonic Tic Number	0.907
		Phonic Tic Intensity	0.878
		Phonic Tic Complexity	0.872
		Phonic Tic Frequency	0.868
		Tic Global (Total) Score	0.858
		Phonic Tic Interference	0.805
		Motor Tic Number	0.759
		Overall Life Impairment	0.747
		Motor Tic Frequency	0.731
		Motor Tic Overall	0.730
		Motor Tic Interference	0.676
		Motor Tic Intensity	0.673
ADHD/OCD	19.7%	ADHD Total	0.857
		ADHD Inattention	0.815
		ADHD Hyperactivity	0.806
		OCD Obsessions	0.662
		OCD Total	0.626
		OCD Doubting/Checking	0.566
		OCD Washing	0.484
		OCD Neutralizing	0.452
OCD	13.6%	OCD Hoarding	0.857
		OCD Total	0.653
		OCD Doubting/Checking	0.577
		Motor Tic Interference	0.490
		OCD Neutralizing	0.451
Tic-related OCD	9.1%	Motor Tic Complexity	0.788
		OCD Washing	0.674
		Motor Tic Overall	0.550

A variable was considered to have loaded a factor if its correlation (loading) with the factor was greater than  $r = 0.450$ . See **Appendix A** for a list of each rating scale's subscales and the questions comprising them.



**Figure 4.12** TS and Control Tic Severity and ADHD/OCD Factors

Individual TS patient and Control ADHD/OCD Factor scores are plotted against Tic Severity Factor scores.

**Table 4.6** Correlations of eye movement factors with diagnostic rating scale factors

EM Factor	Tic Severity	ADHD/OCD	OCD	Tic-related OCD
Inhibition	$r(62) = 0.20$	<b><math>r(62) = 0.39</math></b>	$r(62) = -0.05$	$r(62) = 0.17$
	$p = 0.11$	<b><math>p = 0.001</math></b>	$p = 0.69$	$p = 0.19$
Generation	$r(62) = 0.07$	<b><math>r(62) = 0.27</math></b>	$r(62) = 0.07$	$r(62) = 0.05$
	$p = 0.60$	<b><math>p = 0.03</math></b>	$p = 0.61$	$p = 0.69$
Harder Task	$r(62) = 0.05$	$r(62) = -0.10$	$r(62) = -0.06$	$r(62) = -0.10$
	$p = 0.72$	$p = 0.43$	$p = 0.65$	$p = 0.46$
Easier Task	$r(62) = -0.12$	$r(62) = -0.20$	$r(62) = 0.10$	$r(62) = 0.07$
	$p = 0.36$	$p = 0.12$	$p = 0.44$	$p = 0.60$

EM, eye movement; Bold correlations are statistically significant.

### Part 3 Summary

Separate factor analyses, one of the eye movement variables and another of the diagnostic rating scale totals and subscales, each produced four interpretable factors. The first two eye movement factors represented the voluntary functions of inhibition and generation, respectively. The latter two factors seemed to signify oculomotor function, namely Working Memory and Basic Sensorimotor Performance (**Table 4.3**). Only the Inhibition and Generation factors significantly correlated with the total scores of the three clinical measures (**Table 4.4**). Whereas the subscales loading most heavily on the first diagnostic rating scale factor exclusively evaluated tic severity, those loading the second factor were a mix of ADHD and OCD subscales. The third and fourth factors represented OCD and tic-related OCD, respectively (**Table 4.5**). Tic severity and ADHD/OCD factor scores correlated for Controls, but not TS patients (**Figure 4.12**). Of these diagnostic rating scale factors, only the ADHD/OCD factor significantly correlated with the Inhibition and Generation factors (**Table 4.6**).

## Chapter 5

# Discussion

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Despite the unwanted motor and vocal tics of TS, it is the highly prevalent comorbid conditions of ADHD and OCD associated with increased tic severity that insidiously impair the daily functioning of children with TS. This study clearly assessed the voluntary control abilities of children with TS. As suggested by the Tonic Inhibition Model (Serenio, 1992), frontal cortex regions regulate the basal ganglia's tonic inhibitory output applied on midbrain structures. Thus, it follows that impaired prefrontal cortex function will be evidenced by inferior voluntary performance, perhaps in tandem with enhanced reflexive operation. The neuroanatomical model outlined in **Chapter 2** describes the role of basal ganglia-thalamocortical loops in cognitive and motor control, anticipates behavioral deficits in individuals with TS, and predicts how they are exaggerated by comorbid ADHD and/or OCD. Earlier oculomotor investigations of cognitive control in TS ignored troublesome confounds, including medication, age, and comorbidity. The current study shows cognitive control deficit is not attributable to TS alone, but rather only when affiliated with increased symptom severities. In the final chapter, I will discuss this surprising finding, anchor its conclusion to the literature, and present a revised neuroanatomical model of TS and concomitant ADHD and OCD. In the process I will address three questions: Are comorbid ADHD and OCD additional, or instead inherent, to TS? How can children with only TS, who have obvious outward behavioral differences from typically developing children (i.e., tics), not also display behavioral differences on voluntary saccadic tasks of cognitive control? What, then, causes children with TS and ADHD and/or OCD to show cognitive control deficits? I will close with comments on how this study's conclusions can translate into improved clinical care.

## **Collective Results**

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In TS patients, ADHD and OCD symptom severities correlated strongly with one another. Additionally, tic severity increased positively with the symptom severities of both ADHD and OCD. Thus, symptoms of all three disorders tended to increase in tandem. This finding indicates comorbid ADHD and OCD are not self-contained components that often appear in partnership with TS, but rather that ADHD and OCD symptomatology is present at some level in the majority of TS patients, subthreshold to diagnosis in some and above diagnostic threshold in others.

On the Prosaccade and Antisaccade tasks of Part 1, I expected both TS-only and TS-comorbid patients to have a normally functioning reflexive system (normal Prosaccade response time and error rate), but depleted voluntary control (impaired Antisaccade response time and/or error rate) compared to Controls. This hypothesis was supported only partially.

Whereas TS-comorbid patients did have normal reflexive performance and deficient voluntary control, surprisingly neither TS-only patients' reflexive *nor* voluntary control differed from that of Controls. Just as symptom severities of all three disorders increase with one another and Antisaccade response times and error rates increase in patients with elevated symptom severities (i.e., TS-comorbid patients), perhaps these measures of voluntary function increase on a sliding scale encompassing even TS-only patients. This possibility was corroborated by the strikingly increased Antisaccade error rate evident in TS-only patients of higher tic severity when separately compared to TS-only patients with lower tic severity and Controls. The latter two groups did not differ in Antisaccade error rate. Thus, the data support the notion that as frontal lobe function becomes progressively worse, symptoms become more severe.

On the 0-back and 1-back tasks of Part 2, I expected both TS-only and TS-comorbid patients to have weak voluntary control (impaired 0-back and 1-back response time and/or error rate). Furthermore, I expected the Working Memory Load (response time or error rate performance difference between the 1-back and 0-back tasks) to be progressively greater on TS-only and TS-comorbid patients compared to Controls. Working Memory Load, as a difference measure, is a particularly accurate gauge of working memory, as it specifically captures the impact of increased task demands on an individual and removes the influence of other factors that may differ between the N-back tasks. As in Part 1, only a portion of the hypothesis was substantiated. With elongated response times, elevated error rates, and greater Working Memory Load, TS-comorbid patients demonstrated their voluntary control to be lacking not only in comparison to Controls, but also to TS-only patients, as again TS-only patients and Controls unexpectedly had comparable voluntary performance. The presence of measureable deficits in TS-comorbid patients, who have more severely defective basal ganglia-thalamocortical loops than TS-only patients, supports the idea that as basal ganglia-thalamocortical loops become gradually more damaged, frontal lobe voluntary control suffers.

In the factor analyses of Part 3, eye movement variables loaded onto four orthogonal (non-correlative) factors. Thus, Inhibition and Generation factors likely represent distinct voluntary processes, which correlate with the total scores of all three diagnostic rating scales. Hence, as symptom severities increase, inhibition and generation are progressively lacking. As for the factor analysis of diagnostic rating scales, subscales of the YGTSS are highly related and loaded the first factor. A mix of ADHD-IV and OCI-CV subscales next best accounted for the variance in clinical data. Interestingly, while the Hoarding, Doubting/Checking, and Neutralizing subscales of the OCI-CV loaded the third factor, only the Washing subscale loaded the fourth. Perhaps this division is influenced by the fact that symmetry obsessions and hoarding, touching, and counting compulsions are more common in patients with TS and OCD



than contamination obsessions and washing/cleaning compulsions, which more often afflict patients with OCD alone (de Groot and Bornstein, 1994; Leckman et al., 1994a; Cath et al., 2001).

