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I, Nasrin Shahana, hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Neuroscience/Medical Science Scholars, Interdisciplinary.

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Sensory Dysfunction in Children with Tourette Syndrome

by

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience

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ABSTRACT

Sensory Dysfunction in Children with Tourette Syndrome

By

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The University of Cincinnati, 2015

Under the Supervision of Donald L. Gilbert, MS, MD

Prime symptoms of Tourette Syndrome (TS) constitute motor and vocal tics but observation from clinical standpoints as well as parents or individual patient’s observation has provided evidence for sensory abnormalities associated with TS. One of the well-known phenomenon is tic related premonitory urges (PU’s), described as recurring, intrusive sensory feelings such as discomfort, pressure etc. that precede and in some cases compel performance of tics. Sensory sensitivity or intolerance is often reported to be related to being sensitive to the external sensory information such as intolerance to clothing tags. Some report urges to have subconsciously copying movements (echopraxia) or speech (echolalia) of others. Patients often complain about their tics being enhanced by certain sensory stimuli like sounds or lights. With the exception of Premonitory Urges (PU’s), most of the sensory symptoms have not been addressed by standard clinical practice. PU’s can be evaluated with a standard clinical rating scale called Premonitory Urges in Tourette Syndrome (PUTS) which tends to be well correlated with tics. PU’s seem to be a critical distinguishing factor between TS and other movement disorders. Interestingly, medications treating tics do not diminish the
PU’s. These sensory abnormalities arising from external and internal sources in perceptual and behavioral responses suggest potential dysfunction in the sensory system might play a key role in the pathogenesis of TS. The well-established motor theories involving Cortico-striato-thalamo-cortical (CSTC) pathways may need augmentation with better understanding of the influence of sensory input and processing. An obstacle to understanding the possible role of sensory phenomena in the pathophysiology of tics is that sensory symptoms are subjective and difficult to quantify. In this study, we propose to quantify the sensory measures in children with TS and their age matched peers. To explore the components of the sensory system most relevant to TS in detail, we will evaluate sensory thresholds, both detection and discrimination threshold, sensory adaptation (habituation), perceptual latency and temporal order of judgment (TOJ). We have chosen the tactile system as a model to evaluate the sensory system in part because many of the premonitory urges and self-reported hypersensitivities involve touch. In humans, tactile system is composed of two subsystems: cutaneous and kinesthetic. Here, in this study we will concentrate on the cutaneous subsystem which deals with cutaneous spatiotemporal perceptions of external stimuli mainly via mechanoreceptors located on glabrous surface of finger pads. Three of the core concepts of somatosensory processing are 1) Sensory threshold- the minimum amount of stimulus needed to produce a response; 2) Sensory neuroadaptation – a biological process suggested to be experienced after all types of sensation, where a series of changes occurs over time to the sensory receptors or neurons in relation to the stimuli; 3) Perceptual processing – a fundamental, complex process responsible for recognizing and interpreting of a stimulus. Perceptual
processing encompasses multiple domains including duration of time between a given
stimulus and awareness (perceptual latency) as well as motor and cognitive domains for
proper identification and effective response for given stimulus. Sensory evaluations
were obtained using a brand new device, called cortical metrics 5 (CM-5), specifically
designed to measure sensory function of cortical neurons. CM-5, a portable, a non-
invasive device, functions as a vibrotactile stimulator. It is an electrical stimulator with
dual probe tips specially designed to stimulate two finger tips. Probe tips were designed
as two- point- stimulator and two alternative forced choice tracking protocols (2AFC)
were used for most of the tasks. Objectives of this study were divided into three groups
1) To evaluate sensory thresholds in Tourette Syndrome compared to Typically
Developing children via two tasks- Sensory (electrical impulse) detection threshold and
discrimination threshold. 2) To demonstrate Neuroadaptation through single site
adaptation (ss-AD) in Tourette Syndrome compared to Typically Developing children. 3)
To explore perceptual processing of tactile stimuli in regard to perceptual latency and
time perception via Choice Reaction time (cRT) and Temporal Order of Judgment (TOJ)
thresholds in Tourette Syndrome compared to Typically Developing children. Group
analysis revealed no differences in sensory thresholds. However, children with Tourette
Syndrome had reduced sensory adaptation compared to age matched healthy children.
In addition, decreased level of neuroadaptation negatively correlated with higher (more
severe) clinical tic score. Time perception latency identifying TOJ to two tactile stimuli
was also increased but did not reach statistical significance. This reduced adaptation
and faster perceptual latency might indicate an abnormal processing of somatosensory
information by somatosensory cortex which might ultimately contributes the sensory
hyperawareness observed in TS. The more compelling finding is the negative correlation of sensory adaptation with clinical tic score, meaning the more tics the patient have the less the adaptation they have. This is a novel finding and might contribute an additional impact identifying sensory system as potential pathogenesis in the development of Tourette Syndrome.
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List of Abbreviations

