WHAT MAKES A TIC TICK? MOTORIC DISINHIBITION, AND THE INCIDENTAL ASSOCIATIONS THEORY OF TIC FORMATION

by

B. Duncan McKinlay

A thesis
presented to the University of Waterloo
in fulfillment of the
thesis requirement for the degree of
Doctor of Philosophy
in
Psychology

Waterloo, Ontario, Canada, 2001

I hereby declare that I am the sole author of this thesis.

I authorize the University of Waterloo to lend this thesis to other institutions or individuals for the purpose of scholarly research.

_____

B. Duncan McKinlay

I further authorize the University of Waterloo to reproduce this thesis by photocopying or by other means, in total or in part, at the request of other institutions or individuals for the purpose of scholarly research.

_____

B. Duncan McKinlay

The University of Waterloo requires the signatures of all persons using or photocopying this thesis. Please sign below, and give address and date.

Abstract

OBJECTIVES:
Evidence for inhibitory difficulties in individuals with 'pure' (no comorbid diagnoses) Tourette Syndrome (TS) is inconsistent, and a complete neurological understanding of how tics are formed is lacking.

In Experiments 1 and 2 we postulated that individuals with unmedicated TS, free of unmedicated comorbid symptomatology, would not differ from controls in cognitive inhibition or motor inhibition success at any age. However, individuals with TS would differ from controls in terms of motor inhibition failures once at an age where normal development of motor inhibition is expected to have stabilized.

In Experiments 3 and 4 we hypothesized that tics were the product of incidentally learned associations between various motor movements, elicited due to failures in motor inhibition.

METHODS:
In Experiments 1 and 2 the Stroop task and a tactile variant of the Simon task were used to measure "cognitive inhibition" and "motor inhibition" respectively. Both tasks measure the ability of individuals to inhibit a prepotent response (semantic activation of words in the Stroop, and ipsilateral motor responses in the Simon). Moreover interference in both tasks during incongruent trials depends upon the correspondence between the irrelevant stimulus attribute and the response. Reaction times and errors were analyzed in TS and control groups split into younger (7=9 years) and older (10-21) samples (n=40).

In Experiments 3 and 4 half of the older participants in each group were primed in an incidental motor association. A tactile stimulus, followed by a response button press, was defined as the goal oriented action. A RESET button press, allegedly to prompt the next trial, followed the response button press and was therefore incidentally associated to it. All older participants were later tested for problems inhibiting this association by being told that pressing the RESET button was no longer necessary.

Inhibition problems were assessed in three different ways: number of times the incidental motor association (i.e. RESET Button Press) was engaged in, number of times the incidental motor association was initiated (i.e RESET Button Initiation), and reported urge to engage in the incidental motor association.

RESULTS:

In Experiments 1 and 2 the younger groups did not differ on any measures of cognitive or motor inhibition success or failure. In the older groups, individuals with TS committed significantly more errors than controls on the Simon task.

In Experiments 3 and 4 all participants exposed to the incidental association procedure reported a greater urge to engage in the associated movement than unexposed participants. Only the exposed individuals with TS showed failures in inhibiting this incidental motor association.

CONCLUSIONS:

Experiment 1 suggested that cognitive inhibition difficulties are not present in TS when comorbid conditions are controlled for. Experiment 2 suggested that motor inhibition failures are a feature of TS. Experiments 3 and 4 suggest that stereotypical movements may become associated with numerous goal-directed behaviours. In the absence of appropriate motor inhibition these associations strengthen over time. When inhibition fails, these goal-directed behaviours elicit the stereotypical movements at seemingly random intervals and are considered 'tics'. This model gives direction to future diagnostic testing and treatment methods, provides explanations for a considerable body of phenomenological evidence and past research, and suggests many future areas of exploration.

Acknowledgements

The encouragement and support that my advisor, Mike J. Dixon, provided me is incalculable and is simply beyond description. From his initial intrigue by my ideas to his tireless edits of this thesis I have been overwhelmed by his intellect, graciousness, concern, generousity, and modesty.

Murray J. Guylee and Brandon Wagar provided valuable technical support in apparatus construction, software programming, and data preparation.

I would like to thank the Tourette Syndrome Foundation of Canada (TSFC) for its support of this project. In particular, the TSFC Main Office generated our sample from its membership banks based on our criteria and conducted mailings of the solicitation package.

This project was funded in part by the Natural Science and Engineering Research Council (NSERC); I am grateful for their backing of this project.

Dedication

In many special ways people important to me have demonstrated how much they believed in who I am and what I do. It is through them I found the strength to persevere.

Friends…families…mentors…followers of my work…to all of you who have touched my life…I am what I am because of you. Thank you for helping me to make it.

Duncan

Table of Contents

INTRODUCTION

Tics, defined as sudden, rapid, recurrent, non-rhythmic, stereotyped motor movements or vocalizations (APA, 1994) are the essential diagnostic feature of Tourette's Disorder. Diagnosis of Tourette's Disorder using DSM-IV criteria requires that "both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. The tics occur many times a day…. nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months" (APA, 1994). Symptom onset must be before 18 years, the symptoms must cause marked distress or significant impairment in social, occupational, or other important areas of functioning, and symptoms cannot be due to a substance or general medical condition (APA, 1994).

These criteria for Tourette's Disorder [herein referred to by the more familiar term Tourette Syndrome (TS)] amalgamate the most severe criteria of two other tic disorders found in the DSM-IV. Chronic Tic Disorder requires that tics be present for more than one year (even though the presence of *only* motor *or* vocal tics are required for this diagnosis), and Transient Tic Disorder requires that both motor and vocal tics be present (even though the presence of tics may be *less than 12 months* for this diagnosis). The criteria for TS are comparable to those delineated in the ICD-10 nosology (World Health Organization, 1992).

TS – Prevalence and Epidemiology

TS, once thought to be quite rare, is now believed to be considerably more common than past estimates indicated. In a recent review of the epidemiological literature, Robertson concluded

that, in general, approximately one percent of children experience this disorder (Robertson, 2000; 2001). As recently as 1984 the prevalence of TS was recorded as 5 per 10 000 (Bruun, 1984). Some authors maintain that between 5 and 10 per 10 000 remains a reasonable estimate of the incidence of TS (Zohar, Apter, King et al., 1999; Scahill, Tanner & Dure, 2001) while others have submitted estimates as high as 300 per 10 000 (Mason et al., 1998). A number of factors can cause variance in reported estimates of TS incidence however.

First, one's definition of phenotype is crucial. If one is screening only for the presence of tics, reported frequencies are much higher than those reported for TS. Approximately 10-12% of children may be identified (Robertson, 2001; Scahill, Tanner & Dure, 2001). Costello et al. (1996) reported a prevalence of 4.2% for all tic disorders from a community sample of 4000 (9-13) in North Carolina. Verhulst et al. (1997) estimated 4.3% of 780 adolescents from the Netherlands met the diagnostic criteria for some form of tic disorder (.1% TS, 2% chronic tic disorder, 2.2% transient tic disorder).

Even when looking for TS in particular, different research groups may use different diagnostic criteria. Any studies completed before 1994 used the diagnostic criteria found in the DSM-III-R: criteria that contain important differences from those outlined in the DSM-IV. The criterion pertaining to age of symptom onset decreased from 21 in the DSM-III-R to 18 in the DSM-IV (APA, 1994). Also, many in the TS research community have taken exception to the "marked distress and significant impairment' criterion found in the DSM-IV (e.g. Freeman, Fast & Kent, 1995) – research exists to show that tic severity and impairment correlate poorly (Dykens, Sparrow, Cohen et al., 1999) as does symptom severity and attitude towards one's

disorder (McKinlay, 1998). If one is defining 'disorder' simply from a purely neurological, "medical model" perspective then distress and impairment are indeed irrelevant. Those who define disorder following a medical model have elected to reject criteria pertaining to distress and impairment and adopt their own criteria. The TS Classification Study Group, for example, developed criteria for a diagnosis of "Definite Tourette Syndrome" in 1993. These criteria are more closely based on that of the DSM-III-R than the DSM-IV: the 'impairment' criterion does not appear, a criterion specifying that tics will periodically change in number, frequency, type, location, and severity has been included, and the requirement that 'motor and/or vocal tics must be witnessed by a reliable examiner directly at some point, or be recorded by videotape or cinematography' has also been added (Tourette Syndrome Classification Study Group, 1993). If one is defining 'disorder' from a more functional psychosocial perspective however, assessing the presence of distress and impairment are crucial. From this perspective, the Dykens, Sparrow, Cohen et al. and McKinlay studies could be interpreted as demonstrating the irrelevance of the severity of abnormal neurology and the importance of other factors (such as attitude) in diagnosing 'disorder.'

Types of populations screened are also important when considering prevalence. Selecting a sample of children from special education settings (such as residential schools) results in a much higher prevalence of TS – perhaps as many as 6-12% of these children have TS, and 26-28% have some diagnosable tic disorder (Robertson, 2000; Comings, 1990; Kurlan et al., 1994a). TS also appears to be found in three to five times more males than females (Erenberg, Cruse & Rothner, 1986; Park et al., 1993; Robertson, 2000). Each of 65 sites in 22 countries of the **T**ourette Syndrome **I**nternational Database **C**onsortium (TIC) reported an

excess of males (sites varied considerably in ratios however – ranging from 10:1 to 3:1 with a mean of 4.3:1 Freeman, Fast, Burd et al., 2000). TS can be found in all cultures, countries, racial groups and social classes (Gilles de la Tourette, 1885; Robertson, 1989; Robertson 1994) and the greater prevalence of males relative to females having the disorder also appears to be stable across all cultures (Freeman, Fast, Burd et al., 2000). Despite these commonalities, there may be important cultural differences. Incidence rates tend to vary across different cultural groups: reports indicate that TS is relatively rare among American blacks (Robertson, 1989) and among Japanese (Robertson 2001). Prevalence in terms of particular symptoms also changes in different cultures. Coprolalia appears in only 4% of Japanese samples (Nomura & Segawa, 1982), but appears in 33% of TS samples in Europe and the United States. Some countries like Canada may have an even higher incidence rate of coprolalia among their TS samples (Staley et al., 1997) than the typical 33% cited in the USA and Europe (Robertson, 2000).

When assessing prevalence, the age of the population measured must be taken into account. Sex differences in TS-incidence rates appear to be less pronounced in adults (3:1) than children (5.2:1; Freeman, Fast, Burd et al., 2000). Data collection methods are also important to note. Clinic vs. community samples, parents and teachers vs. clinicians as informants, larger vs. smaller samples, and direct sample observation vs. reliance on already-identified clinical cases can all influence prevalence estimates (Scahill, Tanner & Dure, 2001). Scahill, Tanner and Dure also note that while most epidemiological studies are cross-sectional, more longitudinal analyses are necessary for the reduction of false negatives. The experience of the researcher, such as his/her ability to differentially diagnose TS from other conditions

such as Wilson's disease, Huntington's disease, dystonia, myoclonus, chorea, dyskinesia and athetosis will affect prevalence assessments (Towbin, Peterson, Cohen & Leckman, 1999). Finally, the interest the researcher holds in TS may affect incidence-rate assessments. Robertson (2001) reported on an instance where a clinician's tic diagnoses increased from 5% to 17% after an interest in the area was cultivated.

TS – Course

Although all current diagnostic criteria will consider symptom onset up to age 18, in 96% of cases symptoms present before age 11 (Robertson, 1989). A group from the Yale Child Study Center followed 36 of their TS patients until 18 years of age. Mean tic age of onset was 5.6 years (SD 2.3; Leckman, Zhang, Vitale et al., 1998). This is not dissimilar from findings by the **T**ourette Syndrome **I**nternational Database **C**onsortium (mean tic age of onset was 6.4 years in their sample). Tics continued to worsen from onset until a mean age of 10.0 (SD=2.4) after which time they decreased in most cases (Leckman, Zhang, Vitale et al., 1998). Interestingly, Robertson suggests that vocal tics may follow a different pattern: in an address at the Tourette Syndrome Foundation of Canada (TSFC) 2nd International Research Symposium she reported findings that vocal tics on average commence later -- at age 11 (Robertson, 2000; 2001). This observation has also been made by Leckman, King & Cohen at Yale (1999) who describe a phonic tic age of onset between 8 and 15 years of age. Thus the course of TS appears to move from motor tics at an early age, and begins to encompass phonic tics only at a later age.

During certain points in the course of TS, symptoms have the potential to be quite disabling. Self-injury (body and head punching/slapping, poking, scratching, and inflicting serious eye injuries) is prevalent in 33% of severe cases, and is frequent in hospital-referred samples (Robertson, Doran, Trimble & Lees, 1990). Self-injurious behaviours are positively associated with tic severity, as are scores on measures of obsessionality and hostility (Robertson, Doran, Trimble & Lees, 1990). Leckman and his Yale group found that, during the course of the disorder, 22% of cases at their worst-ever period found that symptoms seriously jeopardized or rendered impossible school functioning (Leckman, Zhang, Vitale et al. 1998). As individuals age, various physiological problems caused by prolonged exposure to violent tics can also arise. Cervical myelopathy may develop in individuals with twisting, extending, and thrusting movements of the neck (Krauss & Jankovic, 1996); this condition has led to a number of complications in adults with TS including gait disturbances, sensory deficits, extremity weakness, and bladder dysfunction (Krauss & Jankovic, 1996). Anecdotal reports of multiple hernias and detached retinas exist as well although more research in this area is needed to determine actual incidence rates of these particular sequelae.

TS was once believed to be a life-long condition. Current evidence on course and prognosis is now at best equivocal. Goetz et al (1992) found that tics persisted in all patients from a sample of 58 adults diagnosed with TS in childhood. Symptoms were moderate to severe in only 24% of these adults as compared to 60% who had moderate to severe symptoms during their periods of poorest functioning earlier in life. Severity of tics in childhood was also not predictive of tic severity in adulthood – according to their data 75% of individuals with moderate to severe tics as children had only a mild condition as adults (Goetz et al., 1992). de

Groot et al. (1994), in a 5 year follow-up of 23 participants in three different age cohorts (7-12, 13-21, 21 and older), found that only 13% had experienced an improvement in tic symptoms: 65.2% were unchanged and 21.7% had worsened. Importantly, de Groot and his colleagues found no significant differences in symptom severity across the three different age cohorts (although the sample size, while argued to be representative by the authors, is small). Another body of research suggests much higher remittance rates however. Robertson (1994) and Bruun and Budman (1992) estimate that 30-40% of children with severe tics will experience complete diminishment of their symptoms by late adolescence. Similarly, Erenberg, Cruse & Rothner (1987), in a sample of 58 adolescents and young adults (aged 15-25; ì 18 years) found that 73% had reported considerable lessening of their tics. Although figures vary widely it seems to be safe to conclude that while tics may or may not disappear in adulthood, they will at least abate somewhat in many individuals. In corroboration of this postulate, Singer and Walkup in a 1991 review estimated that approximately 1/3rd of TS cases will completely remit, 1/3rd will decrease significantly, and 1/3rd will remain symptomatically stable throughout life. It should be noted, however, that even in cases where tic symptoms do reduce or ameliorate entirely, other conditions comorbid with TS (e.g. Obsessive-Compulsive Disorder (OCD) and other anxiety disorders, conduct disorder, substance abuse) may increase (Comings, 1990; de Groot, Bornstein, Spetie & Burriss, 1994).

TS – Symptom Phenomenology:

Although diagnostic criteria differ, there is a universal agreement that tics involve frequent and stereotypical movements and sounds (Comings, 1990), although manifestations are wide-ranging and often unique to each individual. To state this in the opposite way, more novel

movements and noises in an individual's repertoire tend not to become tics. Leckman and colleagues suggest, "Tics may be seen as fragments of normal motor action or vocal productions that are misplaced in context…." (Leckman et al., 2001). Others have echoed this belief that one's symptom repertoire evolves, and is enshrined, from once purposeful movements (Ziemann et al., 1997). As Oliver Sacks eloquently stated, tics may represent 'hieroglyphic, petrified residues of the past….as if the Tourettic body becomes an expressive archive – albeit jumbled – of one's life experiences" (Sacks, 1995).

Motor tics may be simple – abrupt, meaningless movements involving one muscle group such as eye blinking – or motor tics may be quite complex. Complex motor tics (such as head shaking, jumping, touching, echopraxia, and copropraxia) are coordinated and sequenced (Jankovic, 1997), longer and more involved (Leckman et al., 2001) and may or may not seem purposeful. The orchestrated blending of a number of simple motor tics, called paroxysms, can be a form of complex motor tic as well (Leckman et al., 2001).

Phonic tics (argued to be a more accurate description than 'vocal tics' because sounds – such as whistling -- may be produced without utilizing the vocal cords) may also be simple or complex. Single, meaningless sounds define simple phonic tics, while more linguistically meaningful utterances (palilalia, echolalia, coprolalia) are considered complex phonic tics. Interestingly, complex 'phonic' tics (e.g. coprolalia) can also appear during signing in patients who are mute (Lang, 1992).

Tics may be classified as clonic (abrupt, fast, and brief movements), dystonic (slow and sustained movements) or tonic (isometric muscle contractions such as abdominal tensing; Jankovic, 1997). According to Jankovic (1997), tics may be categorized as a suppressible form of involuntary movement. Doing so requires intense mental effort and results in a build-up and eventual 'rebound' effect, however (Leckman et al., 2001). Tics may also be categorized as semivoluntary/unvoluntary in that they occur in response to inner sensory stimuli or unwanted feelings and compulsions. These inner sensations or feelings that precede tics in TS, while sometimes called sensory tics (Karp & Hallett, 1996; Ziemann, Paulus, & Rothenberger, 1997) are more often referred to as 'premonitory urges'.

Premonitory urges are reported to occur in over 80% - 92% of cases (Cohen & Leckman, 1992; Jankovic, 1997); the discomfort usually arises in a part of the body (or is associated with an extracorporeal object) that is involved in the subsequent motor act (Karp & Hallett, 1996). Premonitory urges may also take the form of less specific urges, anger, or anxiety. A graduate student with TS, in a paper on premonitory urges, postulated an "attentional tic" theoretical framework (Kane, 1994). He argued that these urges are not unique sensory events, but rather are manifestations of somatosensory hyperawareness that serve as the aversive stimulus toward which tics are purposively directed. The position that tics are in fact a purposeful execution to relieve involuntary sensations (sometimes requiring a number of repetitions to achieve this 'just right' feeling) is one that is held by many researchers (Jankovic, 1997; Ziemann et al., 1997; Van Amerigan, Mancini & Oakman, 1998). Premonitory urges appear to increase as clients age in that more adolescents and adults report them than children (Leckman et al., 2001). Premonitory urges are also more likely associated

with dystonic tics (Jankovic, 1997), and improve or worsen as the tics do (Leckman et al., 2001).

Tics appear in bouts with brief intertic intervals (Leckman, King & Cohen, 1999). These bouts coincide with burst patterns seen in the neurons of the substantia nigra, and appear in bouts themselves; furthermore these bouts of bouts also appear in bouts. In fact higher order combinations of bouts (bouts of bouts of bouts of bouts) have been measured over weeks and months (Peterson & Leckman, 1998). Thus, individual tics are a consequence of bouts of neuronal firing that occurs across seconds – some seconds there are more tics than others. These sequences of tics occur in bouts across hours – some hours there are more bouts than others. Hourly bouts of tics occur in bouts across days - some days there are more bouts than others. Daily bouts follow a bout pattern across weeks – some weeks there are more bouts than others. Finally, weekly bouts occur in grand bouts across months - there are some months that have more bouts than others. These "grand bouts" may be a contributing factor to another quality of tics: the waxing and waning of symptoms across time and situations.

Much of the research into the waxing and waning of tics has focussed on various physical and psychological stressors as the precipitating factors (Bruun & Budman, 1992). Excitement, anxiety, boredom, fatigue, stress, premenstrual syndrome, dopaminergic drugs, and stimulants have all been suggested as sources of tic exacerbation (Silva, Munoz, Barickman & Friedhoff, 1995; Robertson, 1989; Bruun & Budman, 1992). Likewise, a number of factors have been associated with tic reduction: distraction, intense concentration during highly complex tasks and reading (Bruun & Budman, 1992; Silva, Munoz, Barickman

& Friedhoff, 1995). Tics also seem to subside during what might be described as primal behaviour patterns (i.e. during orgasm or sleep; Robertson, 1989; Silva, Munoz, Barickman & Friedhoff, 1995).

Tics are influenced by attention and are suggestible. Focusing one's attention on a particular movement or noise can exacerbate the urge and/or increase the presentation of that tic. In 1980 Joseph Bliss caught the attention of the research community on this and other phenomenological aspects of tics in a seminal paper concerning his own TS experiences. He wrote, "Intense concentration on the site can, itself, precipitate the action…" (Bliss, 1980). This phenomenon leads to the unfortunate irony that the more one attempts to consciously suppress a tic, the worse the need for expression becomes. It also sets up a paradox: for one to ever lose a tic, one must not ever realize that it is gone.

In closing, a number of anecdotal reports also exist concerning the phenomenology of tics that are worth mentioning. It seems that the longer one has a tic, the more difficult it is to remove from one's repertoire. The quietest time for tics in terms of both premonitory urge and implementing the response is when one first awakes in the morning. Finally, novel environments tend to reduce tics – a good illustration of this is the 'Doctor's Office Syndrome'. Infamous among caregivers, this unfortunate situation occurs when an obviously symptomatic child, to the utter dismay and embarrassment of the concerned and frazzled parent, shows no tics in front of the diagnostician (Silva, Munoz, Barickman & Friedhoff, 1995).

TS – Treatment

A number of sources review the pharmaceuticals used in the treatment of TS (e.g. see Sandor, 1995; Tourette Syndrome Association - Southern California Chapter). In general the first, second, and third lines of defence have become antihypertensives, atypical antipsychotics, and classic neuroleptics respectively (Kurlan, 2001). Literature on non-pharmaceutical interventions for TS is more difficult to find (Chodosh & Messinger, 1997) and many of these treatments have not been adequately studied. Everything from self-hypnosis (Kohen, 1995), acupuncture (Wu, Li & Kang, 1996), tension reduction techniques (Evers & van de Wetering, 1994), botulinum toxin injections (Singer, Wendlandt, Krieger, & Giuliano, 2001), nicotine (Silver, Shytle & Sanberg, 1999), transcranial magnetic stimulation, craniosacral manipulation, immunotherapies, homeopathy and alternative diet (Budman, 2000) has been suggested. In very rare and extreme cases where severe tics were accompanied and complicated by severe OCD and self-mutilation, bilateral limbic leucotomies have been performed. In one case study, lesions to the inferior medial quadrants of the frontal lobes and lesions in the anterior cingulate gyrus were made (Robertson, Doran et al., 1990). In a second case study, lesions in the anterior hypothalamus and the inferior aspects of the cingulate gyrus were performed (Sawle, Lees, Hymas et al., 1993). Both successfully and substantially reduced obsessions and self-injury, however only the frontal lobe-anterior cingulate operation had an effect on tic reduction.

A growing number of physicians believe that the "Neuroleptic Era" of TS is ending – more and more professionals take the stance that medications are not always appropriate and may in fact create more problems than they ameliorate (Walkup, 2000). Perhaps coming years

will provide more empirical studies concerning the costs and benefits of pharmaceutical treatment. Leckman, King & Cohen, in their overview chapter of tics and tic disorders, mention that new therapeutic interventions may arise from a deeper understanding of neuronal plasticity and how it is that tics and premonitory urges can be modified (1999). For example, it is well known that individuals with TS who are self-conscious about their tics and afraid of ridicule, ostracization, or persecution can 'camouflage' their tics by incorporating them into purposeful acts called parakinesias.

Various behavioural techniques have received some attention in the last 30 years – massed negative practice, contingency management and self-monitoring (King, Scahill, Findley & Cohen, 1999). The best-established and most encouraging means of modifying habit or tic symptoms is Habit Reversal Training (HRT). This technique involves a number of steps (taken from Azrin & Nunn, 1973):

a.) ***Recording:*** Habit frequency is documented.

b.) ***Awareness training:*** The client, while looking at him/herself in a mirror, describes each habit. Habits and tics are consistently brought to the client's attention until (s)he is able to recognize them without assistance. Triggers for the habit are identified, including early behavioural warning signs and environments where the habit tends to occur.

c.) ***Competing response practice:*** Clients engage in an opposing and sustainable movement or noise each time (s)he feels the urge to tic or at the tic onset. The competing response is chosen to be socially unobtrusive, compatible with goal-directed

actions, and to strengthen muscles opposite to the tic. Various competing responses used and studied over the years have been tabulated by Carr (1995).

d.) ***Habit control motivation:*** Discussing the negatives of the habit and providing positives (i.e. praise) for habit frequency reduction.

e.) ***Generalization training:*** Rehearsal during imagined exposure, practice, and everyday situation application.

Results from HRT studies have been very positive: the initial study on 12 individuals with various habits and tics found a mean reduction of 90% after one session, and 99% after a 3-month follow-up (King, Scahill, Findley & Cohen, 1999). A 1990 study on 10 TS clients yielded a mean tic reduction of 93% at home and 93.5% in the clinic – HRT worked for motor and phonic tics, in children and adults, reduced tic severity and frequency, and also demonstrated an effectiveness over and above benefits derived from medication (Azrin & Peterson, 1990). Peterson & Azrin in 1992 achieved a 55% reduction in tics using competing response alone: self-monitoring alone resulted in a 44% tic reduction and relaxation training alone reduced tics by 32%. Each of the six TS clients used in this experiment were trained in all 3 techniques and observed for 10 minutes whilst employing the technique. Finally, Peterson and Azrin (1993) conducted a review of controlled group outcome studies of both pharmacological and HRT treatments. It was concluded that HRT reduced tics 30-40% more than classic neuroleptics and 70% more than antihypertensives without producing side effects.