In sum, I interpret the data to indicate (1) ADHD and OCD symptoms are present at some level in most all TS patients, because severities of these three disorders increase together, (2) orienting in TS patients with increased symptom severities follows the cognitive theory that inadequate volitional control produces normal or hyper-reflexive responses, (3) involvement of aberrant basal ganglia-thalamocortical loops leads to progressively more pronounced cognitive control impairments, specifically response inhibition, response generation, and working memory, and (4) eye movement variables and clinical data can be reduced separately into meaningful factors.

### **ADHD and OCD in TS: Additional or Integral?**

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As the controversial revisions of the DSM-IV are currently in committee, the debate whether to define mental disorders categorically or dimensionally is as germane as ever. Current standards use a categorical description, with discrete criteria to place a binary diagnosis on an individual. A dimensional approach, however, acknowledges the effluence of one disease into another and considers continuous severity of symptoms. One could argue the different frontostriatal underpinnings of TS and comorbid ADHD and OCD warrant a categorical approach. Growing evidence, however, calls for a dimensional method encompassing the shared phenotypes and overlapping frontostriatal circuitry of these developmental disorders. Some have doubted that what is currently categorically described as three concomitant, yet independent disorders, may in fact be the random parcellation of a solitary entity (Klein and Riso, 1993). For TS, comorbid ADHD and OCD may not be distinct, but rather intrinsic in TS.

The debate whether ADHD and OCD are additional, or instead integral, to TS started decades ago. Most studies based their stance on behavioral and epidemiological data. Comings and Comings, after extensive study, concluded ADHD is an integral aspect of TS (Comings and Comings, 1984, 1985, 1987). Later, this same group argued for a genetic relationship between ADHD and TS (Knell and Comings, 1993). While the Pauls group acknowledged the concurrence of ADHD and TS (Pauls et al., 1986a), they posited two types of TS with comorbid ADHD, one in which ADHD and TS independently coexist and another in which ADHD is secondary to TS (Pauls et al., 1993). While the evidence for overlap and genetic relationship between OCD and TS is strong (Frankel et al., 1986; Pauls et al., 1986b), some studies still offered controversy (Black et al., 1992; Shapiro and Shapiro, 1992).

Shared clinical manifestations of tics, compulsions, and behavioral disturbances seem to suggest similar neural circuits underlie them. As symptoms worsen, are these circuits involved in succession or in parallel? A scatter plot of the symptom severities of two disorders can reveal clues of their neurobiological relationship. A plot with an initial slope of zero, which at some point spikes upward, signals the additive involvement of neural circuits. Critically, though, if TS and comorbid ADHD and OCD share a common neural substrate, their respective symptoms should correlate (Spessot and Peterson, 2006). Indeed, in my patient sample, TS, ADHD, and OCD symptom severity correlated with one another. Zhu and colleagues also found that tic severity correlated with attention problems and thought problems, as measured by the Child Behavior Checklist (Zhu, et al., 2006). While they did not use global tic severity as I did, their correlation values for YGTSS motor and phonic subscales ranged between  $r = 0.32$  and  $0.52$  ( $p < 0.05$  to  $p < 0.01$ ) for attention problems and  $r = 0.28$  and  $0.33$  ( $p < 0.01$ ) for thought problems. This ADHD-tic symptom severity correlation was stronger than mine ( $r = 0.22$ ) giving greater credence to the claim that ADHD is part and parcel with TS. My study's OCD-tic symptom severity correlation value ( $r = 0.35$ ) is similar to that of Zhu and colleagues. Of interest, Cath and colleagues qualitatively confirm this, stating the primary difference among TS patients with and without OCD is increased symptom severity in TS patients with OCD (Cath et al., 2000). Zhu and colleagues also report significantly increased attention and thought problems in TS children with more severe tics compared to those with less severe tics. This aligns with my findings not only of increased Antisaccade errors in the TS-only patients with high tic severity, but also with impaired voluntary control in TS-comorbid patients (who also tend to have more severe tics). These data point to parallel, gradually increasing symptom severities matching with equivalently escalating behavioral performance deficits. This suggests ADHD and OCD are integral to TS.

ADHD and OCD symptoms commonly coexist in TS, but is their pairing more or less strong in the absence of TS? Mathews and colleagues demonstrated that inattention/hyperactivity and obsessions/compulsions are present together in undergraduate students (Mathews et al., 2004). The strength of their relationship ( $r = 0.28$ ) was less than in the typically developing children in my study ( $r = 0.42$ ), but ADHD symptoms (Faraone et al., 2006) as well as OCD symptoms (Bloch et al., 2009) are known to decline in adulthood. Regardless, in both Mathews' and my non-TS samples, ADHD and OCD symptoms were not as tightly linked as in my TS patients. Therefore, ADHD and OCD uniquely interact in TS.

## **TS-only Patients: Tics, but No Cognitive Control Impairments?**

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Owing to known frontostriatal dysfunction, patients with TS are expected to have neuropsychological deficits in addition to their tics (Eddy et al., 2009). These impairments could include visuomotor deficits, attention deficits, or executive deficits encompassing inhibition and working memory break down. Indeed, cognitive impairments in other movement disorders of basal ganglia origin, like Parkinson's disease (Gabrieli et al., 1996; Weintraub et al., 2005) and Huntington's disease (Lawrence et al., 1998; Montoya et al., 2006), have been linked to basal ganglia-thalamocortical circuit dysfunction. So, too, have many studies reported cognitive deficit in individuals with TS. As in previous eye movement studies, however, most study designs prevent complete attribution of deficit to TS, but rather to the culprits of medication, age, and comorbid status.

Echoing the findings of my eye movement investigation in TS, the neuropsychological literature largely finds cognitive control deficits only in TS children with comorbid disorders. My review here will discuss only studies in children with TS, although the same issues stand in adults (Eddy et al., 2009). On tests of working memory, Verte and colleagues reported children with TS to have impairment, however 22 of 24 subjects had comorbid ADHD and/or OCD (Verte et al., 2005). Poysky and colleagues attributed the working memory deficits in their study to the influence of coexistent ADHD (Poysky et al., 2006). In fact, Martha Denckla, doyenne of ADHD research, remarked that after a decade of research with TS children free of ADHD, she could not find the substandard motor control or executive control typifying children with ADHD alone or TS with ADHD (Denckla, 2006). Perhaps most applicable to my study, children with pure TS showed no confirmation of working memory deficit on an N-back verbal working memory task (Crawford et al., 2005).

With the unintended release of tics in TS, inhibitory control deficits are expected to be central to TS. On a Go-No Go task, children with TS were impaired, although several patients in this study had OCD (Muller et al., 2003). Couple this with another Go-No Go study in which inadequate performance was found only in patients with OCD, not in children with uncomplicated TS or controls (Watkins et al., 2005). In strong corroboration of my findings, Ozonoff and colleagues found reduced inhibitory function on a negative priming task not only exclusive to TS patients with comorbid ADHD and/or OCD, but also patients of high symptom severity (tics, inattention/hyperactivity, *and* obsessions/compulsions), not patients with low symptom severity (Ozonoff et al., 1998). They concluded that cognitive control impairment is a function of both comorbidity and global symptom severity. In sum, children with TS have no

general cognitive impairments, except when accompanied by comorbid conditions (Como, 2001).

Yet, if the presence of tics obviously distinguishes TS-only patients from typically developing children, why do the implicated basal ganglia-thalamocortical circuits not also produce reduced cognitive control? For a possible answer, we can turn to neuroimaging, which provides direct evidence for the involvement of distinct brain areas. Most work in TS has scrutinized subcortical basal ganglia volumes, but recent work has focused on the cortical origins of the multiple basal ganglia-thalamocortical circuits. In a seminal paper, Sowell and colleagues reported thinning of gray matter layers in the sensorimotor cortices of children with TS, providing express evidence for involvement of the Motor Loop in TS (see **Chapter 1**; Sowell et al., 2008). Not only was thinning more pronounced in teens than children, but also was coupled with more severe tics, paralleling the progression of tic severity through adolescence. Specifically, while thinning in dorsal sensorimotor cortices inversely correlated with worst-ever tic severity, thinning was most pronounced in ventral areas and directly correlated with the number of simple facial tics. The ventral sensorimotor cortex is known to control the musculature of the face, mouth, and larynx, the very structures most commonly involved in simple tics. Fahim and colleagues recently replicated these exciting findings, which link anatomy to symptoms, and reported that significant cortical thinning in sensorimotor cortices inversely correlated with tic severity (Fahim et al., 2009).