TS - Tourette Syndrome
TDC - Typically Developing children
SP - Sensory Phenomena
PU’S - Premonitory Urges
PUTS - Premonitory Urges in Tourette Syndrome
CM-5 - Cortical metrics 5
2AFC - Two alternative forced choice
nAD- Amplitude Discrimination without adaptation.
ss-AD- single site adaptation
cRT- Choice Reaction time
TOJ - Temporal Order Of Judgment
*DSM - Diagnostic and Statistical Manual of Mental Disorders*
ADHD - Attention Deficit Hyperactivity Disorder
OCD - Obsessive Compulsive Disorder
YGTSS - Yale Global Tic Severity scale
CT - Computerized Tomography scans
MRI - Magnetic Resonance Imaging
EEG - Electroencephalogram
BG - Basal ganglia
CSTC - Cortico-striatao-thalamo-cortical
GPi, GPe- Globus pallidus interna and externa
SNpr - Substantia Nigra pars reticularis
STN - Subthalamic nucleus
SNpc - Substantia Nigra pars compacta
VL - Ventrolateral
VPL - Ventral posterolateral
MPG’s - Motor power generators
SP - Sensory phenomena
CNS - Central Nervous System
FA - Fractional Anisotropy
SMA - Supplementary motor area
SPD - Sensory Processing
SID - Sensory Integration Disorder
SC - spinal cord
DCML - Dorsal column-medial lemniscus
PCML - Posterior column–medial lemniscus pathway
DRG - Dorsal root ganglia
S1 - Primary Somatosensory cortex
S2 - Secondary Somatosensory cortex
D2 - Index finger
D3 - Middle finger
QA - Quickly adapting
ISI - Inter stimulus interval
ITI - Inter trial interval
LTP - Long-term potentiation
LTD - Long-term depression
TMS - Trans cranial Magnetic Stimulation
PAS – Paired Associative Stimulation
iTBS- Intermittent Theta Burst Stimulation
MEP - Motor Evoked Potential
M1 - Primary motor cortex
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Chapter 1

Introduction of Tourette Syndrome

1.1 History of TS:

Tourette syndrome or Tourette disorder is classified by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition Text Revision (DSM-5) as a "Tic Disorder." The *International Classification of Disease and Related Health Problems*, Tenth Revision (ICD-10) called TS a "combined vocal and multiple motor tic disorder (Gilles de la Tourette's syndrome)." Jean Marc Itard, a French neurologist, described the first known case of Tourette syndrome in the 1825. In which he had recorded the tic and cursing behavior of an aristocratic woman, Madame de Dampierre. Later in 1885 another French physician Georges Gilles de la Tourette, published an article in *Archives de Neurologie*, January issue, reporting a series of patient cases with similar problems. The article was based on nine patients’ case histories with a condition that have similar features, including childhood-onset, multiple motor tics and "involuntary" vocalizations followed by spontaneous waxing and waning. Which was distinct from choreas and hysterias. Later this disease of tics was renamed as “Gilles de la Tourette's", but now is most commonly known as Tourette Syndrome.

1.2 Definition of TS:

Tourette Syndrome (TS) is a neurobehavioral disorder with onset in childhood characterized by multiple motor and vocal tics[1]of duration of one year or greater. According to DSM-5, tic is a sudden, rapid, recurrent, non-rhythmic motor
movement (motor tic) or uttered sound (vocal tic). Tics can be further categorized as simple or complex. Involvement of single muscle group results in simple tics whereas complex tics involve more than one group of muscles and results in coordinated and repetitive movements or vocalization. Eye blinking, head jerking, mouth opening are considered to be examples of simple motor tics and throat clearing, sniffing etc. are considered simple vocal, or phonic, tics. Example of complex motor tics includes twitching of multiple facial muscles, head twisting or shrugging of shoulder, throwing, hitting, copropraxia (performance of obscene gestures), etc. whereas complex vocal tics included echolalia (repetition of other people’s word), palilalia (repetition of one’s own word) or coprolalia (uttering of socially inappropriate, often obscene, words).