TS – Neurological Substrates

Individuals with TS appear to have abnormalities in the cortico-striato-thalamo-cortical (CSTC) circuitry - an interconnected circuit involving the frontal lobes, the basal ganglia and the thalamus. This complex circuit, often referred to as the anterior cerebral system, is believed to be important in inhibition (Harris, Schuerholz, Singer et al., 1995). Deficient inhibitory control in this circuitry has been suggested as the locus of TS symptoms - either a primarily subcortical disorder affecting the motor cortex through disinhibited afferent signals or impaired inhibition directly at the level of the motor cortex or both has been suggested (Ziemann, Paulus & Rothenberger, 1997). The CSTC system also mediates non-conscious forms of learning, called implicit learning, in which the acquisition and expression of information is not accompanied by awareness of its content or its influence on behaviour (Rauch & Savage, 1997). In a paper on perseverative and stereotyped behaviours Ridley (1994) states:

> "Repetitive behaviour is…. a feature of…. some neurological disorders including…. Tourette's syndrome.... Stereotyped behaviour seems to be related mainly to excess dopaminergic activity in the basal ganglia while perseverative behaviour can be produced by lesions of the frontal lobes…. [T]he frontal lobes have a modulating effect on (i) the activation of motor activity by the basal ganglia, (ii) in the generation of self-initiated behaviour, i.e. volition, and (iii) in the neural mechanisms which permit different modes of neural function (e.g. perceiving, remembering or thinking) to be identified. Failures in these three functions could result in excessive and repetitive motor activity [and] stimulus-bound behaviour [i.e. "the excessive execution of the most probable response to the environment"]" (Ridley, 1994).

It makes intuitive sense then that CSTC circuitry might be involved in TS. Not surprisingly a considerable amount of neurological evidence has confirmed the presence of abnormalities in a number of subcortical structures comprising this neurological pathway.

Imaging studies of the lenticular regions (i.e. the putamen and globus pallidus) of 14 neuroleptic-naï ve patients with TS have indicated a loss of the normal L > R neuroanatomical asymmetry found in control samples: this is due to a significant left volume reduction of, on average, 10.7% (Peterson, Riddle, Cohen et al, 1993; Singer et al., 1993; Sandor, 1999). Furthermore, Yazgan, Peterson, Wexler & Leckman, using 11 adult TS patients evidencing this lack of normal L > R lenticular asymmetry, found that a significant lack of the normal functional asymmetries on related neuropsychological measures also existed (Yazgan, Peterson, Wexler & Leckman, 1995). Hyde, Stacey, Coppola et al. (1995) conducted morphometric analyses of the MRI's of MZ twins concordant for tic disorder but discordant for tic severity. Significant volume reductions of the right caudate (î = 6%; particularly the right anterior) and a trend towards left caudate reduction were found in the more severe as compared to the less severe twin. A normal L > R asymmetry in the lateral ventricles was lost: moreover those afflicted members of twin pairs with greater ventricular symmetry had more severe tics (i.e. a significant correlation between ventricular symmetry and tic severity). Finally, bilateral and symmetrical lesions of the globus pallidus with a "tiger's eye" appearance were reported by Demirkol and colleagues when they conducted an MRI scan of an individual with TS comorbid with OCD, Attention-Deficit Hyperactivity Disorder (ADHD), and stuttering who did not respond to a variety of medication classes (Demirkol et al., 1999).

Functional neuroimaging studies (i.e. PET, SPECT) have also found abnormalities in the CSTC circuitry. Studies have generally reported hypometabolism or low regional cerebral blood flow in the basal ganglia (Peterson, 2001). The largest study compared 16 TS cases (14 male, 2 female) to 16 controls (11 males, 5 females) all with an approximate mean age of 33.5

years (Braun, 1993). Relative to the controls, the TS group was reported to have decreased blood flow to the basal ganglia (caudate, putamen and globus pallidus) paralimbic, ventral prefrontal, and brainstem regions, particularly on the left side. No left-right asymmetries were noted for the controls. Interestingly, the TS group showed an *increase* in metabolism to the superior sensorimotor cortex – in a follow-up study "an altered functional relationship between the ventral striatum and sensorimotor cortices" was postulated given that metabolism rates were positively correlated in TS patients but inversely related in controls (Stoetter et al., 1992). Finally, hypoperfusions in the head of the left caudate have been noted in SPECT studies (Moriarty et al., 1995; 1997).

Research has confirmed the existence of numerous CSTC circuits including a "motor" circuit and other more "cognitive" circuits (Alexander, DeLong & Strick 1986); the cortical connections of the five circuits discovered thus far cover almost the entire frontal lobe (Graybeil, 1999). One loop, involving the prefrontal cortex and caudate nucleus, is important in self-regulation, set-maintenance, selective inhibition of verbal and nonverbal responses, cognitive flexibility, planning, prioritizing, organizing, and preparedness-to-act. As many of these functions are characteristic features of ADHD, ADHD has been implicated as one possible result of a dysfunction in this "cognitive" loop (Boucugnani & Jones, 1989). A CSTC circuit linking the lateral orbitofrontal cortex to the ventralmedial caudate has been implicated in TS (Sawle et al., 1993) while others have suggested a circuit involving the primary motor cortex (Brotchie, Iansek, & Horne, 1991) or a "motor" circuit (as described by Alexander, DeLong & Strick, 1986) looping from the sensorimotor strip to the putamen and back up to the supplementary motor areas (Rauch, 1999).

What each loop is responsible for, and which deficits or disorders are associated with each loop, is still not clear. Given this state of uncertainty, we believe that successful inhibition, and the failures that can occur in inhibition, are often under-specified concepts. We view the core deficit in TS to be a failure of "motor inhibition" rather than higher-level "cognitive inhibition" problems. Support for this contention comes from the continuum of severity in TS. Mild forms are characterized by motor and phonic tics whereas only in the more severe forms, and typically only when comorbid conditions are present, does one see more 'complex' tics involving a failure to inhibit higher-level cognitive behaviours (e.g. coprolalia; Freeman et al., 2000). While one may also often see "cognitive inhibition" problems (e.g. attentional problems) in TS beyond those seen in complex tics (e.g. Bornstein, 1991a; Baron-Cohen et al., 1994) these elements may be due to comorbid conditions like ADHD or OCD – problems that are neither required for diagnosis, nor present in all TS cases.

In corroboration of this conception of TS as a "motor inhibition" problem, tasks that emphasize "motor inhibition" such as the Luria Hand Alternation task and motor sequencing tasks have been shown to present significant difficulties for TS samples (Baron-Cohen, Robertson & Moriarty, 1993; Baron-Cohen et al., 1994; Georgiou et al., 1995).

Findings from disciplines other than neuropsychology suggest motor control difficulties as well. Some evidence that ocular motor control circuitry associated with saccade inhibition is mildly affected in individuals with TS (Farber, Swerdlow & Clementz, 1999). Saccade durations were shorter and their mean velocities were higher than in normal controls. In addition, the proportion of anticipatory saccades was higher in individuals with TS (Farber,

Swerdlow, Clementz; 1999). A research group in Germany interested in Restless Leg Syndrome (RLS) has documented that, relative to age and sex matched controls, 7 drug-free individuals with TS demonstrated significantly more periodic limb movements (both legs and arms) during sleep (Voderholzer et al., 1997). Finally, an investigation into motor cortex excitability in TS through transcranial magnetic stimulation (TMS) was conducted by Ziemann, Paulus, and Rothenberger (1997). TMS is accomplished by passing a powerful but brief magnetic current through the skull; this induces highly focal electrical currents in various cortical regions (George et al., 2001). Paired-pulse TMS, the technique employed in the Ziemann, Paulus and Rothenberger study, involves quickly following one pulse with another. The authors delivered the paired pulse TMS to the hand area of the left motor cortex, eliciting motor-evoked potentials and measuring the cortical silent period (the period of time following this motor-evoked potential that the muscles are inactive). Intracortical inhibition and facilitation were produced by a subthreshold conditioning stimulus in a paired stimulus paradigm (see Ziemann, Rothwell & Ridding, 1996) and measured. These researchers found that the 20 right-handed adults with TS that they studied displayed normal motor thresholds, which is indicative of a normal level of excitability at the membrane level. However, they also exhibited both a shortened cortical silent period and deficient intracortical inhibition when electromyographic (EMG) recordings were made. The authors suggest that these deficiencies reflect abnormal inhibition through the basal ganglia-thalamic-cortical motor loop (Ziemann, Paulus, and Rothenberger; 1997) – shortened cortical silent periods reflect problems in the motor cortex, intracortical inhibition difficulties reflect problems in subcortical afferents to the motor cortex.

It is possible that even some of the "cognitive inhibition" difficulties described in this body of literature may, upon closer analysis, be artefacts of underlying motor difficulties. For example, Shucard and colleagues (1997) measured the performance of 22 boys with TS on a Continuous Performance Test and found that, although this group demonstrated a normal capacity for discriminating targets from non-targets during the task, they showed significantly slower reaction times (RT's) than controls – a finding replicated by others (Harris, Schuerholz, Singer et al., 1995). Severity of complex vocal tics was found to be predictive of RT performance – the more severe the tics, the slower the RT's. According to Shucard et al., (1997) possible explanations for these findings included interference associated with tic suppression and a general impairment of motor performance. Thus, although Continuous Performance Test differences are traditionally linked to cognitive inhibition difficulties, the RT deficiencies noted among the TS group in this study may have resulted from participants having to suppress unwanted motor activity (tics), while at the same time making motor responses (key presses) in response to visually presented targets.

While few controlled empirical studies have examined executive functioning in TS, and of those studies comorbidity and medication issues have been generally disregarded, there are a handful of studies that did sample executive functioning in individuals with 'pure' TS (for a review see Pennington & Ozonoff, 1996). These studies involved tasks that emphasized more traditional 'cognitive' measures of inhibition such as a Go-Nogo task, a Negative Priming task and a Continuous Performance task. Results for 'pure' TS samples did not reveal deficits in any of these executive functions (Ozonoff et al., 1994; Ozonoff et al., 1998; Sherman et al., 1998). TS samples with comorbid ADHD, however, demonstrated deficits in impulsivity (Go-

Nogo), the ability to inhibit the processing of irrelevant visual distracter stimuli (Negative Priming), and sustained attention (Continuous Performance). Harris, Schuerholz, Singer et al. (1995) gave 10 executive function tasks to non-medicated groups of individuals diagnosed with TS, ADHD, or both disorders. They found that all three groups had slower RT's than controls. Furthermore, they found that, for all three groups, RT's were more variable than the RT's of controls. The TS-only group had the fewest executive function problems however, followed by the ADHD group and the group diagnosed with both disorders. In corroboration with Pennington and Ozonoff they concluded that executive function difficulties in TS are related instead to comorbid conditions and not TS itself (Harris, Schuerholz, Singer et al., 1995). Therefore studies of executive function difficulties in TS may have produced conflicting results because the various executive function tasks employed may have differentially drawn upon different types of inhibition ("motor", or "cognitive"). Further, although CSTC circuitry is implicated in both TS and ADHD, different and separable circuits may very well be involved in each of these disorders.

If TS indeed reflects a problem in inhibiting motor behaviours, rather than in inhibiting higher-level cognitive behaviours then the anatomical location of the deficit should preferentially involve the subcortical structures of the CSTC circuitry (i.e. the basal ganglia), rather than the frontal-lobe components of this circuit. That being said it is recognized that the subcortical circuits and the cortical circuits must work together to demonstrate successful inhibition. Since developmentally the frontal lobes are the latest to develop, it may be that both children with TS and those without TS may demonstrate inhibition problems early in the developmental sequence. As the frontal lobes develop with age, the entire CSTC circuit may

work more effectively and inhibition failures will be reduced. If this is the case then differences between TS and controls, in terms of failures of inhibition, might only emerge later in the developmental sequence. Succinctly, younger children should have problems with inhibition in general because the frontal lobes are not developed enough to adequately inhibit prepotent motor, or cognitive responses. Older children without TS will have frontal lobes that are developed enough to show normal inhibition of prepotent motor and cognitive responses. Older children with TS, while able to inhibit higher-level COGNITIVE responses due to the adequate development of their frontal lobes, should still have problems inhibiting prepotent MOTOR responses, however, because of dysfunction of the basal-ganglia components of the CSTC circuit.

In deciding what tests would be useful in providing empirical support for our view of TS a number of factors were considered. 1) Tests should be capable of assessing the integrity of the frontal lobes - tests should demonstrate the ability to plan, and implement performance optimization strategies. 2) Tests should differentially draw upon higher-level "cognitive inhibition" or lower-level "motor inhibition".

Using such tests our predictions are that as children both individuals with TS and controls would have problems with "cognitive" and "motor" inhibition, but with increasing frontal lobe development control children would 'grow out' of this problem. As older individuals, participants with TS would be able to 1) invoke performance optimization strategies indicative of integrated frontal lobes, 2) would be able to demonstrate relatively

normal “cognitive inhibition”, but 3) would show problems with lower-level “motor inhibition”.

In the present experiments we chose to use variants of the Stroop and Simon tasks to assess “cognitive inhibition” and “motor inhibition” capability respectively. The Stroop and Simon effects are operationally defined as differences in RT’s between congruent and incongruent trials. Such differences, however, are not always "pure" measures of inhibition. Part of these congruent/incongruent trial differences may reflect the strategies that participants use to carry out these tasks. Logan and Zbrodoff (1979), Lowe and Mitterer (1982), and Cheesman and Merikle (1986) demonstrated strategic influences on the magnitude of the Stroop effect by varying the congruent trial probability (defined as the percentage of congruent, relative to incongruent trials). At low congruent trial probability levels (e.g. 25%) the most cost effective strategy is to do one's best to ignore the interfering word at all times. Since 75% of trials are incongruent (e.g., RED displayed in blue) most of the time the word (e.g. RED) will be incompatible with the required response (blue). Thus the best strategy is to vigorously inhibit the tendency to respond to the word, and focus one's attention exclusively on naming the colour. At higher congruent trial probability levels (e.g., 75%), most of the time the word matches the required response (RED displayed in red). Thus if participants relax their inhibition of words somewhat, overall the strategy will be beneficial. That is, 75% of the time, allowing the word to reach semantic level activation, will serve to increase the activation of the correct colour response, and thereby facilitate correct trial RT’s (e.g., see Cohen, Dunbar & McClelland, 1990). It is only on the 1 trial out of 4 where the word is incompatible with the required colour response where this strategy incurs a cost. The pattern of results driven by

these performance optimization strategies is depicted in Figure 1 below, which shows larger Stroop effects in the 75% congruent trial probability condition than in the 25% congruent trial probability condition.

Figure 1 indicates how Stroop effects in the 75% condition can be parsed into 'pure inhibition' [1] effects plus the effect of participants implementing a performance optimization strategy. A similar pattern of results reflecting 'pure inhibition' at low congruent trial probabilities and a mixture of inhibition and strategic effects at higher congruent trial probabilities can be seen on the Simon task as well (Hommel, 1994a; Hommel, 1994b).

[1]One might argue that in the 25% condition, where most of the trials are incongruent one could read the word and use the word to facilitate naming of the OPPOSITE response (e.g., when the word BLUE is presented, most of the time the correct response will be to say red). If so, then both the 75% and 25% conditions would reflect strategic influences on Stroop effect size. In the 25% condition, however, strategic effects are extremely unlikely to be invoked because using the word to name the opposite colour takes too much time to implement. Dixon & Laurence (1992) demonstrated that it takes at least 250 msec to implement this type of strategy. Since the average Stroop effect is only of the order of about 60 msec, participants are much better off vigorously inhibiting the tendency to say the word, and attempting to name the colour as fast as possible. Furthermore, experiments by Lowe & Mitterer demonstrate that, when RT and errors are taken into account, linear systematic decreases in Stroop effects are found as congruent trial probabilities are decreased from 75% to 50% to 25% (Lowe & Mitterer, 1982). Even in the 50% congruent trial probability condition, one that might be argued to be the "true" strategy-free condition, inhibition is not as free of strategic effects as in the 25% congruent trial probability condition. Thus, although we cannot unequivocally say that the 25% condition is devoid of strategic effects, we will use the term "pure-inhibition" to label this condition with the understanding that, within this context, performance optimization strategic effects are minimized relative to the 75% condition where strategic effects serve to increase the overall size of the Stroop effect

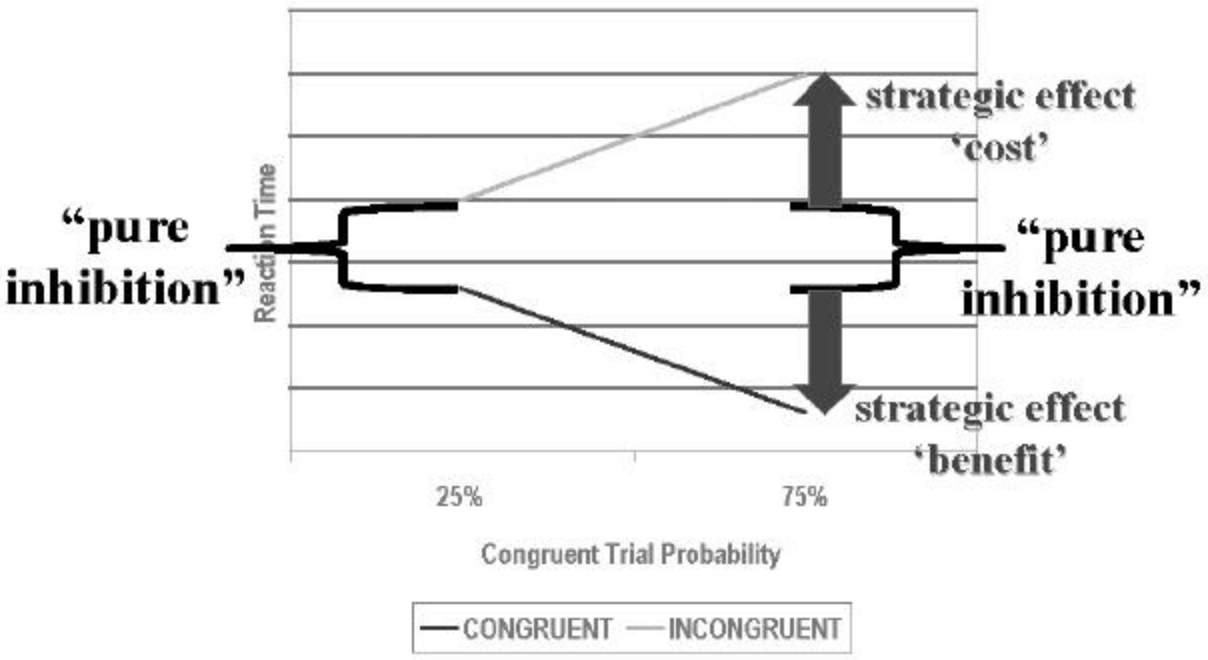

Figure 1: Performance Optimization Effect.

Recall that when deciding what tests to adopt we postulated that 1) Tests should be capable of assessing the integrity of the frontal lobes by demonstrating the ability to implement performance optimization strategies. 2) Tests should differentially draw upon higher-level "cognitive inhibition" or lower-level "motor inhibition". As shown in the figure, the ability of the frontal lobes to implement a performance optimization strategy is reflected by the increased size of the Stroop or Simon effect in high (75%) congruent trial probability conditions. As such these tests are good candidates for fulfilling the first of our requirements.

Next we considered the second of our requirements (tests that can measure "cognitive" or "motor" inhibition). On our variant of the Stroop task participants were presented with colour-words (either RED or BLUE). The colour that the word was displayed in was either congruent with the presented word (e.g., RED was displayed in red), or incongruent with the

presented word (RED was displayed in blue). Participants were asked to ignore the word and simply name the colour of the stimulus as quickly as possible. On our version of the Simon task participants placed one hand atop a box designed to administer different kinds of tactile stimulation (e.g., a buzzing sensation or a drumming sensation). If they felt a buzzing sensation they were to press a response button on the left, **f** they felt a drumming sensation they were to press a response button on the right. Tactile stimulation was presented to either the pinky finger, or to the index finger. For a person with their left hand atop the box, the pinky finger was on the left, and the index finger was on the right, for a person with their right hand atop the box, these relations were reversed. Congruent trials occurred when the finger that was stimulated was on the same side as the button that had to be pressed (e.g., a left finger was stimulated and the type of vibration indicated that the response button on the left must be pressed). An incongruent trial occurred when the finger that was stimulated was on the opposite side of the button that had to be pressed (e.g., a left finger was stimulated, but the type of vibration indicated that the response button on the right had to be pressed).

Thus, on incongruent trials both Stroop and Simon tasks involved the inhibition of prepotent responses. In the Stroop task one had to inhibit the prepotent tendency to read the presented word. In the Simon task one had to inhibit the prepotent tendency to respond on the side of space where the tactile stimulation occurred. Both Stroop and Simon tasks measured the ability of participants to inhibit these prepotent responses, and in both tasks interference during incongruent trials depended upon the correspondence between the irrelevant stimulus attribute and the response (O'Leary & Barber, 1993). The most important difference between the two tasks, for our purposes, was the level and type of inhibition necessary to correctly

respond in each task. We proposed that the Stroop task drew upon higher "cognitive inhibition" because participants were required to inhibit the semantic-meaning level activation of WORDS on incongruent trials. Furthermore, Stroop interference is considered by many to be a classic test of frontal lobe integrity (e.g., Holst and Villki, 1988; Perret, 1974). We proposed that the Simon task, by contrast drew upon "motor inhibition" because on incongruent trials one is required to inhibit the prepotent tendency to make a motor response with a digit on the side of space where tactile stimulation occurred. Indeed, there is a general consensus that Stroop and Simon tasks involve separate response-selection processes – the former being a more cognitive congruence, the latter being a more spatial correspondence (Simon & Berbaum, 1990; O'Leary & Barber, 1993). As such these tests are also good candidates for fulfilling the second of our requirements.

Inhibition capability could be measured in two ways: by its success or by its failure. RT on incongruent trials is a good measure of successful inhibition, (on Stroop and Simon tasks RTs are measured only for correct responses). When measuring successful inhibition, errors rates play the important but relatively minor role of ruling out the possibility that RTs were contaminated by speed-accuracy tradeoffs. When measuring inhibition failures however, error rates take pride of place. An example of an error would be saying 'blue' when the correct response is 'red' in the Stroop task, or pressing the left-most button when the correct response is the right-most button in the Simon task. Most experimental designs involving the Stroop do not consider errors in their analyses. Since we believed TS to be a disorder characterized by sporadic inhibition failure however, errors in the 25% congruent trial probability 'pure

inhibition' condition were considered to be quite meaningful and the best measure of inhibition failure.

In sum then, we proposed that children with TS and control children would have problems with both "cognitive" and "motor" inhibition. As control children age and their frontal lobes develop "cognitive" and "motor" inhibition problems would be alleviated. As TS children age, they would begin to demonstrate normal "**cognitive"** inhibition, but will still demonstrate problems with "**motor**" inhibition - as evidenced by a greater number of "motor inhibition" failures. Our first two experiments were intended to test these general hypotheses. Experiments 3 and 4 were designed to demonstrate how failures in motor inhibition might be used to account for tic phenomenology.

Prior to describing these experiments in detail we wish to note that the ordering of the experiments as they are presented in this thesis do not match the chronology in which they were tested. In actuality Experiment 3 was conducted first; Experiments 1 and 2, run concurrently in a counterbalanced order, followed. Experiment 4 was conducted last. Although this sequence was required for practical reasons, the order in which these experiments are numbered affords a more natural theoretical flow when describing the results. Hence, for the sake of clarity and for ease of explication we present the experiments in an order different from the chronology in which they were conducted.

In addition, when these experiments were initially designed we had not planned to stratify groups by age. Following testing it became clear that younger and older groups were performing these tasks very differently. Upon reflection there were good theoretical reasons

for such age-related performance differences; hence we made predictions concerning older and younger participants based on age-related differences in frontal lobe development.

EXPERIMENT 1 –

STROOP TASK PERFORMANCE OF YOUNGER AND OLDER TOURETTE SYNDROME AND CONTROL PARTICIPANTS

Numerous studies have confounded TS, hypothesized to be a problem in inhibiting lower-level motor behaviours, with ADHD, a commonly comorbid diagnosis associated with "cognitive inhibition" deficits. We sought to demonstrate the lack of "cognitive inhibition" difficulties in a group of individuals diagnosed with TS but free of comorbid ADHD symptomatology. The negative impact of ADHD on Stroop performance is well documented (Lufi, Cohen, & Parish-Plass, 1990; Grodzinsky & Diamond, 1992; Carter, Cameron, Krener et al., 1995; Seidman, Biederman, Faraone, et al., 1997; Katz, Wood, Goldstein et al., 1998; Taylor & Miller, 1997). To the best of our knowledge the Stroop task has never been applied to a TS sample in which ADHD symptoms were either never present or were treated with medication. One extant study tested 12 adults (11 male, 1 female, mean age 29) who met DSM-III-R criteria for TS on the Stroop task. All participants were free of any dementia, but half were medicated (5 with neuroleptics, 2 with Fluoxetine, an SSRI). The TS sample was found to be more depressed, but was matched on age and education and had the same numbers of males to females. For our purposes the most salient finding was that the TS group showed more Stroop interference than the matched controls. Importantly, however, the sample did not appear to have been screened for comorbid ADHD (Georgiou et al., 1995b). Thus it is unclear how much of these Stroop impairments were attributable to TS and how much they were attributable to ADHD symptomatology.