Many imaging studies in TS have found significant changes in the DLPFC, the cortical origin of the Dorsolateral Prefrontal Loop that enables spatial memory, executive function, and attention. An early anatomical magnetic resonance imaging (MRI) study reported *larger* DLPFC volume in children with TS compared to controls (Peterson et al., 2001). Further, bilateral DLPFC thinning correlated inversely with tic severity (Sowell et al., 2008). So, too, in the orbitofrontal cortex (OFC), the frontal lobe origin of the Lateral Orbitofrontal Loop involved in inhibitory control, cortical volume negatively correlated with tic severity (Peterson et al., 2001). Two groups found more white matter under these frontal lobe regions, implying more connectivity with deep brain structures (Fredericksen et al., 2002; Hong et al., 2002).

Because increased DLPFC and OFC brain matter is associated with less tic severity, several authors have interpreted these results as evidence of an adaptive, compensatory mechanism (Peterson et al., 2001; Baym et al., 2008; for review, see Spessot et al., 2004). This view is further supported by a functional MRI (fMRI) study in which effortful tic suppression activated vast areas of the prefrontal cortex (Peterson et al., 1998). Moreover, TS patients had increased electroencephalogram (EEG) coherence among sensorimotor, prefrontal, and

frontomesial regions not only during voluntary tic suppression, but also during a Go-No Go inhibition task (Serrien et al., 2005). Critically, patients had equivalent performance on the task as controls, suggesting the increased coherence was behaviorally compensatory.

As increased tic severity in early adolescence is coupled with the rigid expectations of school and social settings, youth with TS continually tap these prefrontal regions to suppress tics. Over time, activity-dependent enlargement of prefrontal cortices builds the capacity for inhibitory functions (Spessot et al., 2004). This change is known as neural plasticity, which in humans can occur in just days (Pascual-Leone et al., 1995) or minutes (Classen et al., 1998). The prefrontal cortex has long been connected with this type of self-regulatory control, arbitrating working memory and inhibition (Fuster, 1989). The same frontal regions also moderate the cognitive control of voluntary eye movements (Oculomotor Loop; for review, see Hutton, 2008). Thus, in TS, while abnormalities of sensorimotor cortices underpin the presence of tics, the enlarged prefrontal regions of DLPFC and OFC not only adaptively protect against worse symptoms, but also enable the absence of measureable neuropsychological and eye movement deficits.

### **TS-comorbid Patients: What Pathology Causes Cognitive Control Deficits?**

---

Children with TS and comorbid ADHD and/or OCD are known to have cognitive impairment on tasks assessing a wide range of neuropsychological functions. In fact, these deficits are equal or greater to those found in children with ADHD or OCD alone. In a behavioral study, children with TS and ADHD demonstrated no difference from children with pure ADHD (Sukhodolsky et al., 2003). Further, these two groups showed more behavioral, functional, and family disturbances than either controls or children with only TS. In OCD, patients with tic-related OCD were found to have higher incidences of substance abuse, mood disorders, and anxiety than either those with TS or OCD alone (Coffey et al., 1998). This asserts that TS with OCD results in more clinical morbidity than either isolated condition. So, what pathology contributes to inferior cognitive control in these comorbid patients?

Interestingly, the DLPFC and OFC, the same areas posited to compensate for tics and potential cognitive control deficits in pure TS, have been implicated in the functional demise of children with comorbid ADHD and OCD. Children with TS and ADHD were found to have smaller frontal lobes than uncomplicated TS patients (Fredericksen et al., 2002). In particular, Kates and colleagues identified less gray and white matter in the prefrontal cortex of children with TS and ADHD compared to those with only TS (Kates et al., 2002). In a diffusion tensor imaging study of a juvenile TS sample, the strength of the DLPFC connection to the caudate of

the basal ganglia was found to inversely correlate with obsessive-compulsive behavior (Makki et al., 2009). Thus, these abnormal frontal regions likely may lead to functional impairments in children with TS and coexistent ADHD and/or OCD.

The DLPFC is not only abnormally smaller in children with TS and concomitant ADHD, but also in children with ADHD alone. Youth with ADHD have smaller frontal lobes with less underlying connective white matter (Castellanos et al., 2002; Mostofsky et al., 2002). Filipek and colleagues located the cortical shrinkage and white matter depletion in children with ADHD to be in the anterior-superior frontal lobe (region including DLPFC; Filipek et al., 1997). The DLPFC was specifically found to be smaller in children with ADHD alone (Sowell et al., 2003). A longitudinal study reported kids with persistent ADHD have cortical thinning in DLPFC at baseline and at follow-up an average of 5.7 years later compared to controls and patients with remitted ADHD (Shaw et al., 2006). These data indicate abnormalities of the DLPFC contribute to an aberrant Dorsolateral Prefrontal Loop particular to ADHD.

Although pediatric OCD patients have been included in very few neuroimaging studies, the data implicate the OFC in OCD. Carmona and colleagues found decreased gray and white matter in the inferior frontal lobes (region including OFC; Carmona et al., 2007; but see Szeszko et al., 2008). In an fMRI study, both children with OCD and healthy controls completed tests of inhibition – a stop task, a motor Stroop task of spatial interference, and a switch task (Woolley et al., 2008). Children with OCD showed reduced activation of the OFC and its subcortical targets compared to controls, demonstrating dysfunctional frontostriatal circuitry. While patient performance did not differ statistically from controls, patients did show a statistical trend toward worse performance on the Stroop and switch tasks. Limitations of the study included a small patient sample size, 80% of whom were medicated, and all of whom were in partial remission of OCD symptoms. These studies allude to an irregular OFC leading to an impaired Lateral Orbitofrontal Loop in OCD.

The degree of comorbidity in a child has monumental ramifications on the extent of his or her functional impairment. As both the number and severity of comorbidities increase, so, too, do behavioral disturbances (Caron and Rutter, 1991). In fact, the level of comorbidity may represent the extent of underlying pathophysiology in terms of brain function and lead to more symptoms of greater severity (Freeman et al., 2000). For TS, perhaps initially enlarged DLPFC and OFC enable dampened symptom severity and eased cognitive control deficit. But, as volumes of DLPFC and OFC gray and white matter decrease, TS patients inevitably succumb not only to more severe symptoms of TS, ADHD, and OCD, but also more severe functional impairment. Restated, while enhanced DLPFC and OFC allow reduction of symptom severities

and equivalent voluntary eye movement control in TS-only patients, emaciated DLPFC and OFC expose greater overall symptom severity and poor voluntary eye movement control in TS-comorbid patients.

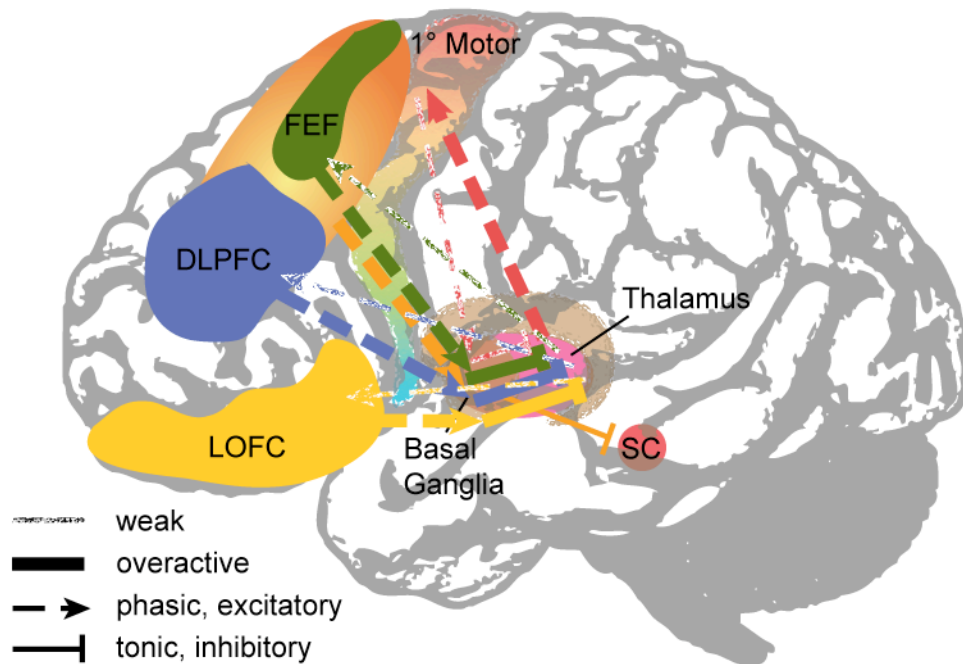
### Updated Model of Orienting in TS

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The original model of orienting in TS (**Figure 2.2**) hypothesized weak frontal areas would lead not only to impaired voluntary eye movement performance, but also to release of the mid-brain reflexive control center from basal ganglia tonic inhibition, allowing normal or hyperreflexive responding. The presence of comorbid ADHD and/or OCD, underpinned by involvement of additional basal ganglia-thalamocortical circuits (see **Figure 2.3**), would motivate further frontal weakness and poorer voluntary eye movement control. Results from both Part 1 and 2, however, unexpectedly revealed TS-only patients to be free of eye movement deficit, whereas only TS-comorbid patients demonstrated the predicted voluntary eye movement dysfunction.