Characteristics of tics in regards to frequency, duration or severity do not follow a regular pattern and have wide interpatient variability yet there is a propensity for them to occur in bouts. When tics occur they usually follow ‘waxing and waning’ over a period of hours, days, weeks, months, or even years [2]. It is estimated that around 3 to 5 in every 1000 school age children has TS worldwide with interracial, geographic and sexual variation [3]. TS is more common in boys compared to girls in a ratio of 4:1 (Freeman et al., 2000). Tic frequency and severity usually decreases by late adolescence in 90% of kids with TS. The peak age of tic onset is considered at 7-10 years [4] and the peak age of tic severity is 9-14 years Tics usually become worst during emotional distress i.e. Anxiety, anger or extreme fatigue [5]. Paradoxically, tics also often increase at the time of relaxation, especially when children come home after long day from school. Although complete absence of tic are rare except during sleep, tic frequency usually diminishes when a patient is concentrating or absorbed in certain activities. Often tics are preceded
by sensory events that can be specific like scratchy feelings in the eye before the eye blinking. Other times, there are nonspecific feelings like inner tension, which is known as premonitory urges [6]. Premonitory urges are commonly described by the patient as buildup of inner tension, pressure, energy, or uneasiness that may enable him to recognize an impending tic.

According to the DSM-5, diagnostic criteria, for a person to be diagnosed with TS, he or she must:

1. Have two or more motor tics (for example, blinking or shrugging the shoulders) and at least one vocal tic (for example, humming, clearing the throat, or yelling out a word or phrase), although they might not always happen at the same time.
2. Have had tics for at least a year. The tics can occur many times a day (usually in bouts) nearly every day, or off and on.
3. Have tics that begin before he or she is 18 years of age.
4. Have symptoms that are not due to taking medicine or other drugs or due to having another medical condition (for example, seizures, Huntington disease, or post viral encephalitis).

1.3 Life-time courses:

According to DSM-5, the onset of TS ranges between births to 18 year with a peak age of diagnosis is 6-7 years[7, 8]. The onset of tics are gradual, most commonly it start with simple motor tics such as eye blinking or some other facial tics between the ages of 3 to 8 years [9], but vocal tics such as throat clearing or sniffing typically comes several
years after onset of motor tics[10]. Tics usually occur multiple times per day, generally in bouts. These bouts are characterized by stable intra tic interval of as short as 0.5 to 1.0 seconds between two successive tics. Over the time course of weeks to months this temporal pattern which displays fractal characteristics will occur many times in a group of “bouts-of-bouts-of-bouts-of-bouts” of tics (Figure 1). This cyclical combination of pattern of tics might be responsible for usual waxing and waning course of TS [2].

**Figure 1.** Fractal character of temporal occurrence of tics from second-hours-days-weeks-months (Leckman JF et al. 2002).
Most cases of TS are thought to be “mild,” that the patient does not seek treatment until they have experienced significant interference in their life from their tics. In uncomplicated cases tic severity usually reaches its peak around the early teen age years and almost half of patients are free of tics by their late teen years with a complete or near complete resolves of symptoms during adulthood (Figure 2) [8]. This spontaneous resolution explains the prevalence rate being 10 times higher in children than adults [11]. The tics that persist in adulthood progressively diminish in their severity and frequency over time, yet about 20% of the children have persistently impairing tics in adulthood [12]. In such cases there can be chronic, progressive lifelong impairments and social disability [13]. New tics in adulthood might represent persistence or recurrence of tics from childhood [14] or in rare situations there are first time occurrences of tics during adulthood [15]. While a good proportion of patients seen in the clinic have a significant remission or improvement in symptoms with age, there are people who do not follow the general norm and instead their tics become worse in adulthood [16]. Pappert et al. (2003) evaluated a “global tic impairment” score considering five tic factors (number of body areas with tics, tic frequency and severity for motor and vocal tics). He performed a longitudinal study in which patients were evaluated using videotape assessment from database during their pre-teen years and after age 20. They have noticed improvement of tic disability in all domains during adulthood although ninety percent of adult patient still have tics. The adults who were thought of as tic-free were often inaccurate in their self-assessment and actually 50% had objective evidence of tics. There are no predictable criteria to characterize which patient might enter into spontaneous remission and which patient falls into lifelong
impairments. Often patients with severe tics during childhood might have a tic free stable life in adulthood although mild tics during adolescence is a better predictor for mild tics as an adult [14].