Although in our studies we would have preferred "pure" participants with TS, practical considerations forced us to include participants with some comorbid diagnoses to ensure an adequate sample size. Since untreated ADHD participants might suffer from "cognitive inhibition" failures, including comorbid ADHD participants in our sample of participants with TS could potentially contribute variance to our data. To minimize this unwanted source of variability it was ensured that these participants had current prescriptions for some form of stimulant medication -- research has shown that individuals medicated for ADHD no longer demonstrate differences on the Stroop task (in fact non-significant group differences between ADHD and control samples on a Stroop task has been used as a gauge of pharmaceutical effectiveness Miller, Kavcic & Leslie 1996; Spencer et al., 1998).[2]

In order to test our developmental predictions participants were divided into two groups – a younger sample (ages seven to nine) and an older sample (ages ten to 21). It was important

[2] We recognized, however, that including participants taking medication for ADHD yielded a further complication - namely the possibility that medications prescribed for ADHD might have influenced TS presentation and therefore our results. In fact it was believed for some time that stimulant medications caused TS (Lowe et al., 1982). This concern was later demonstrated to be unwarranted (e.g. Price et al., 1986). Today it is generally believed that stimulant medications may exacerbate tics in a particular subset of the TS population when the drug is first introduced, but that these initial symptom aggravations often later subside (Gilbert, 2001). Common preventative techniques now employed in clinics include prescribing low dosages of stimulant medications, waiting out flare-ups, and avoiding certain types of stimulant medication known to worsen TS symptoms more regularly (e.g. Dextroamphetamine; Kurlan, 2001). In summary, although we proposed to include participants with TS with comorbid ADHD as long as they were taking medication, as a precautionary measure we tracked the influence of medicated ADHD on performance when analyzing our results.

that one sample represent an age where one would expect frontal lobe function to still be within development while the other sample represent an age where one could reasonably assume that frontal function has stabilized. Some executive function studies have used children as young as six (Harris et al. 1995) and nine (e.g. Ozonoff, Strayer, McMahon & Filloux 1994) years, and Baron-Cohen, Robertson & Moriarty (1993) argue that by age 5 or 6 children develop the capacity to edit simultaneously competing intentions (an example of this would be to attend to one and only one dimension of a compound stimulus such as the colour of the word RED displayed in blue as in the Stroop task). Thus we felt that children who were between six and nine years old would be old enough to complete Stroop and Simon type tasks, but would be young enough to reflect the expanding frontal development of our younger sample.

Ages ten and older seemed an appropriate cut-off point to reflect the stabilized frontal function of our older sample. Stuss (1992) reports that age-related prefrontal RNA development matures by approximately age 9. Motor reaction inhibition develops most between 6 and 8 (Becker, Isaac and Hynd, 1987) and attentional functions (i.e. selective attention, disregard distractions) develop between five and nine (Humphrey 1982). Choosing an age cut-off point slightly higher than those suggested in this literature is additional insurance that these executive functions have fully stabilized in the average child.

In light of our distinction between inhibition successes and inhibition failures our concrete *a priori* hypotheses concerning Stroop performance were specified in terms of what we predicted for RT's and what we predicted for errors.

Reaction Times

- Hypothesis 1) Younger and older participants would demonstrate differences in implementing a performance optimization strategy. We predicted that the pattern depicted by the RT's in Figure 1 would be more pronounced in the older participants (more < shaped patterns) whereas for younger children we predicted less of an effect of congruent trial probability (more = shaped patterns). Statistical support for this prediction would take the form of a congruency (congruent, incongruent) by congruent-trial probability (25%, 75%) by age (older, younger) interaction.
- Hypothesis 2) TS and control groups would not show differential performance in terms of their ability to implement performance optimization strategies. Since we believe the site of TS problems to be the basal ganglia rather than the frontal lobes, we did not predict differences in the frontally mediated ability to implement performance optimization strategies. Support for this prediction would be a non-significant group (TS, control) by congruency (congruent, incongruent) by congruent-trial probability (25%, 75%) by age (older, younger) interaction.

Errors

- Hypothesis 3) As previously argued, the best measure of failures of inhibition are the errors committed in the 25% congruent trial probability 'pure inhibition' condition. We predicted that younger children would show more failures of inhibition than older children. This hypothesis was tested by assessing the significance of the age (younger, older) by congruency (congruent, incongruent) interaction for the 25% 'pure inhibition' condition. Because we were specifically interested in differences between older and

younger children in *failures* of inhibition it was deemed necessary to compare the performance of older and younger children in the condition where such failures should occur most often. Thus in addition to conducting the higher order age by congruency interaction we also conducted a simple main effect of age on incongruent trials in the 25% condition. Here we predict that younger children will make significantly more errors on incongruent trials than older children.

- Hypothesis 4) We predicted that TS and controls would not differ in terms of their failures of "cognitive inhibition", as reflected by the errors committed in the 25% congruent trial probability 'pure inhibition' condition. This prediction would be substantiated by a non-significant interaction between group (TS, control), age (younger, older), and congruency (congruent, incongruent). In addition we also predicted that when either the older subjects were considered in isolation, or when the younger subjects were considered in isolation, there would be no significant difference between group (TS, control) and congruency (congruent, incongruent).

PARTICIPANTS

Volunteers for all experiments were recruited through a solicitation package mailed out by the TSFC. Members within one hour of either testing location (TSFC National Office in Toronto, University of Waterloo Psychology Lab) and between the ages of 7 and 21 were randomly selected through a membership database search (by area code and age) and contacted (n=300). The solicitation package included a letter of invitation from the researchers, a background questionnaire, a consent to be contacted form, and a letter from the TSFC endorsing the project and assuring that a declination to participate would not influence their membership in any way.

Participants were also solicited through short solicitation advertisements appearing in TSFC affiliate newsletters.

Fifty-three interested families returned the background information sheet to the researchers (return addressed, stamped envelopes were provided), and interested members of the family signed the consent to be contacted form (n=96). Individuals with TS either without a comorbid diagnosis of ADHD or medicated for ADHD were preferred. A total of eight individuals with ADHD were included in the sample (four in the older participants and four in the younger); in addition, there were 3 diagnoses of OCD, 2 of learning disorders, 2 of rage, 1 of sleep disorder, and 1 of unspecified anxiety. Two participants were also said to demonstrate obsessive-compulsive behaviours. While Georgiou et al. (1995b) found no significant differences on the Simon task between individuals with TS medicated or unmedicated with conventional neuroleptics or SSRI's, we still chose to accept only participants currently unmedicated with neuroleptics to control for any potential source of variance that variable may present. Siblings under the age of 21, not diagnosed with TS or any other disorder, and in the same age range were preferred as controls. Information regarding diagnoses for both groups was based on parent report. Based on these exclusionary criteria 34 families were contacted (n=45). During the course of arranging and running appointments 7 families discontinued their involvement leaving 27 families participating (n=38). Two children of department members, free of diagnoses, were added to the control group to bring the sample size to 40. Participants were compensated at a rate of $8.00 per hour, and were assigned a number (for family) and letter (for family member) for data entry purposes to ensure anonymity. Both control and TS

groups were split into younger and older samples. Mean ages in the younger sample were 7.78 (control) and 8.5 (TS) and mean ages in the older sample were 13.2 (control) and 12.36 (TS).

Stroop data for seven participants were inexplicably lost through computer error (including three older participants with comorbid TS and ADHD) leaving a final sample size of 33 (see Table 1 below).

	TS (Old)	**Control (Old)**	**TS (Young)**	**Control (Young)**	**TOTAL**
Male	4	3	9	4	20
Female	3	6	0	4	13
TOTAL	7	9	9	8	**33**

Table 1: Participant analysis for Experiment 1.

METHODS

The apparatus was a Macintosh Power PC (7100/66AV) computer interfaced with a 14 inch VGA colour monitor and programmed with PsyScope software (Cohen et al., 1993). One of two colour-words (RED or BLUE) appeared in the centre of the screen displayed in one of two colours (red or blue); 24 point Chicago font was used and trial order was randomized for each participant. Participants were instructed to ignore the colour-words and respond by naming the video display colours as quickly and accurately as possible. Participants spoke into a Sony dynamic microphone connected to the computer via a CMU Button box. Voice RT (operationalized as the time between stimulus presentation and the tripping of the voice key)

was recorded. After the voice key was tripped, the stimuli disappeared from view. The experimenter indicated, via a key-press, whether the participant's response was correct, an "error" (defined as providing the incorrect response in its entirety or blurting a portion of the incorrect response before responding correctly), or a discarded trial due to technical problem (e.g., the voice key being tripped by extraneous noise in the hallway, by a vocal tic, etc.). A 500 ms inter-trial interval separated the experimenter's key press and the presentation of the next stimulus.

Two conditions of 224 test trials each were presented in blocked format. In the first block, congruent trials randomly appeared 25% of the time. In the second block congruent trials randomly appeared 75% of the time. Sixteen practice trials succeeded each block. Practice trials contained the same congruent trial probabilities as the block they preceded. A single five-minute break was offered at each halfway point. Blocks were counterbalanced across participants and interspersed with the sessions of Experiment 2.

RESULTS AND DISCUSSION

Outlier analyses were conducted using the Van Selst & Jolicoeur (1994) technique. As mentioned, because even medicated ADHD could introduce unknown variance into our results (through effects of the medication or inadequate amelioration of the ADHD symptoms) the data were analyzed in two ways as a precautionary measure. Individuals with comorbid but treated ADHD were included in the TS group for one set of analyses to maximize sample size. In the second set of analyses data from these participants were excluded - the TS group was free of participants with comorbid ADHD.

Inhibition Successes in Stroop Performance

Success of inhibition was considered in terms of RT data. RT data was analyzed using a 4-way mixed model ANOVA. Congruency (congruent, incongruent), and congruent trial probability (25%, 75%), were the within subject factors, and age (older, younger) and group (TS, control) were the between subject factors.

ADHD Included: The 4-way ANOVA revealed a significant main effect of congruency (RT was significantly faster for congruent trials than incongruent trials; $F(1,29) = 89.26$, $p < .001$)) and a significant main effect of age (older participants were faster than younger participants; $F(1,29) = 19.21$, $p < .001$). A significant interaction of congruency (congruent, incongruent) and congruent trial probability (25%, 75%); $F(1,29) = 30.45$, $p < .001$ was revealed. There was also a significant interaction between congruency (congruent, incongruent) and age (older, younger); $F(1,29) = 8.68$, $p = .006$. The 4-way interaction of congruency, congruent trial probability, age, and group was non-significant ($F(1,29) = .007$, $p = .934$). Additional main effects and interactions relevant to our hypotheses are listed below:

- Hypothesis 1) Our hypothesis that younger and older participants would demonstrate differences in implementing a performance optimization strategy was supported by a significant 3-way interaction of congruency (congruent, incongruent), congruent trial probability (25%, 75%) and age (older, younger) ($F(1,29) = 5.09$, $p = .032$). We were surprised to find that the patterns demonstrated by the older and younger participants were opposite to what we had predicted – that is, the younger participants in both groups appeared to show greater performance optimization effects (more < shaped patterns) than both groups of older participants. As can be seen in Figures 2 (below),

the most dramatic difference between the younger versus older individuals involves the slope of the lines for congruent trials in the 25% and 75% conditions. Although the younger children show dramatic improvements in RT's, the older participants show little if any improvements in congruent trial colour naming.

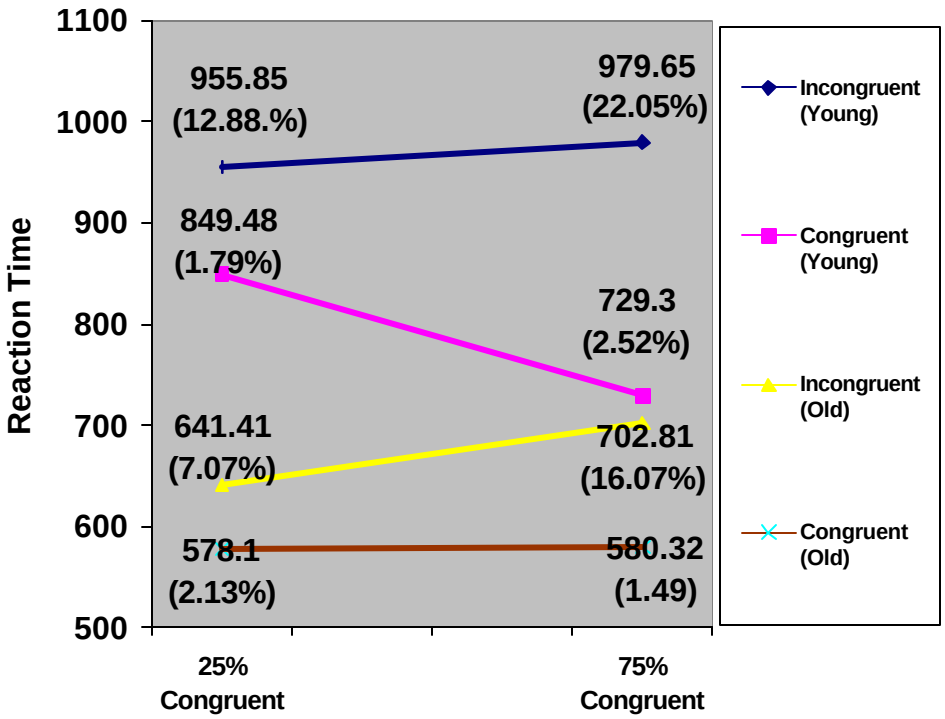

Figure 2: RT as a function of congruent trial probability for both young and old TS and control samples on the Stroop task.

One interpretation of the data presented in Figure 2 is that in a less well-developed frontal inhibition system children would show devastating effects of incongruency. Looking at Figure 2, one can compare the error rates of older and younger children when responding to incongruent trials. Such relatively high error

rates among the younger children might elicit an overall slowing of RT's as a compensatory mechanism. Such an interpretation would account for the large main effect of age in this group (younger children were overall 252.91 msec slower than their older counterparts). The older participants would presumably have better developed inhibition skills than the younger participants and could, given a better ability to 'weather' incongruent trials, afford to respond faster. Hence in the 75% congruent trial probability condition, where relaxing one's inhibition of words somewhat would be an overall beneficial strategy, the younger participants would have considerably more room to improve than the older participants.

- Hypothesis 2) The hypothesis that the TS and control groups would not show differential performance in terms of their ability to implement performance optimization strategies was supported by the lack of a significant group (TS, control) by congruency (congruent, incongruent) by congruent trial probability (25%, 75%), by age (older, younger) interaction ($F(1,29) = .007$, $p = .934$). Because theoretically we had predicted that only the older participants would show frontally mediated performance optimization strategies, we re-analyzed the differences between the older TS and control groups alone. A non-significant group (TS, control) by congruency (congruent, incongruent) by congruent trial probability (25%, 75%), interaction ($F(1,14) = .330$, $p = .575$) also suggested that there were no differences between controls and participants with TS in the ability to implement a performance optimization strategy in the older participants where frontally mediated strategies were predicted to have stabilized.

ADHD Excluded: The four way ANOVA revealed a significant main effect of congruency (RT was significantly faster for congruent trials than incongruent trials; ($F(1,24) = 92.27$, $p < .001$), and age ($F(1,24) = 13.29$, $p = .001$). A significant interaction of congruency (congruent, incongruent) and congruent trial probability (25%, 75%); $F(1,24) = 25.52$, $p < .001$ was revealed. There was also a significant interaction between congruency (congruent, incongruent) and age (older, younger); $F(1,24) = 4.76$, $p = .039$. The 4-way interaction was non-significant ($F(1,24) = .001$, $p = .979$). Additional main effects and interactions relevant to our hypotheses are listed below but in terms of our hypotheses, excluding participants with TS with comorbid ADHD did not lead us to change our interpretation of the data:

- Hypothesis 1) Our hypothesis that younger and older participants would demonstrate differences in implementing a performance optimization strategy was supported by a marginally significant 3-way interaction of congruency (congruent, incongruent), congruent trial probability (25%, 75%) and age (older, younger) ($F(1,24) = 4.1$, $p = .054$).
- Hypothesis 2) The hypothesis that the TS and control groups would not show differential performance in terms of their ability to implement performance optimization strategies was supported by the lack of a significant group (TS, control) by congruency (congruent, incongruent) by congruent trial probability (25%, 75%), by age (older, younger) interaction ($F(1,24) = .001$, $p = .979$). Because theoretically we had predicted that only the older participants would show frontally mediated performance optimization strategies, we re-analyzed the differences between the older TS and control groups alone. A non-significant group (TS, control) by congruency (congruent, incongruent) by congruent trial probability (25%, 75%), interaction ($F(1,13) = .774$, $p = .395$) also suggested that there were no differences between controls and participants

with TS in the ability to implement a performance optimization strategy in the older participants where frontally mediated strategies were predicted to have stabilized.

These analyses supported our hypothesis that there would be no group differences in the employment of a performance optimization strategy. While these analyses supported our hypothesis that there would be developmental differences in strategic ability across younger and older samples, the data configuration was opposite to what we had predicted. The large effect of congruent trial probability demonstrated by the younger sample, however, appeared to be derived from the fact that the younger participants slowed their overall performance to compensate for inhibition difficulties (as evidenced by their high error rates); this slowing enabled them greater room to improve their performance on congruent trials in the 75% congruent trial probability condition. This pattern of results, combined with the fact that there were no differences between participants with TS and controls, suggested that, developmentally, this strategic ability is present in both TS and normal populations by at least age seven and does not vary as one ages.

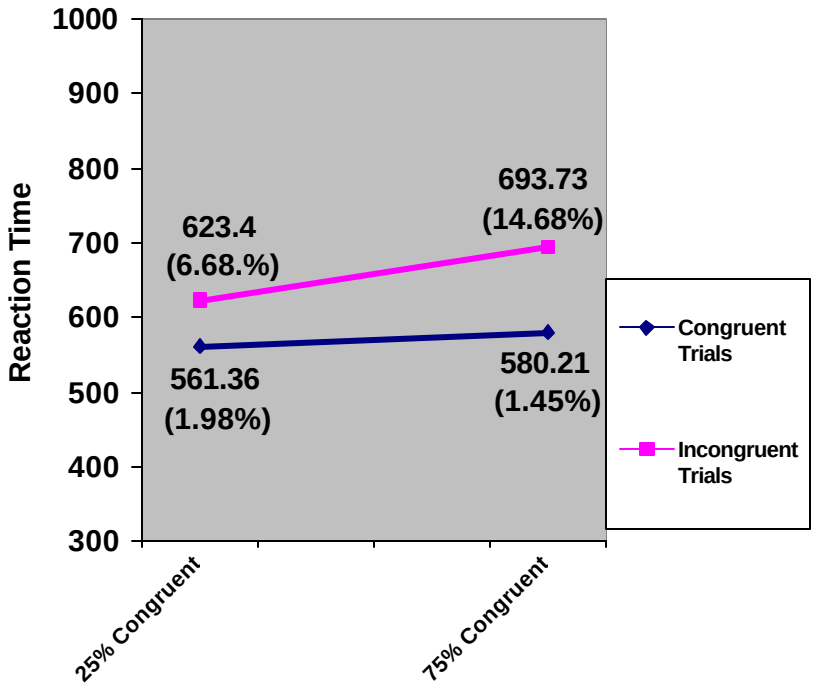

Figure 3: RT as a function of congruent trial probability for the older control sample on the Stroop task.

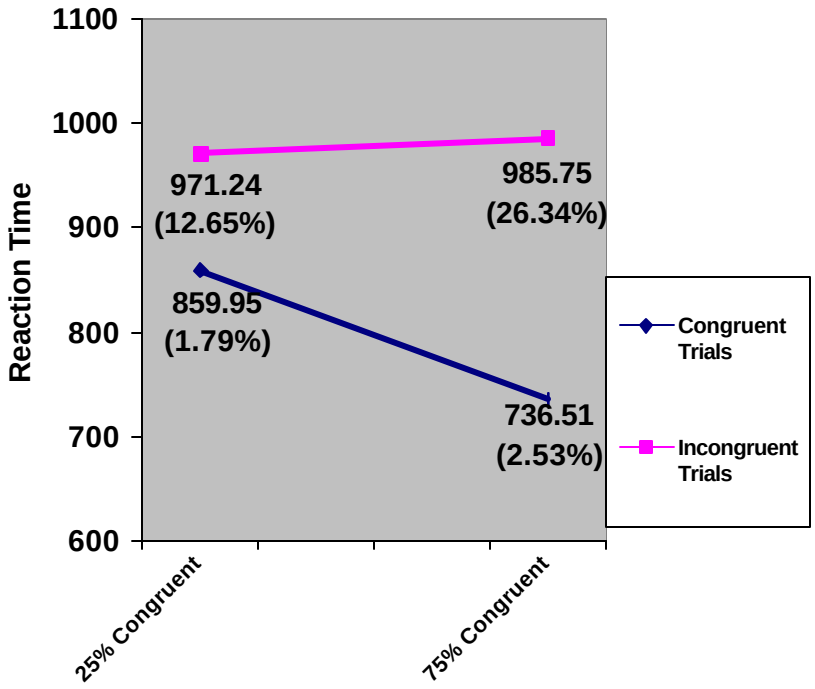

Figure 4: RT as a function of congruent trial probability for the younger control sample on the Stroop task.

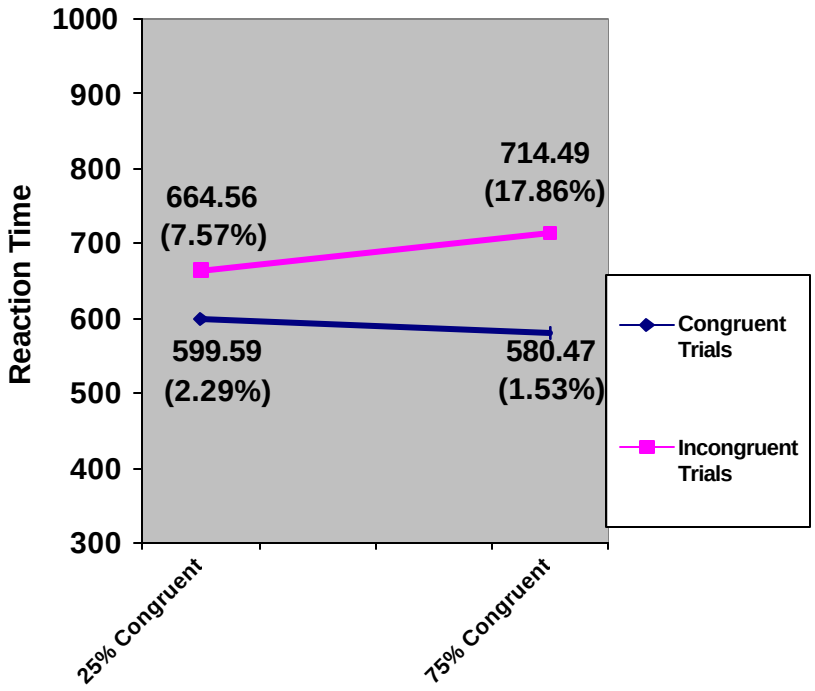

Figure 5: RT as a function of congruent trial probability for the older TS sample on the Stroop task.

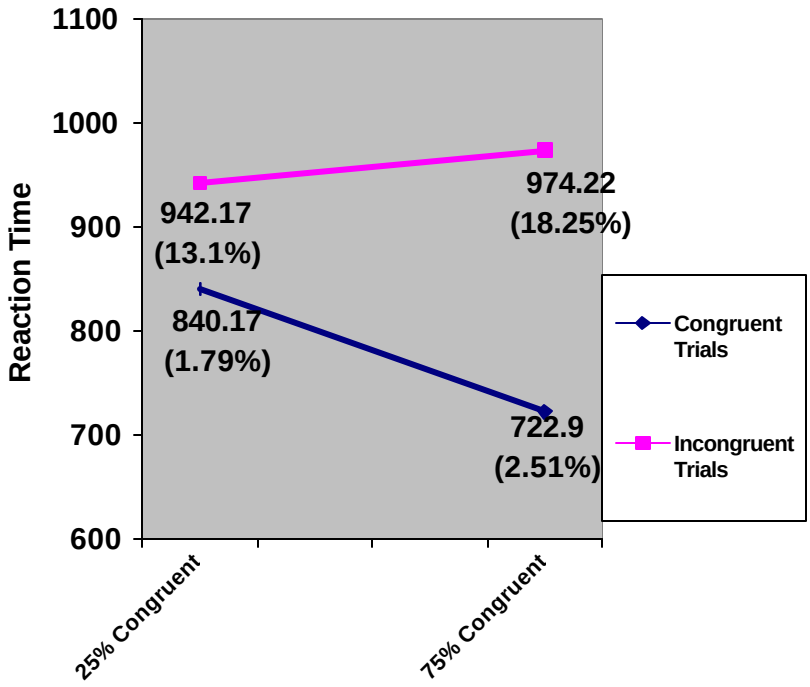

Figure 6: RT as a function of congruent trial probability for the younger TS sample on the Stroop task.

Inhibition Failures in Stroop Performance

Failure of inhibition was considered in terms of errors. Error data from the 25% congruency 'pure inhibition' condition was analyzed using a 3-way mixed model ANOVA. Age (older, younger) and group (TS, control) were the between subject factors and congruency (congruent, incongruent) was the within subject factor.

ADHD Included. This analysis revealed a main effect of congruency (more errors were committed on incongruent trials than congruent trials ($F(1,29) = 27.47$, $p < .001$)). Other main effects and interactions relevant to our hypotheses are listed below:

- Hypothesis 3) Our prediction that younger children would demonstrate more failures of inhibition than older children was not supported; an age (older, younger) by congruency (congruent, incongruent) interaction was non-significant ($F(1,29) = 2.71$, $p = .111$). Because of its theoretical importance a simple main effect was calculated despite the absence of this interaction. To test the hypothesis that younger children would make more errors than older children due to inadequate frontal lobe development, we compared young and older participants on incongruent trial performance (where the most errors would be expected). This one-tailed comparison was significant ($t(31) = 1.67$, $p = .05$).
- Hypothesis 4) We predicted that TS and controls would not differ in terms of their failures of "cognitive inhibition", as reflected by the errors committed in the 25% congruent trial probability 'pure inhibition' condition. This prediction was supported by a non-significant interaction between group (TS, control), age (younger, older), and congruency (congruent, incongruent; $F(1,29) = .002$, $p = .963$.