The updated model of orienting in TS (**Figure 5.1**) reconciles the seeming disconnect between the presence of tics and the absence of voluntary eye movement impairment in children with TS but without comorbid ADHD and OCD. Thinning of the sensorimotor cortex and impairment of the Motor Loop leads to tics. Repeated activation of the DLPFC and LOFC to suppress tics stimulates plastic hypertrophy of these stalwart prefrontal titans, achieving augmented inhibitory reserves. Bolstered Dorsolateral Prefrontal and Lateral Orbitofrontal Loops result in greater capacity for self-regulatory control, keeping otherwise rising symptom severities in check. Benefits of this compensatory mechanism extend to the normalization of potential deficits in eye movement measures of cognitive control.

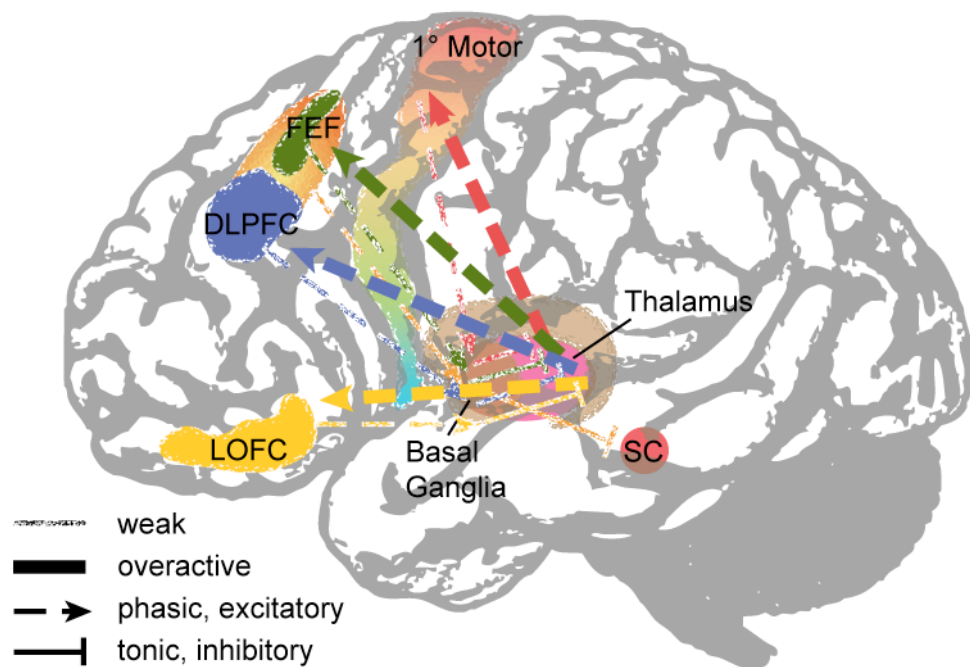
An extension of this model encapsulates the neuroanatomical changes leading to the worsened symptoms and voluntary eye movement deficits characterizing TS patients with comorbid ADHD and/or OCD (**Figure 5.2**). Further thinning of the sensorimotor cortex leads to a growing repertoire of tics, especially if simultaneous with shrinkage or stymied adaptive growth of the DLPFC and/or LOFC. Progressively impaired Dorsolateral Prefrontal and Lateral Orbitofrontal Loops lead to increased severities of ADHD and OCD symptoms, respectively. Consequent reductions in self-regulatory control reveal eye movement deficits indicative of the extent of pathophysiology.



**Figure 5.1** Updated model of orienting in Tourette Syndrome

Thinning of the motor cortex and impairment of the Motor Loop disinhibits the thalamus, leading to tics. Repeated use of the DLPFC and LOFC to suppress tics leads to adaptive growth of these prefrontal volumes and enhanced Dorsolateral Prefrontal and Lateral Orbitofrontal Loops. The resulting boost to self-regulatory control keeps otherwise increasing symptom severities in check and through the FEF and Oculomotor Loop permits normalization of potential eye movement deficits. 1° Motor, primary motor cortex; FEF, frontal eye field; DLPFC, dorsolateral prefrontal cortex; LOFC, lateral orbitofrontal cortex; SC, superior colliculus





**Figure 5.2** Updated model of orienting in Tourette Syndrome patients with comorbidities

Further thinning of the sensorimotor cortex and breakdown of the Motor Loop leads to a growing repertoire of tics, especially if simultaneous with shrinkage or stymied adaptive growth of the DLPFC and LOFC. Progressively impaired Dorsolateral Prefrontal and Lateral Orbitofrontal Loops lead to increased severities of ADHD and OCD symptoms, respectively. Consequent reductions in self-regulatory control involve the FEF and Oculomotor Loop, revealing eye movement deficits indicative of the extent of pathophysiology. 1° Motor, primary motor cortex; FEF, frontal eye field; DLPFC, dorsolateral prefrontal cortex; LOFC, lateral orbitofrontal cortex; SC, superior colliculus

This model is supported by the wealth of neuroimaging data reviewed above, but is not without caveat. This model of orienting in TS holds only for children and adolescents, not adults (who are the extreme minority of TS patients, see **Chapter 1**). While some neuroimaging studies in adults with persistent TS report findings in line with that of children, plenty others do not. For example, while less gray matter in the middle frontal gyrus of adults with TS inversely correlates with tic severity and more white matter underlies this area (Müller-Vahl et al., 2009), critically, adults with TS were found to have smaller DLPFC than age-matched peers (Peterson et al., 2001). These data highlight the developmental nature of TS and underscore the necessity to control for age.

### **Alternative Model**

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In Alexander and colleagues' influential papers describing the neuroanatomy of the basal ganglia-thalamocortical loops, they emphasized the parallel anatomical and physiological nature of each loop (Alexander et al., 1986, 1990). In their description, the circuits all course through the same structures, but never interconnect, establishing segregated, parallel loops. Yet, this model focuses on the basal ganglia's role in selecting and completing learned, coordinated actions or emotions, not its more recently identified ability to learn behaviorally relevant rules (Aosaki et al., 1994). The basal ganglia reinforce behavior, but also integrate current situational cues to allow estimation of future events and execute proper responses. To accommodate these functions, cross talk among functionally distinct loops is necessary (Haber, 2003).

The basal ganglia-thalamocortical loops consult with one another through several mechanisms. First, while the general alignment of anatomical projections through each loop is maintained, the broad dendritic arbors of neurons in adjacent loops often overlap along adjoining functional areas. Further, the sharp reduction of structure size at each circuit level subsequent to the cortex forces convergence of nerve terminals from neighboring functional regions (Percheron and Filion, 1991; Yelnik et al., 1997; Yelnik, 2002). Whereas these means of overlap are primarily at the functional edges of circuits, gross information sharing occurs through several non-reciprocal connections. The motor (Motor), associative (Oculomotor and Dorsolateral Prefrontal), and limbic (Lateral Orbitofrontal and Anterior Cingulate) loops not only form traditionally-described "closed" circuits, which begin and end at the same cortical target, but each loop also has one or more "open" pathways (Joel and Weiner, 1994). The cortical target of an "open" pathway is not the loop's originating cortical structure, but rather that of another basal ganglia-thalamocortical loop. In this way, the motor, associative, and limbic

circuits interact. Inter-loop communication also occurs subcortically, in striato-nigro-striatal (Haber et al., 2000) and thalamo-cortico-thalamic pathways (McFarland and Haber, 2002). In these feed forward routes, limbic regions of a subcortical loop structure (e.g., dorsal SN<sub>pr</sub>) influence associative regions (e.g., medial SN<sub>pr</sub>), which interact with motor regions (e.g., ventral SN<sub>pr</sub>).