![Natural History of Tourette's Syndrome](image)

**Figure 2.** Natural history of TS (Jankovic Josep, NEJM 2001).

1.4 Co-morbidity:

Tics seldom present as single entity. A huge proportion of children with Tourette’s Syndrome who are treated in clinical settings as well as community samples also have symptoms of other disorders or conditions. It is estimated, that as many as 90% of the patients with TS who present for medical attention have other coexistent conditions and around 60% has two or more co-existing disorders [17]. ADHD (60-70%) and OCD (30%) [7] are the most commonly associated disorders of all. In a community based study involving 1,596 children of school age has suggested to have Anxiety disorder, Mood disorders (major depression, mania), oppositional defiant behavior separation anxiety, simple phobia, social phobia, agoraphobia along with ADHD and OCD of the most two common associated disorders [18]. Kurlan and his colleagues have employed
standard psychiatric interviews and standardized rating scales to diagnose childhood behavioral disorders. As we know median age of onset of TS is 6-7 years [7], the most common disorders such as ADHD starts 2-3 years earlier [19] and OCD starts 5-6 years later [20], although comorbid disorders can diagnose at any age beginning as early as 4 years of age (Figure 3) [17]. The association of ADHD and OCD with TS likely has a hereditary origin [21, 22] although genetic association of ADHD and Mood disorders has also been observed in non-TS patient samples [23, 24]. Ratings of quality of life (QOL), social and occupational impairment correlate more with presence and severity of associated disorders rather severity of tics (Eddy CM, 2011- clinical correlates of QOL). In a separate study where QOL was measured based on physical, psychological and social wellbeing, TS patients showed lower scores on all scales compared with healthy controls; furthermore, patients with co morbid depression, anxiety and OCD scored lowest, implying the worst QOL compared to TS- only (K.Elastner, 2000- QOL of patient with GTS). These co-existing conditions are often the cause of more morbidity than the tics themselves [25, 26], and therefore are often the target of treatment.
1.5 Diagnosis:

1.5.a Physical Examinations:

The cardinal features of TS (DSM 5) criteria are tics, multiple motor and vocal tics, appearing before 18 years of age. Neurological examinations in patient with TS are usually normal except during the presence of tics Clinical assessment and diagnosis of TS are typically made in clinic through in-person observation and through collecting information retrospectively using structured interviews, thorough personal, family histories and clinical assessments using DSM -5 criteria (Appendix-1). The disease usually begins with a motor tic at age 6-7 years followed by vocal tics. Multiple rating scales are used for tics and other symptoms. Probably the most frequent of these for

Figure 3. Ages of onset for comorbid disorders among children with Tourette Syndrome (TS). Data points and bars represent median ages at onset and interquartile ranges, respectively (Reproduced from Hirschtritt et al; 2015). ADHD- Attention-deficit/ hyperactivity disorder, OCD – obsessive compulsive disorder)
tics is the Yale Global Tic Severity Scale (YGTSS) [27]. This is used for symptom severity assessment, but is not part of the diagnosis. Once the diagnosis is confirmed, YGTSS (Appendix-3) is administered to rate the severity of tics. It is rated on 0-50-point score, giving 10 items that scores both tics, motor and vocal, on 5-point Likert scales taking into consideration of tic number, frequency, intensity, complexity, and interference as described. Health professionals consider several factors in assessing tics of TS to differentiate it from other hyperkinetic disorders which included patient’s perception, tic modulating factors, and relative lack of tics during sleep. One of the common differential diagnosis of tics in TS is ‘transient tic disorders of childhood’ which is normally present in 25% of the typically developing children [28]. Diminution of tics during sleep and ability to voluntary suppress tics for a short time are the two important distinguishing factors of TS.