In order to highlight contrasts between Stroop task performance (where we predict no group effects at any age) and Simon task performance (where significant group effects are predicted in the older but not the younger participants) we conducted two simple interaction effects tests on each age group separately. The relevant data are presented in Table 2. One simple interaction effect of congruency (congruent,

incongruent) and group (TS, control) in the 25% congruent 'pure inhibition' condition was conducted on the older participants. This 2-way simple interaction effect was not significant ($F(1,14) = .1$, $p = .756$). As can be seen in the left portion of Table 2, older individuals with TS committed approximately as many errors on the Stroop as older controls. A comparable simple interaction effect was conducted on the younger participants. This congruency by group interaction was also not significant ($F(1,15) = .005$, $p = .946$). As can be seen in the right portion of Table 2, younger individuals with TS committed approximately as many errors on the Stroop as younger controls. These non-significant simple interaction effects provide further evidence that failures in inhibition on the Stroop task occur no more frequently in participants with TS than in controls, irrespective of age. These simple interaction effects are expected to be in contrast to parallel calculations on the Simon task conducted in Experiment 2.

	Older	**Participants**			**Younger**	**Participants**
	TS	**Controls**			**TS**	**Controls**
incongruent	12.71	11.22		**incongruent**	22	21.25
congruent	1.29	1.11		**congruent**	1	1

Table 2: Mean number of Stroop errors committed by older and younger TS and control participants in the 25% congruent trial probability 'pure inhibition' condition (ADHD included).

ADHD Excluded. The same 3-way analyses of variance were conducted when those in the TS group with comorbid ADHD were excluded from the analysis. Excluding these participants revealed a pattern of data more consonant with our hypotheses.

This analysis revealed a main effect of congruency (more errors were committed on incongruent trials than congruent trials ($F(1,24) = 31.995$, $p<.001$)) and a significant main effect of age ($F(1,24) = 4.43$, $p=.046$). Other main effects and interactions relevant to our hypotheses are listed below:

- Hypothesis 3) Our prediction that younger children would demonstrate more failures of inhibition than older children was now supported by a significant age (older, younger) by congruency interaction ($F(1,24) = 5.421$, $p=.029$). Simple main effects revealed that younger children on incongruent trials committed more errors than older children on incongruent trials ($t(26)=2.12$, $p=.022$).
- Hypothesis 4) We predicted that TS and controls would not differ in terms of their failures of "cognitive inhibition", as reflected by the errors committed in the 25% congruent trial probability 'pure inhibition' condition. This prediction was supported by a non-significant interaction between group (TS, control), age (younger, older), and congruency (congruent, incongruent; $F(1,24) = .625$, $p=.437$).

Again to highlight contrasts between Stroop (where we predict no group effects) and Simon task performance (where significant group effects are predicted) we conducted two simple interaction effects tests on each age group separately. The relevant data are presented in Table 3. One simple interaction effect of congruency (congruent, incongruent) and group (TS, control) in the 25% congruent 'pure

inhibition' condition was conducted on the older participants. This 2-way simple interaction effect was not significant ($F(1,13) = .146$, $p = .708$). As can be seen in the left portion of Table 3, older individuals with TS committed approximately as many errors on the Stroop as older controls. A comparable simple interaction effect was conducted on the younger participants. This congruency by group interaction was also not significant ($F(1,11) = 1.27$, $p = .284$). As can be seen in the right portion of Table 3, younger individuals with TS committed approximately as many errors on the Stroop as younger controls. These non-significant simple interaction effects provide further evidence that failures in inhibition on the Stroop task occur no more frequently in participants with TS than in controls, irrespective of age. Once again, these simple interaction effects are expected to be in contrast to parallel calculations on the Simon task conducted in Experiment 2.

	Older	**Participants**			**Younger**	**Participants**
	TS	**Controls**			**TS**	**Controls**
incongruent	13.33	11.22		**Incongruent**	22	21.25
congruent	1.5	1.11		**Congruent**	0.8	1

Table 3: Mean number of Stroop errors committed by older and younger TS and control participants in the 25% congruent trial probability 'pure inhibition' condition (ADHD excluded).

GENERAL DISCUSSION OF EXPERIMENT 1

The results of Experiment 1 can be reviewed in terms of both age and group differences for both inhibition successes and inhibition failures. With regards to inhibition successes the younger and older participants were both capable of implementing performance optimization strategies although, contrary to our expectations, significantly slower overall RTs among the younger participants meant that their performance optimization effects were more pronounced than the older participants. Data also indicated that individuals with TS were as capable as controls of adopting performance optimization strategies.

In terms of inhibition failures younger participants committed significantly more errors than older participants overall, however the TS group showed no indication that they are any less successful than controls in inhibiting higher-level prepotent cognitive responses. In sum, data from Experiment 1 provided strong evidence that while "cognitive inhibition" difficulties decrease as one ages, these difficulties are not any more present in TS than in the normal population irrespective of age. This corroborates the conclusions of Pennington & Ozonoff and Harris, Schuerholz, Singer et al. (1995) who suggested that executive functioning is intact in individuals with TS after comorbid conditions have been controlled by medication or eliminated from the sample.

EXPERIMENT 2 –

SIMON TASK PERFORMANCE OF YOUNGER AND OLDER TOURETTE SYNDROME AND CONTROL PARTICIPANTS

After demonstrating the lack of difficulties in "cognitive inhibition" in a TS sample free of uncontrolled comorbid symptomatology we next wished to demonstrate that this population does experience difficulties in "motor inhibition". For comparison purposes we required a more purely "motoric" task: one that would also look at task interference in incongruent trials dependent upon the correspondence between the irrelevant stimulus attribute and an incompatible MOTOR response. For this reason we chose to use the Simon task.

Research has demonstrated that RT to a particular stimulus is significantly faster when the location of the stimulus, although irrelevant, corresponds with that of the response (for example, a stimulus prompting a response with the right hand *appearing* on the individual's right, rather than left). In the tactile domain, if you are exploring the environment by touch, and you feel an object, it makes sense to interact with the object with the hand that felt the object, rather than the opposite hand. Thus, in general, if a stimulus appears on the left, people are better at responding with an appendage on the left. If a stimulus appears on the right, people are better at responding with an appendage on the right. Furthermore, people in general have difficulty inhibiting these prepotent tendencies, (i.e. one takes longer and makes more errors when the location of stimuli, and the appendage used to respond to it, do not correspond). There is "a strong stereotypic tendency to respond initially to the directional component of a stimulus rather than to its symbolic content" (Simon, 1990). This phenomenon is known as the Simon effect.

Most researchers believe the Simon effect is due to the fact that we attend to the position of the stimulus during encoding. While it is easy to understand the evolutionary adaptiveness of encoding an object's position in space relative to oneself, attention to this information can be irrelevant in certain contexts, leading to difficulties in response selection and inhibition (Hommel, 1994b; Buckolz, O'Donnell & McAuliffe, 1996; Stoffer, 1991; Proctor & Wang, 1997; Proctor, 1992). While not all in the field share this view (e.g., see Hasbroucq & Guiard, 1992 for an opposing view), the "response-selection" hypothesis is currently the most commonly accepted one (Lu & Proctor, 1995). The "strong stereotypic tendency" (Simon, 1980) towards automatic activation of ipsilateral response codes in response to location cues is very persistent (even across 1800 trials: Proctor & Lu, 1999) and has been found in species other than humans as well: single-cell recordings in the motor cortex of rhesus monkeys revealed that, in noncorresponding trials, the incorrect but spatially congruent response is still activated to a degree before the proper response is carried out (Georgopoulos et al, 1989).

Only one study testing individuals with TS on the Simon task could be found (Georgiou, Bradshaw, Phillips et al., 1995). Five conditions of progressively increasing complexity were given to 10 male participants diagnosed with TS and with a mean age of 31. All five conditions involved traditional RT responses to the presentation of visuospatial stimuli on a computer screen. In the third condition, which represented a traditional test of the Simon effect, individuals with TS made significantly more errors on incongruent trials as compared with congruent trials – this difference was not found in controls matched for age, sex, IQ, and

Short Test of Mental Status scores (Georgiou, Bradshaw, Phillips et al., 1995). It is not clear, however, whether participants with TS were screened for comorbid ADHD. To the best of our knowledge, no evidence on Simon task performance in the ADHD population exists. In an effort then to clearly demarcate the influences of TS and ADHD on the Simon task we used participants with TS either without a comorbid diagnosis of ADHD or participants with TS who were medicated for their ADHD symptoms. To 'carve' the "motor inhibition" circuitry as cleanly as possible we devised a motoric version of the Simon task in which tactile stimuli cued motor responses.

Tactile stimuli were purposely chosen for their easy discrimination: Hommel (1994a) demonstrated that slowing down the processing of stimulus information reduced the Simon effect and immediate stimulus discrimination allowed for a much greater Simon effect. A within-hand design was also purposefully chosen: Buckolz, O'Donnell & McAuliffe (1996) found a greater Simon effect for within-hand than between-hand conditions (although they had participants use only their right hands). It also seemed that a within-hand design would remove any variance or complicating factors due to any differences in hemispheric asymmetries among the participants with TS and controls.

In light of our distinction between inhibition successes and inhibition failures our *concrete a priori* hypotheses concerning Simon performance were specified in terms of what we predicted for RT's and what we predicted for errors.

Reaction Times

- Hypothesis 1) Younger and older participants would again demonstrate differences in implementing a performance optimization strategy. We predicted that the pattern depicted by the RT's in Figure 1 would be more pronounced in the older participants (more < shaped patterns) whereas for younger children we predicted less of an effect of congruent trial probability (more = shaped patterns). Statistical support for this prediction would take the form of a congruency (congruent, incongruent) by congruent trial probability (25%, 75%) by age (older, younger) interaction.
- Hypothesis 2) TS and control groups would not show differential performance in terms of their ability to implement performance optimization strategies. Since we believe the site of TS problems to be the basal ganglia rather than the frontal lobes, we did not predict differences in the frontally mediated ability to implement performance optimization strategies. Again, support for this prediction would be a non-significant group (TS, control) by congruency (congruent, incongruent) by congruent trial probability (25%, 75%) by age (older, younger) interaction.

Errors

- Hypothesis 3) As previously argued, the best measure of failures of inhibition are the errors committed in the 25% congruent trial probability 'pure inhibition' condition. We predicted that younger children would show more failures of inhibition than older children. Because we are predicting increased errors in older participants with TS on the Simon task (see Hypothesis 4 below), the best test of this hypothesis is to assess the significance of an age (younger, older) by congruency (congruent, incongruent)

interaction among the control group. Because we are interested in differences in error rates between older and younger participants it was deemed necessary to contrast the performance of these samples in the condition where errors would be most pronounced (the incongruent trials of the 25% congruent trial probability 'pure inhibition' condition). Thus in addition to conducting the higher order age by congruency interaction we also conducted a simple main effect of age on performance of incongruent trials in the 25% congruent trial probability 'pure inhibition' condition. Here we predicted more errors in the incongruent condition for younger control participants than for older control participants.

- Hypothesis 4) We anticipated group differences in terms of failures of "motor inhibition" as reflected by the errors committed in the 25% congruent trial probability 'pure inhibition' condition. We expected the TS group to commit more errors than controls but predicted that these group differences would only emerge late in the developmental sequence – we proposed that as children both individuals with TS and controls would have problems with "motor inhibition", but that increasing frontal lobe development would allow controls to 'grow out' of this problem. These predictions would be substantiated by a significant 3-way interaction of congruency (congruent, incongruent), group (TS, control), and age (older, younger). Consequently, simple interaction effects should yield a significant interaction between congruency (congruent, incongruent) and group (TS, control) in the older, but not younger, participants. Because we are interested in differences in error rates between TS and control groups, theoretically it makes sense to contrast the performance of these groups in the condition where errors would be most pronounced (the incongruent trials of the

25% congruent trial probability 'pure inhibition' condition). Thus we assessed the significance of a simple main effect of group on incongruent trials in the 25% condition. Here we predict that older participants with TS will make significantly more errors on incongruent trials than older control participants.

PARTICIPANTS

Participants from Experiment 1 were used. Because the lost data described in Experiment 1 was limited to Stroop data the sample size was higher by seven participants (n=40). Eight members of the TS sample had comorbid diagnoses of ADHD (four in the older sample and four in the younger sample): These participants had current prescriptions for some form of stimulant medication.

	TS (Old)	**Control (Old)**	**TS (Young)**	**Control (Young)**	**TOTAL**
Male	7	4	10	5	26
Female	4	6	0	4	14
TOTAL	11	10	10	9	**40**

Table 4: Participant analysis for Experiment 2.

METHOD

The response box consisted of two sensors 5.5 centimetres apart on the top panel of the box; these sensors connected to speakers controlled by an IBM ThinkPad 380 XD (Pentium 233) laptop computer via an amplifier, and programmed using SuperLab Pro software. Response

buttons a further 2.5 centimetres outside each sensor were built, and connected back to the laptop computer. Participants placed a hand of their choosing on the box so that their index and pinky fingers rested on the sensors; hand was alternated halfway through each session at a programmed break period at which time participants could choose to continue or take five minutes rest. Sensors would emit either a 150 Hz sine wave vibration (eliciting a buzzing sensation) or a 15 Hz square wave vibration (eliciting a drumming sensation), each 250 ms in duration, at random times and on random sides. Participants were told that the 150 Hz sine wave stimuli indicated a leftmost finger response and the 15 Hz square wave stimuli indicated a rightmost finger response regardless of hand and stimuli presentation location. Hence both congruent (where response side indicated by the vibration matches vibration location) and incongruent (where response side indicated by the vibration does not match vibration location) trials existed. As in the Stroop task both 25% and 75% congruent sessions, each with 224 test trials, were programmed. A block (16) of additional practice trials was given at the beginning of each session to ensure that each participant understood the task; practice trials were similar in content to the experimental session that they preceded. The response box emitted different noises depending on whether a sine or square wave trial was occurring. As these audio cues could potentially influence results, participants listened to white noise recorded on cassette over earphones while engaged in the sessions. The experimenter remained in the room to monitor the equipment and to ensure that participants switched hands at the halfway point.

RESULTS AND DISCUSSION

Outlier analyses were conducted using the Van Selst & Jolicoeur (1994) technique. As mentioned, because even medicated ADHD could introduce unknown variance into our results

(through effects of the medication or inadequate amelioration of the ADHD symptoms) the data were once again analyzed in two ways as a precautionary measure. Individuals with TS with comorbid and treated ADHD were included in one set of analyses to maximize sample size. In the second set of analyses these participants were excluded.

Inhibition Successes in Simon Performance

Success of inhibition was considered in terms of RT data. RT data was analyzed using a 4-way mixed model ANOVA. Congruency (congruent, incongruent), and congruent trial probability (25%, 75%), were the within subject factors, and age (older, younger) and group (TS, control) were the between subject factors.

ADHD Included: The 4-way ANOVA revealed a significant main effect of congruency (RT was significantly faster for congruent trials than incongruent trials; $F(1,36) = 109.74$, $p < .001$) and a significant main effect of age (older participants were faster than younger participants; $F(1,36) = 37.83$, $p < .001$). There was also a significant interaction of congruency (congruent, incongruent) and congruent trial probability (25%, 75%); $F(1,36) = 57.51$, $p < .001$. The 4-way interaction of congruency, congruent trial probability, age, and group was non-significant ($F(1,36) = .106$, $p = .747$). Other main effects and interactions relevant to our hypotheses are listed below:

- Hypothesis 1) Our hypothesis that younger and older participants would demonstrate differences in implementing a performance optimization strategy was supported by a marginally significant 3-way interaction of congruency (congruent, incongruent),

congruent trial probability (25%, 75%) and age (older, younger; F(1,36) =3.07, p=.088); the data patterns were in the same direction as in Experiment 1.

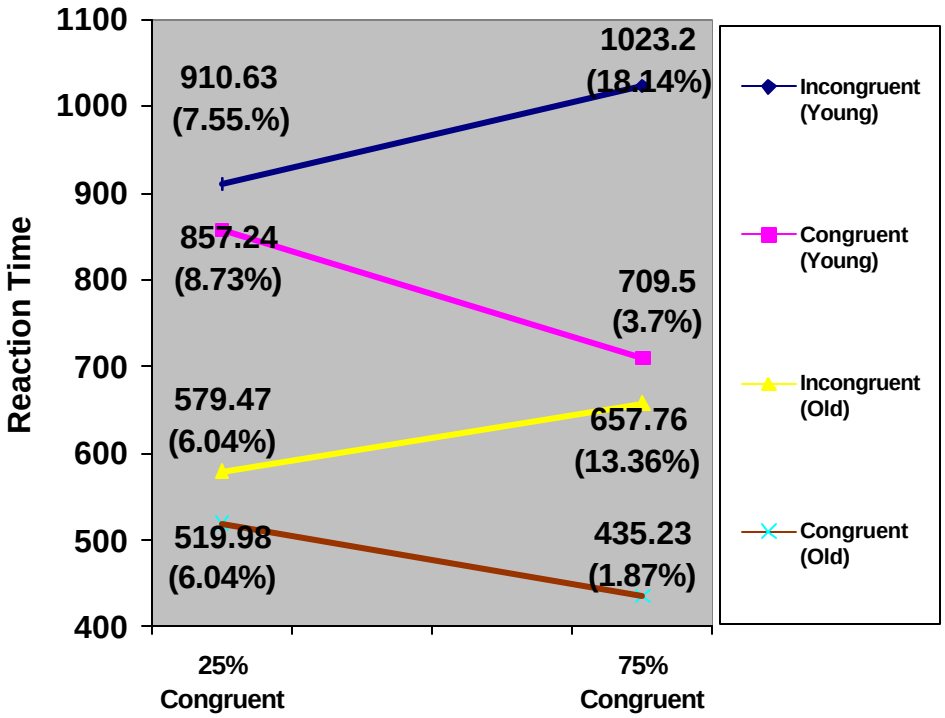

Figure 7: RT as a function of congruent trial probability for both young and old TS and control samples on the Simon task.

- Hypothesis 2) The hypothesis that the older TS and control groups would not show differential performance in terms of their ability to implement performance optimization strategies was supported by the lack of a significant group (TS, control) by congruency (congruent, incongruent) by congruent trial probability (25%, 75%), by age (older, younger) interaction (F(1,36) =.106, p=.747). Because theoretically we had predicted that only the older participants would show frontally mediated performance

optimization strategies, we re-analyzed the differences between the older TS and control groups alone. A non-significant group (TS, control) by congruency (congruent, incongruent) by congruent trial probability (25%, 75%), interaction ($F(1,19) = .373$, $p = .549$) suggested that there were no differences between controls and participants with TS in the ability to implement a performance optimization strategy in the older participants where frontally mediated strategies were predicted to have stabilized.

ADHD Excluded: The 4-way ANOVA revealed a significant main effect of congruency (RT was significantly faster for congruent trials than incongruent trials; $F(1,28) = 67.75$, $p < .001$) and age ($F(1,28) = 26.35$, $p < .001$). There was also a significant interaction of congruency (congruent, incongruent) and congruent trial probability (25%, 75%); $F(1,28) = 42.02$, $p < .001$. The 4-way (congruency by congruent trial probability by age by group) interaction was non-significant ($F(1,28) = .042$, $p = .838$). Other main effects and interactions relevant to our hypotheses are listed below – in general, however, excluding participants with TS with comorbid ADHD did not lead us to change our interpretation of the data:

- Hypothesis 1) Our hypothesis that younger and older participants would demonstrate differences in implementing a performance optimization strategy was not supported by a 3-way interaction of congruency (congruent, incongruent), congruent trial probability (25%, 75%) and age (older, younger; $F(1,28) = 2.4$, $p = .133$); while this interaction was not significant the data patterns were in the same direction as in Experiment 1. As such we concluded that the combined effects of the younger participants being slower, and therefore having more room to improve their performance than the older sample, contributed to the patterns of results seen in Figure 7.

- Hypothesis 2) The hypothesis that the older TS and control groups would not show differential performance in terms of their ability to implement performance optimization strategies was supported by the lack of a significant group (TS, control) by congruency (congruent, incongruent) by congruent trial probability (25%, 75%), by age (older, younger) interaction ($F(1,28) = .042$, $p = .838$). Because theoretically we had predicted that only the older participants would show frontally mediated performance optimization strategies, we re-analyzed the differences between the older TS and control groups alone. A non-significant group (TS, control) by congruency (congruent, incongruent) by congruent trial probability (25%, 75%), interaction ($F(1,28) = .272$, $p = .606$) suggested that there were no differences between controls and participants with TS in the ability to implement a performance optimization strategy in the older participants where frontally mediated strategies were predicted to have stabilized.

These analyses supported our hypothesis that there were no group differences in the employment of a performance optimization strategy, and our hypothesis that there would be developmental differences in strategic ability across younger and older samples. This pattern of results suggested that, developmentally, this strategic ability is present in both TS and normal populations by at least age seven and does not vary as one ages (see Figures 8 to 11 below). As with the data in Experiment 1, any variation in the performance optimization patterns related to age appeared to be a consequence of the overall slowing of RT's among the younger participants. This gave them more room to improve their RT's in the performance optimization condition relative to their older counterparts.

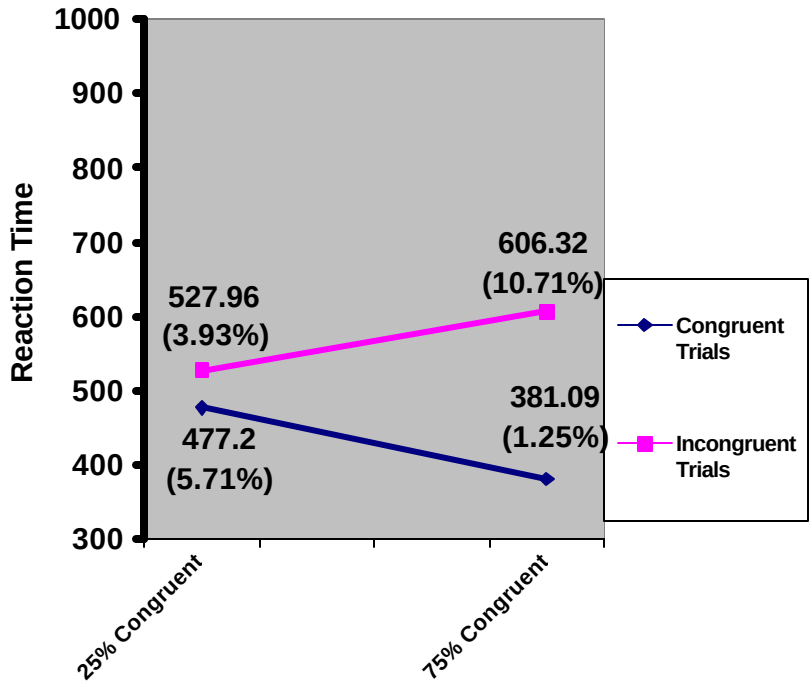

Figure 8: RT as a function of congruent trial probability for the older control sample on the Simon task.

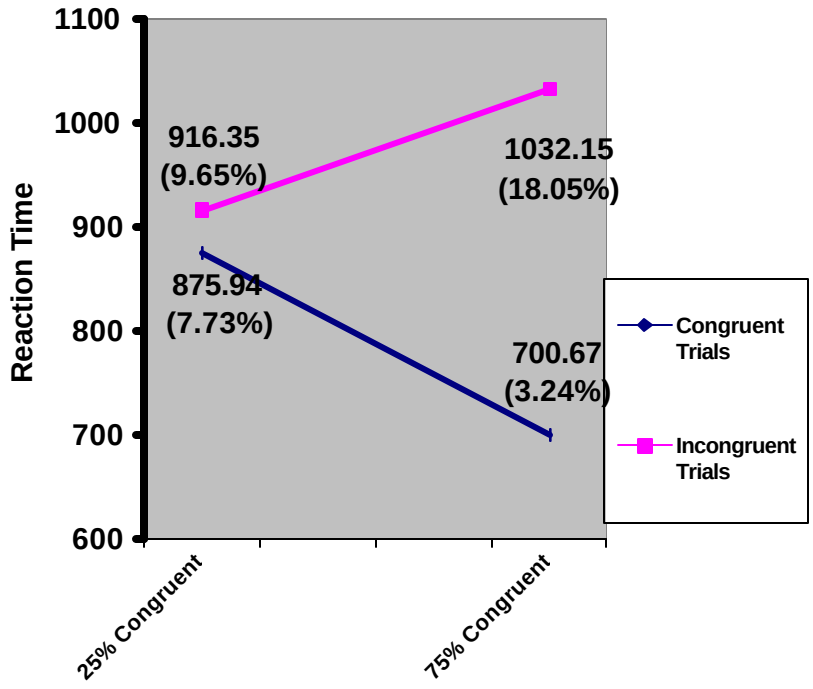

Figure 9: RT as a function of congruent trial probability for the younger control sample on the Simon task.

