PROCESSING OF TACTILE STIMULI IN CHILDREN WITH TOURETTE SYNDROME AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: AN ERP INVESTIGATION

by

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Abstract

Purpose: To investigate and characterize sensory sensitivity in Tourette syndrome (TS) through an evaluation of behaviour, perception and processing of tactile stimuli in children with TS and co-morbid Attention Deficit Hyperactive Disorder (ADHD) compared to typically developing controls (TDC).

Methods: Somatosensory evoked P3 potentials were recorded in TS+ADHD and in TDC children aged 6-12 and compared at midline electrodes. Reported sensory sensitivity was measured using the Sensory Profile, while Semmes-Weinstein filaments were used to determine tactile threshold in the same area stimulated during P3 testing.

Results: 13 TS+ADHD and 12 TDC were studied. TS+ADHD children reported significantly higher sensory sensitivity ($p=.001$) and demonstrated a significantly lower tactile threshold ($p=.027$) than TDC. Furthermore, the amplitude of electrophysiological responses to repetitive tactile stimuli was significantly larger in TS+ADHD ($p=.0009$).

Conclusion: TS+ADHD children are significantly more sensitive to tactile stimulation than controls. ERP differences suggest that central processing alterations could mediate sensory hypersensitivity.

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
BG	Basal Ganglia
CNS	Central Nervous System
CNV	Contingent Negative Variation
CSTC	Cortico-Striato-Thalamo-Cortical
DLPFC	Dorsal Lateral Prefrontal Cortex
fMRI	functional Magnetic Resonance Imaging
FSD	Finger Stimulating Device
GPi	Globus Pallidus Interna
GUI	Graphical User Interface
IBI	Inter-Block Interval
IQ	Intelligence Quotient
ISI	Inter-Stimulus Interval
IT	Inferior Temporal Lobe
OCD	Obsessive Compulsive Disorder
PNS	Peripheral Nervous System
PPI	Prepulse Inhibition
PUTS	Premonitory Urge for Tics Scale
SEP	Sensory Evoked Potential
SI	Primary Somatosensory Cortex
SID	Sensory Integration Disorder
SMD	Sensory Modulation Disorder
SNpc	Substantia Nigra Pars Compact
SP	Sensory Profile

SPD	Sensory Processing Disorder
STN	Subthalamic Nucleus
TDC	Typically- Developing Controls
TS	Tourette Syndrome
WASI	Wechsler Abbreviated Scale of Intelligence
YGTSS	Yale Global Tic Severity Scale

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Chapter 1
Background

1.1 Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by the persistent presence of unwanted movements and vocalizations called tics (American Psychiatry Association, 2000). In addition to tics, TS patients frequently report sensory disturbances that may be equally or more disruptive to their daily functioning than tics. These sensory disturbances include uncomfortable internally generated bodily sensations, as well as heightened sensitivity to externally generated sensation (Cohen & Leckman, 1992; Kurlan, Lichter, & Hewitt, 1989; Kwak, Dat Vuong, & Jankovic, 2003; Leckman, Walker, & Cohen, 1993; Miguel et al., 2000). Despite these reports, heightened sensory sensitivity is often not addressed in standard clinical assessment and has received little attention in investigational research, leading to a limited awareness of these phenomena.

The present research project is concerned with tactile hypersensitivity in children diagnosed with TS and Attention Deficit Hyperactivity Disorder (ADHD). Given the low prevalence of TS sufferers who do not experience co-morbid conditions (10%), this study has focused on the most numerous group children with TS+ADHD (approximately 60 % of the population) while excluding those who have co-morbid obsessive compulsive disorder [(OCD) 27%] (Freeman et al., 2000; Ghanizadeh & Mosallaei, 2009). In addition, to being the most frequent co-morbid condition of TS, children with ADHD have also reported a heightened sensitivity to sensation (Mangeot et al., 2001; Parush, Sohmer, Steinberg, & Kaitz, 2007; Parush, Sohmer, Steinberg, & Kaitz, 1997).

Sensory hypersensitivity as well as tics are proposed to have related pathophysiology, where both symptoms may result from overstimulation of the cortico-striatal-thalamo-cortical (CSTC) circuit, through an excess of unfiltered sensory, motor, and affect input from the thalamus (Mink, 2001a; Mink, 2001b). The characterization and study of sensory phenomena symptoms in TS has the potential to not only inform clinical practice, but to also enhance understanding of how the CSTC circuit functions. This study aims to validate and characterize the frequent clinical

reports of a sensory disturbance in TS and to use physiological and neurophysiological measures to explore mechanisms that may be involved in this perceived sensitivity.

1.2 Tourette Syndrome

1.2.1 Definition of TS

Tourette syndrome (TS) is a chronic neurodevelopmental disorder with childhood onset, characterized by difficulty inhibiting repetitive unwanted movements and vocalizations called tics (Leckman et al., 1997). The disorder is named after a student of Charcot, George Gilles de la Tourette, who described a series of patients with this disorder in 1885 (Gilles de la Tourette, 1885). However Gilles de la Tourette was not the first to describe this disorder. In 1825, French doctor Jean Marc Itard described the Marquise de Dampierre (a refined noble woman with coprolalia), and physician Armand Trousseau, published a description of the disorder's most salient characteristics 12 years before Gilles de la Tourette (Itard, 1825; Rickards, Woolf, & Cavanna, 2010).

Vocal or motor tics may be categorized as simple or complex. Simple tics typically include only one muscle group and are brief or abrupt. Common examples of simple tics include blinking, head-jerking, shoulder shrugging, throat-clearing, sniffing and coughing. Complex tics are coordinated, sequential movements that look like every day movements, but are oddly timed or intense. These include facial gestures, grooming behaviours, touching, smelling objects, using obscene or socially inappropriate words (coprolalia), and repeating one's words (palilalia) or someone else's words or phrases (echolalia) (American Psychiatric Association, 1994; Jankovic & Kurlan, 2011).

Diagnostic criteria for TS according to the fourth edition (TR) of the *Diagnostic and Statistical Manual of Mental Disorders* (1994) include:

1) Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. (A tic is a sudden, rapid, recurrent, non-rhythmic, stereotyped motor movement or vocalization.) These may occur at the same time or at varying periods throughout the illness.

2) The tics occur many times a day (usually in bouts) 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.

3) The disturbance causes marked distress or significant impairment in social, occupational, or other important areas of functioning.

4) The onset is before age 18 years

5) The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or post-viral encephalitis).

TS assessment and diagnosis are typically made in a clinic setting using interviews, thorough personal and family histories, and performing physical and neurological examinations (Robertson, 2011) Though classified as involuntary, many patients are able to suppress tics for minutes or longer. These periods of suppression are sometimes followed by bouts of tics with increased intensity and frequency. During the assessment of tics, examiners need to use peripheral vision, e.g. while taking notes, as patients often suppress tics until they feel that they are not being directly observed (Abi-Jaoude et al., 2010). Tics are also influenced by suggestion e.g. mentioning a particular tic may result in the patient exhibiting the tic shortly afterward (Jankovic & Kurlan, 2011; Robertson, 2011).

Tics can cause a varying degree of impairment and disruption. The impairment caused by tics is often determined by factors other than only the number, frequency, intensity and complexity of tics. These additional factors include the impact of tics on self-esteem, family life, social functioning and physical impairment. A number of scales take all these factors into consideration while determining tic severity, and the most widely used scale is the Yale Global Tic Severity Scale (YGTSS)(Leckman et al., 1989).

The YGTSS begins with a semi-structured interview designed elicit the character and anatomical distribution of motor and phonic tics. Severity is then rated using a 6-point ordinal scale for the following categories: number, frequency, intensity, complexity, interference and impairment. Each point on the scale is marked with descriptors as well as examples (Leckman et al., 1989).

The scale is commonly used in children and adolescents and it has proven validity and reliability (Storch et al., 2007).

1.2.2 Life-time course of tics

By definition the age at onset for this disorder ranges from birth to 18 years of age, with an observed mean age of onset of approximately 6.4 years (Freeman et al., 2000). In most cases the emergence of TS is gradual, typically beginning with a single simple tic such as eye-blinking, or sniffing between the ages of 3 and 8 years of age (American Psychiatric Association, 1994; Leckman, 2003). The life history of tics varies. Over the period of weeks and months tics may appear and disappear, the appearances of new tics sometimes replacing extinguished tics of the past. In a minority of cases elaborate or complex movements and sounds develop, including grooming behaviours, lewd gestures, echolalia, coprolalia and palillia (Leckman, Bloch, Scahill, & King, 2006) . Longitudinal studies found that on average, the highest YTGSS scores occurred between age 10 and 13 and in majority of cases steadily decreased into adulthood (Bloch, Peterson, Scahill, et al, 2006; Leckman et al., 1998). There are reports of a substantial decrease or complete remission of tics by late adolescence in one-half to two-thirds of children with TS (Leckman et al., 1998; Peterson, Pine, Cohen, & Brook, 2001) . This may be an explanation for the disparity in prevalence rates between pediatric and adult populations, where a 10-fold lower prevalence was found among adults versus children/adolescents. (Robertson, Verrill, Mercer, James, & Pauls, 1994) .

The reported life-time prevalence of TS is 1-3% in the Western population, but an average of 1% worldwide (Baron-Cohen, Scahill, Izaguirre, Hornsey, & Robertson, 1999; Freeman et al., 2000; Robertson, 2006) . Proposed explanations for the differences in Western versus world-wide prevalence include societal, racial and cultural issues such as having other medical priorities, having less propensity to seek healthcare, lack of awareness of GTS, ethnic and epigenetic factors, and genetic/allelic differences in different races. In addition, the lack of standardized diagnostic methods for TS diagnosis and the confounding effects of co-morbid disorders that may mask TS have also been suggested (Robertson, 2008).

1.2.3 Co-morbidity, Gender, and TS

Tics rarely occur in isolation. In clinical settings only about 10% of patients can be categorized as "TS-only". TS patients struggle with coexisting conditions such as attention deficit hyperactivity disorder [ADHD (60-70%)], obsessive-compulsive disorder [OCD (30%)] (Freeman et al., 2000; Ghanizadeh & Mosallaei, 2009), learning difficulties and other behavioural problems. These coexisting conditions are often a greater source of social and occupational impairment than the tics themselves (Conelea et al., 2011; Eddy et al., 2011; Leckman, Bloch, Scahill, & King, 2006) and are frequently the primary reason for seeking treatment. It must be noted that only a minority of TS-only patients present in clinical settings or report a diminished quality of life. When functional impairment due to tics and non- tic causes were evaluated in youth, about 50% of caregiver reported tic related impairment while 80% reported impairment due to non-tic causes (Storch et al., 2007).

TS is more prevalent in males than in females with male to female ratio of 4:1(Freeman et al., 2000). Sex differences have been also reported regarding co-morbidities and disease characteristics. For example, co-morbid OCD is far more prevalent in females with TS, while ADHD is more prevalent in males. In families where TS is present, unaffected females have an increased risk of OCD. It has also been suggested that tic remission rates are greater in males than females (Burd et al., 2001).

ADHD is a neurodevelopmental disorder pwith high prevalence (3-7%) among school-age children (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). It is generally characterized by persistent symptoms of inattention, disinhibition, and/ or hyperactivity that lead to poor behavior and impairs educational, and social functioning. ADHD is also characterized by significant gender differences e.g. ADHD boys outnumber girls 3-to-1 in community samples and 9-to-1 in clinical samples. Boys often present with ADHD combined-type, whereas girls are predominantly inattentive. A co-morbid diagnosis of ADHD has been shown to account for a substantial amount of impairment in social, cognitive, and work/school functioning in individuals with TS. Notably, the onset of ADHD tends to occur prior to TS and persist even after tics completely disappear or go into remission (Spencer et al., 2001). Greimal et al (2011) investigated the effect of a tic disorder and ADHD on attention and found that a diagnosis of a tic

disorder had no significant effect on task performance in any of the computerized attention tasks. Furthermore, no evidence has been found to date to indicate that co-morbid ADHD is associated with increased severity or frequency of tics.

1.2.4 Etiology

The etiology of TS is not fully understood. Several lines of evidence are outlined below, including Structural and function imaging, biochemical studies and genetic studies. In general the results support the hypothesis that TS is an inherited, neurodevelopmental disorder involving multiple susceptibility genes, subtle structural and functional CNS abnormalities and disordered neurotransmission.(Abi-Jaoude et al., 2010). The consensus amongst researchers is that TS is largely a disorder of impairred inhibition in the basal ganglia (BG) and its cortical and thalamic connections.

The CSTC pathway contains a several neurotransmitters, however dopamine has been the main focus because of pharmacological evidence indicates that there is an excess of dopaminergic activity in nigrostriatal pathways in patients with TS (Leckman, Bloch, Smith, Larabi, & Hampson, 2010). Excess dopaminergic stimulation has been shown to cause unwanted or excessive movements while dopamine antagonists reduce tic frequency and intensity (Singer, 1994). The clinical experience with neuroleptics in TS suggests that dopaminergic function in TS is abnormal, however, the site of abnormal dopamine transmission remains unknown.

The basal ganglia are comprised of several interconnected nuclei that together initiate and control movement. These nuclei include the striatum (which is further divided into the caudate and putamen), subthalamic nucleus (STN), globus pallidus (interna and externa), and substantia nigra. The striatum and STN receive excitatory input from the cortex, while the globus pallidus interna (GPi) and the substantia nigra pars reticulata (SNpr) are the primary nuclei for BG output. These exiting signals cause increased inhibition in thalamic, cortical and brainstem regions, leading to hypothesis that TS is a disorder of inhibition (Mink, 2001a). Dopamine containing neurons modulate transmission of signals from the cortex to the striatum via inhibitory SNpc pathways. Many other neurotransmitters are involved in the BG such as glutamate in projections from the cortex to the striatum. It appears that the voluntary movements

are modulated in BG by sensory, cognitive, and emotion inputs. (Stern, Blair, & Peterson, 2008).

Several areas of the basal ganglia have been implicated in the pathology of TS. Imaging studies have revealed structural (Peterson et al., 2003; Worbe et al., 2010) and functional abnormalities (Church et al., 2009; Jackson et al., 2011; Plessen et al., 2006; Wang et al., 2011) in the BG, while pharmaceutical evidence has also implicated this structure. Singer et al.(1993) were the first to demonstrate changes in the BG, namely right-sided lateralized dominance in TS. They were also able to use volumetric and dominance changes to differentiate between pure TS subjects and those with co-morbid ADHD. Volumetric differences were further supported by Peterson et al (2003) who conducted a large scale study of children and adults using MRI and found caudate volumes were significantly smaller in children and adults with TS.

Changes in cortical volume have also been found using MRI. Peterson et al (2001) compared 155 TS subjects with 131 controls in a cross sectional study of cortical volumes. They found that children with TS had significantly larger dorsal prefrontal cortex (DLPFC) volumes than controls matched for age and sex, but these volumes were smaller in TS adults than adult controls. These adults had significant and persistent tics in adulthood suggesting that adaptive neurodevelopmental changes did not occur, resulting in smaller DLPFC volumes. These results are consistent with the view that TS is caused by abnormal neural development. Structural studies have also found reductions in cortical thickness in motor, premotor, prefrontal, parietal, sensorimotor and lateral orbito-frontal areas in both adults and children; brain areas that collectively participate in the planning and execution of typical behaviour. These reductions were also correlated with YGTSS severity, though only one of the two studies found a positive correlation between severity and thinning (Sowell et al., 2008; Worbe et al., 2010).

In addition to the changes found in the basal ganglia and cortical areas, thalamic abnormality has also been reported in TS. An MRI investigation of thalamic volume in treatment-naive boys aged 7-14 revealed that TS subjects had a significantly larger left thalamus than controls, with no observed group difference in the right thalamic volume (Lee et al., 2006). The presence of thalamic abnormality in TS is further supported by the finding of larger thalamic volumes bilaterally in TS adults compared to controls using structural MRI (Miller et al., 2010). Taken

together, structural abnormalities in the cortex, basal ganglia, and thalamus support the proposed involvement of CSTC pathways in TS pathology.

Functional abnormalities have also been observed in TS, consistent with proposed disturbances in the CSTC loop. Functional MRI has been used to study areas involved in tic suppression and expression. Investigators found that signals in the BG, thalamus and cortical regions changed during these voluntary processes. Tic suppression increased activity in the frontal cortex and right caudate while decreasing activity in subcortical areas such as the globus pallidus, putamen and thalamus (Peterson et al., 1998). A large amount of data points towards a role for CSTC, however we are only beginning to understand how the function of the CSTC is disturbed in TS. Worb et al. (2012) used fMRI to investigate the 91 proposed areas of interest in the CSTC circuit in 59 adult TS patients and 27 age matched controls. Using global functional integration and graph theory, they found more interactions among anatomical regions and global functional disorganization in the CSTC network of TS patients compared to controls. These networks had a shorter path length, and a greater number of functional connections that were stronger than controls. Functional abnormalities in the premotor, sensori-motor, parietal and cingulate cortices and medial thalamus areas of the cortico-basal ganglia network correlated with tic severity, while tic complexity was correlated primarily with the insula and putamen. These results support the view that in TS subjects the structural abnormalities in the CSTC loop result in abnormal connectivity leading to functional impairments.

1.2.5 Treatment

Historically TS has been treated with medications and more recently also cognitive behavioural intervention. Tics are often managed pharmacologically using clonidine or neuroleptics. No medication is able to permanently extinguish tics, so the goal of pharmacological intervention has been to better manage tics not extinguish them (Bronfeld & Bar-Gad, 2012). Neuroleptics have been successful in decreasing the frequency and severity of tics and reducing disturbances in emotional control, however adverse effects have limited their use, especially in pediatric populations. Atypical antipsychotics that block both serotonin and dopamine receptors have been recommended for use in this population because of a lower risk of extrapyramidal effects. (Parraga, Harris, Parraga, Balen, & Cruz, 2010). Alpha-adrenergic medicines such as clonidine

have also showed positive responses for tic reduction in TS (Singer, 2010). Many patients with a diagnosis of TS only do not require or seek out pharmaceutical intervention. Often the largest challenge in treating TS is the management of co-morbid disorders such as ADHD and OCD which at times involves medications that may exacerbate tics (Debes, Hjalgrim, & Skov, 2009) .

Aside from pharmacological intervention, behavioural intervention has also been employed in TS. Habit reversal is the most extensively documented behavioural intervention used to date (Verdellen, van de Griendt, Hartmann, Murphy, & ESSTS Guidelines Group, 2011) . This treatment helps the patient to become more aware of the tics and especially the premonitory urge while offering training to perform a competing response to avoid or inhibit the tic. This competing response is used to help extinguish the urge to perform a tic (Azrin & Nunn, 1973; Azrin & Peterson, 1988). Several randomized and controlled trials have demonstrated its efficacy in decreasing tic severity and frequency (Piacentini et al., 2010). Cognitive behavioural therapy has also shown success in reducing tics. This therapy challenges patients to evaluate and restructure the way they think about environments or "high-risk situations" where actions such as performing tics may be more stigmatized or stressful situations may occur (O'Connor et al., 2009; Piacentini et al., 2010; Verdellen, van de Griendt, Hartmann, Murphy, & ESSTS Guidelines Group, 2011). Finally, exposure and response prevention has also been used to decrease tics. This treatment views tics as a conditioned response to an unpleasant sensory experiences associated with tics such as the urge to tic. Over time the performance of tics become increasingly associated with the urge sensation. ER aims to disrupt this association by confronting the patient with prolonged exposure to the sensation while requesting resistance or inhibition of the tic. It is thought that with repeated exposure the patient will learn to lessen the urge and decrease tic behaviours (Franklin, Walther, & Woods, 2010; Piacentini et al., 2010; Verdellen et al., 2008).

1.3 Sensory Phenomena and TS

1.3.1 Sensory Phenomena Defined

The presence of tics in TS is often accompanied by a variety of sensory phenomena including sensory tics, premonitory urges and sensory hypersensitivity. Literature on these phenomena is scarce, and the effort to unify diagnosis and classification has only been attempted a few years prior to the genesis of this study. A review by Prado et al.(2008) compiled literature in order to best define these subjective experiences. A sensory tic can be described as a generalized somatic sensation in the bones, muscle joints or skin that lead to voluntary movement for their relief (Bliss 1980;Kurlan et al. 1989;Kwak et al. 2003). A premonitory urge differs from a sensory tic in that the somatic sensation is less generalized, and there is an urge or an uncontrollable impulse that drives a repetitive behaviour or tic (Kane 1994;Leckman et al. 1993). Sensory hypersensitivity is a less specific symptom, where the individual experiences heightened sensitivity to stimuli in a variety of sensory modalities e.g. bright lights, loud noises, and discomfort due to material, fit and tags of clothing (Cohen & Leckman, 1992; Kurlan, Lichter, & Hewitt, 1989) . The sensitivity may be accompanied by a need to have things feel, sound, or look "just right". These particular traits of hypersensitivity in particular are more prevalent amongst TS patients co-morbid with OCD (Miguel et al. 2000b).

Two validated scales have been developed to date for the measurement of sensory phenomena (Sutherland Owens, Miguel, & Swerdlow, 2011), however these scales do not address issues of generalized sensory sensitivity. The Premonitory Urge for Tics Scale (PUTS) is a self-report of subjective experiences preceding a tic (Woods, Piacentini, Himle, & Chang, 2005) . These sensory related behaviours are rated with regard to their presence and frequency. The University of Sao Paulo Sensory Phenomena Scale (USP-SPS) explores the frequency, severity and timing of sensory related behaviours including compulsions and other rituals (Rosario et al., 2009). These validated tools are vital for the clinical and scientific investigation of sensory phenomena in that they provide a behavioural correlate that can be used in neuroimaging and neurophysiological studies.

Despite remaining unrecognized in the DSM-IV, sensory phenomena are common in the clinical spectrum TS. Cohen and Leckman (1992) recruited 28 patients from the Tourette Syndrome

Association as well as neurologist patient lists, and found that twenty-two (82%) of the 28 subjects experienced premonitory urges prior to motor and vocal tics. Of these 22, 13 (57%) found the premonitory urges more bothersome than the tics themselves, and 12 (55%) thought the premonitory urges enhanced their ability to suppress tics. Furthermore, of the 20 patients interviewed about site sensitization, 14 (70%) had heightened sensitivity to tactile, auditory, and/or visual stimuli.

The prevalence as indicated in the Cohen and Leckman study, suggests that these symptoms are common and disturbing enough to investigate. Better recognition and study of the presence of these subjective experiences may increase the patients' ability to suppress tic symptoms (Bullen & Hemsley, 1983) and lead to the development of better pharmacologic or behavioural intervention that address sensory phenomena (Leckman and Peterson 1993). It has also been suggested that the presence of subjective experiences may be a predictive factor of treatment response (Miguel et al., 2000).

In a more recent study, Belluscio et al. (2011) found that 80% of adult TS patients reported a heightened sensitivity to sensation across the 5 sensory modalities. Sixty-five percent reported sensitivity to touch. When specific scenarios were posed, TS patients consistently reported sensitivity to faint, repetitive non-salient stimuli, across modalities. In fact several subjects seemed to prefer more intense tactile stimulations rather than those that are faint. When olfactory and touch sensation was evaluated for threshold and intensity, no significant difference in detection was found between TS participants and healthy controls, however TS patients did characterize stimuli as faint and used lower ratings of intensity to describe stimuli. What this study seems to suggest is that TS patients do not have an enhanced ability to detect stimuli, however an error must be occurring in central processing leading to heightened sensory experiences and discomfort that appear to be inversely correlated with intensity.

1.3.2 Sensory Processing Disorder

It is unclear whether or not the pathology of sensory sensitivity in TS is similar to Sensory Processing Disorder (SPD), but there is a great deal of similarity in their clinical presentation. What is now referred to clinically as SPD was formally introduced as Sensory Integration Theory by occupational therapist and psychologist Dr. A. Jean Ayres (Ayres, 1972a; Ayres, 1974; Ayres, Robbins, & McAtee, 2005; Ayres, 1972b) . Ayres believed that child development relies on the neurological process where sensations experienced in the everyday environment are brought together and organized in order to effectively organize behavior in that environment. Individuals – particularly children –with a decreased ability to process sensation also may have difficulty producing appropriate actions, which, in turn, may interfere with learning and behavior. Ayres theory hypothesized that this atypical behavior was a result of a neurological impairment in detecting, modulating, discriminating, and responding to sensory information. This dysfunction was named Sensory Integration Disorder (SID). Preliminary population studies suggest that 1 in 20 children have an SPD with between 5 and 16% having negative responses to sensation that interfere with daily behaviours (Ahn, Miller, Milberger, & McIntosh, 2004; Ben-Sasson, Carter, & Briggs-Gowan, 2009).

Out of the complex nosology of SID emerged Sensory Modulation Disorder (SMD), as a subtype describing hyposensitivity or hypersensitivity to sensory stimuli (Miller, Anzalone, Lane, Cermak, & Osten, 2007). SMD is further subdivided into sensory-over-responsive, sensory under-responsive and sensory seeking/craving behaviours. Sensory Over Responsive (SOR) individuals react with greater emotion, speed and intensity to stimuli in what might appear as a "fight or flight response (Ayres, 1972a; Miller, Anzalone, Lane, Cermak, & Osten, 2007). Much like TS patients, the most commonly reported symptoms of SOR are sensitivities to touch and sound (Ben-Sasson, Carter, & Briggs-Gowan, 2009; Goldsmith, Van Hulle, Arneson, Schreiber, & Gernsbacher, 2006).

Studies of sensory sensitivity in neurodevelopmental populations do not indicate a peripheral nervous system (PNS) deficit in sensory processing dysfunction (Belluscio, Jin, Watters, Lee, & Hallett, 2011; Parush, Sohmer, Steinberg, & Kaitz, 1997). It is believed that the deficit occurs in higher level processing, within cognitive, affective, attention, memory, and coordination

pathways. According to Ayres, SPD assumes that the immaturity characterizing the brain at birth persists in individuals who experience sensory processing dysfunction. In this theory modulation is defined as the ability of the CNS to regulate its own activity through facilitation and inhibition at the cellular level. Therefore dysfunction is due to immaturity or malfunction in processing discrete sensory stimuli at the central processing level. This hypothesis implies a deficit in inhibiting sensory information from causing excessive CNS arousal – a hypothesis that shares many traits with TS etiology (Ayres, 1972b; Stern, Blair, & Peterson, 2008). If the premise of CNS dysfunction is valid, individuals with SPD should demonstrate brain activity that is different from typically developing individuals. Differences could range from deficits in inhibiting irrelevant sensory information to impaired ability to make appropriate emotional responses to stimuli. Appropriate stimulation through specialized play, for example, is thought to provide the stimulation that will address these brain areas and enable them to mature and function as an integrated whole in the processing of stimulation from the environment. Unfortunately the evidence for the effectiveness of sensory integration therapy is weak at best (Hoehn & Baumeister, 1994; May-Benson & Koomar, 2010;Miller, Schoen, James, & Schaaf, 2007;Miller, Coll, & Schoen, 2007; Polatajko & Cantin, 2010).