1.5.b Laboratory Investigations:
There are no confirmatory medical tests to diagnose TS. Neither standard neuroimaging studies such as routine CT of head or anatomical brain MRI, nor EEG demonstrate any distinguishing abnormalities. Brain imaging should be normal in TS, and EEG, if abnormal, demonstrates non-significant findings with no clinical implications. On a research bases, a number of newer imaging modalities demonstrate TS-associated changes, as discussed in more detail below. However, none of these is specific or can be used to accurately classify individuals as TS vs. non-TS. For example, some studies have shown that caudate nucleus has reduced average volume in TS[29] but there is overlap between the two groups. Of note, another study including 43 children with TS
has suggested that the volume loss of caudate nucleus using MRI significantly correlated inversely with the tic severity in late adolescence and early adulthood [30].

1.5.c Associated factors to consider during Diagnosis:

Although presence of certain associated disorders, i.e. ADHD, OCD, mood disorders, etc. are not diagnostic criteria for TS, their presence can act as supportive evidence. A full family history including extended family members might need to be taken in consideration while assessing TS. There is usually a family history of tics, Tourette Syndrome, ADHD and OCD present in patients with TS, with a complex pattern of inheritance.

1.5.d Verification of Tics:

In most cases patients presenting for clinical attention will manifest their tics in clinic and so the diagnosis is based in part on direct observation in addition to the reported symptom duration and distribution. On occasion the child may not have tics in clinic. In such instances, home video recordings may be provided by the parent.

1.6 Risk factors and Causes:

In US and European populations, the TS occur irrespective of race and ethnicity (CDC: 2012-2013). Male sex poses 4 times more risk to acquire TS compared to females [7], possibly due to greater genetic penetrance. [31]. Precise causes and risk factors for TS remain unknown and have been considered a priority for the researchers for decades.
1.6.a Genetic Risk Factors:

Clinically, it is very common to see children with TS have affected siblings and parents or other family members, suggesting a high heritability. Although the mode of inheritance is unknown [32], larger family and twin studies[33, 34]suggest the mode of inheritance of TS might be of autosomal dominant[35] in nature in which only one copy of the defective gene, inherited from one parent, is required to produce the disorder. But more recent studies have shown that having a parent with TS imposes the risk to carry the gene in their offspring yet does not always expresses the disease suggesting that the pattern of inheritance might be much more complicated than previously thought. So, once the previously accepted single gene hypothesis [31, 36]has been supplanted by data supporting involvement of multiple susceptibility genes interacting with other environmental factors. Specific genetic mutations have been found in less than 1% of patients [37]. Among several genes linked to TS, SLITRK1 on chromosome 13 is one of the first ones[38] expressed in multiple brain regions including the cerebral cortex and basal ganglia. There are mutations in Contactin associated protein 2(CNPAPN2), HDC identified in a few families [39, 40]. CNPNAP2 is located in nodes of Ranvier modulates the K channel in nervous system, disruption of this might influence membrane potential and repolarization leading to unwanted movements in TS. A larger multicenter study with a sample size around 2000 has linked COL27A1, POLR3B, SLITRK6, and SLITRK1 with TS [41]. In trying to determine whether specific genes play a role, patterns of gene expression might be helpful. Since many of the imaging studies using a variety of modalities have shown BG and CSTC pathways producing characteristic motor
symptoms in TS, genes found to be expressed in these locations are more plausible when linked to TS.

1.6.b Non genetic Risk Factors:
Careful investigation identifying potential non-genetic factors that might contribute to the occurrence of disease in higher rates has inconsistent results. Maternal smoking [42], excessive stress during pregnancy and low birth weight [43] have been most consistently implicated. Although other environmental and psychosocial factors have not proven to cause TS, they might influence the severity of the clinical presentation [31]. Autoimmune disorders might have implication in the development of TS are evidenced by elevated antinuclear antibodies [44]. However, the most specific proposed trigger, immune changes induced by streptococcal infections, has been difficult to demonstrate consistently and remains quite controversial[45, 46].

1.7 Motor theory of TS Pathophysiology:
Although involvement of the Cortico-Striato-Thalamo-Cortical (CSTC) pathway [47-49] and over activation motor, premotor, supplementary motor cortex [50] in the development of TS and accompanying neuropsychiatric disorders has been widely studied, an exact location of a primary causative “lesion” has not been established. One of the important areas of focus has been striatum [51]. The stratum contains the input nuclei of basal ganglia (BG) which receive excitatory input from nearly all areas of cortex and then projects to globus pallidus(GP); the output nuclei of BG [52]. These CSTC circuits are involved in the planning and execution of motor movements. Once
basal ganglia co-ordinate the motor planning, it will then relay this plan back to the cortex via the thalamus. Schematic presentation of CSTC circuit is shown on (Figure 4).