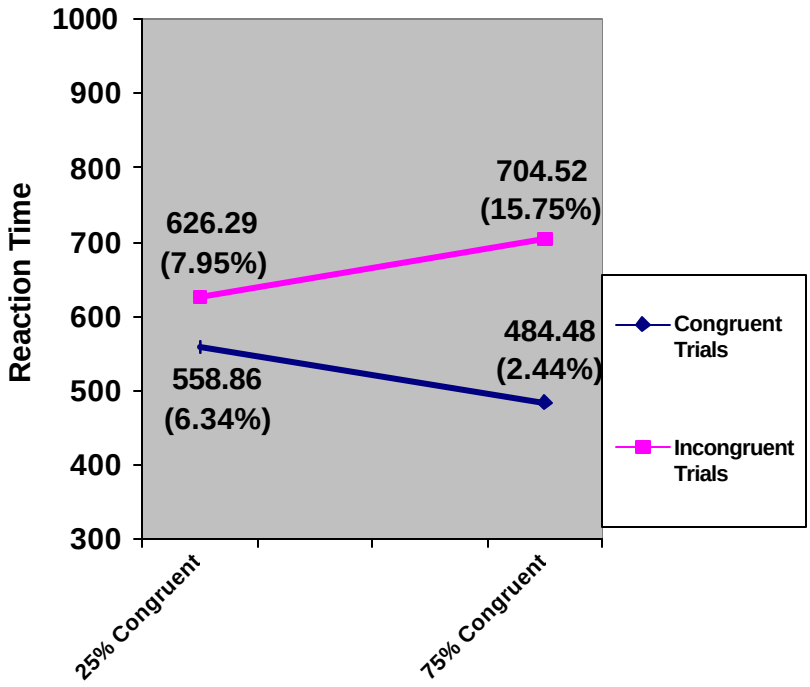

Figure 10: RT as a function of congruent trial probability for the older TS sample on the Simon task.

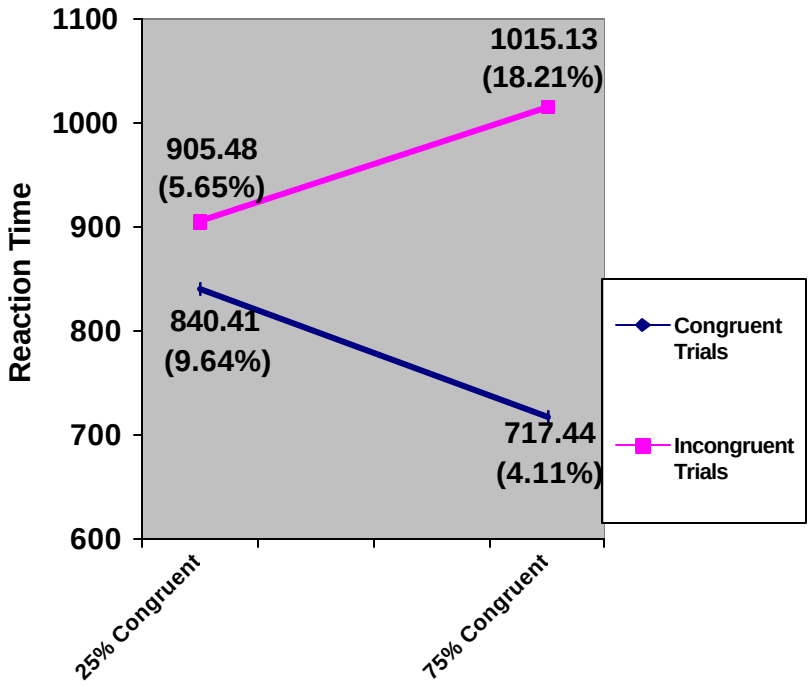

Figure 11: RT as a function of congruent trial probability for the younger TS sample on the Simon task.

Inhibition Failures in Simon Performance

Failure of inhibition was considered in terms of errors. Error data from the 25% congruency 'pure inhibition' condition were analyzed using a 3-way mixed model ANOVA. Age (older, younger) and group (TS, control) were the between subject factors and congruency (congruent, incongruent) was the within subject factor.

ADHD Included. This analysis revealed a main effect of congruency (more errors were committed on incongruent trials than congruent trials ($F(1,36) = 29.61$, $p < .001$)). Other main effects and interactions relevant to our hypotheses are listed below:

- Hypothesis 3) Because we predicted that older participants with TS would not show age related decreases in errors on the Simon task (see Hypothesis 4 below), the best test of this hypothesis was to assess the significance of an age (younger, older) by congruency (congruent, incongruent) interaction only among the control group. This interaction was marginally significant ($F(1,17) = 4.05$, $p = .06$). Simple main effects revealed significantly more errors in the incongruent condition for younger participants than for older participants ($t(17) = 2.26$, $p = .02$). In the analyses above we are interested in documenting 'normal' age-related increases in the ability to inhibit prepotent motor responses; the next set of analyses demonstrates that, with respect to "motor inhibition" capabilities, individuals with TS when compared to controls do not follow this 'normal' developmental sequence.
- Hypothesis 4) We predicted that TS and controls would differ in terms of their failures of "motor inhibition" late in the developmental sequence, as reflected by the errors committed in the 25% congruent trial probability 'pure inhibition' condition by older participants. This prediction was supported by a significant interaction between group (TS, control), age (younger, older), and congruency (congruent, incongruent; $F(1,36) = 7.006$, $p = .012$).

In order to highlight contrasts between Stroop (where we predicted no group effects) and Simon task performance (where significant group effects are predicted) we

conducted a series of simple interaction and simple main effects tests on each age group separately. The relevant data are presented in Table 5. One simple interaction effect of congruency (congruent, incongruent) and group (TS, control) in the 25% congruent 'pure inhibition' condition was conducted on the older participants. This 2-way simple interaction effect was found to be only marginally significant ($F(1,19 = 3.75$, $p=.068$). However a simple main effect of group revealed that participants with TS committed significantly more errors than controls ($t(19) = 1.99$, $p=.03$). As can be seen in the left portion of Table 5, participants with TS committed more errors on incongruent trials of the 25% congruent trial probability 'pure inhibition' condition than controls. A comparable simple interaction effect was conducted on the younger participants. This congruency by group interaction was also marginally significant ($F1,17) = 3.23$, $p=.087$). Looking at the right side of Table 5 however, one can see that the younger controls appeared to commit MORE errors than the younger individuals with TS. However an independent samples T-test of incongruent means in the 25% congruent 'pure inhibition' condition demonstrated that, unlike in the older participants, the TS and control groups did not differ in number of errors ($t(17) = 1.55$, $p=.141$). These simple interaction, and simple main, effects provide further evidence that failures in inhibition on the Simon task occur more frequently in older participants with TS than in older controls. These simple interaction, and simple main, effects are in contrast to parallel calculations on the Stroop task conducted in Experiment 1 where failures in inhibition did not differ between groups at any age. As can be seen in Table 5, the marginally significant simple interaction effect in the younger participants was due to the fact that controls made more errors than individuals with TS. As will be seen in the

next set of analyses, where ADHD is excluded from the TS group, error differences between groups become less pronounced in the younger participants and more pronounced in the older condition. The especially good performance of those individuals medicated for ADHD (see Figure 13) may be attributable to a 'hyperfrontality' effect – an effect discussed more fully addressed in a subsequent section.

	Older	**Participants**			**Younger**	**Participants**
	TS	**Controls**			**TS**	**Controls**
Incongruent	13.36	6.6		**incongruent**	9.5	16.22
Congruent	3.55	3.2		**congruent**	5.4	4.33

Table 5: Mean number of Simon errors committed by older and younger TS and control participants in the 25% congruent trial probability 'pure inhibition' condition (ADHD included).

ADHD Excluded. The same 3-way analyses of variance were conducted when those in the TS group with comorbid ADHD were excluded from the analysis. Excluding these participants revealed a data pattern that was somewhat similar to the data pattern obtained when participants with TS with comorbid ADHD were included.

This analysis revealed a main effect of congruency (more errors were committed on incongruent trials than congruent trials ($F(1,28) = 33.72$, $p < .001$)). Other main effects and interactions relevant to our hypotheses are listed below:

- Hypothesis 3) Because we predicted that older participants with TS would not show age related decreases in errors on the Simon task (see Hypothesis 4 below), the best test of this hypothesis was to assess the significance of an age (younger, older) by congruency (congruent, incongruent) interaction only among the control group. As no control participants were diagnosed with ADHD these results did not differ from those reported above in Hypothesis 3 of the *ADHD Included* analyses. That is, this interaction was marginally significant ($F(1,17) = 4.05$, $p = .06$). Simple main effects revealed significantly more errors in the incongruent condition for younger participants than for older participants ($t(17) = 2.26$, $p = .02$). In the analyses above we are interested in documenting 'normal' age-related increases in the ability to inhibit prepotent motor responses; the next set of analyses demonstrates that, with respect to "motor inhibition" capabilities, individuals with TS when compared to controls do not follow this 'normal' developmental sequence.
- Hypothesis 4) We predicted that TS and controls would differ in terms of their failures of "motor inhibition" late in the developmental sequence, as reflected by the errors committed in the 25% congruent trial probability 'pure inhibition' condition by older participants. This prediction was supported by a significant interaction between group (TS, control), age (younger, older), and congruency (congruent, incongruent; $F(1,28) = 8.39$, $p = .007$).

Again, to highlight contrasts between Stroop (where we predict no group effects) and Simon task performance (where significant group effects are predicted) we conducted a series of simple interaction effect and simple main effect tests on each age

group separately. The relevant data are presented in Table 6. One simple interaction effect of congruency (congruent, incongruent) and group (TS, control) in the 25% congruent 'pure inhibition' condition was conducted on the older participants. This 2-way simple interaction effect was found to be significant ($F(1,15 = 12.55$, $p=.003$). A simple main effect of group revealed that participants with TS committed significantly more errors than controls ($t(15) = 3.93$, $p<.001$). As can be seen in the left portion of Table 6, participants with TS committed more errors on incongruent trials of the 25% congruent trial probability 'pure inhibition' condition than controls. A comparable simple interaction effect was conducted on the younger participants. This congruency by group interaction was not significant ($F(1,13) = 1.38$, $p=.261$). Looking at the right side of Table 5 however, one can see that the younger controls did not commit significantly more errors than the younger individuals with TS. An independent samples T-test of incongruent means in the 25% congruent 'pure inhibition' condition demonstrated that, unlike in the older participants, the TS and control groups did not differ in number of errors ($t(13) = .864$, $p=.403$). These simple main effects and simple interaction effects provide further evidence that failures in inhibition on the Simon task occur more frequently in participants with TS than in controls at an older age. These simple main effects and simple interaction effects are in contrast to parallel calculations on the Stroop task conducted in Experiment 1 where failures in inhibition did not differ between groups at any age[3] (see Table 3).

[3] . For completeness, we analyzed all of the error data from Experiments 1 and 2 together in a 5-way group (TS, control) by congruent trial probability (25%, 75%) by congruency (congruent, incongruent) by task (Stroop, Simon) by age (older, younger) analysis of variance. We expected that we would not have sufficient power to

	Older	Participants			Younger	Participants
	TS	**Controls**			**TS**	**Controls**
incongruent	18.71	6.6		**incongruent**	11.5	16.22
congruent	4	3.2		**congruent**	6	4.33

Table 6: Mean number of Simon errors committed by older and younger TS and control participants in the 25% congruent trial probability 'pure inhibition' condition (ADHD excluded).

These results provided evidence that failures in inhibition occurred equally often for younger TS and younger control participants. As children aged, however, motor inhibition failures occurred significantly more often for participants with TS than controls. Put another way, failures in "motor inhibition" decreased across the developmental path in the normal population but remained the same in the TS population. The conclusion that older participants with TS had significantly more failures in motor inhibition than older controls was based on the results of tests of our a priori predictions concerning the performance of participants with

---

detect significance for this five way interaction; this expectation was fulfilled ($F(1,29) = 1.391$, $p = .248$). Knowing in advance that we would be unlikely to have enough subjects to detect a five-way interaction we chose to make more manageable a priori predictions concerning simple-interaction effects and interactions. Our views coincide with those of Howell who suggest that it is perfectly legitimate to test for simple main effects irrespective of whether or not higher order interactions are significant provided that *the main effects are of sufficient theoretical importance.*

TS and controls in the Simon task. The significant group effects differed from Experiment 1 where the performance of participants with TS was statistically comparable to controls.

Figure 12 demonstrates the effects of including and excluding participants with comorbid ADHD. These data depict the errors on incongruent trials in the 25% congruent trial probability condition. Including those with medicated ADHD in the sample may have led to an underestimation of the average number of errors committed by the older participants with TS. This served to diminish a main effect in failures of motor inhibition across the older participants (where we anticipated individuals with TS would commit more errors). It also served to augment differences in failures of motor inhibition across the younger participants (leading to controls committing marginally more errors than individuals with TS) resulting in a marginally significant interaction effect. Given these unwanted potential complications due to comorbid ADHD symptomatology and/or medications for ADHD symptomatology, we strove to test group differences between individuals with TS who were comorbid for ADHD and individuals with TS who were not.

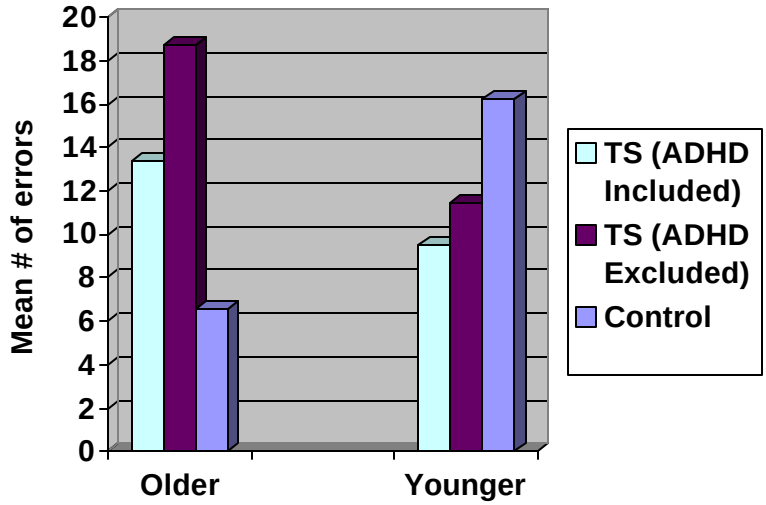

Figure 12: Mean comparisons on incongruent trial errors in the 25% congruent trial probability 'pure inhibition' condition

In most of the analyses contained above, because of our small sample size, we were limited in our ability to directly compare the performances of those TS individuals with a comorbid diagnosis of ADHD (TS +ADHD) and those TS individuals without a comorbid diagnosis of ADHD (TS –ADHD). Only the older TS group contained sufficient numbers of individuals with (n=4) and without (n=7) comorbid ADHD to allow meaningful statistical comparisons directly comparing these two TS groups with controls.

Data pertinent to Hypothesis 4 (data from the 25% congruent trial probability 'pure inhibition' condition), were analysed using a 2 X 3 mixed model ANOVA where congruency (congruent, incongruent) was the within subject factor and group (TS+ADHD, TS-ADHD, control) was the between subjects factor. The analysis revealed a main effect of congruency ($F(1,18) = 21.649$, $p < .001$) and more importantly a significant interaction between congruency and group ($F(2,18) = 9.64$, $p = .001$). Figure 14 graphically depicts this analysis.

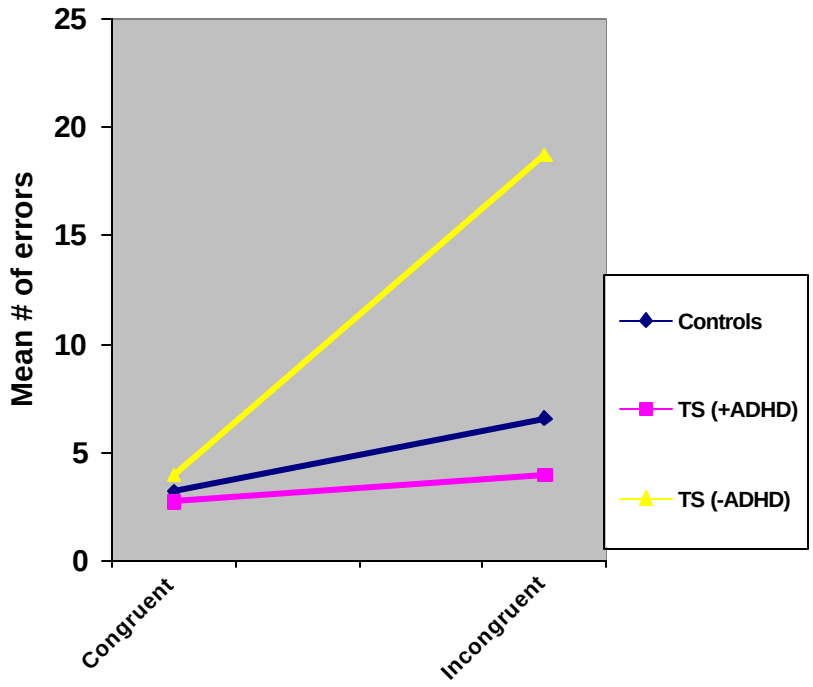

Figure 13: Simon task errors on incongruent trials in the 25% congruent trial probability condition as a function of Group.

What was immediately striking was how much the presence or absence of ADHD changed the performance of the TS group on the Simon task. Those with a comorbid diagnosis of ADHD looked very similar in performance to the age-matched control participants. One interpretation of this result might be that the presence of a stimulant medication, when combined with a short-duration, novel task requiring considerable vigilance, served to heighten the inhibition capabilities of the frontal lobes. Possibly, over the short duration of the test, this 'hyperfrontality' could have temporarily overridden any basal ganglia problems. Support for this interpretation comes from the well-documented finding that tics can be suppressed during periods of intense mental concentration. If the stimulant medication served to heighten such

concentration, it may have served to normalize the error rates of the older participants with TS – making them virtually indistinguishable from controls. Indeed, it was the impression of the experimenter that tics were not apparent in this group during the task. Regardless of the interpretation of these results, the pattern of data presented in Figure 13 provides a striking demonstration of how the presence of comorbid diagnoses and/or medications for these comorbid conditions can alter study results. Further, the profound influence of stimulant medication and or ADHD comorbidity dramatically underscores the importance of controlling for these variables in experimental situations.

GENERAL DISCUSSION OF EXPERIMENT 2

The results of Experiment 2 can again be reviewed in terms of both age and group differences for both inhibition successes and inhibition failures. With regard to inhibition success the younger and older participants were both capable of implementing performance optimization strategies; significantly slower RTs in the younger participants overall meant, though, that their performance optimization effects could be more pronounced. Data also indicated that individuals with TS were as capable as controls of adopting performance optimization strategies. In terms of inhibition failures younger participants committed significantly more errors than older participants overall. From a developmental perspective, it can be seen that failures in motoric inhibition occurred in younger children with and without TS up until at least age 9. Over time inhibition capability appeared to improve in the normal population but not in the TS population. In sum, data from Experiment 2 supported our contention that individuals with TS would have difficulties inhibiting motor movements at an age-appropriate level. However WHEN individuals successfully inhibited movements they did so at a speed

equivalent to normal. This observation fits well with the literature pertaining to tic phenomenon, which describes involuntary movements in TS as intermittent and "burst-like" in nature (Peterson & Leckman, 1998), more "unvoluntary" and suppressible than completely involuntary (Tourette Syndrome Classification Study Group, 1993) and attributable more to the poor regulation of inhibition than an actual global loss of the ability to inhibit.

EXPERIMENT 3 –

THE INCIDENTAL ASSOCIATIONS THEORY OF TIC FORMATION: DESCRIPTION OF THE MODEL AND A TEST ON OLDER TOURETTE SYNDROME AND CONTROL PARTICIPANTS

Having established that failures in motoric inhibition are a feature of TS, we proposed and tested a new model of tic formation based on failures in motoric inhibition and drawing on further neurological findings. The Incidental Associations Theory of Tic Formation, in brief, suggests that many incidental motor associations between frequent, stereotypical movements and other everyday goal-oriented movements (such as walking through a doorway and blinking simultaneously) occur regularly in all individuals. These incidental associations are not appropriately inhibited in individuals with TS however, thus giving the associations the opportunity to strengthen in individuals with TS each time incidentally paired sets of neurons fire together. Eventually these incidental associations become numerous and strong enough to cause the frequent and stereotypical movement to appear at numerous and seemingly random points throughout a day. What emerges then is what we would recognize and describe as "tics".

The basal ganglia are part of the CSTC circuitry that we hypothesized to be the location of the "motor inhibition" difficulties seen in Experiment 2. The basal ganglia are organized anatomically to serve as a system that possesses a reservoir of movement patterns learned through unconscious association (Rauch, 1999; Mink, 2001). The basal ganglia are comprised of a number of excitatory input structures (caudate, putamen, and subthalamic nucleus; STN) and inhibitory output structures (globus pallidus pars interna (GPi) and externa (GPe), and the

substantia nigra pars compacta and reticulata). Numerous inputs from all cortical lobes are received, processed and filtered. The striatum (caudate and putamen) is important in learning and executing sequential skills and habits. Called an "executive secretary" by some (Rauch, 1999), Graybiel (1998) suggests that the basal ganglia may be involved in 'chunking' behaviour patterns for release when exposed to a particular context – after a habit is learned, Graybiel has found that striatum activity is highest at the beginning and end of its production. For example, a rat that has learned the sequence involved in completing a maze evidences high striatum activity only when it begins and finishes the course; during the execution of the learned pattern striatum activity is lower. It is as if a whole motor pattern fires as one interconnected encapsulated module necessitating only activation and cessation (Graybiel, 1999). Based on activation by the cortex, tempered through information of the current situation and of predicted future input, the basal ganglia select the most appropriate movement(s) to execute.

Two different pathways exist for each CSTC circuit. A direct pathway begins with excitation from the cortex to the striatum and progresses from the striatum to the GPi to the thalamus; the thalamus then connects back to the cortex (see the light arrows in Figure 14). Inhibition from the activated striatum prevents GPi from inhibiting the thalamus; thus the thalamus is free to excite the cortex. This general disinhibition is modified through selective re-inhibition or 'pruning' by an indirect pathway. The indirect pathway begins with inhibitory signals sent from the striatum to the GPe and progresses from the GPe to the STN to the GPi to the thalamus; the thalamus then connects back to the cortex (see the **bold arrows** in Figure 14). Inhibition from the activated striatum prevents GPe from inhibiting the STN. The STN is

then free to activate the GPi. Gpi then inhibits thalamus, removing the excitatory influence of the thalamus onto the cortex. Thus the cortex is inhibited.

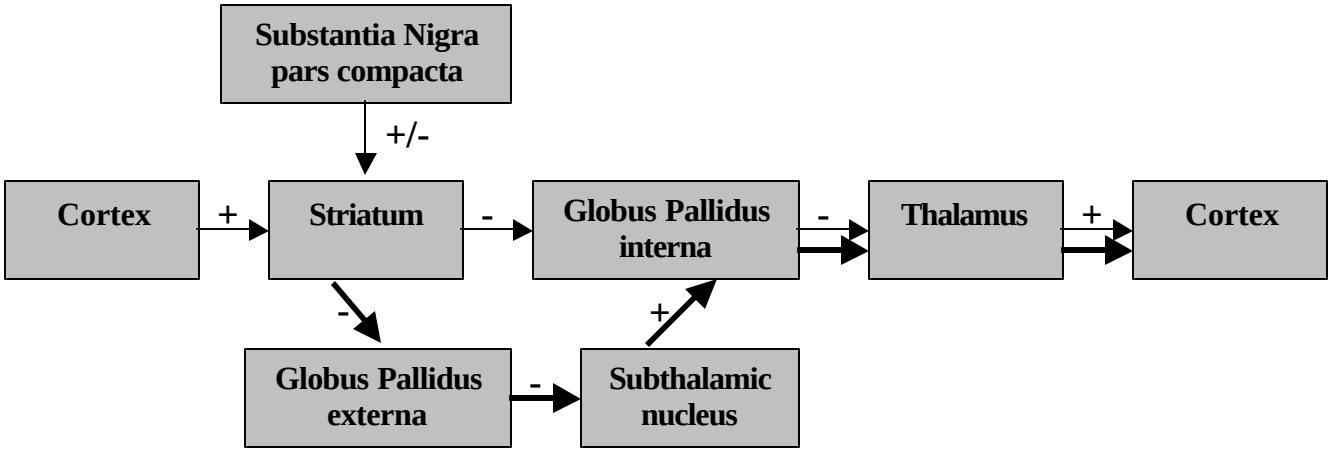

Figure 14: Simplified schematic diagram of basal ganglia circuitry. Light arrows denote the direct pathway and ***bold arrows*** *denote the indirect pathway. "+" signs denote excitatory signals, "-" signs denote inhibitory signals, and "+/-" denotes a modulatory effect.*

Neurological evidence points to problems within the indirect 'pruning' pathway in TS; specifically the locus of this problem seems to lie in dopamine D2 receptors found in the striatum. These receptors are inhibitory, so when activated by dopaminergic neurons sent from the substantia nigra pars compacta (SNpc; see Figure 14), the striatum's inhibitory control over GPe is compromised. With this first step in the indirect pathway disrupted, all subsequent steps are halted: GPe is free to inhibit STN so STN cannot excite GPi to inhibit the thalamus. Hence general cortical activation from the direct pathway (including the activation of any incidental associations) remains unimpeded or 'unpruned'.

Evidence that the inhibitory dopamine D2 receptors are supersensitive in individuals with TS, and that a subsequent chronic disruption of the indirect pathway plays a role in TS, has been obtained from imaging studies (Singer et al., 1992). Most striking are the results from a SPECT study that used increased dopamine D2 receptor binding in the head of the caudate nucleus to predict symptom severity in unmedicated MZ twins (Wolf et al., 1996) – the correlation was nearly perfect (r=.99). Excitatory glutamate in GPi and substantia nigra pars reticulata (SNpr) of individuals with TS is low (Leckman, Peterson et. al. 1997), meaning that STN is not activating the GPi and so the GPi cannot appropriately inhibit the thalamus. Ultimately this results in an excess of motor movement signals being sent to the cortex.