Open, interconnected basal ganglia-thalamocortical loops are important to a comprehensive view of TS. While a dysfunctional Motor Loop underlies symptoms of TS, an aberrant Dorsolateral Prefrontal Loop triggers symptoms of ADHD, and a damaged Lateral Orbitofrontal Loop prompts symptoms of OCD, these clinical signs do not appear or progress independently in TS. In contrast, symptoms of the comorbid triad increase in parallel and may be accommodated by overlapping information flow through basal ganglia-thalamocortical loops. Hence, TS patients with mild overall symptoms and undetectable cognitive control impairments may have moderately affected pathways, while those with more severe global symptoms and measureable cognitive control deficits may have extensive disruption of interconnected loops.

## **Future Directions**

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I personally will use the three diagnostic rating scale scores from this study to develop a single composite score (z-score) for each participant. With this z-score, patients will be divided into those with lower or higher overall symptom severity. This is a more accurate division of symptom severities from my current division into those with or without comorbidities, because it also accounts for tic severity. Analysis of eye movement performance can be repeated to see if a more significant difference exists between patient severity groups, corroborating my model in which cognitive control deficits increase with overall symptom severity.

Another potential direction is to assess the efficacy of common TS pharmacotherapies to improve cognitive control in TS. Children with TS can be tested on tasks of reflexive and voluntary eye movement control before treatment as a baseline measure. After several weeks of drug administration when effectiveness is optimal, patients can be retested to quantitatively determine the improvement of the child's cognitive control due to the medicine.

Finally, as a postdoctoral fellow with Pramod Dash, Ph.D., I will search for candidate salivary protein biomarkers of TS. With high performance liquid chromatography (HPLC) and tandem mass spectrometry, I will investigate Control and TS patients' saliva samples for a protein(s) that is in a significantly different quantity(ies). The identity of this candidate protein biomarker(s) will be confirmed by enzyme-linked immunosorbent assay (ELISA).

## Implications for Changed Clinical Care

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Much evidence supports the deleterious clinical and functional impact of increased tic and comorbid symptom severities in TS. Comorbid conditions, though, are more functionally impairing than tics themselves (Spessot and Peterson, 2006). ADHD is unmistakably the main cause of behavioral, emotional, and cognitive deficit in TS (Spessot and Peterson, 2006). Case in point, children with TS and ADHD have a risk of academic problems four times as great as TS patients without ADHD (Erenberg et al., 1986; Abwender et al., 1996; Schuerholz et al., 1996). Because ADHD leads to more strained social interaction, an early diagnosis of ADHD in TS and subsequent psychosocial coaching may directly improve quality of life (Carter et al., 2000). OCD, too, with increased anxiety, substance abuse, and mood disorders, may bestow a greater functional burden than TS or OCD alone (Coffey et al., 1998). Thus, proactive clinical intervention is direly needed to reduce the effect of comorbid conditions in TS.

Perhaps preventive behavioral therapy could be effective in minimizing future impact of elevated symptom severities in TS. Therapists could employ neuropsychological tasks to strengthen the planning, working memory, and cognitive flexibility of the DLPFC and the reward-motivated, inhibitory processes of the LOFC. This approach has at least two potential benefits. First, reinforced control in these prefrontal cortex regions may produce the activity-dependent plasticity necessary to stave off the progression of symptoms and associated functional impairment. Second, rather than wait until the patient is mired in troubles at school and home, proactive training in recognizing significant triggers, problem events, and associated feelings as well as navigating complex responsibilities (e.g., school demands) can better equip the patient for inevitable struggles.

This study quantitatively established that ADHD and OCD symptoms are present in the majority of TS patients, even if these symptoms are below diagnostic threshold. More exactly, symptoms of comorbid conditions increase together with tic severity. Given tic severity erratically waxes and wanes on both short and developmental time scales, even mild TS patients may face hindering attentional and obsessional symptoms at some time. Thus, clinicians must use vigilance to evaluate all TS patients for the full range of symptom severities. Even families of TS patients presenting with little or no comorbid symptoms should be educated on the possible course and impending impairment of increased symptoms. Pollak and colleagues stress the need for this approach, "TS is itself a risk factor for behavioral problems mandating that children with TS even if without ADHD and OCD still need to be assessed and treated for psychopathology" (Pollak et al., 2009).

To aid this endeavor, inclusion of a dimensional assessment could assist standard categorical diagnostic procedures, not only enabling confirmation of the presence or absence of a condition, but also the degree of expression (Hudziak et al., 2007). As neuropsychological impairment is a function of both comorbid status and overall symptom severity, dimensional assessment is the best predictor of current cognitive status (Ozonoff et al., 1998). In my study, the combinatorial loading of subscales from several clinical measures onto a single factor (e.g., ADHD-IV and OCI-CV subscales) suggest that future work could create a new TS “superscale,” or combination of the three current diagnostic rating scales to most fully evaluate overall symptom severities. Overall, consideration of the complete amalgam of symptoms existing in children with TS will ensure a greater understanding of their functional implications.

Appendix A

# Diagnostic Rating Scales

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## **List of Diagnostic Rating Scales and Subscales**

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### **Attention Deficit Hyperactivity Disorder Rating Scale – IV (ADHD-IV)**

Inattention Subscale	(Odd numbered questions)
Hyperactivity Subscale	(Even numbered questions)
ADHD-IV Total	(Percentile Rank of Total Sum)

### **Obsessive Compulsive Inventory – Child Version (OCI-CV)**

Obsessing Subscale	(Questions 1, 11, 14, and 18)
Washing Subscale	(Questions 2, 10, and 21)
Hoarding Subscale	(Questions 3, 7, and 16)
Doubting/Checking Subscale	(Questions 4, 5, 13, 15, and 20)
Neutralizing Subscale	(Questions 6, 9, and 12)
Ordering Subscale	(Questions 8, 17, and 19)
OCI-CV Total	(Sum of all Questions)

### **Yale Global Tic Severity Scale (YGTSS)**

Motor Tic Number Subscale	
Motor Tic Frequency Subscale	
Motor Tic Intensity Subscale	
Motor Tic Complexity Subscale	
Motor Tic Interference Subscale	
Motor Tic Overall Severity	(Sum of Motor Tic Subscales)
Phonic Tic Number Subscale	
Phonic Tic Frequency Subscale	
Phonic Tic Intensity Subscale	
Phonic Tic Complexity Subscale	
Phonic Tic Interference Subscale	
Phonic Tic Overall Severity	(Sum of Phonic Tic Subscales)
Overall Life Impairment	
Global Tic Severity Total	(Sum of Motor Tic Overall, Phonic Tic Overall, and Overall Life Impairment Subscales)

ID # \_\_\_\_\_

Youth  
Parent \_\_\_\_\_Date \_\_\_\_\_  
Time \_\_\_\_\_

## Rating Scale

Please circle the number that **best describes** your child's behavior **over the past 6 months**.  
This is not a test, so there are no right and wrong answers.

	Never or Rarely	Some- times	Often	Very Often
1. Fails to give close attention to details or make careless mistakes in schoolwork.	0	1	2	3
2. Fidgets with hands or feet or squirm in seat.	0	1	2	3
3. Has difficulty sustaining attention in tasks or play activities.	0	1	2	3
4. Leaves seat in classroom or in other situations in which remaining seated is expected.	0	1	2	3
5. Does not seem to listen when spoken to directly.	0	1	2	3
6. Runs about or climbs excessively in situations in which it is inappropriate.	0	1	2	3
7. Does not follow through on instructions and fails to finish work.	0	1	2	3
8. Has difficulty playing or engaging in leisure activities quietly.	0	1	2	3
9. Having difficulty organizing tasks and activities.	0	1	2	3
10. Is "on the go" or acts if "driven by a motor".	0	1	2	3
11. Avoids tasks (e.g., schoolwork, homework) that require sustained mental effort.	0	1	2	3
12. Talks excessively.	0	1	2	3
13. Loses things necessary for tasks or activities.	0	1	2	3
14. Blurts out answers before questions have been completed.	0	1	2	3
15. Is easily distracted.	0	1	2	3
16. Has difficulty awaiting turn.	0	1	2	3
17. Is forgetful in daily activities.	0	1	2	3
18. Interrupts or intrudes on others.	0	1	2	3



ID # \_\_\_\_\_

Youth  
Parent \_\_\_\_\_Date \_\_\_\_\_  
Time \_\_\_\_\_

# Rating Scale

Please circle the number that **best describes** your child's behavior **over the past month**.  
This is not a test, so there are no right and wrong answers.