SID is truly heterogeneous in its presentation and as a result contains 6 subtypes that Ayres derived from multiple factor analysis studies of the perceptual-motor performance of children with learning disabilities. The heterogeneous and non-specific nature of SID is one of its major weaknesses (Bundy & Murray, 2002). Many neurodevelopmental and behavioural disorders such as autism, TS, ADHD, and OCD report abnormal sensory symptoms. Heilbroner (2005) suggests these sensory processing differences do not represent a distinct disorder but are markers of neurodevelopmental immaturity or symptoms of anxiety. Further, the study of this disorder has been muddled with studies of low sample size, and poor research design, in populations with co-morbid disorders that would seriously alter the functionality of the brain. Additionally, the terms used in describing SID are often confused and interchanged with other terms. A prime example is the term “sensory integration” where Ayres behaviourally focused definition differs from the clinical and neuroscience understanding that refers to the converging of information in the brain from sensory domains (Miller, Nielsen, Schoen, & Brett-Green, 2009). Without a unified clinical definition of SID/SPD and its subtypes it is difficult to distinguish which symptom characteristics and underlying assumptions are being tested (Mulligan, 2002).

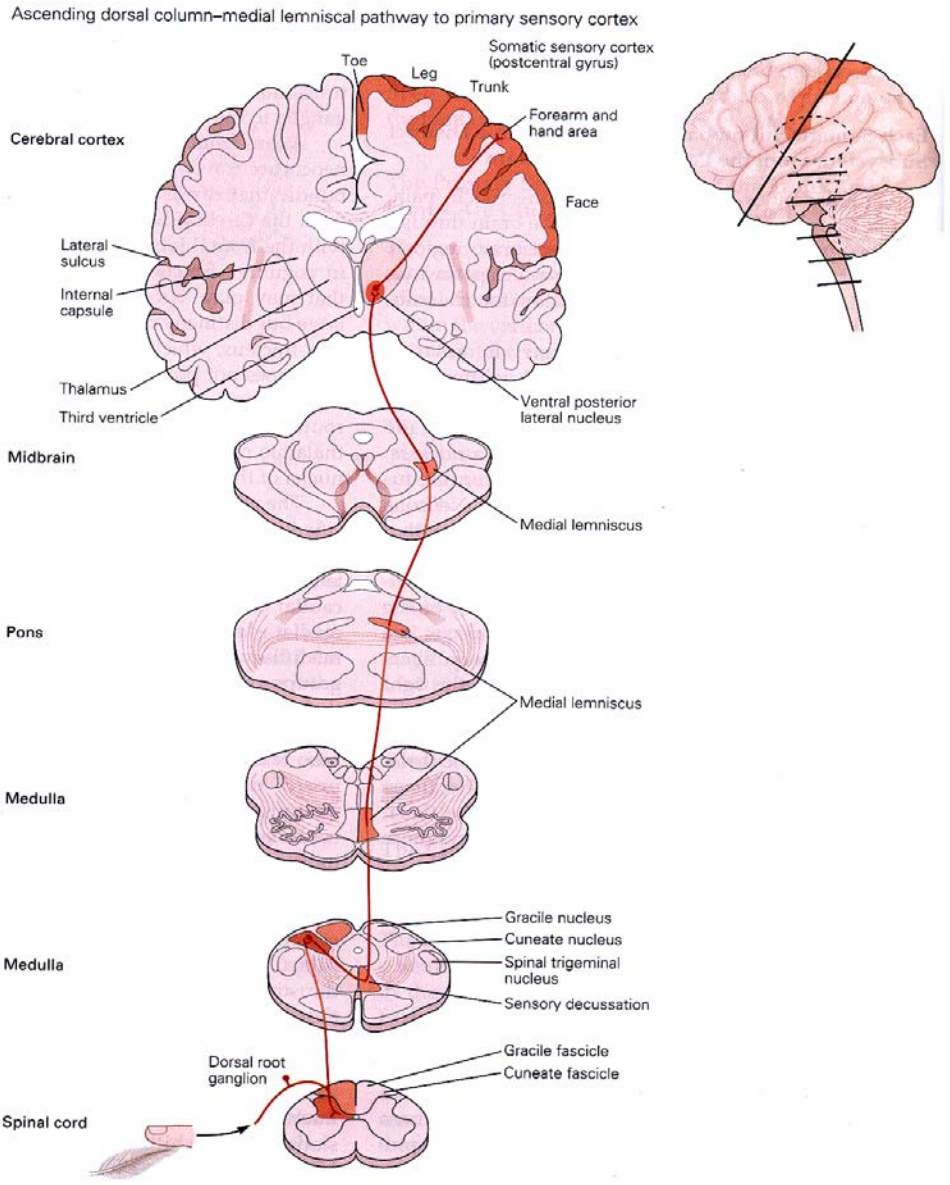
Although the diagnosis of SPD has a relatively long history, many clinicians and researchers have found that there are few, if any objective or validated methods for identifying SID (Miller, Nielsen, Schoen, & Brett-Green, 2009; Smith, Mruzek, & Mozingo, 2005). Nonetheless, the symptoms described under the umbrella of SID do exist and continue to cause a great deal of distress in a number of neurodevelopmental populations (Cascio, 2010). In 1994, Dunn compiled a list of sensory behaviours from histories of sensory dysfunction in the literature. After validating the tool and performing factor analysis the Sensory Profile was created (Dunn & Brown, 1997). The Sensory Profile is a measure of an individual's responses to sensory events in daily life. When used to study children, a caregiver completes the Sensory Profile by assessing the frequency of the child's responses to certain sensory stimuli, modulation, and behavioral/emotional events described in the 125 items. This tool is commonly used by occupational therapists for clinical purposes and in sensory research to describe and quantify the sensory experience in control children as well as those with developmental disorders (Brown, Tollefson, Dunn, Cromwell, & Filion, 2001; Cheung & Siu, 2009; Dunn & Brown, 1997; Ermer & Dunn, 1998; Kientz & Dunn, 1997).

Theories proposed by Ayres continue to be circulated but the etiology of sensory hypersensitivity is still unclear. Though sensory disturbances occur in the general population, a large proportion of the affected individuals appear to have developmental disorders where dopaminergic (DA) dysfunction is implied. This is particularly relevant to the TS+ADHD population where DA dysfunction is proposed in its etiology of inhibition. Studies of children with TS and ADHD have documented widespread reductions in cortical thickness as well as irregularity in sensory-related cortices (Church et al., 2009; Sowell et al., 2008; Tian et al., 2008).

1.3.3 Touch Processing

Understanding how external stimuli generate signals in the peripheral and central nervous systems is key to understanding a possible locus for abnormal sensory experiences. Regardless of the type of sensory receptor, information about the stimulus is transduced via electrical signals that are transmitted to the spinal cord, into various nuclei. The axons are bundled according to their information type (i.e. visual or somatosensory) in order to keep the lines of information separate before reaching relay sites for integrative processing. Tactile stimulation is transmitted

through the dorsal column of the spinal cord via axons that carry somatosensory information to the brain stem. Axons in the touch pathway cluster together in the dorsal root ganglia forming a well-maintained representation or map of the body's surface (somatotopy). It is from this information that the perception of touch begins. Primary afferent fibres carrying somatosensory information ascend to the medulla, then to the medial lemniscus and terminate in the ventral posterior nucleus (VPN) of the thalamus [(Kandel, Schwartz, & Jessell, 2000; Patestas & Gartner, 2009) **Figure 1-1**].



This figure has been reprinted from Principles of Neuroscience by Kandel,E.R et al (4th ed.) 2000 with the permission of McGraw-Hill Companies.

Figure 1-1: The ascending medial lemniscal pathway for somatosensory information. Somatosensory information enters the nervous system through the dorsal root ganglion cells in the spinal cord. This flow of information ultimately leads to processing in the primary somatosensory cortex. The fibres ascend from the peripheral nervous system and relay in an orderly fashion so that information from the entire body surface is maintained on a neural map at each stage of processing**.**

The thalamus is an oval-shaped structure located above the brainstem and under the cerebral cortex. Compromised of 52 nuclei, its major role is to be an essential relay or link between the sensory receptors and the cerebral cortex areas involved in sensory perception and movement. These nuclei are largely the first place for the integration of information from various sensory domains (Tyll, Budinger, & Noesselt, 2011). As a gatekeeper, the thalamus facilitates or prevents the transmission of sensory information depending on behavioural states such as attention and arousal. While some axons project to the primary somatosensory cortex (SI), others participate in motor transmission via the cerebellum, basal ganglia, and frontal lobe (Sherman & Guillery, 2001). Axons projecting to and from the frontal lobe are thought to play a role in memory and attention and project to several distinct areas of the cortex. The thalamus also contains a feedback loop in its outer shell, the reticular nucleus. These fibres do not project to the neocortex, but receive inputs from fibers as they exit the thalamus. In contrast to the majority of thalamic nuclei, the reticular nucleus' primary transmitter is inhibitory, and works to modulate the activity of the other thalamic nuclei (Kandel, Schwartz, & Jessell, 2000).

The somatotopy is maintained in SI where the amount of cerebral cortex representing each body part is proportional to the extent of its innervation. The fingers and the face represent much of the space on the post -central gyrus and as a result these areas are highly discriminative to touch. The post- central gyrus is also the anatomical location where sensory integration occurs at the conscious level (Patestas & Gartner, 2009) . SI is located in the anterior parietal cortex, and it is in Brodmann areas 3, 3a, and 3b that the basic processing of touch occurs. More complex higher order processing takes place in area 1 and in area 2 tactile and limbic information are combined for tactile recognition and memory. The unimodal processing of somatosensory processing becomes multimodal in higher areas where the production of a unified precept and the memory of this precept are created. These higher areas are heavily interconnected with the hippocampus (Kandel, Schwartz, & Jessell, 2000). Prior to this point in the pathway it is believed that afferents travel in parallel but exchange very little information if any at all (S. M. Sherman & Guillery, 2001).

The process of touch occurs in a pathway distinct from pain. Although subjects may incur feelings of discomfort during experiences of hypersensitivity, studies have shown that in

typically developing controls, no correlates can be found between painful and non-painful threshold for touch (Ferretti et al., 2004; Hummel, Springborn, Croy, Kaiser, & Lotsch, 2011).

1.3.4 Habituation

Habituation and sensitization are key processes related to dysfunction in sensory processing. Habituation is a neural marker of inhibition. It occurs in the CNS when neurons identify the stimulus as familiar and decreases transmission or firing rates since continuous evaluation of the stimulus is not required to provide a continued response (Kandel, Schwartz, & Jessell, 2000). In this way habituation represents learning at the neural level, and allows familiar sensations to be filtered so that mental resources can be reserved for salient stimuli and task-relevant sensory input. Whereas habituation decreases mental resources dedicated to perceiving a stimulus, sensitization enhances the attention and mental importance of the stimulus. Sensitization occurs when the response to a stimulus becomes heightened with repeated stimulation and sustained over time. Neuroanatomically, sensitization may increase or sustain the level of neuronal firing, and may even be associated with anatomical changes such as an increase in neuronal connectivity. These processes – particularly habituation – are fundamental in the process of gating sensory information (Braff, Geyer, & Swerdlow, 2001).

The processing of repeated stimulation has been tested by a few investigators interested in electrodermal stimulation. McIntosh et al. (1999) tested children with diagnosed SPD against typically developing children and found that SPD children showed larger and more frequent electrodermal responses and habituated more slowly over repeated trials. In a similar study children with ADHD displayed atypically large reactions to initial presentations of a sensory stimulus, but habituated at rates comparable to controls following subsequent presentations. Electrodermal responses in both groups correlated with sensory profile scores, which were significantly more abnormal in ADHD group (Mangeot et al., 2001). When synthesized, the results of these studies suggest that habituation rates of physiological responses may be used as a method to differentiate different groups with sensory processing deficits (Miller, Nielsen, Schoen, & Brett-Green, 2009).

Similarly, habituation has been tested in fibromyalgia patients using habituation in Event-Related Potentials (ERP). Fibromyalgia patients suffer from long-term, body-wide pain and tenderness in

the joints, muscles, and soft tissues. When tested with auditory and somatosensory stimulation, investigators found that fibromyalgia patients habituated to auditory stimulations, but failed to habituate at a rate comparable to controls during somatosensory stimulation. These results demonstrated a specific somatosensory deficit in information processing, which may be characterized by a lack of inhibitory response to repetitive non-painful stimulation. Combined with the previous studies, these data provide evidence that habituation is an important variable of study in psychophysiological abnormalities in sensory processing.

1.3.5 Etiology of Sensory Phenomena

It has been suggested that the inability to inhibit tics as well as sensory phenomena in TS has been best explained by attributing these symptoms to general problems with inhibitory control in motor function as well as cognitive and emotional function (Leckman, Bloch, Scahill, & King, 2006) . These inhibitory problems are believed to involve errors within basal ganglia circuitry, mediated via the cortico-striato-thalamo-cortical (CSTC) pathway. This pathway carries information from the cortex to the basal ganglia through the thalamus and then returns to the cortex (Bradshaw, 2001; Leckman, 2002). It is proposed that at least three loops (skeletomotor, dorsolateral prefrontal, and orbitofrontal loops) are involved in TS (Stern, Blair, Peterson, 2008) carrying movement, sensorimotor, cognitive, motivation, and affect information (Leckman, Knorr, Rasmusson, & Cohen, 1991). Although these CSTC loops run in parallel, they do interact at the basal ganglia level. Volume reductions in the basal ganglia have been reported in TS patients (Peterson, Riddle, Cohen, Katz, Smith, Hardin, & Leckman, 1993b; Peterson et al., 2003) and this may indicate a developmental lesion that interferes with default inhibitory functions projecting to frontal regions involving prefrontal and primary motor cortices (Mink, 2001a; Mink, 2001b). Deficits in inhibitory control are further evident in transcranial magnetic stimulation (TMS) studies that have found decreased cortical inhibition in TS (Gilbert et al., 2004; Ziemann, Paulus, & Rothenberger, 1997). Leading explanations for sensory phenomena involve the same pathways and pathology. A hypersensitive gating mechanism in the basal ganglia leads to an overflow of afferent signals to the primary and supplementary motor cortex (Peterson, Riddle, Cohen, Katz, Smith, Hardin, & Leckman, 1993) - an area believed to be involved in movement initiation - becomes over stimulated by the excess of unfiltered sensory

input from the thalamus, resulting in the occurrence of these premonitory sensations, sensory tics and hypersensitivities (Fried et al., 1991).

1.3.6 Structural and Functional Imaging in Sensory Phenomena

To date no studies have used imaging methods to investigate correlates specific to measures of sensory phenomena in TS, however inferences can be made from other studies that have found deficits in related tasks and brain areas thought to be implicated in sensory processing.

Thomalla et al. (2009) examined white matter infrastructure in adults with TS and found that there were significant changes in the somatosensory cortex (pre- and post-central gyrus) compared to controls. The thinning was greatest in areas in the sensory and motor homunculi of areas most commonly affect by tics and these changes were found to be positively correlated with tic severity. These results demonstrate a pathology that may directly affect the processing of somatosensory stimulation. The same authors concluded in a subsequent review that data from this study highlight the role of developmental reorganization in the somatosensory system in TS and suggested that sensory phenomena such as premonitory urge be researched in conjunction with imaging and studies of electrophysiology (Munchau, Thomalla, & Roessner, 2011).

1.4 Electrophysiology: Electroencephalography & Event-Related Potentials

Although imaging studies using MRI, fMRI, and PET are able to tell us what brain areas may be implied in the dysfunctional processing of touch through excellent spatial resolution, they lack the temporal resolution to provide online access to the timing associated with the processing of events in the human brain. EEG has the benefit of offering much better temporal resolution as it can make measurements on the order of milliseconds (Picton et al., 2000).

1.4.1 EEG and ERP defined

Electroencephalography (EEG) is the non-invasive detection and recording of electrical activity of the brain via scalp electrodes. The tiny signals (in the range of 1-20 μV) are amplified and plotted graphically as changes in voltage over time (Berger, 1929). The EEG records electrical activity from neural processes of billions of cells. As a result, EEG in its raw form is very

difficult to use in the investigation of specific cognitive and sensory experiences (Luck, 2005). An event-related potential (ERP) is a series of peaks and troughs, which appears in the electroencephalogram (EEG) in response to the occurrence of a discrete event, such as the presentation of an external stimulus or psychological reaction to such a stimulus. These fluctuations in voltage are extracted from the continuous recording using filtering and signal averaging techniques. ERPs can be defined in frequency or time domains however this review will focus on waveforms that change as a function of time. When an ERP is in response to an external stimulation the ERP is called an evoked potential (EP) or an exogenous ERP, while a brain response to a psychological or cognitive event is referred to as endogenous ERP.

1.4.2 Advantages and Limitations of EEG and ERP

ERPs provide an online measure of the processing of stimuli when there is no behavioural response. This allows information about the cognitive response to stimuli to be studied without interpreting behaviours that can be hard to deconstruct, such as reaction time (Luck, 2005). The exact biological events contributing to the production of an ERP are unknown, causing difficulty in interpreting the functional significance of an ERP (Luck, 2005).

ERP also has the benefit of being able to provide an objective measurement of the physical and perceptual qualities of the stimulus (i.e. intensity, loudness, frequency) and through a reliable correlation in normal subjects between these attributes and changes in latency and amplitude it can be used to estimate the subjective experience. This is especially valuable in children, and patients with neurodevelopmental/neurological disorder disorders who are unable to accurately describe their sensory experience.

ERP has the advantage of limited invasiveness, low cost, and excellent temporal resolution, but these advantages come at the expense of poor spatial resolution. Temporal resolution can be as accurate as 1ms or better under optimal conditions. Spatial resolution is poor or undefined due to a great number of neural generators producing electrical output contributing to a given ERP. Voltages recorded at a single electrode reflect the summation of contributions from many different generators, reflecting diverse neurocognitive processes. As a result characterization of the sources and processes contributing to the ERP component (the neural activity that is generated during a specific computational response) is extremely difficult to ascertain with

confidence. At this time localization techniques are only able to *model* electrical activity. Determining the positions and orientations of dipoles using the observed distribution of voltage over the scalp is called the inverse problem. Unless there is only one dipole present with no noise, it is not possible to predict a unique solution in this situation. Several methods have been proposed to get around this issue including the assumption of a small number of equivalent dipoles with small cortical regions and the division of the brains cortical surface into a large number of voxels which can be evaluated by their computed strength. Even within these adjusted models it is not yet possible to estimate the margins of error surrounding these predicted locations (Luck, 2005; Picton et al., 2000).

A final noteworthy shortcoming of ERP is the number of trials required to measure it accurately. The statistical independence between the signal (the response due to the experimental paradigm) and the noise (random background fluctuations due to other computational processes) is assumed in the analysis of ERP. Therefore an ERP is produced under the assumption that if one extracts the segment of EEG within a constant time interval surrounding the stimulus, and average together the single trial waveforms, it is possible to average out the noise and create a replicable waveform in response to the stimulus. In short, averaging N samples of a waveform improves the signal to noise ratio by a factor of $\sqrt{N}$ (Regan, 1989). Therefore, since ERPs are so small and cannot be detected during continuous raw recording, many trials are required to produce a clear average (Luck, 2005; Woldorff, 1993).

1.4.3 Neural Origin of ERP

The electrical activity in the brain originates at the neuronal level. Two types of electrical activity can be measured in a single neuron: action potentials and postsynaptic potentials. Action potentials are the change in electric potential that travels from origin of the axon to the terminal buttons where neurotransmitters are released. Postsynaptic potentials are voltage changes that occur when neurotransmitters bind to receptors on the receptors of another (postsynaptic) cell. The resulting action potential is the opening and closing of ion channels causing a change in potential across the cell membrane (Carlson, 1998). The duration of an action potential is typically 1 millisecond while postsynaptic potentials last between tens and hundreds of milliseconds (Kandel, Schwartz, & Jessell, 2000; Patestas & Gartner, 2009). When measuring

electrical activity at the scalp, action potentials are often not recorded because their duration of firing is short and hence rarely synchronous. As a result action potentials from different axons typically cancel out. From this it can be deduced that electrical activity measured in ERPs reflect the summation of postsynaptic potentials (Luck, 2005; Vaughan, 1982).

1.4.4 ERP Components

The temporal ERP waveform contains several components that occur subsequent to the elicited event. Early components (occurring in the first 200ms) typically measure processes associated with the perception of the stimulus, and are strongly influenced by stimulus parameters such as intensity (Evans & Boggs, 2012). Later components (occurring after 300 ms) are typically task dependent and reflect endogenous or internal processes such as memory, selection and inhibition. These components are identified by a number of factors including the time at which it occurs (latency), its polarity, general scalp distribution (where they are evoked maximally), and its relation to experimental variables. A component name such as P300 indicates that the evoked potential is positive (P), (whereas N represents negative components, and the approximate latency of the component (300 milliseconds post stimulus or event) (Luck, 2005). Clinical and experimental conditions as well as typical inter-subject variation can alter the component latency (and amplitude) of an ERP and as a result many researchers prefer to use notations such as P3 and N1. There are some exceptions to this notation method where waveforms are given proper names related to their experimental conditions such as CNV (contingent negative variation) and Mismatch Negativity.

1.4.5 The P3 Waveform

1.4.5.1 History and Background

Though many components have been identified since the discovery of EEG by Berger, P3 has remained the best studied component in the last 2 decades. The P3 waveform was first reported nearly 50 years ago by Sutton, Braren , Zubin, and John (1965) and is elicited in simple discrimination tasks where the subject is unable to predict whether the next stimulus will be the target stimulus or the non-target stimulus. Original studies manipulated stimulus information conditions to assess their effect on brain activity then turned to studying the role of stimulus

probability and task relevance. They found that a presentation ratio where target stimuli comprised 20% or less, increased the reliability and amplitude of this broad waveform (Donchin, 1981; Duncan-Johnson & Donchin, 1977). The now standard protocol for eliciting P3 has been given the name "oddball paradigm" since 2 stimuli are presented in a random fashion such that one of them occurs infrequently (target). Depending on the stimulus type, stimuli are typically presented at an inter-stimulus interval (ISI) of approximately 1 second, as research has shown that smaller ISI create smaller amplitudes and may not provide enough time for the neural process to reset (Woods & Courchesne, 1986). The oddball paradigm elicits a large positive peak approximately 300 milliseconds post stimulus (in healthy adults) and can be evoked in auditory, visual, and somatosensory paradigms (Friedman, Vaughan, & Erlenmeyer-Kimling, 1978; Picton & Hillyard, 1974;Yamaguchi & Knight, 1991b).

The investigation of different paradigms and stimulus presentations led to the division of the P3 waveform into P3a and P3b. P3a is typically evoked by a novel salient stimulus that is irrelevant to the task and different in quality or modality than the other 2 stimuli in the oddball paradigm. Therefore, the P3a is observed when infrequently presented stimuli interrupt attentional mechanisms engaged in performance of the primary task. P3a is also evoked in fronto -central areas whereas P3b (commonly referred to as P3 in this review) is maximally evoked in parieto-central areas in a typical oddball paradigm (Linden, 2005; Polich, 2007).

Like other components, the P3 waveform is measured by assessing its latency and amplitude (Sutton, Braren, Zubin, & John, 1965). Latency (measured in milliseconds) is defined as the time from stimulus onset to the point of maximum amplitude within the specified range (ie 250-600 ms for P3). Latency is considered a measure of online stimulus classification, or the time needed to detect and evaluate the target stimulus in a train of non-target stimuli (Kutas, McCarthy, & Donchin, 1977; Polich, 1986). Studies have shown that the P3 is not related to any behavioural response selection processes including reaction time, supporting the notion that P3 is sensitive to the neural aspect of sensory processing and not response behaviour (Duncan-Johnson & Donchin, 1979; Duncan-Johnson & Donchin, 1980; Duncan-Johnson & Donchin, 1982; McCarthy & Donchin, 1981). These factors make latency a suitable measure to accurately delineate the timing of when sensory processes are occurring in the brain.

Amplitude is measured in microvolts (μV) and is defined as the difference between the pre-stimulus baseline voltage, and the largest positive going peak between a given post stimulus time range. P3 amplitude is typically relatively large compared to other ERPs, ranging from 10-20 microvolts on average. The P3 amplitude is thought to reflect a neural representation of a sensory process where the incoming stimulus is compared to the mental representation of the previous stimulus and the stimulus environment (context) is updated **(Figure 1-2)**. It is a neural signature of the mechanisms needed to update working memory and make an appropriate response (Donchin, 1981; Donchin & Coles, 1988; Donchin & Coles, 1998; Polich, 2007). An update is required each time the perceived stimulus is different than the previous presentation, and is sensitive to habituation and dishabituation with repeated exposure (Kececi, Degirmenci, & Atakay, 2006; Polich & McIsaac, 1994). Although originally perceived as an endogenous ERP, several exogenous factors are implicit to this cognitive process. These factors include the difficulty of the task, saliency and intensity of the stimulus, as well as the presence and nature of a required response **(Figure 1-3),** each contributing to the amplitude of the waveform (Kok, 2001). When the stimuli are not attended to or ignored, P3 responses are easily extinguished (Duncan-Johnson & Donchin, 1977).

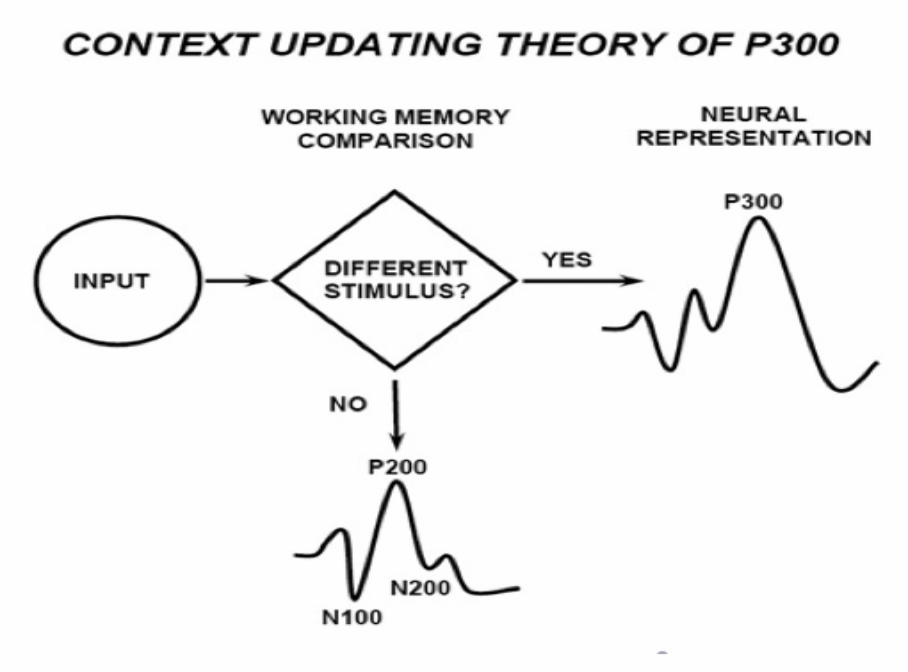


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Figure 1-2: A basic representation of P3 generation. The incoming stimulus is compared to the memory of the preceding stimulus and if the incoming stimulus is the same, early waveforms are evoked representing the basic perception of the endogenous characteristics of the stimulus. If the incoming stimulus is different, P3 is evoked, reflecting the updating of the neural representation of the stimulus environment.