**Figure 4.** Schematic presentation of CSTC circuit. Information comes to brain as sensory input. Cortex sends signals to BG in order to create an ideal motor plan. Once the basal ganglia are done with its work with the motor plan, it then relay this plan back to the cortex via thalamus.
1.7.a Basal Ganglia motor circuit:

Basal Ganglia (BG) motor circuits, most formally known as “cortical-striatal-pallido-thalamo cortical circuits,” are anatomically and functionally interconnected with cerebral cortex and thalamus. The subcortical nuclei include Striatum (Caudate, Putamen), Globus pallidus interna and externa (GPi, GPe), Substantia Nigra pars reticularis (SNpr), and Subthalamic nucleus (STN). These are considered input nuclei of the circuit which receive information from cerebral cortex. All parts of the cerebral cortex including primary motor and sensory cortices, association cortex, and limbic cortices send information to striatum via corticostriate fibers. Other key components are output nuclei, i.e. GPi, GPe and SN, which project information back to the cortex mainly motor and premotor cortex via thalamus (Cortico-Thalamo-cortical fibers). BG mainly works to integrate diverse inputs from the entire cortex while funneling them to mainly motor and premotor cortex [53].

In each circuit, corticostriate fibers representing different cortical areas project into distinct striatal sectors with partial overlapping (Figure 5) of corticostriate information, which subsequently are integrated in later stages of passage through output nuclei of pallidum and STN to the ventrolateral (VL) portion of the thalamus. Thalamocortical fibers originating from thalamus finally brings back the information to single cortical areas[54].
The input and output nuclei are connected via two pathways, direct and indirect. These pathways are modulated by dopaminergic neurons produced from Substantia Nigra pars compacta (SNpc). Dopamine modulates to transfer information from Striatum to the output nuclei i.e. Gpi, SNpr. Output nuclei i.e. Gpi, SNpr finally transfers the

**Figure 5.** Striatum, input nuclei of BG receives information from functionally related cortical areas with partial overlaps. Overlapping signals project to the output nuclei of Pallidum and STN, this in turn projects to the thalamus. Thalamus finally projects the signals back to the cortical areas (Reproduced from Alexender GE et al; 1986).
information back to cortex through thalamus. Ventrolateral thalamus (VL) considers motor thalamus which receives inhibitory impulses from GPi. Output of GPi is inhibitory in nature and provides appropriate level of inhibition to its targets i.e. Motor cortex.

BG circuit as normal physiologic condition has shown in Figure 6. In resting condition, BG is tonically active with strong inhibitory output to thalamus and cortex. This acts as a “brake“ on motor program generators (MPG’s) in the cortex. When a task or movement is desired, a motor program selected by the premotor cortex sends information to the striatum as well to STN. Striatal activation activates the direct pathway and sends information to the output nuclei removing the tonic inhibition (disinhibition), i.e. releases the “brake“ on thalamocortical fibers, which ultimately gives rise to excitatory final output for the desired movements. The parallel cortical fibers to the STN connected to the competing neurons escalate their firing rate so that they increase their inhibition, i.e. apply a brake to the competing neurons. This parallel signaling results in suppression of potential competing motor output, hence permits the desired focused movement and at the same time prevents the competing movements to interfere the task[55].
1.7.b Mechanisms of tics:
Various involuntary movements such as chorea, dystonia or tics arise from dysfunction of distinct but overlapping nodes and pathways of BG circuits. It has been suggested that tics are derived from abnormal activation of striatal neurons. A set of striatal neurons become inappropriately activated, resulting in loss of normal inhibitory nature of BG output to the thalamus and motor cortex. As the disinhibition happens in striatum, the unwanted competing neurons becomes hyper excited which allows the involuntary
unwanted movements. If this cluster of striatal neuron become hyperactive in repeated episodes, then the unwanted movements would be repetitive and stereotyped, tics (Figure 7).

*Figure 7.* Basal ganglia circuit for tics. BG- Basal ganglia, GPi- Globus Pallidus interna, SNpr- Substantia nigra pars reticularis, STN- Substantia nigra (Reproduced from Wink JW et al; 2001)
The mechanism behind over activation of striatal neurons in an inappropriate fashion is in need of further extensive research. It is believed to have multiple mechanisms that might be responsible for the unwanted over activation of striatal neurons including a) Defective intrastriatal inhibition and, b) overactive/over-excitble cortical signaling, possibly resulting in excessive neurotransmission to the striatum that causes downstream dysfunction.