Example	Never	Sometimes	Always
Think a lot about dogs	0	1	2
	Never	Sometimes	Always
1. Thinks about bad things and can't stop.	0	1	2
2. Feels like they must wash and clean over and over again.	0	1	2
3. Collects so much stuff that it gets in the way.	0	1	2
4. Checks many things over and over again.	0	1	2
5. After they have done things, they're not sure if they really did them.	0	1	2
6. Needs to count while they do things.	0	1	2
7. Collects things they don't really need.	0	1	2
8. Gets upset if their stuff is not in the right order.	0	1	2
9. Gets behind in their schoolwork because they repeat things over and over again.	0	1	2
10. Worries a lot about things being clean.	0	1	2
11. Gets upset by bad thoughts.	0	1	2
12. Have to say some numbers over and over.	0	1	2
13. Even after they're done, they still worry they didn't finish things.	0	1	2
14. Gets upset by bad thoughts that pop into their head when they don't want them to.	0	1	2
15. Checks doors, windows, and drawers over and over again.	0	1	2
16. Don't throw things away because they're afraid they might need them later.	0	1	2
17. Gets upset if people change the way they arrange things.	0	1	2
18. If a bad thought comes into their head, they need to say certain things over and over.	0	1	2
19. Needs things to be in a certain way.	0	1	2
20. Even when they do something very carefully, they don't think they did it right.	0	1	2
21. Washes their hands more than other kids.	0	1	2

ID # \_\_\_\_\_

Youth  
Parent \_\_\_\_\_

Date \_\_\_\_\_  
Time \_\_\_\_\_

# Tic Severity Scale

Part I. Please mark the tics below that have been present **during the past week**.

## A. Simple Motor Tics

(rapid, darting, 'meaningless' movements)

- \_\_\_\_\_ Eye blinking
- \_\_\_\_\_ Eye movements
- \_\_\_\_\_ Nose movement
- \_\_\_\_\_ Mouth movements
- \_\_\_\_\_ Facial grimace (wince)
- \_\_\_\_\_ Head jerks/movements
- \_\_\_\_\_ Shoulder shrugs
- \_\_\_\_\_ Arm movements
- \_\_\_\_\_ Hand movements
- \_\_\_\_\_ Abdominal (stomach) movements
- \_\_\_\_\_ Leg, foot, or toe movements
- \_\_\_\_\_ Other \_\_\_\_\_

## B. Complex Motor Tics

(slower, 'purposeful' movements)

- \_\_\_\_\_ Eye gestures or movements
- \_\_\_\_\_ Mouth movements
- \_\_\_\_\_ Facial movements or expressions
- \_\_\_\_\_ Head gestures or movements
- \_\_\_\_\_ Shoulder gestures
- \_\_\_\_\_ Arm or hand gestures
- \_\_\_\_\_ Writing tics
- \_\_\_\_\_ Distorted, abnormal postures
- \_\_\_\_\_ Bending or gyrating (twisting, writhing)
- \_\_\_\_\_ Rotating
- \_\_\_\_\_ Leg, foot, or toe movements
- \_\_\_\_\_ Tic-related compulsive behaviors (touching, tapping, grooming, evening-up)
- \_\_\_\_\_ Involuntary obscene or forbidden gestures
- \_\_\_\_\_ Self-abusive behavior (describe) \_\_\_\_\_
- \_\_\_\_\_ Outbursts of tics (displays), duration \_\_\_\_\_ seconds
- \_\_\_\_\_ Other \_\_\_\_\_

\_\_\_\_\_ Describe any elaborate, choreographed patterns or sequences of motor tics  
\_\_\_\_\_  
\_\_\_\_\_

## C. Simple Phonic Symptoms

(fast, 'meaningless' sounds)

- \_\_\_\_\_ Coughing
- \_\_\_\_\_ Throat clearing
- \_\_\_\_\_ Sniffing
- \_\_\_\_\_ Grunting
- \_\_\_\_\_ Whistling
- \_\_\_\_\_ Animal or bird noises
- \_\_\_\_\_ Other \_\_\_\_\_

## D. Complex Phonic Symptoms

(language: words, phrases, statements)

- \_\_\_\_\_ Syllables (list) \_\_\_\_\_
- \_\_\_\_\_ Words (list) \_\_\_\_\_
- \_\_\_\_\_ Stuttering (list) \_\_\_\_\_
- \_\_\_\_\_ Speech interruption by tongue, lips, or vocal chord freezing \_\_\_\_\_
- \_\_\_\_\_ Involuntary obscene or forbidden words or remarks (list) \_\_\_\_\_
- \_\_\_\_\_ Repeating another's words (describe) \_\_\_\_\_
- \_\_\_\_\_ Repeating one's own words (describe) \_\_\_\_\_
- \_\_\_\_\_ Disinhibited speech (immediate impulsive response) (describe) \_\_\_\_\_
- \_\_\_\_\_ Describe any elaborate, choreographed patterns or sequences of phonic tics  
\_\_\_\_\_  
\_\_\_\_\_

ID # \_\_\_\_\_

Youth  
Parent \_\_\_\_\_

Date \_\_\_\_\_  
Time \_\_\_\_\_

Part II. Rate motor and phonic tics separately, unless otherwise indicated.

Using the following scale, rate the **number** of:

\_\_\_\_\_ motor tics (selected in sections A and B) present **during the past week.**

\_\_\_\_\_ phonic tics (selected in sections C and D) present **during the past week.**

- 0 None
- 1 Single kind of tic (eye blinking, for example)
- 2 Multiple kinds of tics (2-5) (eye blinking and nose movements, for example)
- 3 Multiple kinds of tics (>5)
- 4 Multiple kinds of tics plus at least one elaborate, choreographed pattern of multiple simultaneous or sequential tics where it is difficult to distinguish distinct tics.
- 5 Multiple kinds of tics plus several (>2) elaborate, choreographed patterns of multiple simultaneous or sequential tics where it is difficult to distinguish distinct tics.

Using the following scale, rate the **frequency** of:

\_\_\_\_\_ motor tics (selected in sections A and B) present **during the past week.**

\_\_\_\_\_ phonic tics (selected in sections C and D) present **during the past week.**

- |   |                       |  |
|---|-----------------------|--|
| 0 | <i>None.</i>          | No evidence of specific tic behaviors.   |
| 1 | <i>Rarely.</i>        | Specific tics have been present during the past week. These behaviors occur infrequently, often not on a daily basis. If bouts (attacks) of tics occur, they are brief and uncommon.                                 |
| 2 | <i>Occasionally.</i>  | Specific tics are usually present on a daily basis, but there are long tic-free intervals during the day. Bouts (attacks) of tics may occur on occasion and are not sustained for more than a few minutes at a time. |
| 3 | <i>Frequently.</i>    | Specific tics are present on a daily basis. Tic-free intervals as long as 3 hours are not uncommon. Bouts of tics occur regularly, but may be limited to a single setting or environment.                            |
| 4 | <i>Almost Always.</i> | Specific tics are present virtually every waking hour of every day, and periods of sustained tics occur regularly. Bouts (attacks) of tics are common and are not limited to a single setting or environment.        |
| 5 | <i>Always.</i>        | Tics are present virtually all the time. Tic-free intervals are difficult to identify and do not last more than 5 to 10 minutes at most.   |

ID # \_\_\_\_\_

Youth  
Parent \_\_\_\_\_Date \_\_\_\_\_  
Time \_\_\_\_\_Using the following scale, rate the **intensity** of:\_\_\_\_\_ motor tics (selected in sections A and B) present **during the past week.**\_\_\_\_\_ phonic tics (selected in sections C and D) present **during the past week.**

- |   |                            |   |
|---|----------------------------|---|
| 0 | <i>Absent.</i>             |   |
| 1 | <i>Minimal intensity.</i>  | Tics are not visible or audible (exist only in patient's private experience) or tics are less forceful than comparable voluntary actions and typically are not noticed because of their intensity.  |
| 2 | <i>Mild intensity.</i>     | Tics are not more forceful than comparable voluntary actions or utterances and are typically not noticed because of their intensity.  |
| 3 | <i>Moderate intensity.</i> | Tics are more forceful than comparable voluntary actions, but are not outside the range of normal expression for comparable voluntary actions or utterances. They may call attention to the individual because of their forceful character. |
| 4 | <i>Marked intensity.</i>   | Tics are more forceful than comparable voluntary actions or utterances. Such tics frequently call attention to the individual because of their forceful and exaggerated character.  |
| 5 | <i>Severe intensity.</i>   | Tics are extremely forceful and exaggerated in expression. These tics call attention to the individual and may result in risk of physical injury (accidental, provoked, or self-inflicted) because of their forceful expression.            |