A final piece of evidence comes from pharmaceutical treatment literature. Haloperidol, a classic neuroleptic and the longest used medicinal treatment for tic reduction, works by primarily blocking dopamine from communicating with D2 receptors (Comings, 1990); this prevents the inhibition of the striatum and increases the efficacy of the indirect pathway.

In summary, then, the basal ganglia fire off whole packages of associated movements in response to cortical will. Direct pathway activation of movement patterns are not properly modified, pruned, or selectively reinhibited by indirect pathway activation in individuals with TS. On a neuropsychological level Baron-Cohen et al. (1993, 1994) have theorized that an "intention editor", a conceptual structure that essentially 'prunes' simultaneously activated and competing intentions, may be faulty in TS individuals. The indirect CSTC pathway serving motor function may very well be this speculative structure as it applies to TS.

Our logic was that ALL individuals, whether they are diagnosed with TS or not, fall prey to incidental associations – individuals engage in innumerable and unrelated motor actions simultaneously every day, and Hebbian rules dictate "synapses which are active when a post-synaptic membrane is depolarized are incremented" (Hebb, 1949). Only in individuals where these serendipitous connections cannot be properly extinguished or 'pruned' due to the imperfect operation of the indirect pathway will these 'extra' movements fail to be inhibited though. With each failed inhibition the associations would strengthen. Given that various stereotypical movements (such as eye-blinking) do occur in individuals on a very frequent basis throughout a day, the opportunities for these movements to become incidentally associated with a great number of other goal-oriented movements (such as walking through a doorway) would be great.

In addition to the continual strengthening of an extensive number of incidental associations, a number of normal learning processes could be assumed to occur. Generalization may occur when, for example, an individual learns to blink when walking through a similar doorway to the one in which the incidental association originally occurred. Accommodation in a Piagetian cognitive development sense may occur when, for example, an individual's mental organization around blinking and doorways adjusts; the individual begins to blink when walking through ANY doorway following enough assimilations of individual "blinking-and-walking-through-doorway" learning exposures. A particular frequent and stereotypical movement such as eye blinking provides ample opportunity for incidental associations. Given the sheer number of incidental associations possible (i.e. blinking becomes associated with doorways, with water fountains, with clocks, with looking at one's co-worker,

etc.), assuming the occurrence of generalization and accommodation, and given that observers are likely not cataloguing the various precursors to the frequent and stereotyped movement, this movement would begin to appear at seemingly random intervals. Ultimately this movement gains the appearance of what are diagnostically referred to as 'tics'. In actual fact however, we propose that this "tic" is the product of multiple individual pairing episodes strengthened over time.

According to the proposed model one of the most general claims that could be made is that those with TS would have difficulty breaking the bonds between events that have become associated. As a first test of this model we proposed to teach participants with TS and controls to associate two movements. Specifically, participants placed their hand atop the stimulus box used in the Simon experiments. Participants were told that they would be partaking in a RT task. They were instructed that each time they felt stimulation in one of their fingers they were to make a button press response as quickly as possible, and that RT's would be recorded to see how quickly they could make these responses. Participants were then told to press a RESET button to initiate the next trial. Thus in this task although the primary association was between a tactile stimulus and a button press response, there was also a second, incidental association, between one button press response and a second (RESET) button press response. Once these movements were associated, we predicted that participants with TS would have trouble "pruning" or inhibiting the second movement (the RESET button response) after making the first button press response. To test this hypothesis participants were called back to redo the experiment: now they were told that this RESET button response was no longer required.

We proposed to measure problems with inhibition of a previously learned incidental association in three different ways. The first and most straightforward way was to measure the number of RESET Button Presses during the second session (where they were told that it was no longer necessary to press the RESET button). A second measure of problems inhibiting a previously learned incidental association was the number of movements initiated towards the RESET button (what we referred to as RESET Button Initiations). During the second session, since participants were told that RESET Button Presses were unnecessary, the most efficient means of performing the task was to 1) feel the tactile stimulus, 2) make the required response, and 3) return one's hand to rest upon the top of the tactile stimulator in preparation for the next trial. RESET Button Initiations were operationally defined as a discernable movement towards the reset button, rather than to the position atop the tactile stimulator. This "RESET Button Initiations" measure was thought to be a more sensitive measure than RESET Button Presses because in addition to including complete presses, it also included partial movements towards the RESET button. Such initiations can be construed of as **failures of suppression** (both complete and incomplete) of a formerly associated movement. The third measure of problems inhibiting a previously learned incidental association was a retrospective measure, taken after the experiment was over, in which participants were asked to rate their urge to press the RESET button on a 5 point Likert scale.

If participants with TS pressed or made initiations towards pressing the RESET button more often than controls it would be important to show that this tendency truly reflects the inability to inhibit a formerly associated (but no longer required) response rather than a type of environmental dependency syndrome or simply the random manifestation of tic movements.

In order to rule out these hypotheses it was necessary to include groups of TS and control participants who were presented with the same testing equipment, but were never taught to press the RESET button at time 1. If these groups were not inclined to press the RESET button, then any differences in RESET Button Presses or RESET Button Initiations could be ascribed to inhibition failures.

Finally, recall that the proposed model states that incidental associations would occur in all individuals – these associations would only surface through strengthening, generalization and accommodation when combined with poor "motor inhibition". Hence we anticipated that ALL participants exposed to the incidental association procedure would experience some sense of 'incompletion' at not pressing the RESET button. It followed that those who were capable of inhibiting this second movement – the exposed control group – would nevertheless report some urge to engage in it. It can be hypothesized that those with poor inhibition capabilities – the exposed TS group – may have satiated this urge through their RESET Button Presses and RESET Button Initiations and hence would not report the same degree of urge as the exposed controls. Literature on TS makes clear that individuals with TS tic in order to resolve a feeling of discomfort or anxiety – compelling descriptions of this have been offered by children as young as seven years of age (Leckman, King & Cohen, 1999).

Thus, our concrete *a priori* predictions were as follows:

- Hypothesis 1: RESET Button Presses) Both TS and control groups who were not exposed to the incidental association procedure would not show any propensity to press the RESET button. Participants with TS exposed to an incidental association between

two movements would be poorer at inhibiting the second (RESET Button Press) movement than control participants exposed to this same incidental association. Statistically we sought to analyze RESET Button Presses using a group (TS, control) by condition (exposed, unexposed) analysis of variance in which we predicted a main effect of exposure, and a significant group by condition interaction attributable to exposed participants with TS making more RESET Button Presses than any other group. Contrasts of theoretical interest involved a comparison between exposed participants with TS and unexposed participants with TS (to demonstrate the learning component of the model) and a comparison between exposed participants with TS and exposed controls (to demonstrate the failure-in-motor-inhibition component of the model). Because of their theoretical importance we conducted simple main effects contrasting these groups. Here we predicted that exposed participants with TS would make more RESET Button Presses than unexposed participants with TS, and exposed controls.

- Hypothesis 2: RESET Button Initiations) The same predictions were made for RESET Button Initiations as for RESET Button Presses - a main effect of exposure, and a significant group by exposure interaction due to exposed participants with TS making more RESET Button Initiations than any other group. Contrasts of theoretical interest involved a comparison between exposed participants with TS and unexposed participants with TS (to demonstrate the learning component of the model) and a comparison between exposed participants with TS and exposed controls (to demonstrate the failure-in-motor-inhibition component of the model). Because of their theoretical importance we conducted simple main effects contrasting these groups.

Here we predicted that exposed participants with TS would make more RESET Button Initiations than unexposed participants with TS, and exposed controls.

- Hypothesis 3: Urges) Both TS and control groups who were not exposed to the incidental association procedure would not have any urge to press the RESET button. We predicted minimal urge scores in both groups. Control groups exposed to the incidental association procedure would report a greater urge to press the RESET button than the exposed TS group. Statistically we sought to analyze urges using a group (TS, Control) by condition (exposed, unexposed) analysis of variance. We predicted a main effect of exposure where all exposed groups would report significantly higher urge scores than all unexposed groups. We also predicted a significant group by condition interaction attributable to exposed controls reporting greater urges to press the RESET button than any other group.

PARTICIPANTS

All participants from Experiments 1 and 2 were used (n=40) and were randomly divided between exposed and unexposed procedures. Given the results of Experiment 2, namely that group differences in motor inhibition failures only arise once controls have 'grown out' of the problem and individuals with TS have not, only the older participants were analyzed. Because we had not stratified cell membership by age, this unfortunately resulted in an imbalance of the numbers of exposed individuals with TS and controls in the older cohort.

METHOD

The response box from Experiment 2 was used with one modification. A large red button on the slanted face of the box, positioned so that the heel of the participant's hand rested above it, was activated in this experiment. This RESET button controlled the initiation of each new stimulus in the session following a trial response.

Participants were randomly divided between 2-day and 1-day procedures. Individuals chosen to participate for two days were asked to come to an appointment the day immediately before the Simon and Stroop tasks were given[4]. On this day participants were told that they would take part in a simple RT experiment (720 trials). Both the sine and square wave stimuli were used, but the sine wave consistently occurred in the leftmost sensor and the square wave consistently occurred in the rightmost sensor. Participants were instructed to press the response button on the left when they felt the buzzing sensation (sine wave), and the response button on the right when they felt the drumming sensation (square wave). Participants were then told that in order to initiate each new trial after striking the appropriate response button

[4] This raises an interesting issue. Since our contention is that this first appointment sets up associations, it is possible that the exposed older participants might differ from the unexposed older participants on their Experiment 2 performance. To see if exposure had an effect we conducted a multiple regression on errors in the 25% congruent trial probability 'pure inhibition' condition. Exposure was entered first, followed by group (control, TS +ADHD, TS –ADHD). Beta values indicated significant effects for exposure ($t=3.846$, $p=.001$); however group still accounted for a significant unique amount of the variance remaining once exposure effects were removed ($t=-2.737$, $p=.014$). Although this analysis indicates the results of Experiment 2 cannot be considered an artefact of exposure, in retrospect had we known that exposure would have a significant effect on error rates we would have matched numbers of exposed TS and controls more carefully (i.e. by age).

they would need to press the red RESET button with the heel of their hand. Thus, both TS and control groups were exposed to an incidental motor association – pressing the response button, and immediately afterwards pressing the RESET button. Five breaks were programmed into the task; at each break participants were instructed to switch hands so that each hand was used in alternation three times.

The following day, and before commencing the Simon and Stroop tasks, both the group exposed to the incidental association (the exposed group) and the unexposed group were asked to participate in a RT session of 224 trials without using the RESET button. Participants were misled into believing that the RESET button had only been used prior to that day as a result of computer program limitation, but that the evening before (or, in the case of the exposed groups, between their visits) the researchers had been able to overcome this technical difficulty and had programmed the apparatus to reset automatically. Participants were informed that the RESET button was no longer connected to the computer and no longer required attention, but if they still pressed it there would be no consequence ("The RESET button is now completely disconnected, so if you still feel most comfortable pressing it that's ok, it won't do anything and is no big deal. I just wanted you to know that you don't have to if you don't want to"). Individuals with TS and controls in the 'unexposed' groups, upon their arrival, also participated in this 'RT' experiment. These participants were simply told that all participants prior to themselves had needed to utilize the RESET button; using instructions identical to those given to the exposed groups, these participants were told that the RESET button had been disconnected, making pressing the button unnecessary but inconsequential if one were to do so anyway.

The experimenter remained in the room to conduct measurements. He recorded the number of times each group pressed the RESET button and the number of times participants initiated a RESET movement, defined as a detectable movement towards pressing the RESET button without actually pressing it. Finally, at the conclusion of the session participants were asked to rate on a scale from 1 to 5 how strongly they felt an urge to press the RESET button. Again to combat any audio clues participants wore headphones playing white noise during the trials.

RESULTS AND DISCUSSION

Preliminary data screening revealed violations of the assumption of homogeneity of variance for RESET Button Presses and RESET Button Initiations. Data were therefore transformed using natural logarithms to normalize this data.

RESET Button Presses

Unexposed groups. Data for the participants in the unexposed group are presented in the left hand portion of Table 7. In the control group none of the six unexposed participants pressed the button. In the TS unexposed group one of the four subjects pressed the RESET button (5 times) - the other three subjects did not press the button. This participant with TS who pressed the button, however, retrospectively reported no urge to press this button (his rating on the Likert scale was the minimum urge score). Given that zero RESET Button Presses was the mode in both groups these data lead us to reject the notion of "environmental

dependency". That is neither controls nor participants with TS, upon seeing the red RESET button, felt compelled to press this button.

Exposed groups. The number of RESET Button Presses by the TS and control participants in the exposed groups are reported in the right hand portion of Table 7. Although the TS group on average pressed the RESET button more often than controls (TS = 11.71, controls = 1.75) as can be seen in the table there was tremendous variability in the TS group relative to the controls. Since means were roughly proportional to standard deviations, data were transformed using natural logarithms [because of the large number of zero's the formula used was Y' = log10 (Y+1)].

Transformed data were analyzed using a group (TS, control) by exposure (exposed, unexposed) analysis of variance. The main effect of exposure was significant ($F(1,17)=3.03$, 1-tailed $p=.05$). The group by exposure interaction was not significant ($F(1,17)= .158$, $p=.698$). Simple main effects indicated that exposed participants with TS were not significantly different from unexposed participants with TS ($t(9) =-1.19$, 1-tailed $p=.132$) or exposed controls ($t(9)=-.990$, 1 tailed $p=.174$).

In summary, although exposed groups overall pressed the RESET button significantly more often than unexposed groups, within the exposed groups participants with TS were no more likely to engage in RESET Button Presses than controls. With small sample sizes such as these however, it may be necessary to use a more sensitive measure to detect group differences in the propensity for motor responses to become incidentally associated. One such measure is initiations toward the RESET button (RESET Button Initiations) described next.

Unexposed TS: RESET Button Presses	Unexposed Controls: RESET Button Presses	Exposed TS: RESET Button Presses	Exposed Controls: RESET Button Presses
0	**0**	**64**	**0**
0	**0**	**11**	**1**
5	**0**	**4**	**5**
0	**0**	**2**	**0**
	0	**1**	
	0	**0**	
		0	
Mean = 1.25	**Mean = 0**	**Mean = 11.71**	**Mean = 1.75**

Table 7: Number of RESET Button Presses by groups exposed and unexposed to the Incidental Associations procedure.

RESET Button Initiations

Unexposed Groups. None of the controls initiated any movements towards the RESET button. In the TS group one of the four participants made 5 RESET Button Initiations (in this case, 5 actual RESET Button Presses). Again, this same participant was the one who retrospectively reported no urge to press this button - his rating on the Likert scale was the minimum urge score. These data lead us to reject the "environmental dependency" notion. Using the RESET Button Initiations measure, we conclude that neither controls nor participants with TS, upon seeing the red RESET button, were compelled to press this button.

Exposed Groups. The number of RESET Button Initiations by the TS and control participants in the exposed groups are reported in Table 8. Although the TS group on average made more RESET Button Initiations than controls (TS = 28.86, controls = 8.75) as can be seen in the table there was tremendous variability in the TS group relative to the controls. Since means were roughly proportional to standard deviations, data were transformed using natural logarithms [because of the large number of zero's the formula used was Y' = log10 (Y+1)].

Transformed RESET Button Initiation data were analyzed using a group (TS, control) by exposure (exposed, unexposed) analysis of variance. The main effect of exposure was significant ($F(1,17) = 37.731$ $p<.001$). The group by exposure interaction was not significant ($F(1,17) = 1.332$, $p=.264$). Simple main effects however indicated that exposed participants with TS made significantly more initiations toward the RESET button than unexposed participants with TS ($t(9) = -5.17$, one-tailed $p<.001$) and exposed controls ($t(9) = -2.08$, one-tailed $p=.034$).

In summary, using this more sensitive measure of the propensity for motor acts to become incidentally associated, we were able to show that following exposure to such an incidental association, participants with TS were more likely than unexposed participants with TS and exposed controls to demonstrate difficulties in breaking apart this association even when the resulting motor behaviours were explicitly declared to be of no value.

Unexposed TS: RESET Button Initiations	Unexposed Controls: RESET Button Initiations	Exposed TS: RESET Button Initiations	Exposed Controls: RESET Button Initiations
0	**0**	**86**	**0**
0	**0**	**27**	**18**
5	**0**	**15**	**12**
0	**0**	**16**	**5**
	0	**35**	
	0	**6**	
		17	
Mean = 1.25	**Mean = 0**	**Mean = 28.86**	**Mean = 8.75**

Table 8: Number of RESET Button Initiations by groups exposed and unexposed to the Incidental Association procedure.

Urges

Unexposed Groups. Only one of the six control participants reported any urge at all to engage in the RESET Button Press movement (a rating of 3). In the TS group none of the participants reported any urge. These data lead us to reject the "environmental dependency" notion. Neither controls nor participants with TS, upon seeing the red RESET button, reported any compulsion to press this button.

Exposed Groups. The urges reported by the TS and control participants in the exposed groups are reported in Table 9. The control group on average reported higher urges to engage in the RESET Button Press movement than the TS group (controls = 2.75, TS = 2). A 2 (TS, control) by 2 (exposed, unexposed) ANOVA was conducted on the urge rating data. This analysis revealed a significant main effect of exposure ($F(1,17) = 10.150$, $p = .005$) indicating that, as we predicted, ALL participants exposed to the incidental association felt a greater urge to engage in the second unnecessary movement than unexposed participants. The group by exposure condition interaction was not significant ($F(1,17) = .302$, $p = .590$). Contrary to our hypothesis that exposed controls would evidence higher urge scores than the exposed TS group, and although the data was in the proper direction, the simple main effect comparing exposed controls to exposed participants with TS was not significant ($F(1,17) = 1.473$, $p = .256$). The logic for this somewhat counter-intuitive hypothesis is explained in the introduction to Experiment 3. In order to properly test the hypothesis that any exposed group which engaged in the incidental association would satiate any cultivated urge more than any exposed group which did not, it is necessary that the experimental design create a strong enough incidental association in exposed groups for any decline in urge to be detected. It may be the current design, where exposure to the incidental association was merely a single session of approximately 45 minutes duration, is insufficiently sensitive to investigate this.

Unexposed TS: Reported Urge	Unexposed Control: Reported Urge	Exposed TS: Reported Urge	Exposed Controls: Reported Urge
1	**1**	**3**	**3**
1	**1**	**2**	**1**
1	**1**	**2**	**3**
1	**1**	**1**	**4**
	3	**2**	
	1	**3**	
		1	
Mean = 1	**Mean = 1.33**	**Mean = 2**	**Mean = 2.75**

Table 9: Urges reported by groups exposed and unexposed to the Incidental Associations procedure (1 = no urge, 5 = maximum urge).

Based on these findings, we could conclude that while participants primed in this incidental association may be more tempted to press the button than unexposed participants, only the exposed and motorically disinhibited individuals with TS seem to act upon it. Given the limitations of this experiment in testing the Incidental Associations Model (i.e. 'true' tics would be the product of incidental associations that have strengthened over considerably more time and trials than this design could permit), these results were most encouraging.

EXPERIMENT 4 –

REPLICATION OF DATA FROM EXPERIMENT 3 USING CONTROL PARTICIPANTS FROM NON-RISK FAMILIES

In Experiment 3 the control group was comprised of siblings of the individuals with TS. While using individuals from similar environments can control for many types of variance in a study there is a danger that, because TS is an inherited condition with poorly understood transmission, siblings may carry elements of the disorder. Indeed, a number of control participants in the above experiment seemed to respond more like the TS group than the control group.

Furthermore, participants in Experiment 3 had been randomly selected for exposure to the incidental association procedure. This random selection procedure did not stratify for age (hence seven individuals with TS from the older group were exposed as compared to only four older controls); moreover both individuals and controls were randomly chosen -- participants were not age or sex-matched across exposed groups.

For these reasons we chose to redo the analyses between exposed groups in Experiment 3 using an age and sex matched sample of controls without any trace of TS or comorbid conditions reported in the family. Because in Experiment 3 all measures indicated significant effects of exposure, we focused only on the key contrast between exposed participants with TS and exposed controls.

Our concrete a priori predictions were that exposed participants with TS would make more RESET Button Presses, and more RESET Button Initiations toward the RESET button than exposed controls. In terms of retrospective ratings of urges we hoped to show that controls would report greater urges to press the RESET button than individuals with TS.

METHOD

Seven individuals, age and sex matched to the existing seven individuals with TS who had been exposed to the incidental association procedure in Experiment 3, were sent solicitation packages or contacted by phone through the University of Waterloo Cognition and Perception Subject Pool. Solicited individuals were explicitly asked if they, or to their knowledge any member of their family, was or had ever been diagnosed with TS, ADHD, or OCD. All participants confirmed that they had not. One participant reported a diagnosis of asthma for which he used an inhaler. All other participants reported that they had received no diagnoses nor took any medications of any kind.

The methods used were identical to those delineated in Experiment 3 except that all seven participants were chosen for the 2-day procedure. All seven participants were run out of a lab in the University of Waterloo Psychology Department.

RESULTS AND DISCUSSION

RESET Button Presses

The number of RESET Button Presses by the TS and control participants in the exposed groups are reported in Table 10. Although the TS group on average pressed the RESET button

more often than controls (TS = 11.71, controls = 0.29) the variability of the TS group necessitated transforming the data prior to analysis. As before data were transformed using natural logarithms (Y' = log10(Y+1).

An independent t-test on these log-normalized data revealed that participants with TS pressed the RESET button significantly more often than controls (t(12) =2.14, 1-tailed p=.026).

In summary, when participants with TS were contrasted against controls who were presumed to be free of any genetic predispositions for TS, ADHD or OCD, we were able to demonstrate that participants with TS showed greater difficulty inhibiting an incidental association than this control group.

Exposed TS: **RESET Button Presses**	**Exposed Controls:** **RESET Button Presses**
64	**0**
11	**1**
4	**1**
2	**0**
1	**0**
0	**0**
0	**0**
Mean = 11.71	**Mean = 0.29**

Table 10: Number of RESET Button Presses by groups exposed to the Incidental Associations procedure (replication).

RESET Button Initiations

The number of RESET Button Initiations by the TS and control participants in the exposed groups are reported in Table 11. Although the TS group on average made more RESET Button Initiations than controls (TS = 28.86, controls = 1.57) as can be seen in the table the tremendous variability in the TS group relative to the controls necessitated transforming the data prior to analysis. As before data were transformed using natural logarithms (Y' = log10(Y+1).

An independent t-test on these log normalized data revealed that participants with TS initiated movements towards the RESET button significantly more often than controls ($t(12) = 6.52$, $p < .001$).

Exposed TS: RESET Button Initiations	Exposed Controls: RESET Button Initiations
86	**0**
27	**3**
15	**6**
16	**2**
35	**0**
6	**0**
17	**0**
Mean = 28.86	**Mean = 1.57**

Table 11: Number of RESET Button Initiations by groups exposed to the Incidental Association procedure (replication).

Urges

The urges reported by the TS and control participants in the exposed groups are reported in Table 12. The control group on average reported higher urges to engage in the RESET Button Press movement than the TS group (controls 214, TS = 2,). An independent samples t-test revealed that these differences were not significant (t(12) =.281, 1 tailed p=.392).

Exposed TS: Reported Urge	Exposed Controls: Reported Urge
3	1
2	3
2	2
1	4
2	1
3	2
1	2
Mean = 2	Mean = 2.14

Table 12: Number of Urges by groups exposed to the Incidental Associations procedure (replication).

Based on these findings, we could again conclude that while all participants primed in this incidental association may be equally tempted to engage in the incidentally associated RESET Button Press movement, only the motorically disinhibited individuals with TS act upon it. The strength of this replication lays in the significant difference in actual RESET Button Presses – arguably a cleaner measure of inhibition failures than RESET Button Initiations or the retrospective urge measure. As measurements were coded and recorded in Experiments 3 and 4 by the primary experimenter who was not blind to group membership, these results are less prone to any real or perceived experimenter bias.

GENERAL DISCUSSION

Pennington and Ozonoff (1996), in their review of executive functioning in TS, suggested that until a study differentiates and independently examines multiple components of executive functions no definitive conclusions about inhibitory deficits in TS can be made. The first part of this thesis was an attempt to draw more definitive conclusions about failures of inhibition in TS by parsing inhibition problems into "cognitive inhibition" and "motor inhibition" difficulties. Experiments 1 and 2 demonstrated that although participants with TS do not have problems with "cognitive inhibition", they do demonstrate difficulties in "motor inhibition". Given our efforts to ensure that participants with untreated comorbid symptomatology were not included in the sample (as described in the Participants section of Experiment 1) we were able to show that individuals with TS can be expected to perform normally on the Stroop Colour Word task. We further found that, in corroboration with another study where control of ADHD symptoms was not reported, individuals with TS commit more errors than controls on the Simon task.

A comprehensive model of tic formation, capable of accounting for all available tic phenomenology, has to date not been presented in the literature. The second part of this thesis was an attempt to postulate such a model, drawing and building on the conclusions from Experiments 1 and 2. Experiment 3 demonstrated that incidentally learned associations form between various motor movements serendipitously occurring together and, because of the demonstrated difficulties in motoric inhibition, could continue to strengthen. In every-day application this process may lead to the networking of simple movements (like eye-blinking) to countless daily goal-oriented actions (like walking through a doorway). Experiment 4

replicated and strengthened the results of Experiment 3 by comparing older participants with TS to an age and sex matched sample of individuals free of any potential genetic loading for TS or its comorbid conditions.