1.8 Managements of TS:

Standard pharmacological management of tics is based on concepts from the motor theory of TS. Such medications have been used for decades, and it is important to understand their mechanism of action. However, it is also generally understood that current medicines have only modest benefits. Many severe cases continue to experience tics despite trying all available medicines. This observation suggests increased understanding of the pathophysiology of TS and its involvement with the sensory system will be important to design more effective therapies. During management of TS, the most important first step to take into consideration is to decide whether the patient needs any intervention at all, as in many mild cases education about the condition suffices. When tics do cause impairment, pharmacologic treatment or non-pharmacologic treatments such as behavioral therapy or some combination may be appropriate. Selecting a treatment plan is crucial, tic severity and families views about therapy and medications are important aspects to consider while choosing treatment plans[56].
1.8.a Pharmacologic Agents:

There is no medication that “cures” tics or modifies the course of the disorder; all of the medications are aimed to relieve the symptoms. One medicine might work for a patient but might not fit for other patients, so medications are carefully chosen by the clinicians in collaboration with the individual or family. Assessing the presence of comorbidity and its severity is another important element that needs to be considered during the selection process of drugs. Multiple medications, briefly categorized as neuroleptic and non-neuroleptics, are used to treat the tics. Neuroleptics are usually reserved for the more severe forms of tics and are considered second line treatment.

First line agents: Alpha adrenergic inhibitors in clinical use are alpha 2 receptor (pre-synaptic) agonists which decrease sympathetic output. These are generally considered when tics are less severe. Efficacy is less than neuroleptics but smaller side effect potential makes them first line treatment agents. They also help control impulsive behavior associated with TS. These are also used to treat ADHD without tics.

Second line Agents: Neuroleptics are considered in this group. These are also referred to as antipsychotics as they were originally tested and marketed to suppress unwanted thoughts in schizophrenia. The mechanism of action is blocking dopamine receptors, primarily the D2 receptor. This results in inhibition within the CSTC circuit and reduces any kind of unwanted movement – tics, chorea, etc. This are potent medications usually saved for severe form of tics but often adverse effects outweigh the benefits. This makes them a less popular choice in clinical practice.
Other medications that decrease the excitability of the motor system may also be used. These include benzodiazepines and several anti-seizure medications like topiramate as well as anti-spasmodic medications like baclofen. Finally, injecting botulinum toxin, more directly decreases motor output by reducing signaling at the neuromotor junction. This has also been found in some cases to reduce highly focal, severe tics. In clinical practice, a combination of medications is a standard practice since a vast majority of TS is associated with other disorders, as for example children with TS and ADHD, might get benefit from using combined low doses of stimulants and clonidine.

In some instances where tics are extremely severe and can cause bodily injury, surgery is used. These are generally adult patients with persistent symptoms and suffering refractory to other management. In prior decades ablative surgeries like pallidotomy and thalamotomy were used, again based on motor circuit theories of TS. These surgeries can cause grave side effects. More recently, deep brain stimulation (DBS) of globus pallidus or thalamus [57], which is FDA approved for Parkinson’s disease and a few other motor disorders, has been attempted in TS. Some benefits have been reported in individual cases and small published case series, although the evidence is still emerging and needed further large clinical trials for confirmatory results.

1.8.b Non Pharmacologic managements:

Finally, non-pharmacologic options are increasingly sought by patients and families as well as to caregivers due to the high rate of side effects and low efficacy rate in
conventional medications. Small scale reports of habit reversal training (HRT), a behavioral therapy [58] and biofeedback [59] demonstrated modest benefit. Building on these results plus beneficial results of cognitive behavioral therapy in adolescents with OCD [60], a group of research designed a more rigorous non-pharmacological therapy for TS called “Comprehensive Behavioral Intervention for Tics” (CBIT). CBIT teaches strategies for tic suppression that incorporate increasing the patient’s awareness of the sensory aspects of TS. The patients are taught to focus on their sensory system and sensory urges and practice delaying performance of their tics and substituting small, less-noticeable tics in place of their usual tics. This therapy was studied in a large, sham-controlled, multi-center study in adolescents [61] and found to produce a high degree of benefit in many adolescents with TS. A similarly designed CBIT study in adults also showed benefit although of a smaller magnitude [62].