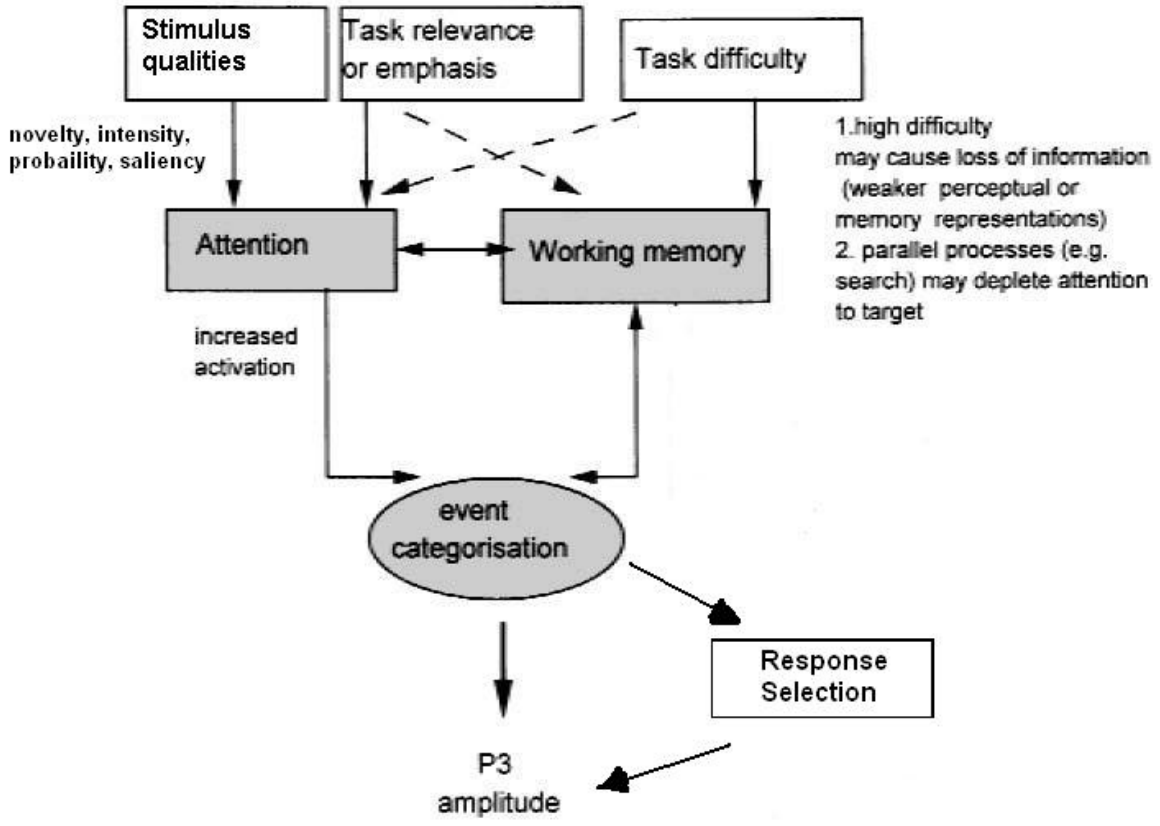

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Figure 1-3: Simplified diagram describing the major determinants of P3 amplitude (white boxes), the underlying mechanisms (dark boxes), and their effects on the event categorization process. Low probability, novelty, and greater saliency and intensity are assumed to increase the neurons recruited in association with event categorization, leading to larger P3 amplitude. Task difficulty plays an inverse role in that as difficulty increases, P3 amplitude decreases. Response selection also modulates P3 amplitude where an overt response such as a button press causes larger amplitudes than a covert response such as mental counting.

1.4.5.2 Neural Generators of P3

In adults the P3 is evoked maximally at midline electrodes Fz, Cz, and Pz, with amplitudes increasing from the frontal to the parietal lobe. (Dujardin, Derambure, Bourriez, Jacquesson, & Guieu, 1993; R. Johnson, 1993). Several studies have proposed that the scalp-recorded P3 is generated in networks that include the temporal-parietal neocortex as well as frontal areas and limbic structures for higher processing (Bledowski et al., 2004; Johnson, 1995; Linden, 2005; McCarthy, Wood, Williamson, & Spencer, 1989). The direct manifestation of stimulus categorization has yet to be determined. It has been suggested that the inferior temporal (IT) lobe cells work to adaptively filter information, thereby increasing or decreasing activity through to upper level pathways (such as the cortex). This theory would also explain why target P3 habituation occurs following repeated stimulus presentation, however many studies have not been able to reliably reproduce IT generator findings. A review of the published literature in source localization and fMRI demonstrates that the generators are not precisely defined, however the areas of brain activation most consistently reported include the prefrontal cortex, temporal-parietal junction, and medial temporal lobes (Nieuwenhuis, Aston-Jones, & Cohen, 2005; O'Connell et al., 2012; Soltani & Knight, 2000; Yamaguchi & Knight, 1991a) . Many of these areas are simultaneously engaged suggesting that multiple individual generators are synchronously involved, or that one central system with multiple connections throughout the brain is being engaged (Duncan et al., 2009).

Neurophysiological responses to electrode pulse stimuli to the fingers have been evaluated in oddball somatosensory paradigm using source localization. It was found that earlier ERPs such as SEP, N60 and N140 were elicited in the primary somatosensory cortex, while P3 was elicited from the medial temporal lobe, parahippocampus, insular cortex, and hippocampus (Tarkka, Micheloyannis, & Stokic, 1996). Yamaguchi & Knight (1991a) explored the contribution of anterior and posterior areas to somatosensory P3 by studying lesioned subjects and comparing them to adult controls. Using a mechanical finger tapping oddball paradigm, they found that subjects with temporal-parietal lesions showed markedly reduced P3 responses at all scalp locations with the largest reduction occurring over the parietal electrodes over the lesioned hemisphere. Patients with parietal lesions had normal P3 responses for target stimuli while

frontal lesions reduced P3 amplitude for novel targets and minimally altered amplitude for target P3 (Yamaguchi & Knight, 1991b). This evidence supports the results of previous P3 neural generator research, and suggests that there may be very few differences in the areas implicated across different stimulus modalities.

1.4.5.3 Clinical Utility of P3

ERPs have been used for decades to identify differences between clinical and developmental populations. The temporal resolution of ERPs make them an exemplary tool for the accurate measurement of the timing behind sensory processing in the brain. Many components including P3 have been proven to be reliable and great value has been placed in their ability to reflect reception and processing of sensory information. P3 latency, for example, has been negatively correlated with mental function in normal subjects, where shorter latencies were associated with superior cognitive performance in controls as well as in patient groups such as those with dementia (Rosenberg, Nudleman, & Starr, 1985) . Because the nature of some cognitive operations in ERP have been delineated and linked to specific brain systems, changes in ERP's can lead to inferences about pathology (Giard, Perrin, Pernier, & Bouchet, 1990; Nieuwenhuis, Aston-Jones, & Cohen, 2005; Yamaguchi & Knight, 1991b). Despite inter-subject variability due to the distinctive folding of the cortex, a meta-analysis study of P3 has estimated a genetic heritability of approximately 60%, furthering the utility of this method in understanding inherited disorders such as TS that is believed to have genetic etiology (van Beijsterveldt & van Baal, 2002) . As with any tool, there are limitations to the utility of P3 because it is influenced by endogenous and exogenous factors such as age, sex, stimulus modality, intelligence and medication. These confounding variables will be explored below.

1.4.5.3.1 Age effect

Goodin, Squires, Henderson, and Starr (1978) were the first to demonstrate changes in the P3 component with age. Using an auditory stimulus in normal subjects aged 6-76, Goodin et al. found that there was a systematic increase followed by a subsequent decrease in latency and decrease in amplitude with age. Their findings mirrored trends in early-evoked potentials that were already being used in clinical disorders of the nervous system, thereby providing validity for the use of P3 in assessing cognitive functioning. Although there are some discrepancies even

in recent investigations, the majority of investigations, including longitudinal studies, show that there is a nonlinear decrease in latency with age, which plateaus in adolescence and early adulthood until middle age where latency progressively increases (Courchesne, 1978; Dujardin, Derambure, Bourriez, Jacquesson, & Guieu, 1993; Fjell & Walhovd, 2001; Johnson, 1989; Polich & Herbst, 2000; Schiff et al., 2008).

1.4.5.3.2 Sex Effect

Studies have shown, that females in all age groups demonstrate significantly larger P3 amplitudes, with no significant changes in latency when compared to males (Brumback, Arbel, Donchin, & Goldman, 2012; Deldin, Duncan, & Miller, 1994; Polich & Geisler, 1991). Deldin et al (1994) found that in addition to larger amplitudes, females also had faster reaction times and in some cases shorter latencies suggesting that women utilized a different form of informational processing that may be more efficient than the processing used by men in the set task. When gender differences were analyzed 46% of the variance was due to season and sunlight, similar to the results found by Polich and Geisler (Polich & Geisler, 1991). This seasonal interaction may also be related to hormones as there is evidence to suggest that gonadal hormones can alter cognitive processing and stimulus evaluation. Unfortunately a measure of gonadal hormones was not conducted in any of the previous studies. It is important to note however that other studies of the effect of gender on P3 have found only slight increases in female P3 amplitude or no effect of gender at all (Kosmidis, Duncan, & Mirsky, 1998; Shelton, Hartmann, & Allen, 2002).

1.4.5.3.3 Intelligence effect

Several studies have related P3 with Wechsler Adult Intelligence Scale (WAIS) and Wechsler Intelligence Scale for Children (WISC) and have consistently found a negative correlation with latency, where higher Intelligence Quotients (IQ) produced shorter latencies (Boucher et al., 2010; McGarry-Roberts, Stelmack, & Campbell, 1992; Pelosi et al., 1992). Although the result has not always been consistent, the majority of studies have found that a higher IQ produces larger amplitudes, and these IQ differences may be specific to particular subtest of the IQ test (Pelosi et al., 1992; Robaey, Cansino, Dugas, & Renault, 1995; Russo, De Pascalis, Varriale, & Barratt, 2008). There is also evidence that suggests that the effect of IQ on amplitude is not a linear relation and that the amplitude is affected only in those with a below average IQ. Thus

there seems to be a difference between those with above average, and those with below average IQ, with little incremental differences within each group (Pelosi et al., 1992).

1.4.5.3.4 Medication Effect

A number of studies have attempted to quantify the effect of everyday substances and prescription drugs on P3 measures. A majority of TS patients carry co-morbid diagnoses of ADHD and/or OCD, and many receive medications for these conditions making it important to consider the effects of SSRIs, stimulants, alpha 2 agonists and antipsychotics, on the P3. To date there have been no studies evaluating medication effects on the P3 in TS patients, however a large body of data is available for consideration from ADHD, OCD, and schizophrenia populations. Typically ADHD subjects produce depressed P3 amplitude during target selection, with the effect size negatively correlated with age. Further, this effect size increases as the proportion of males in the study increase (Szuromi, Czobor, Komlosi, & Bitter, 2011) . Stimulants (methylphenidate) normalize P3 amplitude and latency in ADHD subjects. When medicated ADHD subjects were asked to participate in a P3 go-nogo task, amplitude was significantly greater 2 hours after taking stimulants than when off medication for 36 hours. And this trend was observed both for long-term users and stimulant naive single-trial users (Groom et al., 2010; Lazzaro et al., 1997; Ozdag, Yorbik, Ulas, Hamamcioglu, & Vural, 2004).

Few studies have investigated the effects of SSRIs on P3 in OCD-only patients, however one study observed that drug-free OCD patients had a lower amplitude and longer latency than controls. The P3 amplitude increased after SSRI treatment in these initially drug naïve OCD patients. . The latency remained unchanged (Sanz, Molina, Martin-Loeches, Calcedo, & Rubia, 2001) . Single doses of SSRIs in healthy controls have not caused significant changes to P3 baseline (Oranje, Jensen, Wienberg, & Glenthj, 2008; Wienberg, Glenthoj, Jensen, & Oranje, 2010).

P3 in schizophrenic patients are known to have smaller amplitudes than age-matched controls with no significant differences in latency. Antipsychotic medications in this population decrease the difference in amplitude between patients and controls, though this effect is not dose dependent (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004). Polich and Jeon (2003) conducted another meta-analysis and also found smaller amplitudes and longer latency in P3

among schizophrenic patients, but were unable to find any significant relationship between antipsychotic medications and P3 amplitude.

1.4.5.3.5 Modalities

Unlike early components of the ERP (e.g. P50), the P3 has been shown to be largely independent of the sensory modality (Luck, 2005). Therefore the endogenous properties of P3 are consistent, and P3 is equally evoked across paradigms, demonstrating similar changes across modalities when parameters such as intensity, probability, and response selection are manipulated (Covington & Polich, 1996; Mertens & Polich, 1997; Polich, Ellerson, & Cohen, 1996).

Though auditory and visual P3 are the most commonly studied modalities, the most prevalent clinical reports of sensory hypersensitivity come from the touch and sound domain. Typically P3 modality investigations study differences between visual and auditory paradigms, however Polich and Brook (1991) demonstrated that there was no difference in the effects of probability, ISI, or scalp distribution between auditory and somatosensory modalities. Furthermore, P3 was also maximally evoked at Pz demonstrating that when used in relatively simple discrimination tasks, both modalities produce similar amplitude and latency values.

Typically somatosensory evoked potentials are evoked using peripheral electrodes overlying the nerve, but this type of stimulation can be especially uncomfortable after repeated trials. More recently Piezoelectric stimulators and mechanical tapping devices have been used, but much like nerve electrodes, piezoelectric stimulators provide a vibration stimulation that may continue to activate receptors after the stimulator has ceased to vibrate, making it an imprecise stimulus for ERPs high temporal specificity.

1.4.5.4 Use of EEG/ERP in Neurodevelopmental Populations

1.4.5.4.1 Sensory Processing Disorder

Electrodermal activity provides a measure where PNS effects on the CNS may be inferred but EEG methodologies offer the ability to directly measure brain activity in SPD. Davies and Gavin (2007) sought out to test Ayres' assumptions that there is a relationship between brain function and behavioural manifestations in SPD. They tested 28 children with SPD to determine if there were differences in the central processing of auditory stimuli compared to typically developing controls. The recruited SPD population included 15 children with co-morbid neurological or behavioural disorders. All scores for typically developing children fell within the typical performance range on the Sensory Profile while SPD scores fell within the 'definite difference' and 'probable difference' range in 5 of 6 subscales. Using a paired click paradigm of sensory gating, the study found that both SPD and control children demonstrated ERP inhibition or gating of the second click, but SPD children showed a trend to less gating (this difference did not reach statistical significance). A sensory registration paradigm was also used to test differences in responses to changes in intensity and frequency via early ERPs N1 and P2. SPD subjects had shorter latencies with greater N1 amplitudes and longer latency and smaller P2 than controls, but none of these differences reached statistical significance. Gating data were analyzed for possible factors in variability within and between groups and it was found that for typically developing children there was a significant relationship between gating abilities and age, but this relationship was not present in SPD children. This indicated that children with SPD do not demonstrate improved gating as a function of age, supporting the developmental nature of SPD.

Another ERP investigation was conducted by this group to replicate the above findings and explore differences in P3. As with the former study, group differences were present, especially in P3 amplitude, but these differences did not reach statistical significance (Davies, Chang, & Gavin, 2010). It is likely that these studies did not find statistically significant differences between groups because of the heterogeneity of the SPD population. SPD itself covers a large variety of sensory impairments that represent a continuum. This continuum is further complicated by a co-morbidity rate of approximately 50% in these samples that were also quite heterogeneous. Individuals on the extreme ends of the continuum may represent different brain

pathologies, thus increasing variability in the patient sample, while still resulting in group means similar to controls. These two flaws are common amongst studies of SPD and they make the interpretation of results difficult at best. Recent attempts have been made to select more homogenous samples in the study of SPD ERPs but this improvement has yet to be instituted in studies of P3.

1.4.5.4.2 ADHD

Electrophysiology has been widely used to study information processing in ADHD. Early studies focused on tasks testing functioning of attention within auditory and visually systems as well as processes under frontal lobe control such as inhibition. The most common tasks involve selective attention (e.g. different stimuli presented to each ear or cross-modality presentation) or an oddball task, where age, sex, subtype, and task differences (active vs. passive, use of reward, task difficulty, task performance,) can be evaluated (Buchsbaum & Wender, 1973; Johnson & Barry, 1996; Jonkman et al., 1997; Satterfield, Cantwell, Lesser, & Podosin, 1972).

Tests of selected attention found that that hyperactive children aged 7-14 exhibited attenuated P3 amplitude to attended target stimuli (Jonkman et al., 1997; Loiselle, Stamm, Maitinsky, & Whipple, 1980). During oddball tasks, posterior target P3 amplitude is typically reduced in ADHD subjects compared to controls. This difference is most evident in subjects younger than approximately 12 years of age (Holcomb, Ackerman, & Dykman, 1986; R. Johnson & Barry, 1996; Kuperman, Johnson, Arndt, Lindgren, & Wolraich, 1996; Satterfield, Schell, Nicholas, Satterfield, & Freese, 1990; Satterfield, Schell, & Nicholas, 1994). It has also been suggest that these results are affected by reward or motivation where larger amplitudes are seen in ADHD children than controls when protocols are free of motivation and reward (Johnson & Barry, 1996). Interpretations of the posterior P3 reduction include abnormal capacity allocation, and context-updating deficiency while frontal (Johnstone, Barry, & Anderson, 2001) compensation is mediated by reward networks (Johnson & Barry, 1996).

Mixed results have been reported regarding the relationship between ADHD diagnosis and P3 latency. Some studies have shown that ADHD subjects report shorter latencies than controls (Loiselle, Stamm, Maitinsky, & Whipple, 1980) while other studies have reported no significant difference between populations (Johnson & Barry, 1996; Johnstone, Barry, & Anderson, 2001).

1.4.5.4.3 TS

EEG has been an important research tool in the study of cerebral dysfunction in TS. Preliminary studies sought to discover a physiological marker for TS (Krumholz, Singer, Niedermeyer, Burnite, & Harris, 1983; Obeso, Rothwell, & Marsden, 1982; Shapiro, Shapiro, & Clarkin, 1974; Yordanova, Heinrich, Kolev, & Rothenberger, 2006) but the majority of research yielded no significant or reliable differences in ERPs or routine EEG recordings (Obeso, Rothwell, & Marsden, 1982; Yordanova, Heinrich, Kolev, & Rothenberger, 2006). Few studies have used EEG to explore inhibitory dysfunction (Obeso, Rothwell, & Marsden, 1982; Serrien, Orth, Evans, Lees, & Brown, 2005).

Serrien and colleagues (2005) used EEG to measure cellular coherence during various behavioural inhibition tasks such as Go-NoGo task and tic suppression. They found that when compared to controls, non-medicated TS patients demonstrated increased coherence (a measure of the degree of association between 2 or more brain regions) in sensorimotor areas and the prefrontal and mesial frontal cortex during voluntary tic suppression. Over activity indexed by elevated coherence in these areas was also evident during Go-NoGo task, despite similar task performance between groups. The authors suggest that this increased coherence in these inhibitory pathways likely is an adaptive feature in TS, used in the voluntary suppression of tics. These results align with the findings of Hyde et al (1994) who studied monozygotic twins where at least one twin was diagnosed with TS. The study found that within the twin pair, there was greater frontal coherence and greater amount of noise and irregular artifacts (by visual inspection) in the monozygotic twin with greater tic severity.

Electrophysiology has also been used to study pre-pulse inhibition (PPI). PPI is a behavioural measure that detects inhibitory deficits across all mammals. In this type of experiment a startling stimulus is preceded by a weaker stimulus. In a normal control this weaker stimulus or prepulse signal, attenuates the startle response to the pulse via cortical inhibitory mechanisms (Braff, Geyer, & Swerdlow, 2001). TS children aged 9-17 years had significantly lower percentages of PPI in both the tactile and auditory stimuli trials (Swerdlow et al., 2001). These results demonstrate that there are deficits in inhibition implicit to the process of sensorimotor gating. These deficits in inhibitory gating in TS may be consistent with the diminished ability to

normally inhibit or gate intrusive sensory, cognitive, and motor information in this disorder. The phenomenon of PPI is thought to be mediated by the CSTC brain circuitry (Koch & Schnitzler, 1997; Swerdlow, Bongiovanni, Tochen, & Shoemaker, 2006).

Although this study did find a link between inhibitory dysfunction and TS, it did not provide direct evidence for a link between sensory phenomena and inhibitory function. One patient was mentioned whose percent PPI was 3 standard deviations lower than the mean of the group. The patient also had the highest tic severity score (63 on the Yale Global Tic Severity Scale) of the TS group (Swerdlow et al., 2001). This indicated that tic severity may be influenced by a deficit in inhibitory function, however this was not confirmed or commented on by researchers and no mention was made of the role sensory phenomena may have played in this observation.

Contingent negative variation (CNV) has been examined in TS. It is postulated that this negative ERP represents sensorimotor integration in the CSTC pathway as well as a measure of arousal and attention. Weate et al. (1993) recorded the CNV of 12 TS patients (9 with ADHD, 3 of whom had OCD as well) and found that compared to controls, CNV amplitude was larger in all TS subjects for the warning stimulus. Furthermore, subjects with co-morbid ADHD and/or OCD demonstrated an attenuated response to the imperative or second click. Irregularities in the CNV have been associated with various dopaminergic disorders. Weate et al. suggest that the irregularities in the TS CNV are due to an excess of DA activity in the implied striatal pathway, resulting in a dysfunctional cortex.

Only a few studies have investigated changes in the P3 in TS. Thibault et al. (2008) tested a visual oddball task on 4 groups, TS, TS+OCD, OCD and controls. Between group comparisons revealed significantly larger amplitudes in controls than TS+OCD and OCD patients. No significant difference in amplitude was found between controls and TS-only subjects or OCD and TS+OCD subjects in the anterior region, however the TS-only group had larger posterior amplitudes than all co-morbid groups and controls. Increased obsessive compulsive behaviours (OCB) correlated with a decline in P3 amplitude, while increased tic severity predicted larger P3 target amplitude (Thibault et al., 2008). Zhu and colleagues (2006) also found co-morbidity specific differences during their investigation of auditory P3 in TS, TS+ADHD, and control children. Subjects with co-morbid ADHD showed significantly shorter latency and larger

amplitude than TS-only and control subjects. Subjects with TS-only also showed no significant difference in latency compared to controls, but showed significantly lower amplitude than controls.

Research from both Zhu (2006) and Thibault (2008) indicate that differences in TS P3 are highly influenced by co-morbidity. Thibault found only minute correlations (R=0.1) between P3 amplitude and OCD and tic severity indicating that other factors are involved in the altered TS P3 profile. Previous studies have reported a decrease in the amplitude of the earlier component P2 to non-target stimuli, and suggest that this effect may be caused by disturbances in arousal and focal attention toward non-relevant stimuli. Johannes et al (2001) tested this hypothesis using a simultaneous dual modality P3 oddball task, and found that TS adults demonstrated a decreased ability to accurately respond to target stimuli, but demonstrated lower P3 amplitudes in response to auditory stimuli, when compared to controls. Investigators interpreted these findings as an indication that TS subjects have an altered allocation of attentional resources, leading to the interference of inhibitory mechanisms occurring prior to or during target evaluation and detection processes. This disturbance may occur during the processing of the stimulation at the perceptual stage, during the cognitive response selection phase, or both. P3 presents as an ideal component for the investigation of these differences in TS as the component represents both exogenous and endogenous information processing procedures.

Just as Thibault et al. measured symptom severity and correlated these indexes with P3 latency and amplitude, it is plausible to explore P3 in the context of sensory hypersensitivity. Sensory symptoms are a major part of the phenomenology of TS, and the investigation of tics. The clinical utility of P3 has been well described (Duncan et al., 2009; Hansenne, 2000; Polich, 1998; Polich & Herbst, 2000) and a number of studies recently used ERP as a tool to better quantify differences in groups who demonstrate sensory processing differences (Brett-Green, Miller, Schoen, & Nielsen, 2010; Cascio, 2010; Cheung & Siu, 2009; Gavin et al., 2011; Ghanizadeh, 2011; Miller, Nielsen, Schoen, & Brett-Green, 2009; Parush, Sohmer, Steinberg, & Kaitz, 1997).

Previous studies of electrophysiology in TS subjects have investigated the P3 ERP (van Woerkom, Roos, & van Dijk, 1994; van, Martens, Fortgens, Slaets, & van Woerkom, 1985).

However these investigations aimed to find characteristic differences between the TS individuals and controls in amplitude, latency, and topography. ERPs have already been used to measure habituation in normal subjects and other patient groups experiencing sensory processing deficits (Lin & Polich, 1999; Montoya et al., 2006; Murphy & Segalowitz, 2004; Pan, Takeshita, & Morimoto, 2000; Polich & McIsaac, 1994; Ravden & Polich, 1998; Yamaguchi & Knight, 1991c). This has yet to be done in the TS population, where the investigation of the processing of repetitive tactile stimulation may provide insights into sensory processing deficits when related to measures of tic severity, behavioural sensitivity and premonitory urge.

Furthermore, though Belluscio et al (2011) conducted behavioural tests of sensory behavior in TS patients, no attempts have been made to replicate their findings, using more rigorous assessment of co-morbidities and especially in child populations were the incidence of positive sensory phenomena is greater. Not enough research has been conducted in the field of sensory hypersensitivity in TS population and this work has attempted to close this gap.

1.5 Rationale

Symptoms such as premonitory urges, sensory tics, and sensory hypersensitivity are commonly present in TS and may be related in that these may be linked to a failure to ignore task irrelevant stimuli in order to allocate attention to the relevant task. All of the aforementioned clinical phenomena may involve dysfunction of CSTC circuit. The present study explores the nature of sensory phenomena in TS patients by testing the ability of these patients to ignore task irrelevant stimulation while responding to task relevant stimuli during a tactile P3 oddball task. Furthermore evoked potentials elicited by this task will be analyzed for habituation or automation through the measurement of P3 amplitudes and latencies.

Controlling responses to objects and events in the environment requires selection processes that are modified by attention. Attention modulates behavioural responses by providing information to the brain about what is important in a particular task or environment. The P3 waveform reflects stimulus perception and cognitive processing and is composed of several parts that reflect an information-processing cascade when attention, memory, and stimulus evaluation and categorization mechanisms are engaged (Polich, 2007). Therefore this waveform has the capability of demonstrating the influence of tactile sensitivity on both pre-perceptual and post-perceptual stages of information processing- information that would be valuable to the study of sensory phenomena in TS.

The comparison of P3 amplitude and latency between TS children and typically developing controls will indicate if there is an overall group difference, while the investigation of processing trends over blocks of trials will provide information about differences occurring over repeated stimulation. It is believed that the presentation of a new stimulus during the P3 oddball paradigm elicits a change or update in the schema the brain forms of the previous stimuli (Donchin, 1987). Therefore it is plausible that the P3 waveform represents the inhibition of previous sensory information in order to process new information. This process has been thought of as a rapid neural inhibition where irrelevant information is gated out to facilitate the transmission of necessary information from external input (attention) to event processing and response (Linden, 2005; Polich, 2007). It has been suggested that the inappropriate allocation of attention may play a role in the etiology of TS sensory phenomena as well as tics. This hypothesis proposes that tics

and sensory phenomena emerge because of a failure to gate irrelevant unnecessary movement, sensation and behaviour (Mink, 2001a; Mink, 2001b). Given that sensory phenomena can be more disturbing to the patient than the tics themselves, it is hoped that the present study can add to the minimal literature on tactile hypersensitivity and help researchers and clinicians to better understand and develop interventions for these symptoms.