Excellent reviews by Mink (2001) and Peterson et al. (1999) describe in intricate detail the physiology and neuroanatomical circuitry relevant to TS including the direct and indirect CSTC pathways. Mink stresses that while certain disruptions in the functions of the basal ganglia (the 'editing' or 'pruning' of competing responses) would readily account for unwanted competing motor patterns, to explain tics one must "account for their stereotyped, repetitive nature". While Leckman has suggested that pre-wired rather than learned movements may be what are disinhibited in the TS brain, this explanation would have difficulty accounting for much of the tic phenomenology reported in the introduction to this thesis. While Mink postulates a number of mechanisms that could potentially be responsible for an "unwanted…. specific set of striatal neurons [becoming] overactive in discrete repeated episodes", the learning model proposed in this thesis may be one of the final pieces to this most intriguing puzzle, providing a framework from which to comprehensively explain both the findings pertaining to tic phenomenology as well as providing a further context for understanding some of the more puzzling research findings reported in the literature. Outlined below are accounts of each tic feature cited in the introduction to this thesis, by means of the model's central assumptions. These assumptions provide many predictions that subsequent research can support or refute based on empirical testing.

Phenomenological Findings

Tics are frequent, stereotyped movements and sounds – movements and sounds that occur rarely in a given individual tend not to become tics. The Incidental Associations model postulates that stereotyped movements or noises may become associated with goal-directed behaviours, actions and sounds. When these associations become strong enough that the goal-directed actions or sounds can elicit the stereotyped movement or noise, and when a sufficient number of these goal-directed actions or sounds are associated with the movement or noise, the appearance of these movements or noises occurs frequently and at seemingly random intervals. These movements or noises then 'become' tics. Given these principles, the only movements or noises that COULD be considered as 'tic candidates' are ones that occur often enough, and similarly enough each time, to be incidentally associated to countless goal-directed actions. Conversely, while a unique movement or noise for the individual can be assumed to still be incidentally associated with whatever other goal-directed actions were being performed concurrently, this unique movement occurs only once or occurs differently on each occasion of its execution. Hence the opportunity for numerous incidental associations of this movement or noise with goal-directed actions to occur or strengthen does not exist. Therefore this unique movement or noise will not be elicited regularly and would not ever develop into a tic.

Tics may be seen as enshrined fragments of normal motor action or vocal productions that are misplaced in context. To discuss incidental associations in terms of 'goal-directed actions' and 'movements or noises' is really no more than a linguistic convenience to aid in understanding. In actual fact both behaviours are purposeful when they initially serendipitously occur together; the only difference between them is that the movement

or noise that will eventually 'become' a tic occurs on a regular enough basis and in a standard enough fashion to be susceptible to multiple learning opportunities. To illustrate, blinking may become a tic in that it is a movement that is stimulated to occur each time an individual walks through a doorway, sits at their desk, picks up a book, and so on. There was, however, initially a point at which each of those blinks occurred at each of those times because they served a purpose (i.e. to lubricate the cornea). In that sense tics are 'normal' movements and noises – what is 'abnormal' is that these normal movements or noises, through strengthened incidental associations, have had the timing of their emergence usurped: they have been coupled to various other actions or sounds. Hence they no longer only occur when there is a function to them – they can also be elicited out-of-context by stimuli to which they have become incidentally associated.

Tics are environmentally influenced. Tics tend to "follow" the environment of the individual. For instance, someone who works in physical labour seems to experience more motoric tics and less phonic tics than an individual whose job emphasizes verbal skills. Incidental associations develop from one's daily routines – it would seem most plausible then that tics reflect those daily routines. Tics may even be unique to a particular environment. Based on the present model, one would predict that environmentally unique tics would be comprised of movements or noises and goal-directed actions or sounds that are performed, and have been incidentally associated, in that select environment alone. A personal example of the first author would be a flicking of the left wrist. This tic only occurs in summer, in his backyard, when watering plants and holding an active garden hose in his left hand. Holding a garden hose and flicking one's wrist to aim the water stream in the desired direction are related

(hence ripe territory for incidental associations to occur) yet holding a garden hose is a very context-specific action (hence many months will pass and memory of the tic disappears until gardening season again arrives).

Tics appear between the ages of 5 and 6. Our results from Experiment 2 suggest that the failures of motoric inhibition seen in individuals with TS are the result of a developmental delay – in other words, the improper firing of the indirect CSTC circuit in individuals with TS is only abnormal in that this population does not eventually grow out of this deficit. Assuming this is true, incidental associations must be occurring and strengthening in all children from birth. Why is it then that most young children don't have tics? While a high percentage of children DO evidence tics and tic disorders as they grow (as reviewed in the introduction to this thesis) the vast majority of children do not. It seems safe to conclude then that motoric inhibition develops and strengthens before any incidental associations become strong enough and numerous enough to begin eliciting frequent and stereotyped movements out of context. Considering the sheer number of associations needed to give the impression of random expression, and given the time it would take for these serendipitous, simultaneous occurrences to occur together by chance often enough to achieve the strength necessary for one action or sound to elicit another movement or noise, it is not surprising that many years of infancy and childhood may pass before tics emerge in an individual. For some, it is during this time period that motor inhibitory skills develop and prevent the expression of incidentally associated movements and sounds. For others, these skills are delayed and so tics emerge.

Tics follow a pattern of increasing severity throughout childhood. Continuing with the above logic, if motor inhibition remains delayed or sporadic in an individual then this affords these incidental associations opportunity to continually strengthen over time. In addition, a person develops a greater repertoire of learned motor patterns as they grow, develop, learn and engage in new activities and sounds. All of these 'new grounds' are fertile for incidental associations to potentially develop. Also recall from the introduction of this thesis evidence that complex tics develop later than simple tics. Complex tics involve more involved combinations of complex goal-directed behaviours and incidentally associated movements and noises. It may well be that these more involved combinations of goal directed behaviours and movements require more time to develop. One type of complex tic, called a paroxysm, was described in the introduction as being an orchestrated chaining together of numerous simple tics. It is straightforward to see how a tic, once established, could begin to develop incidental associations to a new movement or noise in a sort of second- third- or fourth-order conditioning. By this reasoning complex tics ipso facto must follow simple tics ('first order' incidental associations) developmentally.

Tics are preceded by, and are unvoluntary responses to, an "itch" or premonitory urge sensation. By definition, according to the Incidental Association model, tics are elicited – they do not simply occur in a vacuum. An individual is compelled to engage in a particular movement or noise as part of a learned and strengthened sequence of behaviours – to not do so disrupts a pattern acquired over a great deal of time and experience. Suppression then would bring about a sense of motor or phonic "incompletion", focussed on the area of the body or on the object that has been incidentally associated to 'engage' at that point in the pattern. The

sensation would be akin to the angst of being pulled away from a task (for example the writing of a letter) before finishing it. Just as the associations between each component of the pattern grow stronger with additional pairing of eliciting stimuli and tic response, premonitory urges grow over time. In this sense tics are a mirror to the strength of incidental associations: as these associations become more or less primed in different circumstances the tics likewise will wax and wane.

Tics wax and wane with stress. Experiment 2 provides evidence that individuals with TS are not completely incapable of motoric inhibition – RT's for successful inhibitions did not differ from those of controls. Moreover, the fact that the magnitude of the Simon effect in the TS group was indistinguishable from controls reveals that while inhibiting a prepotent motor response incurs a cost in terms of RT, individuals with TS *are* capable of successfully inhibiting these prepotent motor responses. That failures of inhibition were higher in the TS group may indicate that this ability to inhibit is simply more sporadic. Given these motor inhibition fluctuations, while incidental associations would be ever-present they would only be acted upon (i.e. tics would only be elicited) during times of motor inhibition failure. Recall from the introduction to this thesis that stress has been found to be a determinant in the waxing and waning course of tics. It is not difficult to see how physical or psychological strain could negatively impact one's normal neurological functioning and exacerbate existing vulnerabilities. In the case of TS, stress would result in an even less efficient use of the indirect 'pruning' CSTC pathway resulting in more activation of incidentally associated movements and, to the eye, a waxing of symptoms. Peterson and colleagues have conducted some promising research in this area (1998). In their study 22 adult patients (18-55 years; ì

35.7 years) underwent functional magnetic resonance imaging during periods of voluntary tic suppression and spontaneous tic expression. Considerably more activation of the basal ganglia, thalamus, and connecting cortex were noted during suppression periods. More importantly, however, the magnitudes of regional signal change in the basal ganglia and thalamus correlated inversely with the severity of tic symptoms. In other words, using a 'leaky brakes' analogy, more severe tics were predictive of less capability in engaging the appropriate CSTC circuitry for suppression (Peterson et al., 1998). While this study considered severity between subjects, assuming constant neurology in each subject, a similar study conducted within-subject, where patients are asked to suppress under varying stress levels, could be most beneficial in helping to explain the waxing and waning course of TS. It is reasonable to presume that, since stress plays a role in symptom severity, this could be demonstrated on the neurological level. Perhaps also tying into this picture is neurological research that dopamine release from the substantia nigra is burst-like in fashion. In addition to perhaps explaining the relative increases and decreases in inhibitory capability (reflecting the waxing and waning of tics) these findings may also explain 'micro' waxing and waning – the typical burst-like pattern that tics follow on an hourly and daily basis.

Tics disappear during highly complex tasks involving considerable focus and/or concentration. While movements or noises incidental to a goal-directed action will become somewhat associated with that action, the purposeful components associate as well. Indeed, the purposeful components of a complex goal-directed behaviour will occur together much more reliably and in a much more consistent order each time that behaviour is performed than the incidental movement or noise will. For example, when walking through a doorway one

always must first extend one's arm and twist the doorknob with one's hand BEFORE moving one's legs. On the other hand, a blink may occur at any point in this sequence. Moreover, doorknob twisting and striding will ALWAYS be components of walking through a doorway whereas blinking may only occasionally occur during this pattern. Thus it is safe to believe that incidental associations to any one of the purposeful components of a complex goal-directed behaviour will not be as strong as the associations between the purposeful components of the complex goal-directed behaviour themselves. The fact that incidentally associated movements still occur is evidence that the general disinhibition of the direct CSTC pathway is sufficient to spread to these 'lesser' associations and activate them. It is conceivable, however, that in the case of a highly complex task with a variety of simultaneous demands the cognitive resources required to carry out the tic are all devoted to the orchestration of the required purposeful movements. In this situation the incidental associations still exist but they are not activated; this would exhibit as an absence of either premonitory urges or tics.

Tics are suggestible. Drawing from the 'spreading activation' notion suggested above, attracting one's attention to a particular body part, object, or behaviour would trigger the arousal of any associations to it, including incidental ones. Thus a premonitory urge to engage in these movements or noises is induced. This could help explain the well-known observation that individuals with TS, exposed to another's symptoms, can begin to pick up those symptoms themselves (Ziemann, Paulus, & Rothenberger, 1997).

Tics do not appear to infiltrate primal behaviour patterns such as sexual relations. Deeply ingrained, phylogenetic "action patterns" are relatively fixed and automatic from birth

– they are unlearned. Given this, these patterns would not susceptible to incidental learning either.

The longer one has a tic, the more difficult it is to eliminate it from one's repertoire. While an anecdotal report, this is an observation that could be readily predicted from this model. An 'older' tic is one that is more deeply "entrenched" in its associations, has had opportunity to attach itself to many more goal-directed behaviours, and is more generalized and accommodated.

Premonitory urges and tics are at their quietest when one first wakes in the morning. Before an individual rises in the morning, daily routines and customary movements and sounds have yet to be engaged in. Since tics are joined TO these customary routines, no impetus for their expression exists yet. Only after one initiates one's first goal-directed actions or sounds of the day can the urge to complete any movements or noises tied to those actions or sounds be activated.

Tics wane in novel environments or during novel experiences and/or actions. The common example of this phenomenon, cited in the introduction to this thesis, is the Doctor's Office Syndrome. Besides the obvious fact that suppression may play a role, by definition a novel circumstance is one in which you have no past associations. This would include incidental associations as well. Hence any novel tasks, sights, or individuals are free of linked movements and noises. Common solutions used by experienced clinicians to thwart the Doctor's Office Syndrome are: extended durations of time in the office and/or multiple visits to

the doctor's office until tics start to manifest, and 'catching' the individual (via videotape or two-way mirrors) in a more accustomed environment where the tics commonly occur. In the language of the Incidental Associations Model, the first technique affords opportunities for incidental associations to form in (or perhaps more accurately generalize to) the new environment. The second technique removes or minimizes the novel environments so that the doctor may observe the pre-existing incidental associations.

Habit-Reversal Training is a highly effective technique for tic management. Based on the premises of the model, pharmaceutics and HRT approach tic reduction in completely different ways. The former attempts to ameliorate the problems in motor inhibition failures without any concern for pre-existing incidental associations. This is perhaps why some parents anecdotally report that their children continue to tic, but do so in slow motion as if under water – medications merely thwart the expression of tics rather than fixing the fundamental problem. HRT, on the other hand, confronts and eliminates the associations themselves. That HRT generalizes better after treatment than medications is of little surprise then since HRT, when successful, extinguishes each incidental association so that tic movements, along with any urges to engage in them, are gone. It is interesting to note that, despite the fact that a learning model of tic formation did not exist in 1973, Azrin and Dunn in their original conception of HRT included the identification of signs, people, places and situations that triggered tics (Azrin & Nunn, 1973).

Past Research

Conditioned blocking is impaired in individuals with TS (Oades & Muller, 1997). The Incidental Associations Model provides new context for this peculiar finding. Conditioned blocking refers to the transient suppression of learning that a new stimulus has the same consequences as an already present conditioned stimulus. An example would be if an individual, after learning that an appearance by an ice-cream truck on one's street is contingent upon a ringing bell, did not learn that the appearance of the truck is also contingent upon a particular time of day (4:07 p.m.). Time of day as a reliable predictor of an ice-cream truck was blocked from learning because another reliable stimulus had already been conditioned – in other words the learning is redundant and unnecessary. Oades and Muller demonstrated that associations, even when unnecessary, were made nonetheless in TS patients – conditioned blocking was independent of age. Children 11 years of age and older with TS were significantly worse at conditioned blocking than controls and children with ADHD (Oades & Muller, 1997). Not being able to inhibit new, unnecessary associations is the hallmark of the proposed model of tic formation, and so these findings can be construed as a rather elegant demonstration of the model's principle tenets and a fortuitous find in the literature.

Georgiou, Bradshaw et al. (1995) found evidence that motor sequencing in the absence of external cues was poor in 12 individuals with TS (after controlling for medication and depression). They found that reductions in external cues for sequenced movements did not affect movement initiation but did slow movement execution (moving from one button to next). They hypothesized that motor sequencing generated by the basal ganglia may be faulty, and so external cues that are accessed through the lateral premotor cortex must be relied upon.

When these cues are removed, the authors proposed, participants with TS would then have to rely on internal cues from the faulty basal ganglia. Perhaps internal cueing is a problem, and causes slow movement execution, because of competition between numerous incidentally associated responses. When adequate external cues are provided, these help the appropriate goal-directed response to be "louder" than other incidentally associated responses competing for activation and so the appropriate response is more easily and quickly initiated.

Neurological findings discussed in the introduction to this thesis can now be better understood as well. Hypoperfusions and hypometabolism in basal ganglia structures can all be understood as being the result of underdevelopment of the 'pruning' functions these structures are supposed to engage in as components of the indirect CSTC pathway. Braun et al. (1993) and Stoetter et al. (1992) noted a hyp*er*metabolism of the sensorimotor cortex in individuals with TS – if appropriate inhibition of unnecessary movements and noises is not being signalled by the basal ganglia due to a defective indirect pathway then overactivity of the sensorimotor cortex is to be expected.

Should the Incidental Associations Model of Tic Formation be accurate, this would have significant and broad clinical implications. Diagnostic tests for TS could seek the susceptibility of an individual to engage in serendipitous motor associations, and treatments that focus on the extinguishing of learned associations, like HRT, could be further developed and emphasized. It may also be a striking demonstration of the concept of neuronal plasticity – the idea that pre-wired neurology can and will be modified by learning.

Potential challenges for model are discussed below:

Why do tics often end or decrease in adulthood? First, symptoms do not always abate over the life course of people with TS (see the review of this literature in the introduction to this thesis). Second, the Incidental Association theory rests on two premises, both of which must remain true for tics to be exhibited: incidental associations must form through environmental experience, and the individual must experience a failing of motor inhibitory ability through their altered neurological organization. Recall that results from Experiments 3 and 4 demonstrated that incidental associations can be engendered in individuals without TS as well – exposed control participants retroactively reported significantly stronger urges to engage in the RESET Button Press movement than both unexposed controls and individuals with TS. Given that incidental associations are not unique to those with TS, the reason controls did not succumb to them is because their motor inhibition exceeded that of the TS group (as demonstrated in Experiment 2). Also recall that failing in motor inhibition in individuals with TS appears to be a maturational delay. While for some this may be a permanent impediment, for others this delay may eventually completely or partially ameliorate over time. In the first scenario, tics would be life-long. In the second scenario, tic frequency and number would decrease or disappear altogether.

Why do tics appear spontaneously? If tics are the product of incidental associations occurring for years, why do we not see a more gradual onset of individual tics? Using a rising submarine as a metaphor for the gradual strengthening of incidental associations, the "sudden" breaking to the surface is only an illusion of spontaneity – in actual fact its ascent might simply

have gone undetected. Incidental associations likewise are concealed until they are of sufficient strength for one action to elicit another. Only the appearance of the actual tic movement, wrenched from its appropriate context, is abrupt: its origin is not.

Why do we not see thousands of different tics in an individual instead of rather constant repertoires? In other words, if countless goal-directed actions and sounds are involved in the development of tics, why aren't countless movements and noises too? Why isn't a person's every movement and noise tied to every other movement and noise? One answer is that we can assume, if in a given setting multiple competing responses exist, the strongest association 'wins' and is the determining factor.

A better answer can be offered however. The Incidental Association model states that it takes many repetitions of the same serendipitous associations to strengthen into one tic. While it is true that countless incidental associations between innumerable actions and sounds must take place, it is important to consider that a single random association event would not be sufficient to engender a conscious compelling urge to engage in the elicited movement or noise (i.e. become a tic). Incidental associations will not adequately strengthen to the point where tics are elicited unless the same association randomly takes place on a consistent enough basis. Given this constraint, while an immeasurable number of incidental associations could and would occur in an individual with TS, the number that would randomly yet consistently occur is considerably lower. Hence a potential tic repertoire is radically smaller than one's repertoire of incidental associations.

The Incidental Associations model provides a multitude of directions for future research. Concerning the failure-of-motor-inhibition component of the model, further and different tests demonstrating this preferential deficit in individuals with TS should be performed to replicate the findings of Experiments 1 and 2. An important question to ask is whether even severe forms of TS are purely disorders of motor inhibition. In asking this question it would be important to carefully operationalize the term "severity". One should not confound 'severity of tic symptoms' with 'comorbidity', where other more "cognitive" CSTC circuitry components are likely involved. One should also be careful to not confound 'increased frequency and number of tics', and 'the introduction of complex tics', which again may be more likely to involve more "cognitive" CSTC circuitry (such as the disinhibition of words as in coprolalia or echolalia). Freeman et al (2000), in their epidemiological analysis of international data, state that impressive levels of complex tics are only seen when comorbid conditions exist. Given this, perhaps complex tics only occur in comorbid cases of TS and are an indication that further diagnoses are warranted. An interesting future study could be to analyze the relationships between tic symptom severity, comorbidity of ADHD and OCD, and complex tics – can one have "severe" TS without having complex tics and/or any comorbid diagnoses, and if so would these cases demonstrate failures in domains other than motoric inhibition?

Additional tests of the learning component of the model are also required. Substantiations of anecdotally reported tic phenomenology reported to fit the model, and the proffered explanations for why these phenomena may be occurring, require confirmation. For example, it was suggested that tics might wane during orgasm because this behaviour pattern

is primal and occurs independently of ANY form of learning. If this is true, can research demonstrate corresponding wane periods during other 'fixed patterns' like fighting, mastication, and/or sucking/swallowing? Also, while complex tics do appear to develop from simple tics (Leckman et al., 2001), and while this fits well with the Incidental Associations model, is it the case that complex tics *always* follow simple tics and are initial tics *always* of the simple variety?

Further studies into the 'rules' of incidental associations need to be performed. In the present study a stimulus (tactile vibration) and response button press were defined as the goal oriented action, and the subsequent RESET Button Press was another movement not specifically (or explicitly explained to be) related to the principal stimulus response association. One shortcoming of this design was that a RESET Button Press followed each and every response button press. This would be analogous to an individual reliably blinking EACH TIME they walk through a doorway. Obviously this does not occur in everyday life – in fact if it did one might expect that the basal ganglia in ALL individuals would learn to consider eye blinking to be a purposeful component of walking through a doorway. Thus this association would be indistinguishable from all others within the stored "walking-through-doorway" motor pattern, and eye-blinking movements would occur in all individuals walking through doorways. In the future one might wish to make the learning even more 'incidental' by changing the probability with which the RESET Button Press might follow the response button press. That is, one could tell participants that there is a "bug" in the program that causes it to get "stuck" every so often. Participants could be informed that they can "unstick" the program by pressing the RESET button each time the program hangs. The software could be

programmed to randomly hang according to various responses-to-RESET-Button-Pressing ratio schedules. Such an experiment would more closely mimic the incidental associations that occur in every day life – motor responses happen to become chained on a certain percentage of trials, rather than all the time.

The Incidental Associations model could also guide neurological research. Future projects might look at the neurology of learning and how these processes may differ in individuals with TS. Does stress impact the functioning of the indirect pathway of the basal ganglia and, if so, are tics more likely to form from incidental associations occurring during stressful conditions? Does suppression of tics ("extinction of incidental associations") ultimately lead to a better adult prognosis, and does relaxation of suppression ("unrestrained strengthening of incidental associations") ultimately lead to more severe symptoms and a lessened ability to suppress?

Given the wide range of phenomena that the Incidental Associations Model of Tic Formation can account for, the authors hope that others will consider the model to be a helpful framework for understanding how tics are formed and strengthened, and for guiding exploration of TS diagnosis and treatment. This model may have some utility as well in understanding other disorders thought to involve inhibition failures outside of an exclusively motor realm, such as ADHD, OCD, and schizophrenia. Applying an analogous model to schizophrenia, for example, would help to explain the tangential thinking, clanging, and loose associations diagnostic of this debilitating condition. If an individual were experiencing a more profound inability to inhibit or prune incidental associations than that seen in TS – the

inability to prune stray cognitive connections to one's present string of thought – one would be fated to wander idiosyncratically through a spreading activation of incidental associations, robbed of the ability to stay with a coherent theme. In terms of OCD, certain deeply encoded thoughts (such as grooming, cleanliness, and safety) have evolved to occur frequently in individuals. Should incidental associations between these "pre-wired" thoughts and goal-directed thoughts occur in a fashion identical to that described for TS, these "pre-wired" thoughts would begin to appear on a regular and seemingly random basis devoid of context. By this logic obsessions and compulsions could be viewed as simply cognitive versions of premonitory urges and tics respectively; alternatively premonitory urges and tics would be somatic and motor versions of obsessions and compulsions.

Reference List

Alexander, GE; DeLong, MR; Strick, PL (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review Neuroscience, 9, 357-381.

Azrin, NH; Nunn, RG (1973). Habit reversal: A method of eliminating nervous habits and tics. Behavior Research and Therapy, 11, 619-628.

Azrin, NH; Peterson, AL. (1990). Treatment of Tourette Syndrome by habit reversal: A waiting-list control group comparison. Behavior Therapy, 21(3), 305-318.

Baron-Cohen, S; Cross, P; Crowson, M; Robertson, M (1994). Can children with Gilles de la Tourette syndrome edit their intentions? Psychological-Medicine, 24(1), 29-40.

Baron-Cohen, S; Robertson, MM; Moriarty, J (1993). The development of the will: a neuropsychological analysis of Gilles de la Tourette syndrome. In Cicchetti, D; Toth, SL; et al. (Eds.), Disorders and dysfunctions of the self. Rochester Symposium on Developmental Psychopathology, Vol. 5 (pp.57-77). New York: University of Rochester Press.

Becker, MG; Isaac, W; Hynd, GW (1987). Neuropsychological development of nonverbal behaviours attributed to "frontal lobe" functioning. Developmental Neuropsychology, 3, 275-298.

Bliss, J (1980). Sensory experiences in Gilles de la Tourette syndrome. Archives of General Psychiatry, 37, 1343-1347.

Boucugnani, LL; Jones, RW. (1989). Behaviors analogous to frontal lobe dysfunction in children with attention deficit hyperactivity disorder. Archives of Clinical Neuropsychology, 4(2), 161-173.

Bornstein, RA (1991a). Neuropsychological performance in adults with Tourette syndrome. Psychiatry Research, 37, 229-236.

Braun, AR, Stoetter, B, Randolph, C; et al. (1993). The functional neuroanatomy of Tourette's syndrome: An FDG-PET study. I. Regional changes in cerebral glucose metabolism differentiating patients and controls.. Neuropsychopharmacology, 9, 277-291.

Brotchie, P; Iansek, R; Horne, MK (1991). Motor function of the monkey globus pallidus: neuronal discharge and parameters of movement (also cognitive aspects of movement and phasic neuronal activity). Brain, 114, 1667-1683 (also 1685-1702).

Bruun, RD; Budman, CL (1992). The natural history of Tourette syndrome. In TN Chase, AJ Friedhoff (Eds.), Tourette syndrome: Genetics, neurobiology, and treatment. Advances in neurology, Vol. 58 (pp. 1-6).

Buckolz, E; O'Donnell, C; McAuliffe, J (1996). The Simon effect: evidence of a response processing "functional locus". Human Movement Science, 15(4), 543-564.

Budman, CL (2000). Treatment of Tourette syndrome. Symposium conducted at the 2000 Tourette Syndrome Association convention, Washington D.C., USA.

Carr, JE. (1995). Competing responses for the treatment of Tourette syndrome and tic disorders. Behaviour Research and Therapy, 33(4), 455-456.