Using the following scale, rate the **complexity** of:\_\_\_\_\_ motor tics (selected in sections A and B) present **during the past week.**\_\_\_\_\_ phonic tics (selected in sections C and D) present **during the past week.**

- |   |                    |  |
|---|--------------------|--|
| 0 | <i>None.</i>       | If present, all tics are clearly 'simple' (sudden, brief, purposeless).  |
| 1 | <i>Borderline.</i> | Some tics are not clearly 'simple' in character.   |
| 2 | <i>Mild.</i>       | Some tics are clearly 'complex' (purposive in appearance) and mimic brief 'automatic' behaviors, such as grooming, syllables, or brief meaningful utterances such as 'uh huh,' or 'hi,' that could be readily camouflaged.   |
| 3 | <i>Moderate.</i>   | Some tics are more 'complex' (more purposive and sustained) and may occur in elaborate bouts (attacks) that would be difficult to camouflage, but could be rationalized or 'explained' as normal behavior or speech (picking, tapping, saying 'you bet' or 'honey,' brief repeating of another's words).   |
| 4 | <i>Marked.</i>     | Some tics are very 'complex' in character and tend to occur in sustained elaborate bouts that would be difficult to camouflage and could not be easily rationalized as normal behavior or speech because of their duration and/or their unusual, inappropriate, bizarre, or obscene character (a lengthy facial contortion, touching genitals, repeating another's words, longer bouts of saying 'what do you mean' repeatedly, or saying 'fu--' or 'sh--'). |
| 5 | <i>Severe.</i>     | Some tics involve lengthy bouts of elaborate behavior or speech that would be impossible to camouflage or successfully rationalize as normal because of their duration and/or extremely unusual, inappropriate, bizarre, or obscene character (lengthy displays or utterances often involving self-abusive behavior or involuntary obscene or forbidden gestures, words, or remarks).  |

ID # \_\_\_\_\_

Youth  
Parent \_\_\_\_\_

Date \_\_\_\_\_  
Time \_\_\_\_\_

Using the following scale, rate the **interference** of:

\_\_\_\_\_ motor tics (selected in sections A and B) present **during the past week**.

\_\_\_\_\_ phonic tics (selected in sections C and D) present **during the past week**.

- |   |                  |   |
|---|------------------|---|
| 0 | <i>None.</i>     |   |
| 1 | <i>Minimal.</i>  | When tics are present, they do not interrupt the flow of behavior or speech.  |
| 2 | <i>Mild.</i>     | When tics are present, they occasionally interrupt the flow of behavior or speech.  |
| 3 | <i>Moderate.</i> | When tics are present, they frequently interrupt the flow of behavior or speech.  |
| 4 | <i>Marked.</i>   | When tics are present, they frequently interrupt the flow of behavior or speech, and they occasionally disrupt future intended action or communication. |
| 5 | <i>Severe.</i>   | When tics are present, they frequently disrupt future intended action or communication.   |

Using the following scale, rate the **impairment** of:

\_\_\_\_\_ motor and phonic tics combined (selected in sections A-D) present **during the past week**.

- |    |                  |   |
|----|------------------|---|
| 0  | <i>None.</i>     |   |
| 10 | <i>Minimal.</i>  | Tics are associated with subtle difficulties in self-esteem, family life, social acceptance, or school or job functioning (infrequent upset or concern about tics compared to the future; periodic, slight increase in family tensions because of tics; friends or acquaintances may occasionally notice or comment about tics in an upsetting way).  |
| 20 | <i>Mild.</i>     | Tics are associated with minor difficulties in self-esteem, family life, social acceptance, or school or job functioning.   |
| 30 | <i>Moderate.</i> | Tics are associated with some clear problems in self-esteem, family life, social acceptance, or school or job functioning (feel depressed, anxious, or irritable; periodic distress and upheaval in the family, frequent teasing by peers or social avoidance).   |
| 40 | <i>Marked.</i>   | Tics are associated with major difficulties in self-esteem, family life, social acceptance, or school or job functioning.   |
| 50 | <i>Severe.</i>   | Tics are associated with extreme difficulties in self-esteem, family life, social acceptance, or school or job functioning (severe depression with thoughts or plans about suicide, disruption of the family [separation/ divorce, residential placement], disruption of social ties – severely restricted life because of social stigma and social avoidance, removal from school or loss of job). |

# Background Questionnaire

ID#: \_\_\_\_\_

TASK ORDER \_\_\_\_\_

DATE OF BIRTH: \_\_\_\_\_ SEX: M F HANDEDNESS: L R

EDUCATION: 3<sup>rd</sup> 4<sup>th</sup> 5<sup>th</sup> 6<sup>th</sup> 7<sup>th</sup> 8<sup>th</sup> Fr So Jr Sr

ETHNICITY:

Ethnicity / Racial Category	Hispanic or Latino	Non-Hispanic or
American Indian / Alaska		
Asian		
Hawaiian or Islander		
Black or African American		
White		
More than one race		
Unknown		

VISION: Normal Nearsighted Farsighted

None Glasses Contacts

SURGERIES, OTHER NEUROLOGICAL DISORDERS OR DISEASES: NO YES  
(e.g., car accident, brain injury or tumor, cerebrovascular disease, epilepsy, stroke, eye surgery, ADHD, OCD)

FIRST DEGREE RELATIVES WITH NEUROLOGICAL DISORDERS: NO YES  
(e.g., Bipolar, Schizophrenia, Autism, Parkinson, Huntington, Tourette, ADHD, OCD)

=====

DATE: \_\_\_\_\_ TIME: \_\_\_\_\_ AM PM

CONDITION: ON OFF Control

CURRENT MEDICATIONS: NO YES

Type: \_\_\_\_\_

Dosage: \_\_\_\_\_

Time since last Dose: \_\_\_\_\_

DRUG ABUSE HISTORY: NO YES  
ALCOHOL in last 24 hours: NO YES  
SMOKING: NO YES \_\_\_\_\_per day  
Time since last cigarette: \_\_\_\_\_  
CAFFEINE in last 24 hours: NO YES

VIDEO GAMES: \_\_\_\_\_ hours per day/week

TV WATCHED: \_\_\_\_\_ hours per day/week

Have you ever had a streptococcal infection? If so, when? \_\_\_\_\_

Have you ever taken nasal steroid spray medication? \_\_\_\_\_

TS PATIENTS: Age of Onset / Duration: \_\_\_\_\_

Motor tics \_\_\_\_\_

Vocal tics \_\_\_\_\_

During what situations are you most likely to have tics? \_\_\_\_\_

Are you able to suppress your tics? If so, for how long? \_\_\_\_\_

How do you know a tic is about to happen? \_\_\_\_\_

YGTSS: Motor \_\_\_\_\_ Phonic \_\_\_\_\_ Impairment \_\_\_\_\_ Global \_\_\_\_\_

ADHD: Inattention \_\_\_\_\_ Hyperactivity/Impulsivity \_\_\_\_\_ Total \_\_\_\_\_

OCD: Washing \_\_\_\_\_ Checking \_\_\_\_\_ Ordering \_\_\_\_\_ Total \_\_\_\_\_

Obsessing \_\_\_\_\_ Hoarding \_\_\_\_\_ Neutralizing \_\_\_\_\_

IQ: Full Scale \_\_\_\_\_ T-Score \_\_\_\_\_ Percentile \_\_\_\_\_

Clinical Measures:

## Appendix B

# Sample Data Files

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## Sample Data Output File – Task parameters and practice trials preceding a 0-back trial block

Testing TS7 at 10:03:55 AM on Saturday, August 30, 2008.

Number of trials = 96 Experiment is S.