Because of the heterogeneity of the TS population, the present investigation will focus on the most prevalent co-morbidity, ADHD. Tactile hypersensitivity has been observed in both TS and ADHD. It has been hypothesized that these groups have a common pathophysiology involving the somatosensory system where preliminary studies have shown hyper-excitability of the primary somatosensory cortex in both TS and ADHD populations. (Krumholz, Singer, Niedermeyer, Burnite, & Harris, 1983; Miyazaki, Fujii, Saijo, Mori, & Kagami, 2007; Parush, Sohmer, Steinberg, & Kaitz, 2007; Parush, Sohmer, Steinberg, & Kaitz, 1997). These studies have also implied inhibitory deficits in the basal ganglia related to CSTC dysfunction in ADHD; a key region of interest in the study of sensory phenomena and tics in TS.

1.6 Objectives

In response to the lack of studies characterizing and exploring the sensory experience in Tourette syndrome patients, the present study aims to provide behavioural data on the sensory experience of TS+ADHD children, while also examining the neurophysiological differences in sensory processing between TS+ADHD and typically developing children. The main study question is "Do TS individuals with sensory hypersensitivity process tactile stimulation differently than typically developing controls?" This question will be explored by investigating the following objectives:

1) To characterize the sensory experience of TS children to stimuli across all 5 modalities using parental reports from the Caregiver Sensory Profile and compare their behavioural results to those of typically developing controls.
2) To test the hypothesis that TS patients may have an enhanced ability to perceive tactile stimuli compared to typically developing controls as determined by their tactile threshold using Semmes-Weinstein filaments..
3) To use tactile ERP to investigate CNS differences between TS children and typically controls in sensory processing and decision-making. First, overall differences in amplitude latency and topography will be explored. Second, trends in P3 amplitude between successive trial blocks will be explored to investigate the hypothesis that sensory hypersensitivity results from an inability to ignore, gate, or habituate to repetitive stimuli.
4) To relate these 3 aforementioned behavioural and physiological measures to clinical measures of tic severity, ADHD severity, intelligence and positive sensory phenomena scales to understand correlates of sensory sensitivity in TS+ADHD as well as typically developing children.

1.7 Hypotheses

1) Reported behavioural sensitivity as determined by Caregiver Sensory Profile will be significantly greater in TS vs. TDC across all 5 modalities and TS participants will be rated as significantly more sensitive on the "Sensitivity" quadrant score of the Sensory Profile.
2) TS subjects will demonstrate a significantly lower threshold to tactile stimuli compared to TDC as tested with Semmes-Weinstein filaments.
3) P3 amplitude will be significantly greater in TS+ADHD vs. TDC. No significant differences in latency will be present between TS+ADHD and TDC. Between-block analysis will reveal that TS patients demonstrate slower rates of habituation over successive trial blocks compared to TDC. There will be no significant changes in latency across blocks in either group.
4) Behavioural measures such as tic severity, and ADHD severity, will be correlated with P3 amplitudes. There will be an inverse relationship between sensory hypersensitivity scores on the Sensory Profile and the rate of habituation within TS subjects.

Chapter 2
Methods

2.1 Participants

Fifteen TS patients with co-morbid ADHD (TS+ADHD), aged 6-12 years old, were recruited through postings in the Tourette Syndrome Neurodevelopmental Clinic (TSNC), Toronto Western Hospital. Sixteen typically developing control (TDC) participants, aged 6-12 years old were recruited through a local private school and staff members at University Health Network. All subjects were recruited between March 2011 and April 2012. The study was approved by the University Health Network Research Ethics Board, Toronto, Canada. Informed consent for participation was obtained from the parents of all children and consent or assent was obtained from all child participants. Parents were reimbursed for parking and travel costs while children were rewarded with a gift certificate upon completion of the study.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion Criteria

The participants in the TS group were approached for recruitment purposes only if they carried the clinical diagnosis of TS and ADHD according to DSM IV criteria. Control subjects were required to be naïve to psychotropic drugs. TS participants were included whether or not they were receiving medication for tics and/or ADHD symptoms.

2.2.2 Exclusion Criteria

Exclusion criteria for all participants included the presence of OCD, psychosis, and depression according to DSM IV criteria. Subjects were excluded when history of significant head or spinal cord injury, stroke, or family history of psychosis in a first-degree relative was present. Subjects were also excluded if their IQ was ≤75 or they were unable to comply with task instructions.

2.3 Clinical Assessment

Diagnoses of TS, ADHD and rule-outs for disorders listed as exclusion criteria were made according to DSM IV criteria by P.S. and M.P., experienced staff psychiatrists at the TSNC. A preliminary screening was conducted upon first contact. This screen confirmed briefly, age, diagnosis, and medication criteria for both groups. Control children were screened by A.N. using selected items from the screening questionnaires used for patient intake at the TSNC (Conners, Sitarenios, Parker & Epstein, 1998; Cooper, 1970; Paul & Hurst, 1987) (See **Appendix 1**). This tool was used to interview parents and participants regarding medical history, medication, family history, and possible ADHD, OCD, or tic behaviours of the child. TS symptom severity was assessed using the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) and Premonitory Urge for Tics Scale (PUTS) (Woods, Piacentini, Himle, & Chang, 2005b).

The PUTS is a behavioural measured used to describe sensory experiences associated with tics. Eleven questions about sensory experiences preceding and following tics are posed and patients or caregivers are asked to provide responses using a Likert scale. Two versions of this scale were used. The first scale employed (Version 1) required yes or no responses to the presence of premonitory symptoms while the second scale (Version 2) asked for responses to the same questions on a Likert scale (See **Appendix 2**). YGTSS and PUTS were administered by A.N. to the parents and children of the TS+ADHD group. Parents in both groups also completed the Conner's Parent Short Rating Scale for ADHD and the Caregiver Sensory Profile questionnaire, a validated tool used to describe patterns in sensory processing across all modalities in control children, autism and schizophrenia patients (Brown, Cromwell, Filion, Dunn, & Tollefson, 2002; Brown & Dunn, 2002; Dunn, 1994; Ohl et al., 2012).

The parent Conner's rating scale is an instrument that uses parent ratings to help assess ADHD and evaluate problem behavior in children and adolescents. The short parent version contains behavioural items for response using a Likert scale. These items can be organized into various subscales to provide estimates of ADHD symptoms or impairments such as inattention, hyperactivity, oppositional behaviour, etc. Responses are tabulated and compared against

normative values taken from 8000 children aged 3-17, providing an indication of any difference observed between the evaluated child and standardized age and sex matched norms.

The caregiver Sensory Profile is designed to promote caregiver (parent/guardian) awareness of a child's behavioural responses to everyday sensory experiences. It also offers a standardized method for clinical and research professionals to characterize sensory processing. Using this scale it is possible to characterize the child's reported behaviour on 125 items into quadrants scores such as registration, seeking, sensitivity, and avoiding. Standardized scores indicate if the child's behaviours are typical or if there is a probable difference between the child and the standardized norm (i.e. greater sensitivity or less sensitivity than others). These quadrant scores involve items from each modality section of the SP. Sensory processing can also be analyzed by modality (i.e. auditory, visual, touch, and oral processing) in order to pinpoint in which sensory modalities differences occur.

Estimates of IQ were also attained by A.N. for each child using the 2-subtest Wechsler Abbreviated Scale for Intelligence (WASI), which tested vocabulary (verbal subtest) and matrix reasoning (non-verbal subtest) to estimate IQ.

2.4 Tactile Threshold Measurement

Absolute tactile detection threshold was assessed in both the TS+ADHD and TDC groups using a validated series of Semmes-Weinstein monofilaments (North Coast Medical Inc., California, USA) to perform an ascending method of limits test. Each subject was tested with their eyes closed while seated at a table across from A.N. who carried out the testing. The palmar aspect of the distal phalanges of the non-dominant hand was chosen as the test site. Increasing successively from the smallest available monofilament (0.0008g), subjects were presented with the stimuli and asked to lift the corresponding finger if they detected a touch. Each monofilament was presented in a randomized fashion with each phalanges being tapped once, in order to correct for guess responses. Once the correct detection response was given by the subject the monofilament target force was recorded. Data were recorded for the 2nd digit (index finger) only. The examiner was not blinded to the group status of the participant.

2.5 Electrophysiology

2.5.1 Stimulation Machine Development

We aimed to develop a device to which would deliver consistent non –painful mechanical finger stimulation as described in (Yamaguchi & Knight, 1991a). The design required that stimuli onset and subject response signals could be transmitted to EEG software where they could be time-locked with EEG recordings online. The device was designed by Allison Needham and Paul Sandor, while engineering and software design were contracted to Mohanad Elshafi, mechanical and electrical engineer.

The Finger Stimulator Device (FSD) was comprised of a black Plexiglas frame, 2 solenoids mounted with 4 degrees of freedom in movement in each, and an IEEE Botboard ’07 powered by a microchip 18F4620 microcontroller (see **Appendix 3** for image of the device). The circuit board and microcontroller were used to communicate stimulation instructions from the stimulation a computer to the FSD as well as to transmit outgoing signals to the acquisition computer via BNC cables. These outgoing signals produced signals of 5 volts, which were transduced to an equivalent but smaller signal that could be processed by the EEG amplifiers.

The FSD was controlled via a graphical user interface (GUI) **(Figure 2-1)** compatible with Windows 98/2000/Vista Net 2.0 computer systems. The FSD software allowed the setting and control of parameters such as inter-stimulus interval (ISI), the randomized timing jitter of the ISI, inter-block interval (IBI), the number of blocks, and the number of sub-blocks (or identical repeated sequences) within each block. User controls were also available to manipulate the duration of the tap or solenoid extension (≥300ms), percentage of target vs. non-target stimuli, and the total number of trials (strokes) per block. Once these parameters were set the computer was able to generate a randomized presentation of stimuli that could either be executed immediately or saved for repeated use at a later date.

The FSD was electrically powered by 2 power supplies, 9V DC, 2A and 12V DC, 1.5A respectively. One power supply works to power the solenoids, while the other works to power the Botboard. All electrical conducting devices were connected to the chassis ground and all power supplies were approved by the Canadian Safety Association for medical use. The device was also inspected by the Medical Engineering Department at Toronto Western Hospital, University Health Network and approved for use with patients and volunteers.

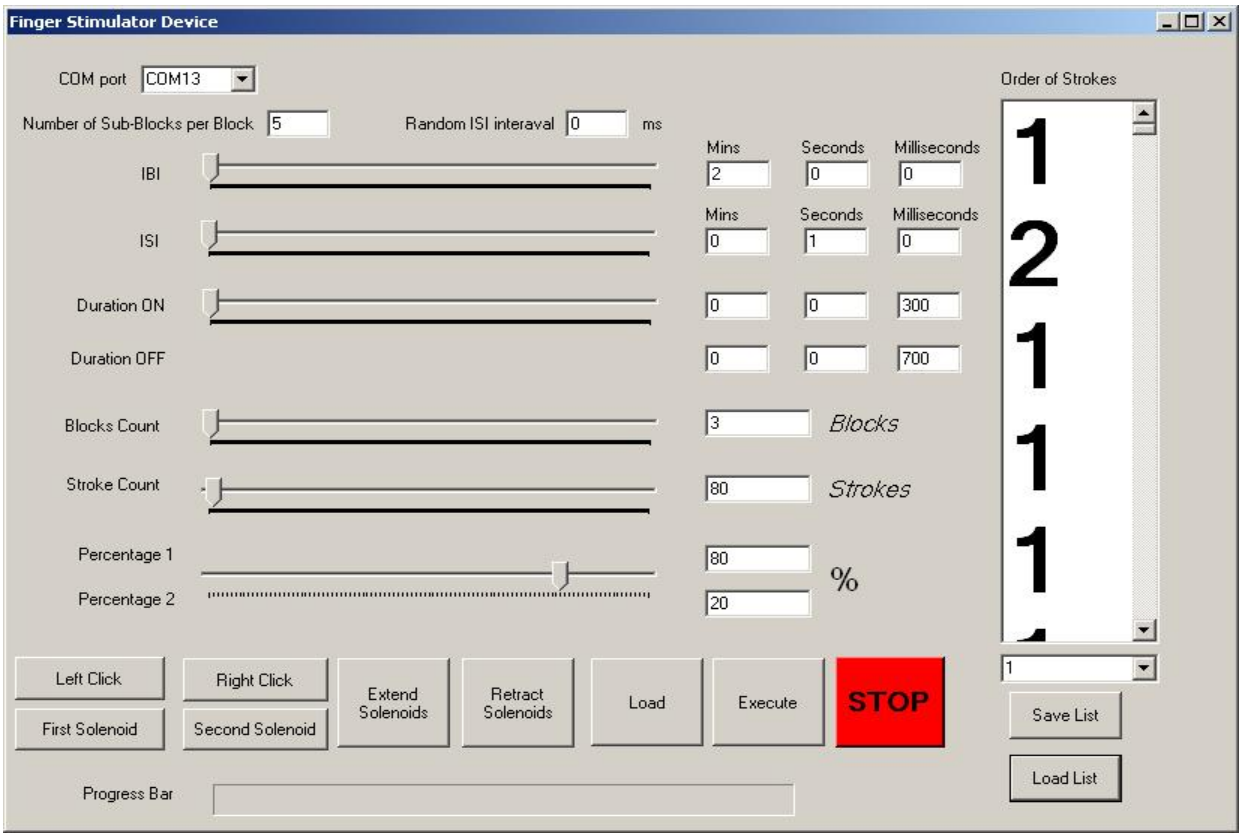

Figure 2-1: Graphical User interface(GUI) for programming control of the Finger Stimulating Device. The GUI allowed for control of the tactile stimulation by entering desired parameters for ISI, IBI, target trial percentage, number of stimuli per block, number of sub-blocks, and the duration of the stimulation.

2.5.2 FSD pilot study

Protocol for the FSD pilot study was approved by the UHN Research Ethics Board.

A small preliminary pilot study was conducted in order to test the technical and mechanical properties of the device and to confirm that the study protocol was suitable for TDC and TS+ADHD children. The former goal could be carried out using human subjects of any age and thus adult subjects were chosen. P3 amplitudes decline and latencies increase with age (Schiff et al., 2008), thus I proposed that if P3 waves were evoked using the FSD in adults, P3 waves would be evoked in even greater amplitude in children. Since we sought to measure a decline in ERP amplitude over time it was important that we were able to elicit a large initial ERP response.

The proposed protocol for the adult pilot study commenced with testing a stimulus paradigm consisting of 3 trial blocks including 500 stimuli /trial block. Each trial block was broken into 5 identical sub trial blocks, with a non-target to target ratio of 4:1. Inter stimulus (ISI) presentation was 1 msec. This meant that during each block 500 finger taps from the mechanical rod (each of equal pressure and duration of 500 ms per tap) were delivered every second to either the target finger or the non-target. Each block took 8.3 minutes. Between each block the subject was given a 2-minute resting period where no stimuli were presented and no response was required. The time to complete this protocol was 28 minutes (adapted from methods in (Lindin, Zurron, & Diaz, 2004). Initial physiological and behavioural data showed the appearance of the P3 component however the amplitude was approximately 7 μV in the first two subjects which was significantly smaller than expected for somatosensory stimulation (Nakajima & Imamura, 2000; Yamaguchi & Knight, 1991a; Yamaguchi & Knight, 1991c). We proposed that smearing (due to the short ISI of 1 second may have been responsible for the attenuated amplitude (Woldorff, 1993), however a longer ISI was not feasible as subjects reported that they found the protocol too long to maintain attention. Furthermore solutions such as increasing the ISI and decreasing the number of target stimuli to shorten the experiment adequately for sustained attention across 3 blocks typically resulted in a low number of target trials (Picton et al., 2000). It was expected that a number of infrequent trial blocks would be discarded in a child and neurodevelopmental population (due to tics, hyperactivity, inattention, and the difficulty of remaining still while seated for long periods of time. As a compromise solution, FSD settings were set to 100 ms ISI

randomization to resolve potential data smearing and the numbers of stimuli per sub-block were reduced from 100 to 80. These changes reduced the average block by 2 minutes to about 6.5 minutes and ultimately produced better results amongst adult pilot participants. After sufficient pilot testing the randomized presentation of stimuli was selected and saved for subsequent testing in the main study.

A demographic survey of our clinic population revealed a smaller number of eligible subjects than previously understood. Conducting pilot study testing with children from our potential sample pool could reduce our overall collection numbers, as the study called for protocol-naive participants. Instead, the decision was made to proceed directly to the main study using the aforementioned adjusted protocol for P3 ERP collection. If the first 4 child subjects from each group (recruited according to inclusion/exclusion criteria) were able to complete the task we would proceed with no changes to the protocol. **Figure 2-1** displays the finalized FSD settings for operation of the finger-tapping device. A random ISI interval jitter of 100 ms was also employed.

2.5.3 Tactile Oddball Paradigm

A button-response tactile somatosensory oddball paradigm was used for P3 recording. A solenoid powered mechanical tapping device delivered gentle taps to the volar surface of proximal phalanges of the 2nd (80%) and 4th (20%) digits of the left hand with an inter-stimulus interval of 1000 ± 100 ms **(Figure 2-2)**. The hand was immobilized on a pressure pad using 2 Velcro restraints at the elbow and wrist as well as individual Velcro rings for the target and non-target finger. Each solenoid was activated by a 30 ± 2ms square wave electric pulse resulting in a downward 3.175 mm movement of the tapping rod. Each rod had a contact diameter of 6mm and produced a maximum applied force of 0.83 N or 84.67 g of pressure. Subjects were instructed to press a button in response to stimulation of the 4th (target) digit and to ignore stimulation to the 2nd (non-target) digit. Stimuli were delivered in 3 blocks with 400 stimuli per block and a 2 min rest period between blocks. Subjects were given time to practice the task and become familiar with the procedure prior to recording. Participants were seated at a desk and asked to focus on a fixation point approximately 1m away in order to minimize eye-blink artifacts in the recording. White noise was presented through headphones to mask the sound produced by the rod movement throughout the experiment.

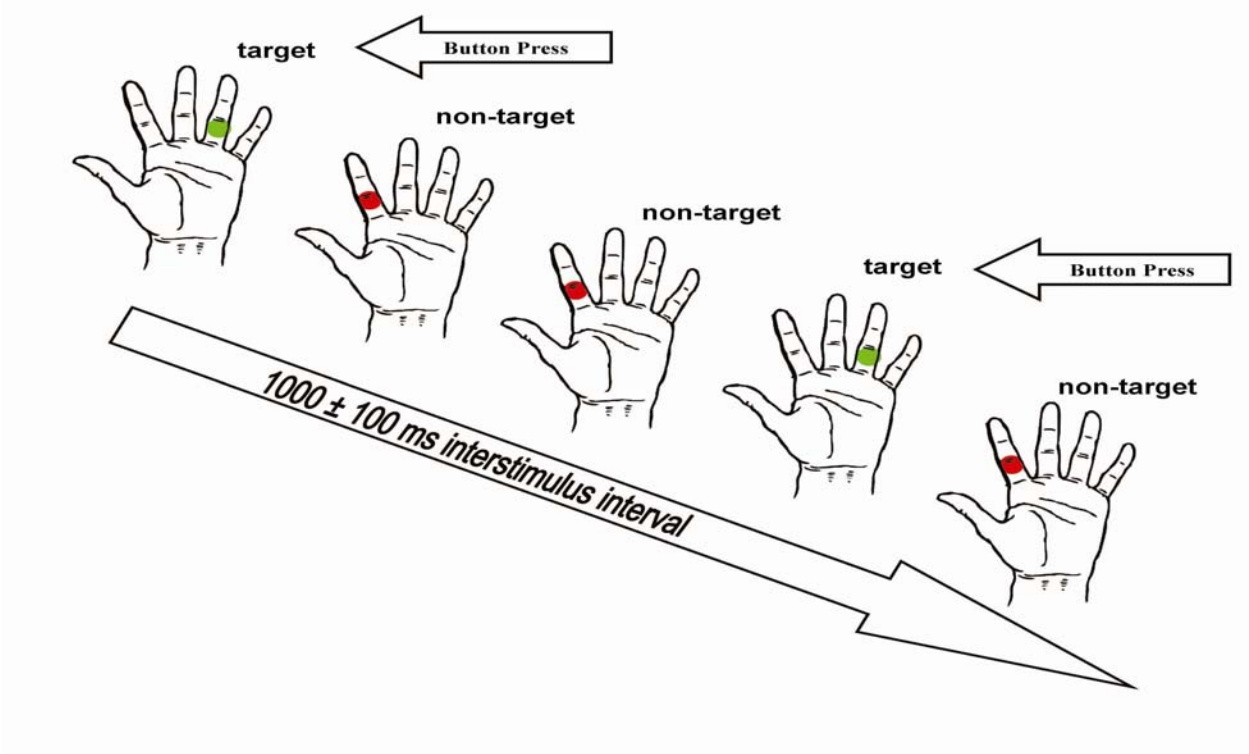

Figure 2-2: Illustration of the tactile button press oddball task. A solenoid-powered tapping device delivered non-painful taps to the volar surface of the 2nd (non-target) and 4th (target) digit of the non-dominant hand. Subjects were instructed to use their dominant index finger to quickly press a button in response to a perceived tap to the 4th digit of their left hand without responding to non-target stimuli**.**

2.5.4 ERP Recording Procedures

All electrophysiological brain recordings were acquired using Ag/AgCl electrodes (Grass Technologies, Rhode Island, USA) placed at 9 electrode sites Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, and above the left eye at Fp1 using the International 10-20 recording system. All electrodes were referenced to linked-earlobes with impedance values kept below 5 KΩ. EEG data were acquired using Neuroscan SynAmps amplifier. EEG recordings were continuously sampled at 1000Hz ADC and amplified with a calibrated gain of 5000 with a 0.05-30 Hz band-pass filter. Recordings were stored on a hard drive disk for off-line analysis.

2.5.5 EEG and ERP Signal Extraction

EEG data were analyzed offline using SCAN 4.4 (Neuroscan, USA). P3 analysis was completed for target stimuli only. Stimulus presentation and subject response were automatically recorded online on raw continuous EEG. Trials in which the waveforms in the EEG or EOG exceeded ± 80 μV in amplitude were automatically rejected, while smaller ocular artifacts were corrected using regression analysis combined with artifact averaging. Corrected data were time-locked to the infrequent stimulus onset and analyzed in 1000ms epochs with 200 ms pre-stimulus baseline correction before being averaged. Minimums of 60 trials were included per block, while within-block (sub-block) analysis included the first 30 trials per sub-block for block 1 data only. The sub-block analysis was designed as an intra-block analysis where electrophysiological trends in P3 occurring within each respective block could be measured and analyzed. This would not be possible in the block analysis since all trials within each respective block are averaged together to form the block average for between block analysis.

The P3 component was scored baseline to peak for correct target responses and defined as the most positive peak between 250 to 650 ms. This window was defined after inspection of individual TS patient data, as neurodevelopmental patient data often deviates from norms determined for typically developing adult controls (250-450msec). Task performance data during P3 oddball testing was collected for each subject. The average reaction time and percentage of correct responses was tabulated offline for each subject by block then tabulated into group averages. Trials containing incorrect responses, ocular artifacts or amplifier saturation were excluded from ERP averages.

2.6 Statistical Analysis

2.6.1 Sample Size

Prior to conducting the study an estimate of the appropriate sample size was calculated. The primary objective of this study is to measure the difference in evoked P3 amplitude between TS+ADHD and typically developing controls. A survey of P3 oddball-task research involving studies of TS or habituation in controls revealed an N of 12-20 participants per group (Thibault, et al., 2008; Zhu et al., 2006; Polich, & McIsaac, 1994). Due to differences in stimulus presentation and modality (visual, tactile, auditory), the present study expected that P3 amplitude outcomes would differ from those reported in the aforementioned papers, where a high degree of variance was present in mean amplitude and standard deviation between studies.

A review of the literature describing mechanical tactile stimulation in studies of P3 (Yamaguchi, & Knight, 1991) suggests that, depending on the electrode site, control P3 ERP (the primary outcome) in response to target stimuli range in amplitude from 10 μV to 22 μV. Using the average of this range we predict that there will be an effect due to group (Control versus TS+ADHD) of at least 25% or 4 μv. Using the predicted average standard deviation of 5.8 uV, a standardized effect size of 0.69 was calculated.

The sample size was then calculated using the method proposed by Rochon (1991) for two-group repeated measures experiments. A type I error rate of 0.05 and power of 0.8 were used in order to detect a standard effect size of 0.7 between TS+ADHD and control groups with AR correlation structure assumed for three repeated measurements at each electrode location for amplitude. Using these values to test a hypothesis for the main effect of group with a repeated measures correlation coefficient of 0.35 (from preliminary data), the sample size required for each group was calculated to be 18 subjects.

2.6.2 Statistical Analysis Procedures

Statistical analysis was performed using Statistical Analysis System (SAS) version 9.2. Descriptive analyses were conducted on all variables collected. Mean, standard deviation, maximum, and minimum were reported for the continuous outcomes. Percentages were reported

for categorical outcomes otherwise stated. T-test was used for analysis of normally distributed outcomes.

T-tests were used to analyze normal continuous data such as age, and IQ. Categorical demographic information (such as sex, handedness, OCB, and medication) as well as Sensory profile results were analyzed using Chi-square or Fischer's exact test (where the total sample size was less than 25). Conner's Parent ADHD ratings, YGTSS, and PUTS were analyzed using Wilcoxon non-parametric test and, Pearson correlations and linear regression analysis respectively.

Previous studies have found P3 to be evoked maximally at midline electrodes Fz, Cz, and Pz, with amplitudes increasing from the frontal to the parietal lobe. This pattern is not altered by stimulus modality (Dujardin, Derambure, Bourriez, Jacquesson, & Guieu, 1993; Johnson, 1993). The aim of the present study was to determine if differences between TS+ADHD and TDC exist in a number of sensory processing measures. A full electrode array would not contribute valuable information relating to the objectives of the study that could not be obtained from the key midline sites. Therefore, midline electrodes were chosen for analysis of P3 latency and amplitude using several univariate repeated-measures mixed model analyses. Amplitude and latency data were analyzed separately. Variables with mixed model univariate p values less than 0.1 were entered into a multivariable repeated mixed analysis with the following factors, group (TDC and TS+ADHD), block (levels 1-3), age, sex (male and female), electrode (Cz, Fz, Pz). An interaction term for group*block was studied using mixed model analysis to determine if the rate of change in amplitude or latency was significantly different between groups. A similar multivariable mixed model analysis was conducted for sub-block data to determine trends occurring within Block 1. Separate repeated mixed model analyses were used to analyze the capacity of Sensory Profile, YGTSS and Conner's ADHD symptom ratings to predict changes in P3 amplitude and latency. Reaction time and task performance criteria were compared between groups using multivariable repeated mixed modeling. Fixed effects of age, sex, block, and electrode were tested. Tukey-Kramer adjustment was used for mixed model post-hoc comparisons. Finally, Semmes-Weinstein sensory threshold data were compared using Wilcoxon rank sum, non-parametric test. Statistical analysis was performed using Statistical Analysis System (SAS) version 9.2. The significance level was set at 5% (two tailed) for all tests.