Carter, CS; Krener, P; Chaderjian, M; Northcutt, C; et al. (1995). Abnormal processing of irrelevant information in attention deficit hyperactivity disorder. Psychiatry Research, 56(1), 59-70.

Cheesman, J; Merikle, PM (1986). Distinguishing conscious from unconscious perceptual processes. Canadian Journal of Psychology, 40(4), 343-367.

Chodosh, J; Messinger, R (1997, October). Stress and coping in families who have a child with severe Tourette syndrome: Educating families and service providers. Poster presented at the Tourette Syndrome Foundation of Canada International Symposium "Tourette Syndrome: The Complexities of Treatment", Quebec City, QC, Canada.

Cohen, JD; Dunbar, K; McClelland, JL(1990). On the control of automatic processes: A parallel distributed processing account of the Stroop effect. Psychological Review, 97(3), 332-361.

Cohen, AJ; Leckman, JF (1992). Sensory phenomena associated with Gilles de la Tourette's syndrome. Journal of Clinical Psychiatry, 53, 319-323.

Cohen, JD; MacWhinney, B; Flatt, M; Provost, J (1993). PsyScope: A new graphic interactive environment for designing psychology experiments. Behavioral Research Methods, Instruments, and Computers, 25(2), 257-271.

Comings, DE. (1990). Tourette Syndrome and Human Behavior. California: Hope Press.

Comings, DE; Hines, JA; Comings, BG (1990). An epidemiologic study of Tourette's syndrome in a single school district. Journal of Clinical Psychiatry, 51, 563-569.

Costello, EJ; Angold, A; Burns, BJ, et al. (1996). The Great Smoky Mountains study of youth: Goals, design, methods, and the prevalence of DSM-III-R disorders. Archives of General Psychiatry, 53, 1129-1136.

de Groot, CM; Bornstein, RA; Spetie, L; Burriss, B (1994). The course of tics in Tourette syndrome: a 5-year follow-up study.. Annal of Clinical Psychiatry, 6(4), 227-233.

Demirkol, A; Erdem, H; Inan, L; Yigit, A; Guney, M (1999). Bilateral globus pallidus lesions in a patient with Tourette syndrome and related disorders. Biological Psychiatry, 46, 863-867.

Dixon, M; Laurence, J-R (1992). Hypnotic susceptibility and verbal automaticity: Automatic and strategic processing differences in the Stroop color-naming task. Journal of Abnormal Psychology, 101(2), 344-347.

Dykens, EM; Sparrow, SS; Cohen, DJ; Scahill, L; Leckman, JF (1999). Peer acceptance and adaptive functioning. In JF Leckman, DJ Cohen (Eds.), Tourette's syndrome, tics, obsessions, compulsions: Developmental psychopathology and clinical care (pp. 104-117). New York: John Wiley and Sons.

Erenberg, G; Cruse, RP; Rothner, AD (1986). Tourette syndrome: An analysis of 200 pediatric and adolescent cases. Cleveland Clinic Quarterly, 53, 127-131.

Erenberg, G; Cruse, RP; Rothner, AD (1987). The natural history of Tourette's Syndrome A follow-up study. Annual Neurology, 22, 383-385.

Evers, RA; van de Wetering, BJ (1994). A treatment model for motor tics based on a specific tension-reduction technique. Journal of Behavioral Therapy and Experimental Psychiatry, 25(3), 255-260.

Farber, RH; Swerdlow, NR; Clementz, BA (1999). Saccadic performance characteristics and the behavioural neurology of Tourette's syndrome. Journal of Neurology, Neurosurgery, and Psychiatry, 66(3), 305-312.

Freeman, RD; Fast, DK; Burd, L; Derbeshian, J; Robertson, MM; Sandor, P. (2000). An international perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries. Developmental Medicine & Child Neurology, 42, 436-447.

Freeman, RD; Fast, DK; Kent, M. (1995). DSM-IV criteria for Tourette's [letter]. Journal of the American Academy of Child and Adolescent Psychiatry, 34, 400-4001.

George, MS; Sallee, R; Nahas, Z; Oliver, NC; Wassermann, EM (2001)., Transcranial magnetic stimulation (TMS) as a research tool in Tourette syndrome and related disorders. In DJ Cohen, CG. Goetz, J. Jankovic (Eds.), Advances In Neurology Vol. 85. Tourette Syndrome (pp.1-14). Philadelphia: Lippincott Williams & Wilkins.

Georgiou, N; Bradshaw, JL; Phillips, JG; Bradshaw, JA; Chiu, E (1995a). Advance information and movement sequencing in Gilles de la Tourette syndrome. Journal of Neurology, Neurosurgery, and Psychiatry, 58, 184-191.

Georgiou, N; Bradshaw, JL; Phillips, JG; Bradshaw, JA; Chiu, E. (1995b). The Simon effect and attention deficits in Gilles de la Tourette's syndrome and Huntington's disease. Brain, 118(5), 305-1318.

Georgopoulos, AP; Lurito, JT; Petrides, M; Schwartz, AB; Massey, JT (1989). Mental rotation of the neuronal population vector. Science, 243, 234-236.

Gilbert, D (2001, March). Treatments for TS. Symposium conducted for the Tourette Syndrome Association Ohio Chapter Annual Convention, Cleveland, OH, USA.

Gilles de la Tourette, G. (1885). Etude sur une affection nerveuse caracterisee par de l'incoordination motrice accompagnee d'echolalie et de coprolalie. Archive of Neurology, 9, 19-42, 158-200.

Goetz, CG; Tanner, CM; Stebbins, GT; et al. (1992). Adult tics in Gilles de la Tourette's syndrome: Description and risk factors. Neurology, 42, 784-788.

Graybeil, AM (1998). The basal ganglia and chunking of action repertoires. Neurobiology of Learning and Memory, 70, 119-136.

Graybeil, AM (1999, June). Repetitive behavior in Tourette syndrome. Symposium conducted for the 3rd Tourette Syndrome Association International Symposium, New York, New York, USA.

Grodzinsky, GM; Diamond,R (1992). Frontal lobe functioning in boys with attention-deficit hyperactivity disorder. Developmental Neuropsychology, 8(4), 427-445.

Harris, EL; Schuerholz, LJ; Singer, HS; Reader, MJ; Brown, JE; Cox, C; Mohr, J; Chase, GA; Denckla, MB (1995). Executive function in children with Tourette syndrome and/or attention deficit hyperactivity disorder. Journal of the International Neuropsychological Society, 1, 511-516.

Hasbroucq, T; Guiard, Y (1992). The effects of intensity and irrelevant location of a tactile stimulation in a choice reaction time test. Neuropsychologia, 30(1), 91-94.

Hebb, DO (1949). The organization of behavior. New York: Wiley.

Holst, P, Vilkki, J (1988). Effect of frontomedial lesions on performance on the Stroop test and word fluency tasks. Journal of Clinical and Experimental Neuropsychology, 10, 79 (Abstract).

Hommel, B (1994a). Effects of irrelevant spatial compatibility depend on stimulus complexity. Psychological Research, 56(3), 179-184.

Hommel, B (1994b). Spontaneous decay of response-code activation. Psychological Research, 56(4), 261-268.

Howell, DC (1987). Statistical methods for Psychology, 2nd edition. Duxbury Press: Boston.

Humphrey, MM (1982). Children's avoidance of environmental, simple task internal, and complex task internal distractors. Child Development, 53, 736-745.

Hyde, TM; Stacey, ME; Coppola, R; Handel, SF; Rickler, KC; Weinberger, DR (1995). Cerebral morphometric abnormalities in Tourette's syndrome: A quantitative MRI study of monozygotic twins. Neurology, 45(6), 1176-1182.

Jankovic, J (1997). Phenomenology and classification of tics. Neurologic-Clinics, 15(2), 267-275.

Karp, BI; Hallett, M (1996). Extracorporeal 'phantom' tics in Tourette's syndrome. Neurology, 46(1), 38-40.

Katz, LJ; Wood, DS; Goldstein, G; Auchenbach, RC; Geckle, M. (1998). The utility of neuropsychological tests in evaluation of attention-deficit/hyperactivity disorder (ADHD) versus depression in adults. Assessment, 5(1), 45-51.

King, RA; Scahill, L; Findley, D; Cohen, DJ (1999). Psychosocial and behavioural treatments. In JF Leckman, DJ Cohen (Eds.), Tourette's syndrome: Tics, obsessions, compulsions. Developmental psychopathology and clinical care (pp. 23-42). Toronto: John Wiley & Sons, Inc.

Kohen, DP. (1995). Coping with the stress of Tourette syndrome in children and adolescents: Use of self-hypnosis techniques. Australian Journal of Clinical and Experimental Hypnosis, 23(2), 145-157.

Krauss, JK; Jankovic, J (1996). Severe motor tics causing cervical myelopathy in Tourette's syndrome. Movement Disorders, 11(5), 563-566.

Kurlan, R (2001). Workshop on pharmaceutical interventions for Tourette syndrome and associated disorders. Symposium conducted at the 2nd TSFC International Symposium on Tourette Syndrome and Other Neurodevelopmental Disorders, Mississauga, Canada.

Kurlan, R; Whitmore, D; Irvine, C; McDermott, MP; Como, PG (1994a). Tourette's syndrome in a special education population: a pilot study involving a single school district. Neurology, 44, 699-702.

Lang, AE (1992). Clinical phenomenology of tic disorders: selected aspects. In TN Chase, AJ Friedhoff, DF Cohen (Eds.), Advances in neurology, Vol. 58. Tourette syndrome: Genetics, neurobiology, and treatment (pp. 25-32). New York: Raven Press.

Leckman, JF; King, RA; Cohen, DJ (1999). Tics and tic disorders. In JF Leckman, DJ Cohen (Eds.), Tourette's syndrome: Tics, obsessions, compulsions. Developmental psychopathology and clinical care (pp. 23-42). Toronto: John Wiley & Sons, Inc.

Leckman, JF; Peterson, BS; Anderson, GM; Arnsten, AFT; Pauls, DL; Cohen, DJ (1997). Pathogenesis of Tourette's syndrome. Journal of Child Psychology and Psychiatry, 38(1), 119-142.

Leckman, JF; Peterson, BS; King, RA; Scahill, L; Cohen, DJ (2001). Phenomenology of tics and natural history of tic disorders. In DJ Cohen, CG. Goetz, J. Jankovic (Eds.), Advances In Neurology Vol. 85. Tourette Syndrome (pp.1-14). Philadelphia: Lippincott Williams & Wilkins.

Leckman, JF; Zhang, H; Vitale, A; Lahnin, F; Lynch, K; Bondi, C; Kim, Y-S; Peterson, BS (1998). Course of tic severity in Tourette syndrome: The first two decades. Pediatrics, 102(1), 14-19.

Logan, GD; Zbrodoff, NJ. (1979). When it helps to be misled: Facilitative effects of increasing the frequency of conflicting stimuli in a Stroop-like task. Memory & Cognition, 7, 166-174.

Lowe, DG; Mitterer, JO. (1982). Selective and divided attention in a Stroop task. Canadian Journal of Psychology, 36(4), 684-700.

Lowe, TL; Cohen, DJ; Detlor, J; Kremenitzer, MW; Shaywitz, BA (1982). Stimulant medications precipitate Tourette's syndrome. Journal of the American Medical Association? (Journal of the American Medical Association), 247(8), 1168-1169.

Lu, CH; Proctor, RW (1995). The influence of irrelevant location information on performance: A review of the Simon and spatial Stroop effects. Psychonomic Bulletin & Review, 2, 174-207.

Lufi, D; Cohen, A; Parish-Plass, J. (1990). Identifying attention deficit hyperactive disorder with the WISC--R and the Stroop Color and Word Test. Psychology in the Schools, 27(1), 28-34.

Mason, A; Banerjee, S; Eapen, V; et al. (1998). The prevalence of Tourette syndrome in a mainstream school. Developmental Medicine & Child Neurology, 40, 292-296.

McKinlay, BD (1998). You say lemon, I say lemonade: The impact of attitude when dealing with disorder. Unpublished master's thesis, University of Waterloo, Waterloo, Ontario, Canada.

Miller, DC; Kavcic, V; Leslie, JE (1996). ERP changes induced by methylphenidate in boys with attention-deficit hyperactivity disorder. Journal of Attention Disorders, 1(2), 95-113.

Mink, J. (2001). Neurobiology of basal ganglia circuits in Tourette syndrome: Faulty inhibition of unwanted motor patterns? In D.J. Cohen, C.G. Goetz, J. Jankovic (Eds.), Advances in Neurology Vol. 85. Tourette Syndrome (pp. 113-122). Philadelphia: Lippincott Williams & Wilkins.

Moriarty, J; Campos Costa, D; Schmitz, B; Trimble, MR; Ell, PJ; Robertson, MM (1995). Brain perfusion in Gilles de la Tourette's syndrome. British Journal of Psychiatry, 167, 249-254.

Moriarty, J; Eapen, V; Costa, DC; et al. (1997). HMPAO SPECT does not distinguish obsessive-compulsive and tic syndromes in families multiply affected with Gilles de la Tourette's syndrome. Psychological Medicine, 27, 737-740.

Nomura, Y; Segawa, M. Tourette syndrome in oriental children: Clinical and pathophysiological considerations. Advances in Neurology, 35, 277-280.

Oades, RD; Muller, B (1997). The development of conditioned blocking and monoamine metabolism in children with attention-deficit-hyperactivity disorder or complex tics and healthy controls: an exploratory analysis. Behavioral Brain Research, 88(1), 95-102.

O'Leary, MJ; Barber, PJ (1993). Interference effects in the Stroop and Simon paradigms. Journal of Experimental Psychology: Human Perception and Performance, 19(4), 830-844.

Ozonoff, S; Strayer, DL; McMahon,WM; Filloux, F (1994). Executive function abilities in autism and Tourette syndrome: An information processing approach. Journal of Child Psychology and Psychiatry and Allied Disciplines, 35(6), 1015-1032.

Ozonoff, S; Strayer, DL; McMahon, WM; Filloux, F (1998). Inhibitory deficits in Tourette syndrome: a function of comorbidity and symptom severity. Journal of Child Psychology and Psychiatry and Allied Disciplines, 39(8), 1109-18.

Park, S; Como, PG; Cui, L; et al.(1993). The early course of the Tourette's syndrome clinical spectrum. Neurology, 43, 1712-1715.

Pennington, BF; Ozonoff, S (1996). Executive functions and developmental psychopathology. Journal of Child Psychology and Psychiatry and Allied Disciplines, 37(1), 51-87.

Perret, E (1974). The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. Neuropsychologia, 12, 323-330.

Peterson, AL; Azrin, NH (1992). An evaluation of behavioral treatments for Tourette syndrome. Behaviour Research and Therapy, 30(2), 167-174.

Peterson, AL; Azrin, NH (1993). Behavioral and pharmacological treatments for Tourette syndrome: A review. Applied and Preventive Psychology, 2(4), 231-242.

Peterson, BS (2001). Neuroimaging studies of Tourette syndrome: a decade of progress. In D.J. Cohen, C.G. Goetz, J Jankovic (Eds.), Advances In Neurology Vol. 85. Tourette Syndrome (pp. 261-271). Philadelphia: Lippincott Williams & Wilkins.

Peterson, BS; Leckman, JF. The temporal dynamics of tics in Gilles de la Tourette syndrome. Biological Psychiatry 44 (1998): 1337-1348.

Peterson, BS; Leckman, JF; Arnsten, A; Anderson, GM; Staib, LH; Gore, JC; Bronen, RA; Malison, R; Scahill, L; Cohen, DJ (1999). Neuroanatomical circuitry. In J.F. Leckman, D.J. Cohen (Eds.), Tourette's syndrome--Tics, obsessions, compulsions: Developmental psychopathology and clinical care (pp.118-139). New York: John Wiley and Sons, Inc.

Petersen, B; Riddle, MA; Cohen, DJ; et al. (1993). Reduced basal ganglia volumes in Tourette's syndrome using three-dimensional reconstruction techniques from magnetic resonance images. Neurology, 43, 950-956.

Peterson, BS; Skudlarski, P; Anderson, AW; Zhang, H; Gatenby, JC; Lacadie, CM; Leckman, JF; Gore, JC (1998). A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. Archives of General Psychiatry, 55(4), 326-333.

Price, RA, Leckman, JF, Pauls, DL, Cohen, DJ & Kidd, KK. (1986). Gilles de la Tourette's syndrome: tics and central nervous system stimulants in twins and nontwins. Neurology, 36(2), 232-237.

Proctor, RW; Lu, CH; Van-Zandt, T (1992). Enhancement of the Simon effect by response precuing. Acta Psychologia, 81(1), 53-74.

Proctor, RW; Wang, H (1997). Enhancement of the Simon effect by response-location precues: Evaluation of the stimulus-identification account. Acta-Psychologica, 95(3), 279-298.

Proctor, RW; Lu, CH (1999). Processing irrelevant location information: Practice and transfer effects in choice-reaction tasks. Memory and Cognition, 27(1), 63-77.

Rauch, SL; Savage, CR (1997). Neuroimaging and neuropsychology of the striatum: Bridging basic science and clinical practice. Psychiatric Clinics of North America, 20(4), 741-768.

Rauch, SL (1999, June). Neuroimaging and OCD. Symposium conducted for the 3rd Tourette Syndrome Association International Symposium, New York, New York, USA.

Ridley, RM (1994). The psychology of perseverative and stereotyped behaviour. Progress in Neurobiology, 44, 221-231.

Robertson, MM (1989). The Gilles de la Tourette syndrome: the current status. British Journal of Psychiatry, 154, 147-169.

Robertson, MM. (1994). Annotation: Gilles de la Tourette syndrome – an update. Journal of Child Psychology and Psychiatry, 35(4), 597-611.

Robertson, MM. (2000). Tourette syndrome, associated conditions and the complexities of treatment. Brain, 123, 425-462.

Robertson, MM. (June, 2001). Diagnosing Tourette syndrome. Is it a common disorder? Symposium conducted at the 2nd TSFC International Symposium on Tourette Syndrome and Other Neurodevelopmental Disorders, Mississauga, Canada.

Robertson, M; Doran, M; Trimble, MR; Lees, AJ (1990). The treatment of Gilles de la Tourette syndrome by limbic leucotomy. Journal of Neurology, Neurosurgery and Psychiatry, 53(8), 691-694.

Sacks, O (1995). An Anthropologist on Mars: Seven Paradoxical Tales. New York: Alfred A. Knopf Inc. 81.

Sandor, P. (1995). Clinical management of Tourette's syndrome and associated disorders. Canadian Journal of Psychiatry, 40, 577-583.

Sandor, P. (1999, May). Images of TS…The new frontier. Symposium conducted at the Tourette Syndrome Foundation of Canada Conference "Towards Enlightenment", Ottawa, ON, Canada.

Sawle, GV; Lees, AJ; Hymas, NF; Brooks, DJ; et al. (1993). The metabolic effects of limbic leucotomy in Gilles de la Tourette syndrome. Journal of Neurology, Neurosurgery and Psychiatry, 56(9), 1016-1019.

Scahill, L; Tanner, C; Dure, L. (2001). The epidemiology of tics and Tourette syndrome in children and adolescents. In D.J. Cohen, C.G. Goetz, J Jankovic (Eds.), Advances In Neurology Vol. 85. Tourette Syndrome (pp. 261-271). Philadelphia: Lippincott Williams & Wilkins.

Seidman, LJ; Biederman, J; Faraone, SV; Weber, W; et al. (1997). Toward defining a neuropsychology of attention deficit-hyperactivity disorder: Performance of children and adolescents from a large clinically referred sample. Journal of Consulting and Clinical Psychology, 65(1), 150-160.

Sherman, EMS; Shepard, L; Joschko, M; Freeman, RD (1998). Sustained attention and impulsivity in children with Tourette syndrome: Comorbidity and confounds. Journal of Clinical and Experimental Neuropsychology, 20(5), 644-657.

Shucard, DW; Benedict, RH; Tekok-Kilic, A; Lichter, DG (1997). Slowed reaction time during a continuous performance test in children with Tourette's syndrome. Neuropsychology, 11(1), 147-155.

Silva, RR.; Munoz, DM.; Barickman, J.; Friedhoff, AJ. (1995). Environmental factors and related fluctuation of symptoms in children and adolescents with Tourette's disorder. Journal of Child Psychiatry, 36(2), 305-312.

Silver, AA; Shytle, DS; Sanberg, PR (1999). Clinical experience with transdermal nicotine patch in Tourette syndrome. CNS Spectrums, 4(2), 68-76.

Singer, HS; Walkup, JT (1991). Tourette syndrome and other tic disorders. Medicine, 70, 15-32.

Singer, HS; Wendlandt, J; Krieger, M; Giuliano, J (2001). Drug therapies for Tourette syndrome-related tics tested in clinical trials. Neurology, March 13 Volume.

Simon, JR. "The effects of an irrelevant directional cue on human information processing." Stimulus-response compatibility: An integrated perspective. Advances in psychology, Vol. 65 Ed. Proctor, RW; Reeve, TG; et al. 1990. 31-86.

Simon, JR; Berbaum, K (1990). Effect of conflicting cues on information processing: The "Stroop effect" vs. the "Simon effect". Acta-Psychologia, 73(2), 159-170.

Singer, HS; Wong, DF; Brown, JE; Brandt, J; Krafft, L; Shaya, E; Dannals, RT; Wagner, HN Jr (1992). Positron emission tomography evaluation of dopamine D-2 receptors in adults with Tourette syndrome. Advances in Neurology, 58, 233-239.

Singer, HS; Reiss, AL; Brown, JE; Aylward, EH; Shih, B; Chee, E; Harris, EL; Reader, MJ; Chase, GA; Bryan, RN; Denckla, MB (1993). Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. Neurology, 43, 950-956.

Spencer, T; Biederman, J; Wilens, T; Prince, J; Hatch, M; Jones, J; Harding, M; Faraone, SV; Seidman, L (1998). Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. American Journal of Psychiatry, 155(5), 693-695.

Staley, D; Wand, R; Shady, G (1997). Tourette disorder: a cross-cultural review. Compr. Psychiatry, 38, 6-16.

Stoetter, B; Braun, AR; Randolph, C; et al. (1992). Functional neuroanatomy of Tourette syndrome. Limbic-motor interactions studied with FDG PET. Advances in Neurology, 58, 213-226.

Stoffer, TH (1991). Attentional focussing and spatial stimulus-response compatibility. Psychological Research, 53(2), 127-135.

Stuss, DT (1992). Biological and psychological development of executive functions. Brain and Cognition, 20, 8-23.

Taylor, CJ; Miller, DC (1997). Neuropsychological assessment of attention in ADHD adults. Journal of Attention Disorders, 2(2), 77-88.

Tourette Syndrome Association – Southern California Chapter. Tourette syndrome medication reference. TSA-SC.

Tourette Syndrome Classification Study Group (1993). Definitions and classification of tic disorders. Archives of Neurology, 50, 1013-1016.

Towbin, KE; Peterson, BS; Cohen, DJ; Leckman, JF (1999). Differential diagnosis. In J.F. Leckman, D.J. Cohen (Eds.), Tourette's syndrome--Tics, obsessions, compulsions: Developmental psychopathology and clinical care (pp.118-139). New York: John Wiley and Sons, Inc.

Van Selst, M; Jolicoeur, P (1994). A solution to the effect of sample size on outlier elimination. Quarterly Journal of Experimental Psychology, 47a, 631-650.

Verhulst, FC, vander Ende, J; Ferdinand, RF; et al. (1997). The prevalence of DSM-III-R diagnoses in a national sample of Dutch adolescents. Archives of General Psychiatry, 54, 329-336.

Van Amerigen, M; Mancini, C; Oakman, JM. (1998). Locating trichotillomania in the obsessive-compulsive disorder spectrum. Manuscript submitted for publication.

Voderholzer, U; Müller, N; Haag, C; Riemann, D; Straube, A (1997). Periodic limb movements during sleep are a frequent finding in patients with Gilles de la Tourette's syndrome. Journal of Neurology, 244(8), 521-526.

Walkup, JT (2000, June). How Not to Let TS Confuse You or Take Over Your Family. Symposium conducted at the Tourette Syndrome Foundation of Canada "Reaching New Horizons" conference, St. John's, Nfld, Canada.

Wolf, SS; Jones, DW; Knable, MB; Gorey, JG; Lee, KS; Hyde, TM; Coppola, R; Weinberber, DR (1996). Tourette syndrome: prediction of phenotypic variation in monozygotic twins by caudate nucleus D2 receptor binding. Science, 273, 1225-1227.

World Health Organization. International statistical classification of diseases and related health problems: ICD-10. 10th revision. Geneva: World Health Organization. 1992.

Wu, L; Li, H; Kang, L (1996). 156 cases of Gilles de la Tourette's syndrome treated by acupuncture. Journal of Traditional Chinese Medicine, 16(3), 211-213.

Yazgan, MY; Peterson, B; Wexler, BE; Leckman, JF (1995). Behavioral laterality in individuals with Gilles de la Tourette's syndrome and basal ganglia alterations: a preliminary report. Biological Psychiatry, 38(6), 386-390.

Ziemann, U; Paulus, W; Rothenberger, A (1997). Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. American Journal of Psychiatry, 154(9), 1277-1284.

Ziemann, U; Rothwell, JC; Ridding, MC (1996). Interaction between intracortical inhibition and facilitation in human motor cortex. Journal of Physiology, 496, 873-881.

Zohar, AH; Apter, A; King, RA; Pauls, DL; Leckman, JF; Cohen, DJ. (1999). Epidemiological Studies. In J.F. Leckman, D.J. Cohen (Eds.), Tourette's syndrome--Tics, obsessions, compulsions: Developmental psychopathology and clinical care (pp.177-193). New York: John Wiley and Sons, Inc.