EMs (well radius in pixels):

fixation = 110 pixels target = 80 pixels

target distance : 266

Durations (ms):

fixation = 399 ms

target (pred exps) = 2998 ms timeout = 1492 ms

anticipation cutoff = 93 ms

anticipation trials discarded = 0 [0=keep, 1=discard]

Averages and speed criteria:

Fixn = 2 Speed = 2 Below = 2 Above = 8

Colors:

background = 0, fixation = 120, cue = 50, target = 255

Landmarks ON

Number of Targets = 4

Config Type = 1761605440 [0=On-Axis, 1=Off-Axis]

NBack ON

This was a 0 Back Run

Min locations in 1B sequence: 2

Max locations in 1B sequence: 3

Sequence Type [0=Random, 1=From file] : 1

Sequence File : FullSeq\_4pos\_96trials

Delay in 1B sequence: 350 msec

Target duration in 1B sequence: 80 msec

Fixation Off Delay: 500 msec

Last Target Off

Iscan sampling rate = 4

Screen refresh rate = 13328 microsec

Time between distance points 26 ms.

NOTE: for delayed & remembered, disinhibitions: -2 = correct, -3 = wrong

Eye Pos: 1=to the target, 2=to diagonally/vertically opposite side of target,  
otherwise the location of the target closest to the eye position (target location labelled from 3 to  
8, starting at [hor=right, vert=0] going anticlockwise)

Ts = response time relative to start of a trial (i.e. once stable fixation is achieved)

Tb = response time relative to the begin of first target presentation

Te = response time relative to the end of last target presentation

Error position within a trial: 1 = Before target presentation, 2 = Before fixation erased in gap  
paradigm

Error position within a trial: 3 = After fixation erased in gap paradigm, 4 = After target presented  
but before target erased

Error position within a trial: 5 = After target erased but before fixation erased, 6 = After target  
presented but before fixation erased

Error position within a trial: 7 = After go signal

Error position within a trial: 10+a = Error position within a trial: 10+a = During the N back  
sequence when a=ordinal number of stimulus in sequence

Begin \_\_\_\_\_

Trial No	TargHF (L=-) (R=+)	TargVF (T=-) (M=0) (B=+)	TargID	Seq	Eye	Cor Pos_H (err=0) (in=1)	RT (ms)	Duration (ms)	NinSeq (ms)	Ts (ms)	Tb (ms)	Te (ms)	EP
1	0.00	-1.00	4	6-4-	1	1	459.0	53.8	2	0	0	0	0
2	-1.00	0.00	5	3-6-5-	1	1	252.2	53.8	3	0	0	0	0
3	1.00	0.00	3	6-5-3-	1	1	239.8	24.8	3	0	0	0	0
4	0.00	-1.00	4	3-6-4-	1	1	272.9	37.2	3	0	0	0	0
5	1.00	0.00	3	4-3-	5	0	454.8	20.7	2	0	0	0	0
6	0.00	1.00	6	4-6-	1	1	339.1	41.3	2	0	0	0	0
7	-1.00	0.00	5	3-5-	1	1	301.8	53.8	2	0	0	0	0
8	0.00	1.00	6	3-5-6-	1	1	264.6	70.3	3	0	0	0	0

There were 2 retrievals because of eye movement.

#### Discarded Trials

Correct Column Codes: 2=MoveOut, 3=MoveOutGap, 4=Blink, 5=Timeout, 6=Antic

Trial No	TargHF (L=-) (R=+)	TargVF (T=-) (M=0) (B=+)	TargID	Seq	Eye	Cor Pos_H (err=0) (in=1)	RT (ms)	Duration (ms)	NinSeq (ms)	Ts (ms)	Tb (ms)	Te (ms)	EP
1	0.00	1.00	6	0-0-0-	0	2	-4.1	0.0	3	26	-13	-13	1
2	-1.00	0.00	5	4-5-6-	6	2	-4.1	0.0	3	1212	799	-13	13

#### Eye position data (Valid trials only)

Trial	TargHF	TargVF	TargID	Dist1	Dist2	Dist3	Dist4	Dist5	Dist6	Dist7	Dist8	Dist9	Dist10
1	0.00	-1.00	4	-260	-262	-262	-265	-266	-278	-281	-274	-272	
2	-1.00	0.00	5	-250	-252	-246	-253	-248	-250	-262	-265	-251	
3	1.00	0.00	3	246	246	246	250	249	238	246	249	252	
4	0.00	-1.00	4	-254	-248	-254	-254	-254	-248	-248	-248	-248	
5	1.00	0.00	3	252	253	250	250	242	243	242	246	251	
6	0.00	1.00	6	301	300	300	300	313	308	313	319	314	
7	-1.00	0.00	5	-284	-284	-287	-284	-281	-284	-280	-284	-294	
8	0.00	1.00	6	-299	-299	-293	-299	-299	-287	-275	-275	-274	

End

# **Sample Eye Coordinates File – Part of a single trial**

0	271		
Sample	X	Y	
1	491	366	3997717
2	491	366	3997721
3	500	354	3997721
4	500	354	3997721
5	503	361	3997721
6	498	367	3997721
7	498	367	3997717
8	498	367	3997717
9	502	367	3997721
10	506	367	3997721
11	502	367	3997717
12	502	367	3997717
13	498	373	3997721
14	497	385	3997721
15	497	379	3997721
16	504	380	3997721
17	498	373	3997717
18	498	373	3997721
19	501	379	3997721
20	497	385	3997717
21	497	385	3997721
22	500	385	3997721
23	503	392	3997721
24	504	380	3997721
25	505	373	3997721
26	504	386	3997717
27	504	380	3997721
28	504	380	3997721
29	501	379	3997721
30	489	384	3997721
31	494	372	3997713
32	498	367	3997717
33	503	361	3997721
34	498	367	3997717
35	484	365	3997721
36	491	366	3997721
37	498	367	3997717
38	498	367	3997721
39	491	366	3997721
40	495	366	3997721
41	496	354	3997721
42	500	354	3997713
43	496	354	3997717
44	492	360	3997717
45	499	360	3997721
46	499	360	3997721
47	499	360	3997717
48	495	366	3997721

# **Sample MATLAB Summary Output File – 0-back task variables for all control participants**

Subject	Trial Trim	%Errors	RTTrials	Mean RT (msec)	SEM RT (msec)	Median RT (msec)	SE of Median RT (msec)
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\*\*\*\*\*

Data for Task: 0 Back

\*\*\*\*\*

CTS01	84	4.76	80	328.64	12.75	296.70	17.56
CTS02	91	3.30	86	309.46	8.89	307.40	10.73
CTS03	95	1.05	90	312.98	9.57	303.30	9.67
CTS04	91	1.10	90	294.30	7.17	288.00	10.05
CTS05	89	6.74	80	440.02	12.35	443.00	17.32
CTS06	94	9.57	84	409.18	13.99	386.20	17.31
CTS07	96	3.12	91	322.02	6.61	319.60	8.38
CTS08	82	3.66	79	382.19	16.85	355.60	25.98
CTS09	92	0.00	89	365.65	10.97	363.60	12.00
CTS10	88	5.68	81	463.62	15.47	440.90	19.65
CTS11	93	0.00	92	341.36	9.69	328.60	12.13
CTS12	90	3.33	84	355.61	8.51	359.40	10.81
CTS13	90	3.33	85	360.84	11.06	343.00	11.13
CTS14	90	1.11	89	351.00	12.00	338.64	17.27
CTS15	70	15.71	58	234.36	9.22	195.50	18.81
CTS16	85	3.53	79	260.57	7.00	253.40	11.88
CTS17	95	1.05	92	282.62	5.76	281.10	7.63
CTS18	92	1.09	88	324.73	9.42	307.60	11.00
CTS19	74	5.41	69	271.27	12.97	195.50	22.82
CTS20	94	1.06	92	329.61	13.53	307.80	20.72
CTS21	95	11.58	82	348.00	11.90	321.90	12.97
CTS22	95	1.05	92	416.77	15.72	396.50	20.25
CTS23	88	0.00	86	337.31	11.12	312.10	9.51
CTS24	88	1.14	85	295.24	8.42	282.90	10.41
CTS25	93	2.15	88	393.69	9.62	386.80	10.37
CTS26	94	3.19	89	353.90	7.81	339.00	9.73
CTS27	92	1.09	88	276.95	7.18	275.90	6.49
CTS28	93	1.08	90	299.78	9.59	303.70	10.50
CTS29	94	3.19	88	386.93	9.78	367.80	10.91
CTS30	88	4.55	81	448.13	11.26	436.20	12.90
CTS31	92	2.17	87	348.69	8.50	334.00	10.71
CTS32	92	0.00	88	320.56	8.32	308.85	10.88
CTS33	84	4.76	79	321.08	13.34	305.75	22.67
CTS34	92	2.17	86	311.70	6.04	306.30	6.19

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# Vita

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