Previous P3 research designs have employed a general linear model repeated measures ANOVA analysis (Kececi, Degirmenci, & Atakay, 2006; Lindin, Zurron, & Diaz, 2004; Murphy & Segalowitz, 2004; Pfueller et al., 2011) however there are several advantages in using a mixed model repeated measures design. A mixed model was chosen for this current study, as it would allow for all patient data to be analyzed without dropping participants from the analysis due to missing data for 1 of 3 trial blocks. Furthermore, the mixed model repeated measures design allows for data to be missing without affecting other scores from that same patient (Gueorguieva, 2004; Littell, Henry, & Ammerman, 1998; Wolfinger, 1997) . The mixed model also does not require that time intervals for repeated measures be consistent between subjects. Finally, a very important advantage of mixed with repeated measures commands is that it allows one to specify different covariance structures (Littell, Henry, & Ammerman, 1998), whereas repeated measure ANOVA models of repeated measure analysis assume sphericity or compound symmetry (Gueorguieva, 2004). The sphericity assumption presumes that all measures at all times of measurement have the same variances and each measurement pair will be equally correlated. More clearly stated, this covariance assumption dictates that each subject within each group changes in the same way over trial blocks. Typically a Greenhouse-Geisser correction is applied to ERP data to correct for violations of sphericity (Luck, 2005). Greenhouse-Geisser correction works by attempting to adjust the degrees of freedom in the ANOVA test in order to produce a more accurate significance (p) value. If sphericity is violated the p values need to be adjusted upwards (and this can be accomplished by adjusting the degrees of freedom downwards). The Greenhouse-Geisser correction is a conservative correction (it tends to underestimate epsilon when epsilon is close to 1) and therefore tends to over-correct (Gueorguieva , 2004). In using a mixed model design we chose a model that, instead of assuming sphericity, allows one to choose the covariance model that best reflects the present data avoiding the application of corrections such as the Greenhouse-Geisser. Choosing the mixed model design also allows us to predict dependent variable outcomes (such as amplitude or latency) based on variables in the model such as age or sex.

Chapter 3
Results

3.1 Participant Demographics

Sixteen control and 15 TS+ADHD subjects were recruited for study screening. Four control participants were excluded from the study including a child found to have ADHD, a child suspected of having an undiagnosed tics disorder, and two children exhibiting inattentive and hyperactive behaviour who were not able to comply with the task requirements of the study. Two children in the TS+ADHD group were also excluded; one female child whose IQ was determined to be <75 and a male child who was unable to comply with task requirements and whose behaviour produced many artifacts during EEG collection.

Demographic and clinical characteristics were tabulated for the remaining subjects and compared for significant statistical differences between groups **(Table 3-1)**. The study sample included 12 TDC participants and 13 TS+ADHD participants with mean ages of 9.46 ± 2.024 years and 10.25 ± 1.77 years respectively. The mean age between groups was not statistically different ($p = 0.312$). The TS+ADHD group contained a significantly higher percentage of boys than the TDC group ($p=0.005$). Testing using the Wechsler Abbreviated Scale for Intelligence revealed a significant difference in IQ between groups ($p=0.005$), where the mean test scores differed by 16 points. TS participants exhibited average IQ score while TDC had superior IQ scores. TDC IQ scores ranged from 97-135, while TS+ADHD IQ ranged from 83-128. There were no reports of serious head injuries, however the parents of 2 control children and 1 TS+ADHD child suspected a single incidence of mild concussion. These incidents were not accompanied by blackouts or headaches lasting over night and were not followed up or assessed clinically.

The TS+ADHD group contained 85% right-handed participants, while all TDC's were all right handed. Though participants with OCD diagnoses were excluded from the study, subjects with sub-clinical obsessive-compulsive behaviours (OCB) were retained. Fifty-four percent of TS+ADHD children exhibited OCB. No signs of OCB were found amongst TDC subjects.

Ninety-two percent of control subjects were medication free (one TDC was prescribed inhaled corticosteroid to control asthma symptoms) and 100% free of psychotropic medication, while only 8% of TS+ADHD remained un-medicated at the time of study. All other TS+ADHD subjects were receiving psychotropic drugs. For medications taken by TS+ADHD group at the time of the study see **Table 3-2**.

	Control N=12	TS+ADHD N=13	Test Statistic	p
Mean Age ±SD	9.46 ± 2.02	10.25 ± 1.77	t test	0.312
Sex (% male)	25	85	Fisher's exact	0.0048
Mean WASI IQ ±SD	118.7± 12.18	102.8 ± 13.48	t test	0.005
Handedness (% right-handed)	100	85	Fisher's exact	0.4783
OCB (% with OCB)	0	54	Fisher's exact	0.0149
Family history of psychiatric illness (% with history present)	58	58 *	Fisher's exact	1.00
Medication (% medicated)	0	92	Fisher's exact	0.00003

* 1 subject missing

Table 3-1: Demographic and clinical characteristics data by participant group

	Alpha-agonist	Atypical antipsychotic		Stimulant		SSRI	SNRI	Natural hormone	Benzodiazepine
	Clonidine	Aripiprazole	Risperidone	Methylphenidate	Vyvanse	Citalopram	Atomoxetine	Melatonin	Temazepam
TS01	*							*	
TS02		*		*					
TS03				*		*			
TS04			*	*					
TS05		*							
TS06	*						*		
TS07									
TS08	*			*					*
TS09	*			*				*	
TS10			*						
TS11				*					
TS12	*			*					
TS13					*			*	
TS14	*			*					
TS15				*					

Table 3-2: Medication taken by participants of the TS+ADHD group.

3.2 Clinical Results

Clinical interviews and questionnaires were employed to assess the severity of TS (YGTSS and PUTS), symptoms of ADHD (Conner's Parent Scale), symptoms of OCB, and Sensory Sensitivity (Sensory Profile) **(Table 3-3)**.

							Conner's		YGTSS			SP
Subject	Sex	Age	Handedness	ADHD Sub-Type	Co-Morbid Diagnoses	OCB	Inattention Score	Hyperactivity Score	Current Total Tic Score	Total Tic Score	PUTS	Sensitivity
TS01	F	10.25	Right	Combined	Delayed sleep phase disorder, Anxiety, Rage	Yes	90	90	23	N/A	N/A	71
TS02	M	9.33	Left	Combined	None	Yes	90	71	29	34	13	43
TS03	M	10.5	Right	Combined	Initial Insomnia	Yes	79	76	0	11	N/A	67
TS05	M	10.16	Right	Inattentive	None	No	82	65	8	24	32	77
TS06	M	9.08	Right	Inattentive	Anxiety, Initial Insomnia, Learning disability	Yes	90	83	27	40	29	57
TS07	M	7.16	Right	Hyperactive/ Impulsive	None	No	55	72	5	21	12	74
TS08	M	10.92	Left	Combined	Rage, Anxiety	Yes	89	90	19	43	12	58
TS09	M	12.92	Right	Combined	ODD	No	90	90	25	30	30	59
TS10	M	12.33	Right	Combined	None	No	90	90	0	22	34	66
TS11	F	11.16	Right	Inattentive	Anxiety	Yes	81	66	23	31	13	70
TS12	M	8.58	Right	Combined	Learning disability	No	78	88	0	16	N/A	83
TS13	M	12.67	Right	Combined	Rage	No	74	79	18	30	31	84
TS15	M	8.16	Right	Combined	NO	No	79	63	3	13	15	84

Table 3-3: TS+ ADHD Patient Characteristics. Higher scores on Conner's' Parent Scale, Premonitory Urge for Tics scale (PUTS) and the Yale Global Tic Severity Scale (YGTSS) represent greater severity while lower scores (<80) on the Sensory Profile indicate greater sensitivity than the standardized norm**.**

3.2.1 Tic Severity Results

Tic severity was rated in all subjects using the YGTSS. While the YGTSS was used to assess severity in the TS+ADHD group, we also used the YGTSS to screen for tics in the control group. With the exception of the excluded control child who presented with previously undiagnosed tics, no tics were reported in the control group, resulting in a total and average score of 0 on all items. Current and lifetime tic severity was measured twice for each TS+ADHD subject. The current scores reflected the tic frequency and intensity during the week prior to the study assessment and for the lifetime scores represent the tic frequency and intensity at their worst. Mean current and worst-ever total tic severity scores were 13.8 ± 11.34 and 26.2 ± 10.20 respectively out of a total possible score of 50 points. Total tic severity for current and worst ever measurements spanned 0-29 and 11-43 points respectively. A Pearson product-moment correlation coefficient was computed to assess the relationship between current total tic severity and worst-ever tic severity. A positive correlation was found between the two variables ($R=0.854$, $n=12$, $p=0.0004$). The YGTSS global tic severity score includes an estimate of impairment in addition to the number, frequency, and intensity of phonic and motor tics calculated in the total tic severity score. A Pearson product-moment correlation coefficient was analyzed for current and worst-ever global severity and a positive correlation was also found between these two variables ($R=0.763$, $n=13$, $p=0.0024$).

3.2.2 Premonitory Urge for Tics (PUTS) Results

The Premonitory Urge for Tics Scale (PUTS) was used to rate positive sensory phenomena associated with tics in the TS+ADHD group. Two versions of the questionnaire were given, the first version asked subjects to indicate the presence or absence of 11 examples of sensory phenomena relating to tics. The second version of the questionnaire asked subjects to rate the frequency and intensity of the previous 11 examples. For each item, subjects indicated the presence (or absence) and frequency of the sensory phenomena in question using a numbered scaled anchored descriptors such as “1 = not at all true, 2 = a little true, 3 = pretty much true, and 4 = very much true”. Analysis of the first questionnaire demonstrated a group mean score of 5 where subject scores ranged from 0 to 11. A mean score of 5 indicates that on average the TS+ADHD group experiences 5 out of 11 symptoms on the PUTS. Results from this scale show

that 46% of TS+ADHD subjects reported feeling a sensation inside their body before performing a tic. An equal percentage of participants also felt as though there was energy inside that needed to be released, or felt wound up or tense inside. Of the 54% of subjects reporting premonitory urge phenomena, 100 % reported that the itchiness, energy, pressure, tense feelings or feelings that something isn't "just right" or complete, went away for at least a little while after performing a tic. When intensity/frequency was measured using the PUTS as developed by Woods (2005) the group mean was 22.1 ± 9.71 out of a possible 44 points. A Pearson's moment correlation coefficient was evaluated to assess the relationship between the PUTS and current and worst ever tic scores measured by the YGTSS. No significant correlation was found ($p=0.739$ and $p=0.860$ respectively).

3.2.3 Conner's 3–Parent Short Form ADHD assessment results

The Conner's 3 Parent Short rating scale was used to assess the presence and severity of ADHD symptoms in the control group and the TS+ADHD group. The questionnaire produces continuous percentile scores for symptoms in the following categories: defiance, executive functioning, hyperactivity/impulsivity, inattention, learning problems, and peer relations. Descriptive statistics were calculated for each category by group. Wilcoxon non-parametric exact test was selected for group comparison as Q-Q plots for each category demonstrated a data distribution that was not normal. No control subject produced individualized categorical scores outside the standardized norms for their age and sex. Control group mean scores in each category fell within the 49^{th} and 53^{rd} percentile. These scores were found to be average against standardized populations, validating clinical judgement for inclusion of these participants in the control group. The mean categorical scores for the TS+ADHD group fell within the 64^{th} and 82^{nd} percentile while individual scores ranged from the 38^{th} percentile (average) to the 90^{th} percentile. Group mean comparisons for each category revealed a significant difference in percentiles for all categories in the TS+ADHD ($p<0.0001$ except for defiance where the significance level was lower, $p=0.0027$). P values for group comparisons in hyperactivity/impulsivity and inattention were $p=2.75 \times 10^{-5}$ and $p=7.31 \times 10^{-6}$ respectively (see **Figure 3.1** for group means by category).

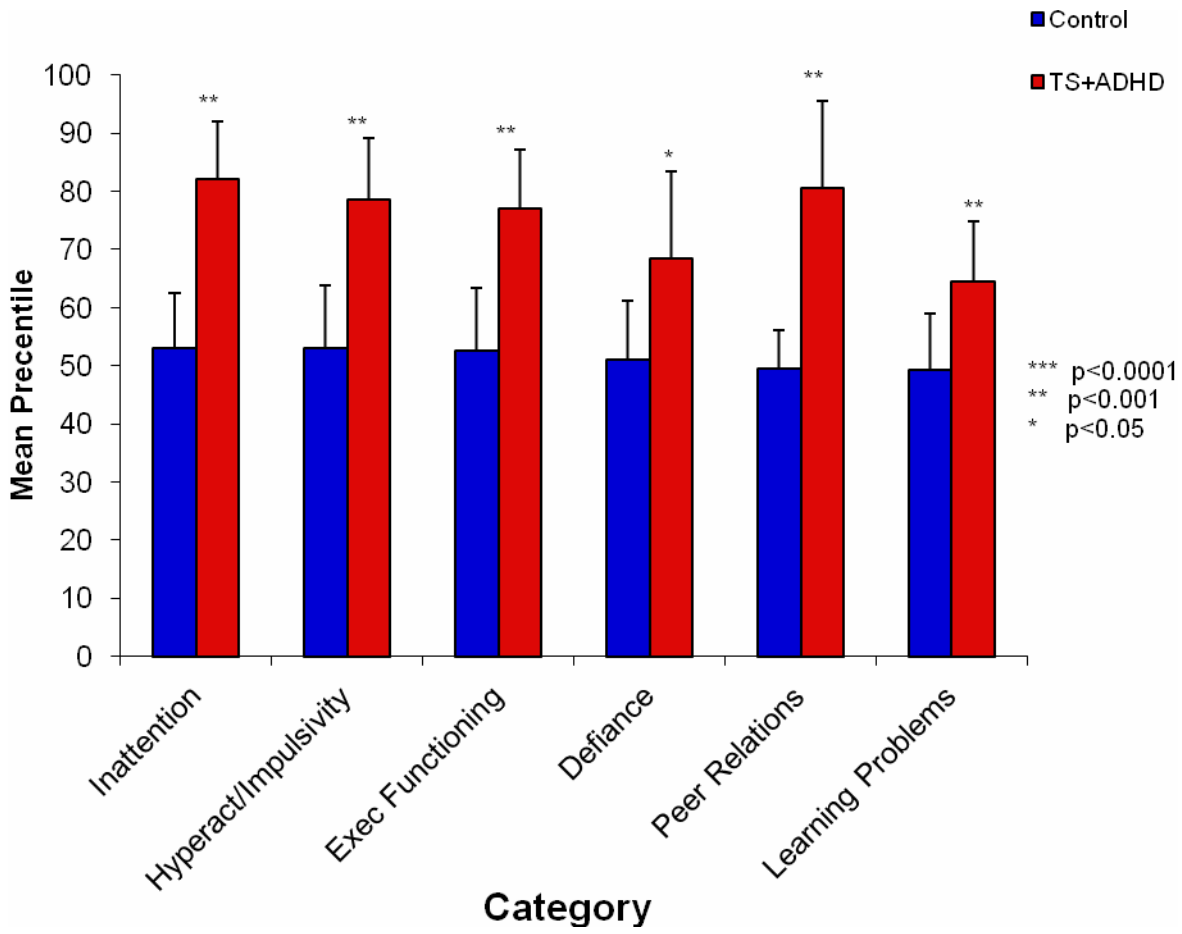

Figure 3-1: Conner's Parent Rating Scale mean percentile results by category. Parents were asked to rate their child's behaviour on a number of items tabulated into the above categories. Individual participant results are compared against a standardized population by age and sex in order to compute percentile scores before group means are tabulated. Statistically significant differences between TS+ADHD and TDC subjects are indicated with an asterisk.

3.3 Sensitivity Test Results

3.3.1 Sensory Profile Sensitivity Results

Subjective sensory experiences across modalities were obtained using the Caregiver Sensory Profile (SP). Parents were instructed to complete the questionnaire with input from the child participant. Because this is a caregiver questionnaire, the items are designed to ask questions about everyday behavioural responses to sensory stimuli that would be noticeable to an observer. Ordinal data responses tabulated by sensory category/modality were compared according to group using Fisher's exact test. For each statement of behaviour a response is given according to a Likert scale from 1-5 where 1 = Always and 5= Never. An example of a behaviour statement is "is sensitive to certain fabrics (for example is particular about certain clothes or bed sheets". Caregiver SP responses for all 125 items are tabulated then standardized against a normal distribution of scores to determine the subjects sensory classification. These classifications are: much less than others, less than others, similar to others, more than others and much more than others. To measure and compare sensory sensitivity between groups we examined the "Sensitivity Quadrant score" which assesses sensory sensitivity across modalities. SP results revealed that 87% of TS+ADHD subjects were either more or much more sensitive than the norm, compared to controls where 92% of subjects were similar in sensitivity to the standardized population **(Figure 3-2)**. A comparison of the mean group differences in the sensory sensitivity quadrant score confirmed a significantly higher frequency of sensory sensitivity in the TS+ADHD group vs. TDC ($p<0.0001$). Further evaluation of SP responses demonstrated significant group differences in sensory processing across modalities. Auditory ($p<0.0001$), visual ($p=0.0024$), vestibular ($p<0.0001$), touch ($p<0.0001$), oral ($p=0.0187$) and multi-sensory ($p<0.0001$) processing were assessed **(Figure 3-3)**. Examining touch sensitivity specifically, 77% of TS+ADHD children were sensitive to certain fabrics compared to only 8% of TDC and 69% of TS+ADHD children were reported as being irritated by shoes and socks compared to 0% of TDC. Differences occurred between groups in items pertaining to human touch, but these differences though significantly different between groups, were not as a common (i.e. rubs or scratches out a spot that has been touched, TS+ADHD 23% vs. 0%).

A Spearman correlation coefficient was evaluated to assess the relationship between worst ever and current total tic severity and SP sensitivity scores. A significant negative correlation was found in both comparisons, where a stronger correlation existed between worst ever tic scores and SP sensitivity [(current YGTSS R=-0.571; p=0.0417 and worst ever YTGSS R=-0.630; p=0.0280)(**Figure 3-4**)].

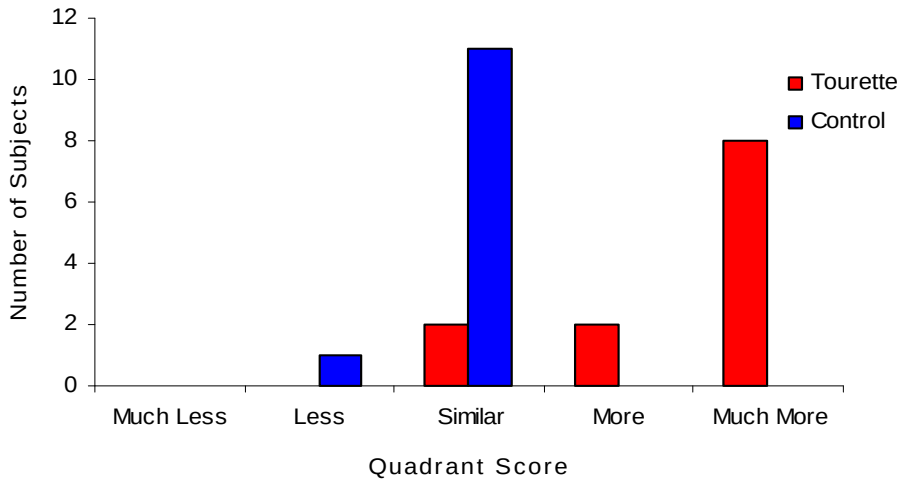

Figure 3-2: Caregiver Sensory Profile standardized Sensory Sensitivity quadrant frequencies by group.

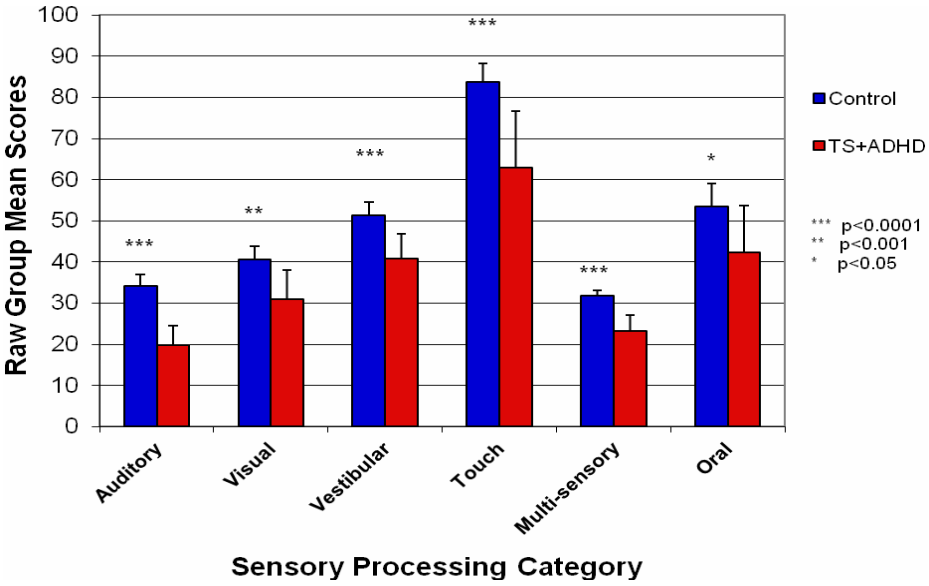

Figure 3-3: Subjective reports of sensitivity made by parents using the Caregiver Sensory Profile. One hundred and twenty-five questions regarding sensory experiences across multiple modalities were tabulated per subject and categorized by the modalities seen above. Generally, lower raw scores indicate greater sensitivity than the standardized norm, however touch is represented by the largest number of items per modality on the scale. Statistically significant differences between TS+ADHD and TDC subjects are indicated with an asterisk, error bars indicate standard deviation.

A Spearman correlation coefficient was evaluated to assess the relationship between Conner's scores of inattention, hyperactivity/impulsivity and SP sensitivity scores. A significant negative correlation was found in both comparisons, where a stronger correlation existed between inattention scores and SP sensitivity than hyperactivity/impulsivity and SP Sensitivity [(inattention R=-0.826; p<.0001 and hyperactivity/impulsivity R=-0.706; p<.0001 (**Figure 3-5)**. A student's t-test was used to evaluate the influence of OCB symptoms on SP sensitivity by dividing the TS+ADHD subjects into two groups according to OCB presence. Analysis revealed that TS+ADHD subjects with OCB symptoms (M=61.0, SD=10.64) were significantly more sensory sensitive according to the SP than TS+ADHD participants without OCB (M=75.3, SD=9.72), t(11)=2.20, p=0.028).

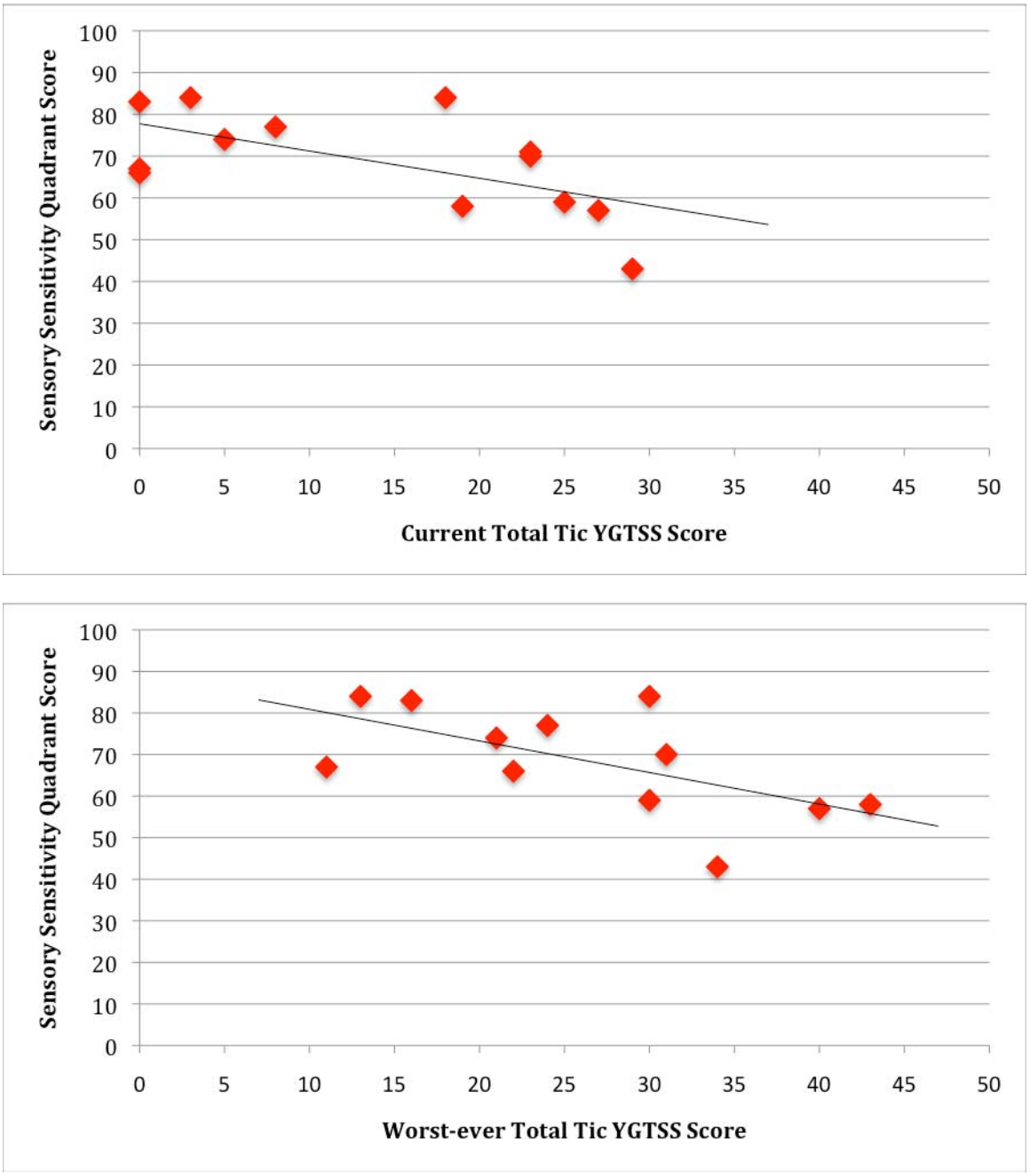

Figure 3-4: Scatter plot representations of the negatively correlated relationship between Sensory Profile sensory sensitivity scores and current (R=-0.571; p=0.0417) or worst-ever YGTSS tic severity R=-0.630; p=0.0280) for TS+ADHD subjects. A lower sensitivity score indicates greater sensitivity compared to the normative population. Therefore the data suggests that symptoms of sensory sensitivity are positively correlated with tic severity.

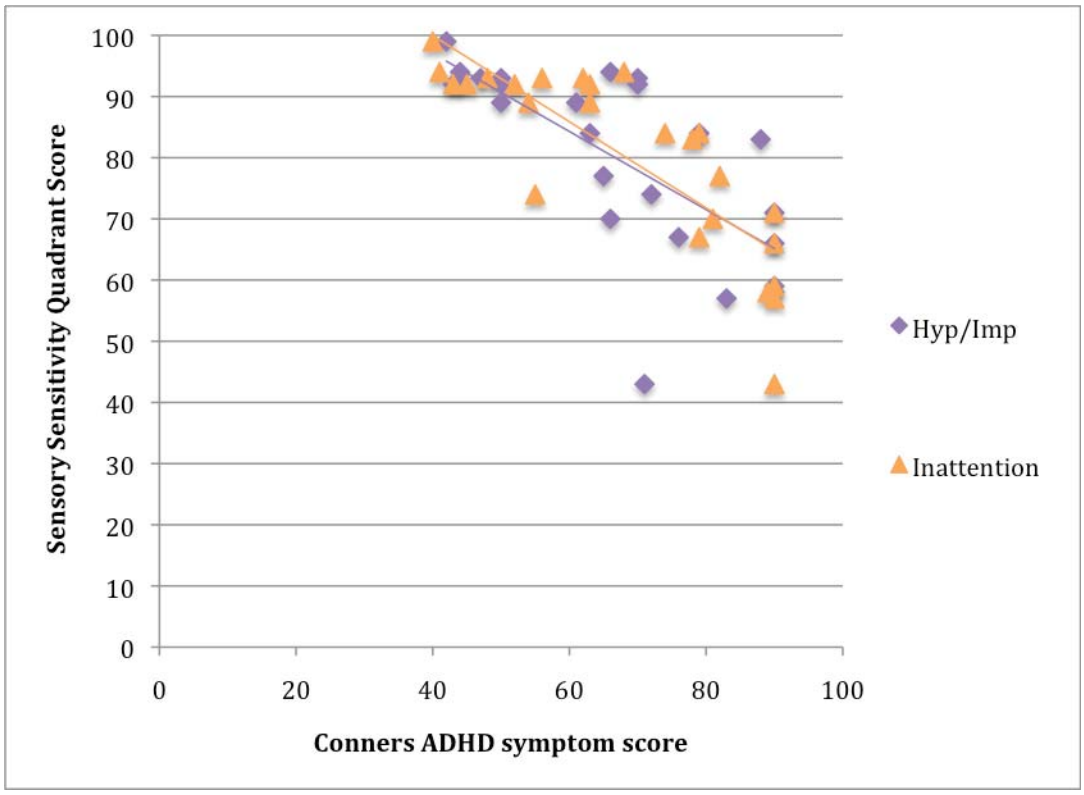

Figure 3-5: Scatter plot representations of the negatively correlated relationship between Sensory Profile sensory sensitivity scores and Conner's symptoms of hyperactivity/impulsivity ($R=-0.706$; $p<.0001$) and inattention ($R=-0.826$; $p<.0001$) for all subjects. A lower sensitivity score indicates greater sensitivity compared to the normative population. Therefore the data suggests that symptoms of sensory sensitivity are positively correlated with hyperactivity/impulsivity, and inattention.

3.3.2 Semmes-Weinstein Tactile Threshold Test Results

Tactile thresholds were measured in both groups using Semmes-Weinstein filaments **(Table 3-4).** On average the TS+ADHD group had significantly lower tactile threshold than control children (p=0.0268). Though the difference was statistically significant, both groups were within the normal clinical range for touch sensitivity. A Spearman correlation coefficient was calculated to assess the relationship between tactile sensory threshold and sensitivity quadrant scores measured by the SP for each subject. A significant positive correlation was found (R=0.575; p=0.0051). A similar assessment performed for tactile threshold and touch sensitivity using SP scores was also statistically significant (R= 0.518; p=0.0135). No significant correlation was found between tactile threshold and current or worst ever YGTSS scores(R=0.279; p=0.4048 and R=0.240; p=0.476 respectively).

	Mean (g)	SD	Median	Maximum	Minimum	p
Control	0.04	0.020	0.04	0.07	0.02	0.0268
TS+ADHD	0.02	0.011	0.02	0.04	0.01	-

Table 3-4: Tactile threshold descriptive statistics for control and TS+ADHD participants.

3.4 Electrophysiology Results

3.4.1 Behavioural Observation

Electrode set-up and testing protocol was well tolerated by 15 of 16 TDC subjects tested. One subject reported discomfort and presented with extreme irritation and behavioural decline. This subject was excluded from analysis due to his inability to tolerate and cooperate with electrophysiology protocol as mentioned in the demographic results section. Four of fifteen TS+ADHD subjects reported difficulty tolerating white noise during testing, including one participant who experienced nausea and dizziness. Despite discomfort, every TS+ADHD subject

was able to complete the task. Some accommodations such as an extended time interval between blocks, lower volume of white noise or no white noise were made in the protocol for the four subjects who indicated discomfort during the study. Therefore IBI varied between 2- 6 minutes across subjects. Each subject was able to correctly execute the oddball response task after less than 3 minutes of practice. During the testing period the majority of subjects reported feeling tired or drowsy by the 2nd ERP testing block. This behavioural observation coincided with the increased presence of alpha waves in the continuous EEG recording. It was thought a priori that tic behaviour would present as a challenge by increasing artifacts during data collection however only one TS+ADHD subject presented with a tic frequency or intensity that resulted in complete exclusion from the study.

A mixed model analysis was performed to assess reaction time and the percentage of correct responses for group differences during the oddball task **(Table 3-5)**. The mean percentage of correct responses across blocks was found to be higher in the control group however this trend did not reach statistical significance (p=0.0715). A significant difference in percent correct responses across trial blocks was not found (p=0.5515). Finally, assessment of reaction time revealed no significant differences between groups (p=0.1615) or between trial blocks (p<0.8082). These results show that there were no significant group or block differences in P3 task performance.

	Control (n=12)			TS+ADHD (n=13)			Group comparison	
	Block 1	Block 2	Block 3	Block 1	Block 2	Block 3	Test	p
Reaction Time (Mean ± SD)	562 ± 63	555 ± 51	550 ± 65	525 ± 79	528 ± 58	530 ±95	F	0.1615
% Correct Responses	80.8	80.0	82.0	69.8	80.0	72.8	F	0.0715

Table 3-5: Mean reaction time and % correct responses by block and group for control and TS+ADHD subjects

3.4.2 P3 Waveform

Though data was collected from all 25 subjects included in the study, some portions of data were rejected from analysis when too many artifacts were present or the minimum criteria for the number of accepted epochs was not met. As a result, a total number of 219 observations were included in each of the multivariable models for latency and amplitude. Each accepted mean amplitude or latency for 1 individual at a specific electrode and block is considered as one observation. The P3 component peaked at an average latency of 461 ms post stimulus and demonstrated typical morphology across blocks previously found in pediatric populations **(Figure 3-6)**.

A number of models were tested within the mixed design however the data best fit a linear model. Therefore the estimates described below describe the linear predicted effect of the independent variable on dependent variables, latency and amplitude respectively.

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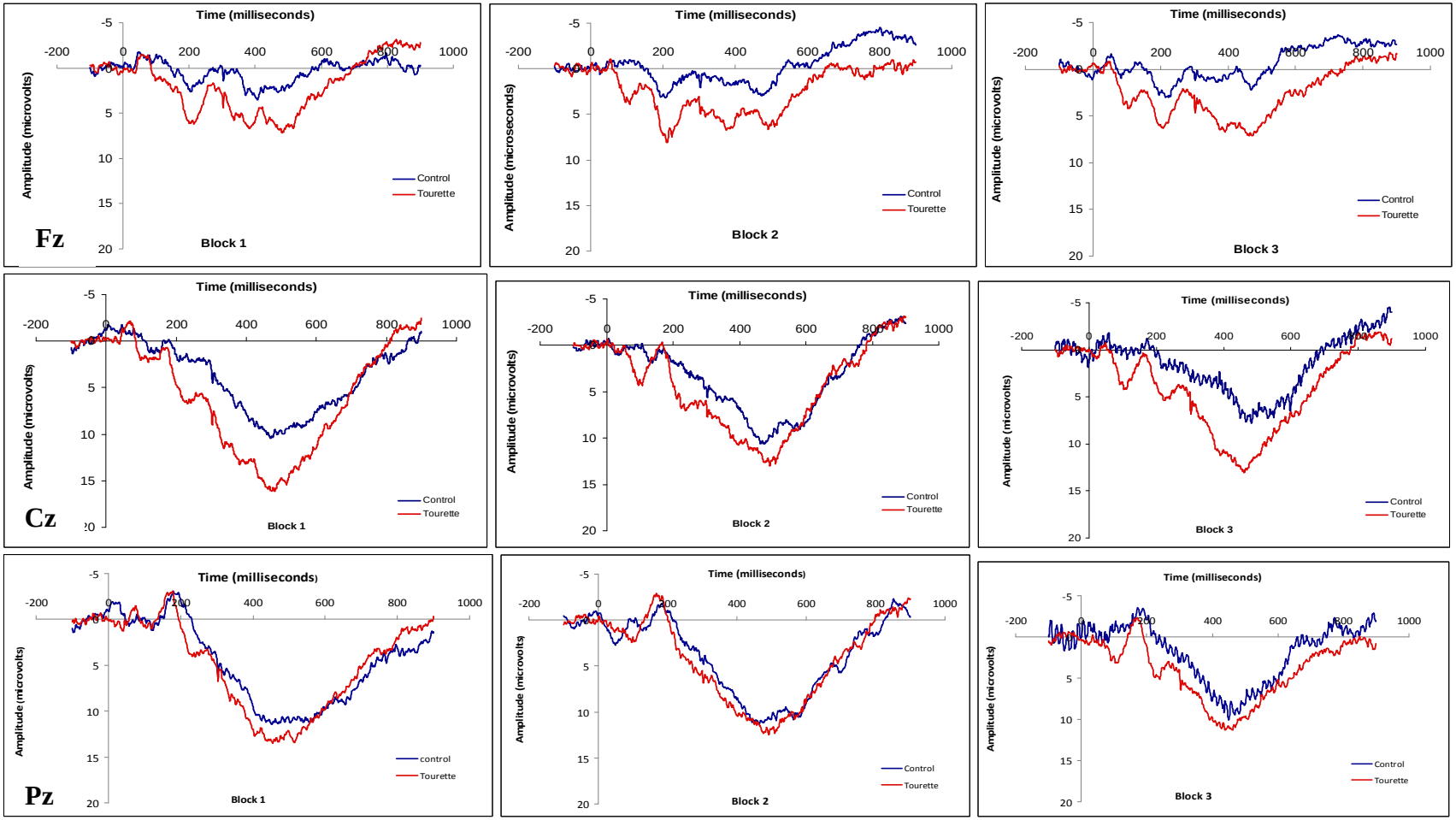

Figure 3-6: Stimulus- locked P3 ERP grand average waveforms for block 1-3 at Fz, Cz, and Pz (from top to bottom). The P3 component showed increased amplitude in the TS+ADHD group compared to TDC across all three blocks demonstrating an increased oddball effect in the patient group.

3.4.2.1 Latency

Univariate mixed model analysis of latency was used to assess for independent variable effects on latency and revealed a significant effect of age ($p<0.0001$), electrode ($p<0.0001$), YGTSS current total tic severity score ($p=0.0293$), and Conner's inattention ($p=0.0411$) and hyperactivity/impulsivity ($p=0.0036$) scores. No significant effect on latency was found for group ($p=0.484$), sex ($p=0.5882$), block ($p=0.0698$), or medication ($p=0.4418$), **Table 3-6.**

Variable	Estimate	SE	t value	p
Age	-25.67	4.488	-5.72	<.0001
Sex (F vs. M)	10.48	19.267	0.54	0.5882
IQ	0.01	0.635	0.02	0.9838
Group (TDC vs TS)	13.48	19.162	0.70	0.484
Electrode	-	-	-	<.0001
Block	-	-	-	0.0698
Handed-ness	11.51	34.135	0.34	0.7369
Medication	-14.81	19.153	0.77	0.4418
Presence of Psychiatric Family History	13.65	19.423	0.70	0.4844
Presence of OCB	-20.42	21.561	-0.95	0.3468
YGTSS Current Total Tic Score	2.08	0.915	2.27	0.0293
YGTSS Worst Total Tic Score	1.86	1.102	1.69	0.1006
Conner's Inattention score	-1.05	0.503	-2.08	0.0411
Conner's Hyperactivity/Impulsivity	-1.56	0.518	-3.01	0.0036
ADHD combined	-0.69	0.263	-2.61	0.0112
Tactile threshold	-18.37	45.787	-0.40	0.6897
Sensory Profile Sensitivity Score	-0.07	0.666	-0.11	0.9159

Table 3-6: Mixed model univariate analysis results for effects on P3 latency.

A combination of statistical and clinical judgment was used to select independent variables of interest to investigate the main research questions surrounding group differences in P3 latency. Although many items were inspected for the univariate analysis of latency, our sample size could not withstand the reduction in power that would occur in a large model constructed with every statistically significant variable from univariate analysis. Mixed model multivariable analysis of selected variables, age, sex, group, electrode, and block further validated univariate results by demonstrating a significant effect of age ($p<0.001$), and electrode ($p=0.0063$) while controlling for all other selected variables (see **Table 3-7**). This model shows that when controlling for age, electrode and block, there is no significant effect of group in predicting P3 latency outcomes. The model predicated a negative linear relationship between age and latency where latency decreases by 24.2 ms for every yearly increase in age. Post hoc analysis of latency data by electrode revealed significant differences between Cz and Fz ($p=0.0184$) electrodes and Pz and Fz electrodes ($p=0.0128$) where latency at Fz is significantly shorter than both Pz and Cz latencies.

Variable	Estimate	SE	DF	t value	p	Tukey - Kramer Adjusted p
Age	-24.19	4.144	69	-5.84	<.0001	
Sex (F vs. M)	0.85	18.597	69	0.05	0.9638	
Group (TDC vs TS)	-3.09	18.692	69	-0.17	0.8692	
Electrode (Cz vs Pz)	-2.42	18.224	69	-0.13	0.8949	0.9904
Electrode (Fz vs Pz)	-53.29	18.224	69	-2.92	0.0047	0.0128
Electrode (Cz vs Fz)	50.87	18.224	69	2.79	0.0068	0.0184
Block (1 vs. 3)	23.88	11.505	69	2.08	0.0417	0.1024
Block (2 vs. 3)	15.09	13.269	69	1.14	0.2595	0.4949
Block (1 vs. 2)	8.80	14.452	69	0.61	0.5448	0.8159

Table 3-7: Mixed model multivariable analysis of independent variable effects on latency**.**

3.4.2.2 Amplitude

The P3 component peaked at the average amplitude of 13.20 μV. Univariate mixed model analysis of amplitude was used to assess for independent variable effects on amplitude. Univariate analysis revealed a significant effect of group, IQ, electrode, block, medication, OCB, Conner's Inattention score, Conner's Hyperactivity/Impulsivity, Sensory Profile Sensitivity Score in predicting amplitude **(Table 3-8)**. Within these significant effects, group, medication, presence of OCB and tactile threshold predicted greater magnitudes of effect in determining amplitude.

Variable	Estimate	SE	t value	p
Age	0.957	0.3822	0.25	0.803
Sex (F vs. M)	-1.291	1.3637	-0.95	0.3472
IQ	-0.105	0.0435	-2.42	0.0179
Group (TDC vs TS)	-4.313	1.2679	-3.4	0.0011
Electrode	-	-	-	<.0001
Block	-	-	-	0.006
Handed-ness	0.598	2.4305	0.25	0.8065
Medication	4.414	1.2701	3.48	0.0009
Presence of Psychiatric Family History	2.138	1.3698	1.56	0.1231
Presence of OCB	-5.191	1.4545	-3.57	0.0006
YGTSS Current Total Tic Score	0.048	0.0695	0.7	0.4911
YGTSS Worst Total Tic Score	-0.037	0.0770	-0.48	0.635
Conner's Inattention score	0.011	0.0290	3.8	0.0003
Conner's Hyperactivity/Impulsivity	0.082	0.0324	2.54	0.0132
ADHD combined	0.051	0.0158	3.26	0.0017
Tactile threshold	-5.695	3.0106	-1.89	0.0633
Sensory Profile Sensitivity Score	-0.150	0.0445	-3.36	0.0013

Table 3-8: Mixed model univariate analysis results for effects on P3 amplitude.

Similar to latency analysis, the final multivariable model used to investigate group difference in amplitude was constructed using a combination of statistical and clinical judgment. A statistically significant difference in IQ was found between study populations. Univariate analysis demonstrated a significant effect of IQ on amplitude (p=0.0179). As previously mentioned, evidence suggests that differences in IQ can contribute to differences in P3 amplitudes amongst controls suggesting that IQ should be analyzed in the multivariable model for amplitude. When the effect of IQ was analyzed along with group, block, electrode, age and sex, IQ no longer yielded a significant effect on amplitude (p=0.3834; **Table 3-9**).

Variable	Estimate	SE	DF	t value	p	Tukey - Kramer Adjusted p
Age	-0.1737	0.2722	68	-0.64	0.5256	
Sex (F vs. M)	1.970	1.2368	68	1.59	0.1157	
IQ	-0.03512	0.04003	68	-0.88	0.3834	
Group (TDC vs. TS)	-4.9324	1.4137	68	-3.49	0.0009	
Electrode (Cz vs. Pz)	0.3235	1.2031	68	0.27	0.7888	0.9610
Electrode (Fz vs. Pz)	-6.6926	1.2031	68	-5.56	<.0001	<.0001
Electrode (Cz vs. Fz)	7.0161	1.2031	68	5.83	<.0001	<.0001
Block (1 vs. 3)	2.1558	0.7572	68	2.85	0.0058	0.00159
Block (2 vs. 3)	1.3388	0.5616	68	2.38	0.0199	0.0515
Block (1 vs. 2)	0.8170	0.06038	68	1.35	0.1805	0.3711

Table 3-9: Mixed model multivariable analysis results for effects on P3 amplitude.

The multivariable model for amplitude reveals that when differences in age, sex, and IQ are controlled there is a significant group difference in amplitude between controls and TS+ADHD children (p=0.0009). The model predicts an average difference of 4.93 μV between controls and TS+ADHD subjects. This prediction is roughly approximated in the data where across all 3 blocks TS amplitude is significantly higher than controls (**Figure 3-7**). There was no significant effect of age or sex on amplitude (p=0.5256 and p=0.1157 respectively).

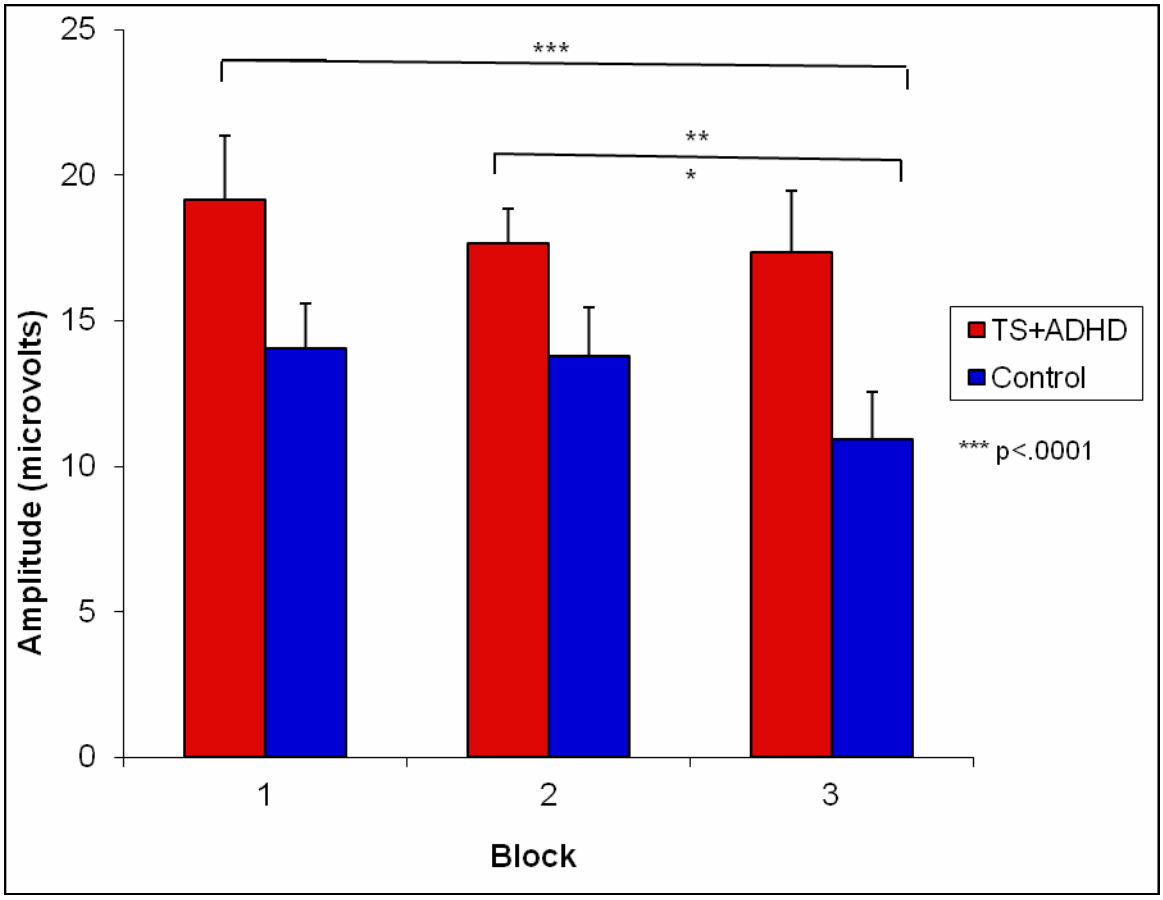

Figure 3-7: Mean P3 amplitude comparison at Cz by group and by block. TS+ADHD subjects demonstrated significantly higher amplitudes than controls at each block (p<.0001).

A significant effect of electrode was found for amplitude ($p<0.0001$). Post hoc analysis showed that Cz>Pz>>Fz, however the significant difference occurred between Cz and Fz ($p<0.0001$) and Pz and Fz ($p<.0001$) electrode comparisons only. No significant difference in amplitude was found between Cz and Pz electrodes ($p=.9610$).

A significant effect of block was found for amplitude ($p=0.0164$) where amplitude decreased successively between blocks. A significant decrease in amplitude was found between blocks 1 and 3 ($p=0.0159$) and blocks 2 and 3 ($p=.0515$). An interaction term GROUP*BLOCK was evaluated to determine the effect of group in the rate of habituation between trial blocks. Though the slopes characterizing changes in amplitude by block differed between groups in magnitude **(Figure 3-8)**, the interaction between block and group was not significant ($p=0.6281$).

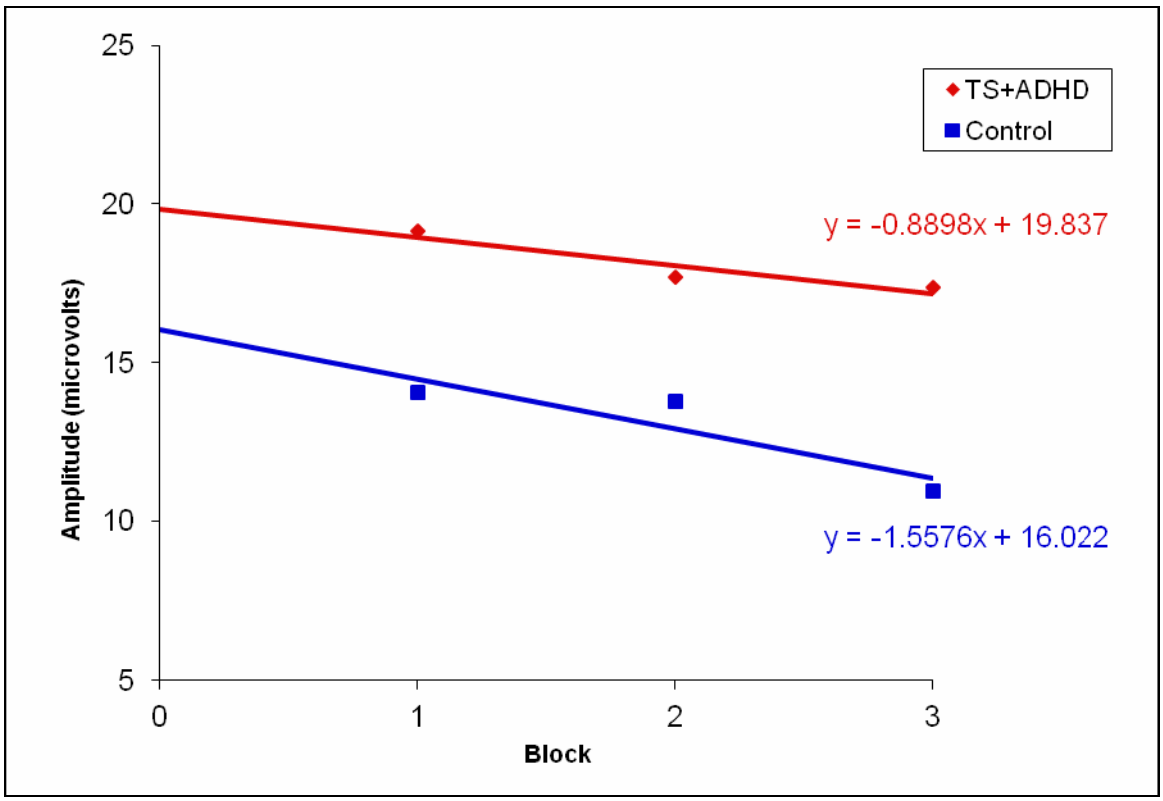

Figure 3-8: P3 mean peak amplitude trends by block and at Cz. Both groups demonstrated a significant decline in P3 amplitude across successive blocks ($p=0.0028$), however the trend for a faster rate of decline in controls did not reach statistical significance ($p=0.6281$).

3.4.3 4.4.3 Sub-block trends

A sub-block analysis was evaluated on block 1 data in order to explore any intra-block trends or differences between groups. Sub-block analysis was conducted on 7 TDC and 5 TS+ADHD children. Mixed model analysis indicated a significant main effect of electrode (p=0.0001) in sub-block amplitude, while main effects for group and sub-block were insignificant (p=0.0950 and p=.0920 respectively,) **(Table 3-10).** Similar to block trends, sub-block amplitude was consistently larger at electrodes Pz and Cz than Fz.

Variable	Estimate	SE	DF	t value	p
Group (TDC vs TS)	-3.0895	1.7959	32	-1.72	0.095
Electrode (Cz vs Pz)	0.036	2.1688	32	0.02	0.9869
Electrode (Fz vs Pz)	-9.0875	2.1688	32	-4.19	0.0002
Sub-block (A vs B)	2.081	1.1979	32	1.74	0.092

Table 3-10: Sub-block mixed model multivariable analysis effects on amplitude.

Sub-block analysis for main effects for latency indicated a significant effect of sub-block where P3 latency during sub-block A was significantly less than sub-block B. No significant main effect for group (p=0.5802) or electrode (p=0.190) was found for latency outcomes **(Table 3-11)**.

Variable	Estimate	SE	DF	t value	p
Group (TDC vs. TS)	13.1069	23.4566	32	0.56	0.5802
Electrode (Cz vs. Pz)	-29.0316	28.3266	32	-1.02	0.3131
Electrode (Fz vs. Pz)	-52.909	28.3266	32	-1.87	0.071
Sub-block (A vs. B)	-38.5833	16.9828	32	-2.27	0.03

Table 3-11: Sub-block mixed model multivariable analysis for effects on amplitude

Chapter 4
Discussion

4.1 Summary of the Main findings

The results of this work demonstrate a significant difference between children with a co-morbid diagnosis of Tourette's syndrome and ADHD and age-matched controls in their behavioural, and physiological processing of touch. Behavioural reports revealed that 87% of TS+ADHD children were more or much more sensitive than the standardized norm. When compared to our control group, the significant increase in sensitivity ($p<0.0001$) to sensory stimulation in TS+ADHD appeared to be generalized across modalities with the greatest differences in sensitivity occurring in auditory, vestibular, and touch domains ($p<0.0001$). Behavioural results were mirrored in physiological threshold testing, as TS+ADHD children were demonstrably more sensitive to touch when tested with mechanical stimulation ($p=0.0268$). Furthermore significant differences were also seen in the electrophysiological response of TS+ADHD children, indicating central nervous system dysfunction that may mediate the heightened ability of this group to detect stimuli.

4.2 Behavioural responses of Tourette's children in the sensory environment

4.2.1 Summary of Results

This study represents the first study to assess behavioural sensitivity in children with Tourette syndrome. Of the 13 TS+ADHD children assessed in this study, 11 children (87%) were reported as being significantly more or much sensitive to sensory stimulation when measured using the standardized SP tool. Increased sensitization was not limited to specific modalities as the TS+ADHD group differed significantly from the controls across all modalities measured including auditory ($p<0.0001$), visual ($p=0.0024$),

vestibular ($p<0.0001$), touch ($p<0.0001$), oral ($p=0.0187$) and multi-sensory ($p<0.0001$) stimuli.

4.2.2 Review of Behavioural results in other studies of TS

Cohen and Leckman (1992) conducted a phone interview with 28 participants aged 6-90 and found that of the 20 that reported sensory sensitivity, 14 individuals (70%) indicated hypersensitivity to tactile, auditory, and visual stimuli. No significant difference was found in age or tic severity. Likewise, a more recent study assessed sensory behaviours in adult TS subjects across all 5 senses using a questionnaire adapted from the Sensory Profile. The results indicated that 80% of their TS group indicated a general heightened sensitivity to touch compared to 19 controls (Belluscio, Jin, Watters, Lee, & Hallett, 2011) . With the exception of taste, Belluscio et al found a significant increase in sensitivity across each modality in the TS group ($p<.01$) with the largest proportion of sensitivities occurring in smell (70% TS: 25% CTL), touch (65% TS; 25%), and light (TS 60% : CTL 15%).

4.2.3 Influence of Age and Co-morbidity in Behavioural Response to Sensory Stimulation

4.2.3.1 Age

Although three studies of sensory sensitivity in TS population reported generally similar results, there were some differences in the incidence of sensory hypersensitivity both in TS and in controls. These may have been mediated by age and co-morbidity. The age range studied in the aforementioned studies were: mean age: 20.4; range 9-60 (Cohen and Leckman 1992) and mean age: 36.2±8.4; range:23-50 (Belluscio et al, 2011). The present study recruited TS participants with the youngest mean age of 10.25 ± 1.77, within the range of 6-12 years of age. At 87% these children demonstrated the largest incidence of sensory sensitivity consistent with the clinical experience that the prevalence and severity of sensory sensitivity decreases with increasing age. A search of the literature did not uncover any previous work establishing the life history of behavioural reports of sensory sensitivity in control or developmental populations.

The human brain follows a complex developmental trajectory, where neuroanatomical changes are age-specific and are accompanied by age specific skills. It is plausible that the sensory hypersensitivity within younger age populations (both neurodevelopmental and control) reflect a lack of maturity within networks that mediate cognitive and emotional control during somatosensory stimulation (Chatham, Frank, & Munakata, 2009; Cox, Mills-Koonce, Propper, & Gariepy, 2010). It has been suggested that once the brain development allows for better inhibitory function thus yielding improved behavioural control, the sensory hypersensitivity may become extinguished in adults leading to lower prevalence of behavioural sensitivity (Koziol, Budding, & Chidekel, 2011). If the deficit in the implied pathways for behavioural processing of sensory stimulation persists this may result in an adult with hypersensitivity that does not resolve with age. This hypothesis is supported by evidence that age negatively correlates with physiological sensory sensitivity; indicating that developmental changes are occurring that may foster decreased sensory sensitivity with age (Lin, Hsieh, Chao, Chang, & Hsieh, 2005; Sosenko, Kato, Soto, & Ayyar, 1989).

4.2.3.2 Co-morbidity

None of the aforementioned studies recruited a large enough population to explore the contribution of co-morbidity to heightened sensitivity, however an exploratory sub-group analysis of behavioural sensitivity in the research of Belluscio et al (2011) revealed that 60% of patients with mild TS (YGTSS total tic severity <20 of 50) and 90% of those with co-morbid OCD/OCB reported heightened sensitivity. Data was not provided on the incidence of heightened sensitivity in co-morbid ADHD. The present study excluded subjects with OCD, however more than half of subjects had the presence of OCB (54% TS+ADHD). Of the 10 OCD/OCB subjects in the Belluscio study, 8 were also co-morbid for ADHD diagnosis. Co-morbid diagnoses were not described in the research of Cohen and Leckman (1992).

There is research that suggests a potential link between sensory hypersensitivity and performance of excessive rituals in OCD (Baranek, Foster, & Berkson, 1997; Dar, Kahn, & Carmeli, 2012b; Hazen et al., 2008). One particular study of sensory sensitivity in

children with OCD found a significant association between ritualistic and anxious behavior and behavioural sensory sensitivity to oral and tactile stimuli reported by parents on the SP. A larger pool of adults were polled in a self-report questionnaire of present and childhood behaviours and similarly a significant correlation was found between oral and tactile sensitivity and anxious or ritualistic behavior (Dar, Kahn, & Carmeli, 2012). Sensory differences in adult OCD groups have also been found using SP, where significant sensory sensitivity was present, entailing difficulty ignoring stimuli and readily responding to them (Brown & Dunn, 2002; Rieke & Anderson, 2009). This is consistent with the findings of the present study as well as the results of Belluscio et al. (2011) where close to 50% of subjects experienced OCB or OCD in both studies, and nearly all of these subjects reported heightened sensory sensitivity. Furthermore, the present study found that when compared to the remaining population without OCB, those with OCB reported significantly higher sensory sensitivity measured by the SP ($p=0.028$).

In addition to OCD, ADHD symptoms have been associated with sensory difficulties as well. The present study found that ADHD symptoms of inattention ($R=-0.826$; $p<.0001$) and hyperactivity/impulsivity ($R=-0.706$; $p<.0001$) were highly correlated with SP reports of sensory sensitivity. Studies have found that the incidence of sensory processing problems in children with ADHD is higher than the general population (Dunn & Bennett, 2002; Mangeot et al., 2001; Parush, Sohmer, Steinberg, & Kaitz, 1997; Sosenko, Kato, Soto, & Ayyar, 1989). Dunn and Bennett (2002) used the Sensory Profile to measure sensory processing patterns in children with ADHD compared to children without developmental disability. They found that ADHD children were significantly more sensitive to perceived sensory stimuli, and differed behaviourally from controls in their SP auditory, tactile, visual processing scores ($p<.0001$) indicating behavioural evidence of dysfunction in these sensory domains. Generally, children typically characterized as sensory sensitive are also significantly more likely to be hyperactive and distractible and Dunn suggests that this may be due to overactive neural systems lacking the ability to habituate responses to the constant presentation of stimuli in the environment (Dunn, 1997). This may indicate that a greater presence of ADHD co-

morbidity in a TS study population may increase the incidence and perhaps severity of sensory processing disturbances including touch processing.

Furthermore, children with ADHD typically present with behavioural and neuropsychological testing deficits in emotional control, planning, inhibition and working memory (Sjowall, Roth, Lindqvist, & Thorell, 2012). These behaviours have been supported with imaging research, where these functions have been shown to be mediated by fronto-parietal and sensorimotor areas implied in TS etiology (Church et al., 2009; Cortese et al., 2012; Fahim et al., 2010; Wittfoth et al., 2012). Decreases in lateral frontal cortex volumes in both groups have been associated with impairments in representation and execution of goal-directed behaviour (Fuster, 2002). Deficits in these areas would clearly influence everyday behaviour including the selection and execution of responses to sensory stimulation. A diagnosis of ADHD may increase the difficulty in controlling emotional responses towards stimuli that are perhaps annoying or aversive, but not painful. Collectively these trends in age and co-morbidity offer insight into the factors that may contribute to small differences in the incidence of sensory sensitivity in TS investigations.

4.3 Changes in External Sensitivity Measured in TS

4.3.1 Summary of Tactile Threshold Results

Increased behavioural sensitivity in TS is thought to result from central processing changes in behavioural inhibition combined with dysfunctional affect control (Leckman, Bloch, Scahill, & King, 2006; Stern, Blair, & Peterson, 2008). In the present study the tactile sensory threshold the TS+ADHD group was able to perceive tactile stimulation of a lower intensity, indicating that these children have a lower sensory tactile threshold than controls. Furthermore, this sensitivity was positively correlated with both generalized behavioural sensitivity ($R=0.575$; $p=0.0051$) and behavioural touch sensitivity ($R= 0.518$; $p=0.0135$). No significant relationship was found between tic severity scores and tactile threshold, as would be expected if tactile hypersensitivity was directly involved in tic generation.

A significant decrease in sensory threshold (p=0.0268) indicates that behavioural sensitivity may be mediated by a peripheral sensitivity to stimulation, i.e. an enhanced ability to detect tactile stimuli, although differences in central processing could also account for this observation. This was an unexpected result as it was hypothesized a priori that peripheral changes in sensory processing would not be found. Previous studies of sensory sensitivity do not indicate a PNS deficit in sensory processing dysfunction in neurodevelopmental disorders (Bar-Shalita, Vatine, Seltzer, & Parush, 2009; Belluscio, Jin, Watters, Lee, & Hallett, 2011; Parush, Sohmer, Steinberg, & Kaitz, 1997). Belluscio et al (2011) measured tactile thresholds at two locations: the peroneal nerve below the knee and the region of most active tic and sensory urge and found that TS and controls did not differ significantly in their thresholds of detection at either of the sites. Furthermore thresholds were not related to tic severity and no relationship was found between the presence of OCD and tactile threshold. Children with SMD were tested with Semmes-Weinstein filaments and vibration stimulation and no difference were found when the lips and palmar fingertips were tested and compared against controls (Bar-Shalita, Vatine, Seltzer, & Parush, 2009).

Unlike some of the other sub-classifications of SPD, SMD has been specifically associated with physiological changes including heightened electrodermal response to tactile sensation (McIntosh, Miller, Shyu, & Hagerman, 1999) . Similar to the adults measured in Belluscio et al.'s adult TS study, the children with SMD did not report more extreme stimuli as more intense, as was hypothesized in both TS and SMD groups. Instead, both research groups reported greater aversive response in comparison to controls to less intense stimulation (Bar-Shalita, Vatine, Seltzer, & Parush, 2009; Belluscio, Jin, Watters, Lee, & Hallett, 2011) , similar to individual case reports in TS (Cohen & Leckman, 1992). This indicates that individuals with SMD or TS share the experience of perceiving non-painful stimulation as aversive, and suggest that sensory sensitivity may be due largely to the evaluation of the stimulus.

However, differences exist between individuals with SMD and those with TS in their sensory experience. The TS group described repetitive, non-salient, faint stimulation to be aversive and preferred intense stimulation indicating that this sensitivity diminishes in

the presence of more intense or deep touch (Belluscio, Jin, Watters, Lee, & Hallett, 2011). Similarly, the SMD group did not show greater aversive responses than typically developing controls to more intense extremely aversive stimuli. In fact, the differences in response to stimuli between SMD and control children narrowed as the aversive nature of the stimuli increased, such that there was no difference in sensitivity (Bar-Shalita, Vatine, Seltzer, & Parush, 2009) . This has been supported by previous SMD research (Miller, Anzalone, Lane, Cermak, & Osten, 2007; Reynolds & Lane, 2008) informing the recommendation of deep touch for hypersensitive children. Deep touch is though to circumvent activation of the reticular formation reducing alertness and arousal due to faint, tickling or fluttery sensory information (Dunn, 1997). Considering these data in light of our lowered threshold findings, there is reason to believe that this heightened sensitivity may be limited to non-painful stimulation, where a difference between groups vanishes when the stimulation reaches aversive intensity.

4.3.2 Implications of Stimulation Location and Statistical Methods in the Analysis of Sensory Threshold Data

The unexpected difference in tactile sensory threshold between previous studies and the present study may be due to differences in study design and analytical methodology. The somatotopic map of the somatosensory cortex is distributed in such a way that areas that are more sensitive or discriminative because of denser peripheral innervation represent larger areas of the cortex (Kandel, Schwartz, & Jessell, 2000). As a result, the ability to detect and discriminate between smaller amounts of pressure delivered by the Semmes-Weinstein filaments may require testing in areas of the body that are better innervated, such as the fingers or the tongue. These areas can provide the tactile sensitivity required to detect a subtle difference in tactile sensitivity between groups. In one particular study of ADHD children, several perceptual threshold tests were performed involving several different body locations. Of these tests the only significant difference between groups was found in the touch test involving finger (Parush, Sohmer, Steinberg, & Kaitz, 2007) . Therefore it is possible that Belluscio et al (2011) may have found a significant difference in tactile threshold between TS participants and controls had they tested the fingertips of subjects as opposed to areas with less innervation, such as the knee.

Furthermore, the Semmes-Weinstein filaments set contain numbered mono- filaments with increasing diameters with a linear and proportional relationship between the ordinal rank of the monofilament and the logarithmic value of the bending force. The bending force of each successive filament follows a linear relationship when transformed into a logarithmic value. In order to analyze this data as a continuous variable, the data must be converted into a logarithmic value first (Werner, Rotboll-Nielsen, & Ellehuus-Hilmersson, 2011). Data analyses in studies of tactile threshold using Semmes-Weinstein filaments that were reviewed by the present author were all flawed since their data was analyzed using the raw bending force as a continuous variable without the required logarithmic transformation. The present study opted to analyze the data as raw bending force, but analyzed the data as ordinal thereby using a non-parametric test for comparison between groups. Before statistical comparison, distribution graphs and Q-Q plots were used to assess the normality of the data. The data did not present as normal and thus Wilcoxon rank sum tests were employed. It is important to note however that if the present study did choose to analyze the sensory threshold data as continuous, the t test procedure would still have produced a significant p value ($p=0.03$) indicating an enhanced ability to perceive tactile stimulation in the Tourette's population.

4.3.3 Support for the Role of Central Nervous System Dysfunction in Lowered TS Thresholds

The finding of increased tactile sensitivity may also be mediated by changes in the central nervous system, consistent with the structural changes reported in the brains of TS patients. When compared with healthy controls, TS patients showed bilateral increases in white matter underlying the post- and precentral gyrus, below the left supplementary motor area, and in the right ventro-postero-lateral part of the thalamus (Thomalla et al., 2009). The pre and post central gyrus areas represent the motor and primary somatosensory cortex respectively, while ventro-postero-lateral areas of the thalamus are critical relay centers for the flow of sensory information from the periphery to the cortex (Kandel, Schwartz, & Jessell, 2000). Increased innervations in the somatosensory cortex, or decreased activity of inhibitory neurons could mediate greater sensory sensitivity

through the summation of a greater number of neurons firing in response to a tactile stimulus.

In addition to structural changes Thomalla and colleagues were also interested in assessing the major pathways that pass through the area of increased white matter in TS patients. The investigation utilized probabilistic tractography, a technique that produces a likelihood map of the diffusion path between two regions of interest. Using this technique researchers identified ipsilateral pathways to adjacent primary somatosensory and motor cortices, connections to the ipsilateral VPL, contralateral sensorimotor areas and connections to the superior peduncle of the cerebellum, with no differences in tract pathways in TS compared to controls. This means that although white matter changes occur in TS, the functional connectivity remains unchanged. Furthermore, white matter changes were correlated with an improvement in tic control suggesting that increases in white matter are adaptive plastic changes that represent resilience to persistent tics in adulthood. This complements the findings of Sowell and colleagues who found cortical thinning in children with TS that was positively correlated with tic severity (Sowell et al., 2008). These studies cannot be directly compared since one used tractography, while the other used a volumetric approach, however this evidence does allow speculation that cortical thinning indicates abnormalities in brain maturity in the somatosensory cortex of TS patients and this cortical thinning could mediate a greater severity of TS that may include dysfunction in sensory processing.

Grey matter changes have also been found in the somatosensory and prefrontal cortex of TS subjects where an increase in grey matter in adults has been interpreted as a correlate of adaptive structural plasticity in areas involved in inhibitory control and reduction in tic severity. This inhibitory control may also be involved in processing of tactile sensation since grey matter changes have been associated with changes in neurological soft signs in schizophrenia (Dazzan et al., 2004). Schizophrenia patients who show neurological soft signs (including a difficulty perceiving and integration sensory stimulation) demonstrate decreases in grey matter (Dazzan et al., 2004). Higher rates of soft neurological signs (both motor and sensory) were associated with a reduction of grey matter volume of subcortical structures (putamen, globus pallidus and thalamus). Signs of sensory

integration deficits were additionally associated with volume reduction in the cerebral cortex, including the pre-central, superior and middle temporal, and lingual gyri. This study may provide preliminary evidence for CNS changes that mediate peripheral sensitivity.

4.4 Increased Amplitudes in Cognitive measures of Sensory Processing in TS

4.4.1 Summary of ERP findings

The primary aim of this study was to explore sensory differences in TS patients using objective methodology. ERP provides an indication of sensory processing differences without being limited by age appropriate descriptors of the sensory experiences or subconscious biases of parents in their reports of child behaviour in the sensory environment. Since functional and behavioural disturbances in emotional control and decision-making are part of the symptomatology of TS and ADHD and OCD, the present study sought to understand the effects of cognitive stimulus processing in sensory differences between individuals with TS+ADHD and TD using P3. P3 latency and amplitude were used as measures of temporal online stimulus classification, and sensory stimulus event categorization (influenced by attention, task relevance and working memory) in response selection (Kok, 2001; Kutas, McCarthy, & Donchin, 1977; Polich, 1986). In addition to the electrophysiological response, behavioural responses in the cognitive decision-making task were also used as indicators of group differences in performance.

In the present study TDC subjects responded correctly more often then TS+ADHD subjects to a repetitive mechano-tactile stimulation in an oddball discrimination task, though this difference did not reach statistical significance ($p=0.0715$). Furthermore no significant difference or trends in reaction time were found between TS+ADHD and TDC indicating that there are no significant differences in task performance between groups. Multivariable analysis of independent variable effects on latency demonstrated that latency was significantly affected by age ($p<.001$) and electrode ($p=0.006$) but not by group ($p=0.870$), sex ($p=0.964$) or block ($p=0.092$). This shows that the ability to classify

tactile stimuli in the present study was influenced by age and was not due to any differences among diagnostic groups.

In contrast, amplitude of the ERP was significantly ($p=0.0009$) affected by group, without significant effects of age ($p=0.525$), sex ($p=0.116$), or IQ ($p=0.383$). The small number of participants in the study did not permit inclusion of additional variables in the multivariable model, however scores of inattention, hyperactivity, pharmaceutical treatment (medication) seem to significantly predict higher amplitudes. It is difficult to analyze the significance of this particular finding since all of these variables are confounded with group. This significant effect of group on amplitude implies a difference in cognitive processing of touch within the domains of attention, working memory and event categorization between TDC and TS+ADHD.

In addition to the significant effect of group, a significant effect of block was found supporting a trend for habituation in both groups i.e. a decreasing ERP amplitude over time ($p=0.016$). Though the TS+ADHD group showed a slightly greater rate of amplitude decline over time, the difference between groups was not statistically significant. Therefore the data failed to support our hypothesis for impaired habituation in TS+ADHD children.

In summary these results indicate that ERP sensory processing differences exist between TS+ADHD and TDC, and suggest that these differences are not due to differences in online stimulus classification speed but instead are due to group differences in stimulus event categorization mediated by behavioural sensitivity, increased stimulus salience and attention.

4.4.2 Influence of age, sex IQ differences on group differences in P3 outcomes

Subjects with IQ significantly below average (≤75) were excluded from the present study in order to control for the effects of low IQ on P3 amplitude and latency. Despite these exclusion criteria a significant disparity in IQ ($p=0.005$) was found between TDC (118.7± 12.18) and TS+ADHD (102.8 ± 13.48) and exploration of the potential effects on P3

was required. Univariate analysis did not reveal a significant effect of IQ on latency (p=0.983) however there was a significant univariate effect of IQ on amplitude (p=0.018) that predicted a small decrease in amplitude (-0.15 uV) with an increase in IQ of one point. This effect of IQ became non-significant when analyzed in a multivariable model for amplitude (p=0.383) further supporting our observation that the difference in P3 amplitude is due predominantly to the group difference (p=.0009). The lack of effect of IQ on both amplitude and latency in this study conflicts with multiple studies that have consistently found a correlation between IQ and latency where lower IQs produce longer latencies (Boucher et al., 2010; McGarry-Roberts, Stelmack, & Campbell, 1992; Pelosi et al., 1992). This discrepancy is probably due to our having excluded subjects with lower IQ, since it has been shown that differences in IQ will not mediate significant effects on ERP among subjects with average or above average IQ scores (Pelosi et al., 1992).

The two groups in this study were not well matched for sex due to the predominance of males in TS and ADHD populations and the inability of the study staff to recruit young boys for participation in the TDC group. Despite the significant difference in sex (p=0.005), sex did not prove to be a significant contributing variable to the multivariable effects on amplitude (p=0.116). The estimated effect (though insignificant) was consistent with the literature in estimating an increase in amplitude of approximately 2 uV in females compared to males matched on all other variables such as age, IQ, group, electrode and block (Brumback, Arbel, Donchin, & Goldman, 2012; Polich & Geisler, 1991). This study found no significant effects of age on amplitude in both the univariate and multivariable analyses (p=0.803 and p=0.526 respectively), but proved to be a significant factor in the P3 latency (p<.0001) consistent with the literature (Adrover-Roig & Barcelo, 2010; Fjell & Walhovd, 2001; Pfueller et al., 2011). The multivariable modeling predicts a decrease in latency of 24 ms for each annual increase in age, but when age differences were controlled for, group differences in latency were not found to be significant (p=0.869).

Nevertheless, the age difference may contribute to the ERP profile but this may not have been apparent in this dataset because of a deliberately narrow age range of our subjects. This narrow age range was chosen precisely to minimize the effects of age and therefore

developmental changes that occur over time. In summary, this data suggests that the diagnosis of TS and ADHD is the most significant variable explaining the group differences in ERP amplitude evoked by repetitive tactile stimulation.

4.4.3 Contribution of TS and ADHD to ERP profile and behavioural performance

A significant difference in behavioural performance between groups was not found in the electrophysiology results of the present study, but it is interesting to note that there was a trend for faster reaction time and increased variance in both reaction time and response accuracy in the TS+ADHD group. Faster reaction time and greater response variability are hallmark characteristics of ADHD behavioural testing (Sjowall, Roth, Lindqvist, & Thorell, 2012; Szuromi, Czobor, Komlosi, & Bitter, 2011). These behavioural characteristics are reflected in the variability of the behavioural performance scores that fluctuate within the mean range of 69.8 - 80.0 % in TS+ADHD groups while remaining fairly stable between the mean average range of (80.0-82%) in controls. Standard deviations for the mean scores were also approximately two times greater in the TS+ADHD vs. TDC, indicating greater variability.

Univariate analyses were used to provide exploratory insight into the group differences in amplitude seen in this study. Current and worst-ever total tic scores were analyzed for their effects on P3 amplitude and the results were insignificant indicating that tic severity as measured by the YGTSS did not significantly predict P3 amplitude.

Van Woerkom et al. (1988) investigated auditory P3 in TS adolescents and adults and found no differences in amplitude or latency compared to controls. Because the present study did not investigate P3 in a TS-only nor ADHD-only groups it is difficult to speculate on the contribution of TS, however the lack of effect of tic severity on the P3 combined with the work of van Woerkem et al. seems to suggest that the P3 amplitude is not influenced by a diagnosis of TS alone. This is also supported by other cognitive based studies that seem to suggest pure TS subjects do not differ from controls on several

behavioural, neuropsychological and neurophysiology measures (Sukhodolsky, Landeros-Weisenberger, Scahill, Leckman, & Schultz, 2010; Yan et al., 2006).

It is also possible that no correlations were found between the total tic YGTSS severity and ERP results because the age range in the present study was relatively narrow due to the fact that we included young children who had not yet reached their peak tic severity. This would keep the variance in the scores low. It is also possible that there is no relationship between tics and sensory sensitivity, and though the proposed etiology of both symptoms may involve the same brain areas, the two dysfunctions are mediated through separate parallel pathways.

Unlike tic severity, indexes of inattention and hyperactivity were significant univariate predictors of both amplitude and latency, suggesting that ADHD dominated in its effects on the ERP profile. It is unlikely however that ADHD was the driving contributing factor in the TS+ADHD increases in amplitude since statistical modeling estimates very small increases in amplitude in individuals with increased inattention and hyperactivity (<0.5 μV per 1 point increase on the Conner's scale). Furthermore, if ADHD symptoms were the driving force behind increased amplitudes in our TS+ADHD group it would be expected that P3 amplitudes would be attenuated by an ADHD diagnosis as seen in studies of pure ADHD subjects and previous work in TS subjects with combined ADHD (Kuperman, Johnson, Arndt, Lindgren, & Wolraich, 1996; Szuromi, Czobor, Komlosi, & Bitter, 2011; Yan et al., 2006) . In these studies ADHD only subjects as well as TS+ADHD subjects produced reduced P3 amplitudes compared to controls, though this observation did not reach significance in the latter group. These results suggest that another variable must be contributing to the increase in amplitude between groups in the present study.

ADHD and tic disorders such as TS have been described as hyperkinetic disorders i.e. a persistent neurodevelopmental disorder that manifests with excessive movement, restlessness and impulsive behaviour. Hyperkinetic disorders have an early onset and are highly associated with other dysfunctional behaviour such as poor social and academic performance (Taylor et al., 2004). Individually both TS and ADHD have sensory

components, and these sensory symptoms may share a common pathophysiology. To test the hypothesis that sensory dysfunction in these disorders is mediated by hyper-excitability in the primary somatosensory cortex, Miyazaki et al (2007) examined somatosensory evoked potentials in TDC as well as children with ADHD and tic disorders. These early-evoked potentials reflect early aspects of perception of physical stimuli before cognitive processes are activated (Evans & Boggs, 2012). The median nerve was stimulated with electrical stimuli during sleep and early somatosensory responses were measured in the cervical vertebrae and scalp using electrodes. They found giant SEP and larger peak-to-peak amplitude in early ERPs N20-P25 in both tic disorder ($p<0.01$) and ADHD ($p<0.05$) groups vs. controls, providing physiological evidence for sensory sensitivity in TS and ADHD and its influence in the CNS. Similar results have been found in ADHD children with tactile defensiveness where children who were tactile defensive produced significantly larger somatosensory evoked potential amplitudes than controls (Parush, Sohmer, Steinberg, & Kaitz, 2007). This research supports an interactive effect between ADHD and sensory processing deficits in increasing the amplitude of ERPs.

Greater P3 amplitude in TS+ADHD vs. controls may also indicate that greater cognitive effort is required when TS+ADHD subjects perform with the same stimulus classification speed and level of accuracy as control subjects. This increase in mental effort may also suggest that TS+ADHD patients nay have some difficulty with automating the task.

4.4.4 P3 habituation

The present study was unable to detect a significant group difference in rates of habituation to repetitive tactile stimulation, between and within blocks however alterations in the protocol may explain this result. Modulating IBI time in order to give more sensory sensitive or restless children a longer break may have interfered with the mechanisms of neural inhibition. It may have also been more useful to measure habituation to the standard or non-target stimuli in order to study the perception of persistent task-irrelevant stimulation, however P3 is not reliably evoked observed with

non-target stimulation and early ERPs were not consistently seen in the ERP profile of the children studied.

4.5 Sensory Sensitivity in Tourette Syndrome: A General Discussion of Behavioural, External and Central Processing Changes

The present study aimed to investigate the cognitive, physiological and behavioural processing of touch in children suffering from Tourette syndrome with co-morbid ADHD. The results of this study demonstrate an increase in hypersensitivity in children with TS and ADHD compared to controls in their cognitive, physiological and behavioural processing of tactile stimuli. These observations can be understood in terms of dysfunction in 3 key areas in the CSTC loop; the dorsolateral prefrontal cortex (DLPFC), the basal ganglia (BG), and the cerebellum. In addition one may invoke functional immaturity across brain regions in TS as discussed below.

4.5.1 Evidence for the involvement of the Dorsolateral Prefrontal Cortex, Basal Ganglia, and Cerebellum in TS sensory hypersensitivity.

Stimulus intensity is mediated by the sensory nerve response where greater stimulus intensity is conveyed in the nervous system as a larger nerve response through the recruitment of more nerve fibers (Patestas & Gartner, 2009). It is possible that enhanced tactile sensitivity in the peripheral nervous system of TS+ADHD subjects could mediate increased firing all the way up to the CNS activating more neurons in the primary somatosensory cortex. This is especially likely if top down control pathways do not mediate activation of inhibitory interneurons that modulate sensory information flowing towards the CNS (Kandel, Schwartz, & Jessell, 2000). This increase in firing could provide an exogenous contribution to the endogenous components of P3 noted in previous ERP investigations, thereby increasing amplitude through the amplification of the sensation in the PNS (Chica, Lasaponara, Lupianez, Doricchi, & Bartolomeo, 2010; Hopfinger & West, 2006; McCullagh, Weihing, & Musiek, 2009; Nakajima & Imamura, 2000).

It cannot be concluded from this study that differences in tactile threshold between controls and TS+ADHD subjects are mediated by changes in the PNS since none of the measures in this study separate central from peripheral mechanisms. The reason for using electrophysiological methods was to find an objective measure to observe the evaluation and processing of repetitive tactile stimulation. As a result, a later component P3 was selected a priori and evaluated for group differences. Differences in these later waves suggest that there are differences in the way that TS+ADHD children evaluate and categorize tactile stimuli. These differences in processing may not be limited to cognitive aspects of sensory processing, as post hoc visual inspection of group averages in **Figure 3-6** would indicate that there are group differences in earlier components that might suggest dysfunction in detection as well as in the evaluation of stimuli.

Between stimulus onset and 200 ms post-stimulus, TS+ADHD children evoked larger amplitude potentials than controls. These differences in amplitude are consistently seen across all 3 blocks at frontal and central electrodes (Fz and Cz respectively) and in block 3 grand averages for Pz, particularly in the areas at approximately 100 and 200 ms post stimulus. Statistical analysis was not performed on these differences, but the magnitude of the difference in the grand averages suggest that the significant differences apparent in cognitive aspects of processing may also be present in these earlier ERP components reflecting detection, arousal and attention towards the stimulus (Hamalainen, Kekoni, Sams, Reinikainen, & Naatanen, 1990; van Woerkom, Fortgens, Rompel-Martens, & van, 1988; van Woerkom, Roos, & van Dijk, 1994). This is not an unexpected finding as Miyzazki and colleagues also found that children with TS and ADHD evoked larger amplitudes in early somatosensory evoked potentials than controls. They suggest that this may be due to cortical hyperactivity in the somatosensory cortex. When combined with evidence of increased metabolism in the sensorimotor cortices and hypoperfusion in the BG (Braun et al., 1993), this data supports the involvement of CSTC pathways in both disorders.

P1 and P2 have also been key components in understanding the role of the DLPF, a major centre for attention. Bolton and Staines (2011) transiently inhibited the DLPFC using continuous theta burse stimulation and compared brain responses in a tactile oddball task

to pre-inhibition baseline responses in controls. It was found that P1 amplitude was attenuated following DLPFC inhibition. These results suggest that increased amplitudes in our patient group in the area of P1 and P2 may represent hyperactive DLPF cortices responsible for impaired sensory gating of stimuli in the earlier stages of central processing. Considering these early ERP findings in the present study as well as the supporting evidence described, it is probable that the sensory threshold differences documented in this study are primarily due to changes in the CNS and hyperactive automatized attention that is stimulus-driven, rather than increased peripheral sensitivity.

Decreased tactile thresholds may be a result of abnormal top down control. Top-down control or executive functioning in the CNS involves the ability to control and coordinate behaviours and actions. When attention is paid to a stimulus certain inputs are selected for cognitive processing and while other sensory inputs are suppressed. This is supported by neural response to tactile stimulation in monkeys. Mean firing rates in S2 increase when the monkey attends to the stimulus and decrease when the stimulus was ignored (Cohen & Maunsell, 2010; Hsiao, O'Shaughnessy, & Johnson, 1993). Cohen and Maunsell (2010) showed that trial-by-trial differences in attention are the main cause of variations in performance in perception tasks. In addition this group demonstrated that top down attention control can select the specific neural population that is involved in providing the sensory information upon which the task-response is based. Physiological evidence for attention selection exists in humans as well (Johansen-Berg & Lloyd, 2000), providing a possible explanation for increased amplitudes in TS+ADHD children. If a child is unable to use this selection process then sensory inputs will constantly be selected for cognitive processing and very little information will be suppressed resulting in increased resource utilization hence larger amplitude ERPs.

Top-down attention, and perceptual decisions are commonly thought to be represented in the frontal lobe. Neuropsychological testing combined with functional imaging indicate a disturbance in frontostriatal circuitry in TS (Cavanna, Eddy, & Rickards, 2009; Wang et al., 2011). Subjects with TS (especially those with co-morbid ADHD) present strong connections in motor pathways but weakened connections in parts of the cortico-striato-thalamo-cortical circuits that exert top-down control such as the caudate and anterior

cingulate cortex (Wang et al., 2011). These weakened connections may be responsible for failure to control tic behaviours, premonitory urge, and attentional selection for stimulation that is typically suppressed. Dysfunction in the frontal area may also be consistent with significant group differences in amplitude in frontal and central electrodes, but minimal differences at parietal sites seen in the present study, however firm conclusions about neural generators of the P3 response are beyond the scope of this study.

Increased P3 amplitudes in a visual oddball task were also found in TS-only subjects (Thibault et al., 2008). Furthermore the loss of normal PFC function is associated with an impaired ability to gate irrelevant sensory information, and a loss of excitatory control over sensory pathways carrying task-relevant information to S1 (Knight, Staines, Swick, & Chao, 1999). Altogether this leads the present author to suggest that the larger amplitudes in TS+ADHD children may be attributed to an overactive cortical area that is substantiated by evidence of a hyperactive dorsolatoral prefrontal cortex demonstrated in GTS using fMRI (Peterson et al., 2001). There is also evidence to suggest that increased PFC volumes in adults may be a compensatory development to aid in the semi-voluntary control of tic suppression strengthening the hypothesis for the role of PFC dysfunction in symptom severity (Peterson, Pine, Cohen, & Brook, 2001).

A recent investigation of prefrontal cortex found distinct populations of neurons that are capable of selectively encoding stimulus presence or stimulus absence (Merten & Nieder, 2012). These cells would ultimately contribute to resolving the need to constantly select what to attend to and what behaviours to engage in. The BG aids in this selection process by using its inhibitory signaling system to correct or mold the excitatory cortex signals. Activity within the direct pathway selects a perception or behaviour by releasing GPi inhibition of the thalamus, which activates the cortex. Activity in the hyperdirect pathway quickly inhibits behaviour starting in the frontal area through direct projections to the STN while the indirect pathway increases inhibition therefore suppressing cortical activity (Alexander, DeLong, & Strick, 1986; Houk, Davis, & Beiser, 1994). Path segregation of inhibitory and excitatory signals in the basal ganglia allow for the coordination of control over multiple behaviour domains including attention, motor

behaviour and limbic emotional control (Kandel, Schwartz, & Jessell, 2000). This allows for the differential expression of co-morbidities despite similar structures being involved in their etiology. The BG exerts its control by using inhibition to allow activation of the modality specific region in the cortex as well as through lower level responses via orienting pathways mediated through connections with the cerebellum. Weaker connections in these areas could cause desynchronous and independent operation that could lead to competing behaviours and ultimately the facilitation of distracting sensory input and dysfunctional sensory gating (Koziol, Budding, & Chidekel, 2011).

The role for BG and frontal areas in sensory phenomena has been addressed in TS literature (Leckman, Bloch, Scahill, & King, 2006; Peterson, Riddle, Cohen, Katz, Smith, Hardin, & Leckman, 1993; Stern, Blair, & Peterson, 2008), however little has been said about the influence of the cerebellum. The cerebellum regulates and fine-tunes the acquisition of sensory input by controlling the force by which sensory information is experienced through inhibition (Bower, 1997). Evidence for this ability has been uncovered in tactile processing in the rat brain as well as in the olfactory system. Odor concentration and sniff volume in a rat are proportional and the cerebellum modulates the force of the sniff (Brown & Bower, 2002; Sobel et al., 1998; Zatorre, Jones-Gotman, & Rouby, 2000). The Purkinje cells mediate cerebellar output via noradrenergic activity. These cells are completely inhibitory and project to deep structures and back to the thalamus and cortex placing them in a strategic position to influence affect, sensation and heaviour (Koziol, Budding, & Chidekel, 2011; Stoodley & Schmahmann, 2010). Insufficient inhibition in any of these areas could cause hypo and hypersensitivities and changes in cognition and affect that have been noted in a number of pediatric cases of cerebellum pathology (Schmahmann, Weilburg, & Sherman, 2007).

Investigations in TS have revealed structural abnormalities in the cerebellum where significantly decreased bilateral volume in TS compared to controls is significantly correlated with tic severity and differences are larger amongst men consistent with the more prevalent expression of TS in males (Tobe et al., 2010). Noradrenergic deregulation has also been suggested in GTS patients (Alsene, Rajbhandari, Ramaker, & Bakshi, 2011; Chappell et al., 1996; Swerdlow, Bongiovanni, Tochen, & Shoemaker, 2006),

leading to over arousal, and dysfunction in the regulation of working memory and attention in the prefrontal cortex. Administration of clonidine, an adrenergic agonist, has been very effective in improving clinical symptoms of TS (Pringsheim et al., 2012) and has even been shown to reduce the oddball effect in humans (Halliday et al., 1994) and decrease sensory sensitivity in rats (Deyama et al., 2011). It is therefore possible that regulation of the adrenergic system could normalize the elevated P3 response in TS and help control sensory dysfunction. Collectively these data support the implication of noradrenergic dysfunction in multiple areas implied in sensory dysfunction, and could suggest that larger P3 amplitudes observed in our TS group collectively reflect frontal dysregulation and a greater state of arousal, increasing the difficulty of maintaining selective attention oddball to the discrimination task.

4.5.2 Functional Immaturity in TS

Though the structural abnormalities in TS that may support sensory processing dysfunction have been addressed in this chapter the influence of functional connectivity has not been discussed. Studies of functional connections in the TS brain in both adults and children have revealed that TS patients appear to have immature brains that are delayed in development when compared to same age controls. Worbe (2012) studied the connections among anatomical regions in TS adults and found significantly more connections in the TS brain with a shorter path length between connections, with no significant effects of medication or gender. The connections showing this pattern were located in the supplementary motor areas responsible for planning and coordinating movement as well as the cerebellum, left anterior caudate, and medio-dorsal thalamus. This pattern resembles the pattern seen in healthy children, before stronger long range connections develop and strengthen in adulthood (Fair et al., 2007). Similarly, Church (2009) compared the maturity of functional connections in TS patients and controls aged 7-31. This group found that TS adolescents appeared to have the connectivity pattern similar to the pattern found in control children between the ages of 7 and 9, demonstrated by shorter and weaker connections in the parietal lobe and between cerebellum ad frontal lobe. Fewer fronto-parietal connections in children are also a sign of brain immaturity that may be altered during development (Fair et al., 2007). These connections in frontal-

parietal network are thought to be involved in adaptive control during moment to moment information processing including goal directed behaviour and initiation, maintenance and adjustment (Dosenbach et al., 2007; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). These are all required components for top down control that would help to mediate the finding of increased tic control with stronger connectivity in the posterio-parietal lobe (Worbe et al., 2012).

Further evidence for developmental immaturity in TS has been found in studies of neuropathology. Investigation of the cell populations that mediate decreases in caudate and putamen volumes led to the postmortem analysis of cells in the BG. In this study Kalanithi et al (2005) found an imbalance in the distribution of striatal parvabumin (PV) interneurons. These interneurons form inhibitory synapses through the striatum and coordinate the firing activity of the majority of cells responding to cortical inputs. In these post-mortem brains PV neurons were increased by over 100% in TS patients in the absence of changes in the total number of PV cells in the basal ganglia that is consistent with aberrant firing patters in the BG. The authors attribute these major abnormalities to a defect in PV cell migration during development.

Lower populations of neurons in the caudate or putamen of TS patients may contribute to disordered inhibition in sensory processing, via the BG and connections to the cortex where GABAergic PV neurons play a role in crucial cognitive processes involved in executive control. Evidence for GABA control in PV cells comes from animal studies. GABAergic blockade through the injection of GABA antagonists in the cat somatosensory cortex changed the receptive field, but when GABA injection followed the sensory threshold was increased and spontaneous tactile firing was abolished (Hicks & Dykes, 1983). Cellular selectivity is also seen in the cat and monkey visual cortex where stimulus orientation selectivity in neuronal firing is eliminated following GABA antagonist injection (Sillito, 1979). This means that without PV inhibition, neurons lose selectivity and respond to stimuli that did not previously elicit a response.

Collectively these data provide mechanisms underlying the deficits in stimulus selection that would contribute to deficient sensory gating in the BG of TS patients and emergence

of tics. CNS maturity is achieved by the development of mature connections in the brain. These connections are established via a number of processes including neuron migration and myelination. The same mechanisms can be offered to explain the eventual decrease or even disappearance of tics in late teens experienced by many TS patients. Moreover these mechanisms may also be invoked to explain the response to behavioural treatment for tics.

4.6 Limitations

There are several limitations to the present study. The most significant limitation may be the lack of additional control groups such as a pure ADHD and pure TS group. Without such control data it has been more difficult to interpret the results of this study. In its earliest version this study was designed to study sensory phenomena in TS+ADHD and TDC as well as a pure ADHD group, but the inclusion of this group would have led to too large a project that could not be completed within the time limitation of a master's level research project.

Though the study attempted to provide preliminary evidence for the role of inhibition in TS sensory phenomena, the protocol was not optimally designed to directly test inhibition specific to the processing of repetitive stimulation presentation. Children with sensory hypersensitivity found it difficult to tolerate the white noise and repetitive stimulation over time, as a result strict IBI limitations could not be maintained for each child. Group differences in habituation were not found, however had these been found, this inconsistency in the protocol would have made the findings difficult to interpret.

The Sensory Profile allows one to measure and quantify an array of sensory experiences. As a result it is not a uniform construct and it is difficult to use to diagnose any one particular disorder. The use of quadrant and factor scores however allow for users to gain an understanding of the trends in specific behaviours. The present study was examining sensory hypersensitivity and therefore focused on the sensory sensitivity quadrant score as a result. This is useful in the present study as the specific nature of sensory sensitivity in TS has not yet been quantified. Moving forward however, it may be necessary to create a more specific tool that may also be useful in identifying the neuroanatomic underpinnings that drive the behaviours captured by the SP; particularly those that are relevant to TS.

The patient population in this study was also largely medicated at the time of study, and though subjects did not take methylphenidate for over 24 hours, it is difficult to quantify the effect medication may have had on our observations, especially since most subjects

were currently taking a variety of psychotropic medication. Most research has shown however that psychotropic medicines typically used in TS normalize P3 amplitudes (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Halliday et al., 1994; Pringsheim et al., 2012). It would therefore be expected that the main findings of increased P3 amplitude in TS+ADHD would not be a result of exposure to pharmacological agents.

Finally another limitation is the small group sample size which made it difficult to perform any concrete exploratory analyses on the variables that might contribute to the P3 results.

Nonetheless our study was still able to quantify a very significant group difference in the ERP profile ($p=0.009$) with a sample size that compares favourably to other ERP study samples that ranged from 6-24 TS or ADHD subjects (Kuperman, Johnson, Arndt, Lindgren, & Wolraich, 1996; Thibault et al., 2008; van Woerkom, Fortgens, Rompel-Martens, & van, 1988; van, Martens, Fortgens, Slaets, & van Woerkom, 1985; Yan et al., 2006).

4.7 Conclusions

The present study is the first to investigate the sensory experience of TS using not only behavioural but also neurophysiological methods. As such this study is also first to present the novel finding of a significant difference between children with TS and ADHD and controls in their cognitive, behavioural and physiological processing of tactile stimuli, offering validation for the previously reported altered subjective sensory experience in TS. Although TS+ADHD children performed equally well as controls on the oddball task (no significant difference in percent error or reaction time), they produced significantly higher P3 amplitudes in a repetitive oddball task. This difference in P3 amplitude may reflect the greater cognitive effort by TS+ADHD children to perform the task as mediated through frontal, basal ganglia and cerebellar pathways. An increase in mental effort may also explain why TS+ADHD subjects appeared less able to automate and therefore habituate at the same rate as controls, though this trend did not reach statistical significance. Latency was not altered in the TS+ADHD group indicating normal tactile stimulus classification speed in the sensory experience of TS patients. Furthermore, although P3 is thought to be largely reflective of cognitive processing, it is also affected by the qualities of a stimulus, where more intense stimuli can produce larger P3 amplitudes. Lower tactile sensory threshold combined with an increased reported sensory sensitivity; indicate that the TS+ADHD patients are more physiologically sensitive, potentially leading to an amplification in signals sent to the CNS from the PNS, and thereby contributing to larger P3 amplitudes. These findings support behavioural reports of sensory sensitivity and suggest that hypersensitivities reported in TS may be related to an underlying aberrant electrophysiological response mediated through an abnormal CSTC.

4.8 Directions for Future Research

The information presented in this study provides only preliminary evidence regarding the group differences that contribute to the altered sensory experience in TS. In order to address some of the limitations of this study, the present study should be extended to include other comparison populations such as pure ADHD, pure TS and pure OCD groups, with well balanced gender ratios. More studies in electrophysiology can be quickly and cost-effectively employed to specifically study the influences of inhibition in TS patients with sensory sensitivity using early ERP gating paradigms and habituation to stimuli that do not require task-relevant responses. Electrophysiological methods could also be used to further explore peripheral sensitivity by measuring early SEPs both on the scalp and the spinal cord.

Functional imaging may be able to provide information as to which structures or connections mediate the differences in TS children who have elevated sensitive scores on the sensory profile compared to those who do not. It would be interesting to know whether sensory differences affect primary processing areas such as the primary somatosensory cortex, association areas or both. Larger longitudinal or cohort imaging studies are also needed to follow the developmental course of sensory sensitivity in order to understand how maturation and development helps to resolve some of these sensory differences over time. Finally, functional imaging may also be used to examine and contrast neural connectivity in patients with high and low sensory profile and with controls.

The use of YGTSS in all studies has become fairly standard, it is hoped that this research will draw the necessary attention to sensory phenomena such that measures like the PUTS and SP will be employed as indicators of TS symptomatology in a diverse collection of TS investigations including studies of functional and social impairment. This will contribute to the knowledge in sensory phenomena without drastically increasing the financial burden of repeating study protocols to understand how previously explored brain areas and tasks contribute to the presentation of sensory phenomena.

More information should also be collected about the possible indication of pharmaceutical intervention, exposure response treatment or habit reversal for sensory sensitivity as these have shown to be effective in controlling tic symptoms and sensory phenomena such as sensory tics

and sensory urge (Piacentini et al., 2010; Singer, 2010; Swain & Leckman, 2005; Verdellen et al., 2008).

Finally, the field of occupational therapy has likely identified the most cases of sensory dysfunctional behaviour in neurodevelopmental populations, but more work is needed to create a clear nosology of SPD so that investigators can be unified in their descriptions and quantifications of different sensory processing behaviours. As with many areas of investigation, sensory processing in TS would be best investigated by a multi-disciplinary approach where a common language and shared theoretical understanding would provide a platform for the discussion of neurodevelopment sensory issues.

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Appendices

Appendix 1: Participant Sheet for Screening

Study Participant Information Sheet - Parent

Study Title Sensory perception in Tourette's syndrome: An EEG study

Investigator Dr. Paul Sandor (416-603-5974)

Research assistant Allison Needham (416-603-5794)

Please complete the following information about your child:

Would you like to be contacted about participation in any future studies? _____
If YES, how would you prefer to be contacted? _____

Current Age: ___/___(years/ months)

Currently taking any medication, drugs, or pills (please circle one)? YES or NO

If YES, list name and dosage:

History of neurological problems (disorders related to the nervous system including the brain, spinal cord, nerves, etc.)? YES or NO

If YES Describe: _____

Has your child ever had a head injury or a concussion? YES or NO

Has your child ever had a spinal cord injury? YES or NO

Has your child been diagnosed with epilepsy? YES or NO

Has your child had a stroke? YES or NO

Has your child been diagnosed with a genetic disorder such as Down's syndrome, Fragile X Prader-Willi Syndrome, Williams Syndrome, etc.? YES or NO

Is your child right handed?	YES or NO
Does your child have a need to repeat certain actions (turning a light off/on, opening/closing a door, flushing the toilet) a particular number of times?	YES or NO
Does your child frequently count objects e.g. fence posts, tiles on the floor, people in the room, books on the shelves, etc?	YES or NO
Does your child wash their hands an exceptional number of times daily?	YES or NO
Do these behaviours interfere with every-day activities?	YES or NO
Does your child have a great fear of acquiring germs? Diseases?	YES or NO
Does your child fear they may hurt themselves or others?	YES or NO
Has your child experienced unreasonable urges to do sudden and reckless things?	YES or NO
Does your child have an obsession with symmetry?	YES or NO
Do these fears or thoughts cause distress?	YES or NO
How many hours per day does your child spend engaging in these activities or thoughts?	_____ hours
Does your child have a family history of mental illness?	YES or NO

If YES, please describe the illness and how the family member(s) is related to your child in the space provided.

Does your child have trouble staying seated i.e. at school, work, or dinner table?	YES or NO
Is your child restless?	YES or NO
Does your child have trouble staying on task?	YES or NO

Does your child have trouble finishing one thing before moving onto the next?	YES or NO
Does your child have trouble paying attention?	YES or NO
Does your child have trouble following instructions?	YES or NO
Does your child have trouble doing things that must be done in certain order or series of steps?	YES or NO
Have any of these symptoms been present before age 7?	YES or NO

What were the teacher comments on your child's latest report card (hyperactivity, inattentiveness, distractibility, disruptive:

Has your child experienced, or have others noticed them having, involuntary and "purposeless" bouts of (please circle one):

Eye Blinking	Never	Ever	Currently
Shoulder Shrugging	Never	Ever	Currently
Sniffing	Never	Ever	Currently
Humming	Never	Ever	Currently
Coughing	Never	Ever	Currently
Snorting	Never	Ever	Currently
Throat Clearing	Never	Ever	Currently
Nose twitching	Never	Ever	Currently
Face grimacing	Never	Ever	Currently

For Office Use Only: Diagnosis (please place an X in the box of all that apply)

- ❑ TS or TD
- ❑ ADHD
- ❑ OCD
- ❑ DPR
- ❑ PSYCH
- ❑ AL/DAB
- ❑ HD

Appendix 2: Premonitory Urge for Tics Scale - Version 1

Premonitory Urge for Tics Scale

Office use only: Study ID# _____

Group: ☐ TS ☐ ADHD ☐ CONTRL

AGE: ☐☐ DATE: dd ☐☐ / mm ☐☐ / yyyy ☐☐☐☐

GENDER: ☐ Male ☐ Female

Shade in the circle to indicate whether or not your son/daughter currently demonstrates these behaviours:

	Yes	No
Right before I do a tic, I feel a sensation inside my body.	○	○
Right before I do a tic, I feel like my insides are itchy.	○	○
Right before I do a tic, I feel pressure inside my brain or body.	○	○
Right before I do a tic, I feel "wound up" or tense inside.	○	○
Right before I do a tic, I feel like something is not "just right."	○	○
Right before I do a tic, I feel like something isn't complete	○	○
Right before I do a tic, I feel like there is energy in my body that needs to get out	○	○
I have these feelings almost all the time before I do a tic.	○	○
These feelings happen for every tic I have.	○	○
After I do the tic, the itchiness, energy, pressure, tense feelings, or feelings that something isn't "just right" or complete go away, at least for a little while.	○	○
I am able to stop my tics, even if only for a short period of time.	○	○

Revised: September 23, 2008

Appendix 3: Premonitory Urge for Tics Scale - Version 2

Subject ID:_____

Premonitory Urge for Tics Scale

Date: _____ Birthday: _____
Month / Day / Year Month / Day / Year

Age: _____ _____
Years Months

Group: ( ) TS ( ) CTL Gender: ( ) Male ( ) Female

Please respond to each statement by circling the number that describes your child best. Use the following key to mark your responses: 1 = not at all true, 2 = a little true, 3 = pretty much true, 4 = very much true.

1) Right before I do a tic, I feel a sensation inside my body.	**1**	**2**	**3**	**4**
2) Right before I do a tic, I feel like my insides are itchy.	**1**	**2**	**3**	**4**
3) Right before I do a tic, I feel pressure inside my brain or body.	**1**	**2**	**3**	**4**
4) Right before I do a tic, I feel "wound up" or tense inside.	**1**	**2**	**3**	**4**
5) Right before I do a tic, I feel like something is not "just right."	**1**	**2**	**3**	**4**
6) Right before I do a tic, I feel like something isn't complete	**1**	**2**	**3**	**4**
7) Right before I do a tic, I feel like there is energy in my body that needs to get out	**1**	**2**	**3**	**4**
8) I have these feelings almost all the time before I do a tic.	**1**	**2**	**3**	**4**
9) These feelings happen for every tic I have.	**1**	**2**	**3**	**4**
10) After I do the tic, the itchiness, energy, pressure, tense feelings, or feelings that something isn't "just right" or complete go away, at least for a little while.	**1**	**2**	**3**	**4**
11) I am able to stop my tics, even if only for a short period of time.	**1**	**2**	**3**	**4**

Appendix 4: Photograph of the Finger Stimulating Device (FSD)