An important implication of treatment studies is that pharmacological interventions based on motor system circuits often fail to help many patients. The behavioral therapies, which incorporate sensory phenomena, have some success, so this shows that understanding and working with the sensory system provides an alternate route to improve tics. However, the CBIT treatment was developed without any specific understanding of sensory physiology or processes in TS. And clinically meaningful benefits only occurred in about half of those receiving treatment. The somewhat larger benefits in children also suggest that it is very important to study the sensory system early and to intervene early for the best outcomes. However, more research into the
sensory components of TS is needed to have a better opportunity to design more effective medication and behavioral treatments.
Chapter 2

Involvement of Sensory Systems in TS

2.1 Clinically reported sensory components in TS:

Despite the fact that sensory phenomena are frequently reported in TS in the clinical setting, there is no description of sensory disturbances or sensory phenomenon included in the DSM5 criteria for TS. Sensory phenomena (SP) can arise both from external and internal sources and within their bodies. Most described SPs’ are external sensory sensitivity or intolerance that seems to originate from external sources like clothing tags or socks, etc. A key feature for many individuals with TS are premonitory urges (PU’s), which are somatic sensations or internal stimuli associated with an urge to tic. There has been limited work addressing sensory phenomena in standard clinical practice or in research studies. This is surprising given that SP are so frequently observed in patients with TS and, according to many patients, SP can be equally troublesome as tics [63][64].

2.1.1 External sensory sensitivity/Intolerance:

A typical everyday life complaint among children with TS is the intolerance of clothing tag; this is considered as external sensory sensitivity or intolerance to external stimuli. This phenomenon is the least studied but one of the most common observations by parents, teachers and patients. In one study around two third (13 out of 20) of patients complained about intolerance of clothing tag[64]. This heightened sensitivity is usually accompanied by feelings of ‘just right’ which is patient’s need to have things feel, sound
or look “just right”. These particular traits of SP are more prevalent amongst TS patients co-morbid with OCD [65]. Patients often experience increased sensitivity to external stimuli of other varieties of sensory modalities e.g. light, sound, smell. Belluscio et al. 2011 has studied external sensitivity and suggested as many as 80% (15/19) subjects have increased sensitivity to external stimuli in all five sensory modalities [66]. Although these type of SP do not provoke tics, they do produce a constant irritation, discomfort and distraction [64] to the patients and ultimately leads to functional impairments.

2.1.2 Hyperawareness of internal sensation AKA Premonitory urges (PU’s):

A special type of disturbed sensations also arises within their bodies known as premonitory urges (PU’s). This aversive sensation first documented by a patient named Joseph Bliss with long 62-year history of TS. He who described that this sensation leads to tics and decrease with performance of tic. Bliss’s own words were “I came to be aware of the faint signals that precede a movement. I kept watching these preliminary symptoms year after year, I described them as vague, unfulfilled sensations “[67]. Successive studies acknowledged this observation and stated that it is indeed experienced by a vast majority of patients with TS[6, 64, 68]. Cohen et.al. 1992 suggested around round82% (22 out of 28 patients) patient experience this SP [64]. Based on these observations of SP, TS is not only a motor disorder. Instead TS involves a central mechanism of hypersensitivity to somatosensory stimulation to at least some extent. These sensations in PU’s are a type of increased sensory awareness described as tension, pressure, tickle, or an itch at or below the skin.
involving muscle, joints that often lead to behavioral response like motor or vocal tics (Chee & Sachdev, 1997). Different types of PU’s are described on Table 1.

**Table 1.** Definitions and Descriptions of Different Types of Premonitory Urges (PU’s)
(Reproduced from Cavanna AE et. al: 2013).

<table>
<thead>
<tr>
<th>Types of PU’s</th>
<th>Definition</th>
<th>Description of physical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory tic</td>
<td>Somatic sensation in the body, especially in bones, muscles, and joints that leads the individual to perform voluntary movements to relieve the sensation.</td>
<td>Uncomfortable tactile, visceral, or musculoskeletal sensation that comes immediately before or accompanies the repetitive behavior. The individual is driven to repeat certain movements until he/she experiences a sense of relief.</td>
</tr>
<tr>
<td>Sensory phenomenon/premonitory experience</td>
<td>Uncomfortable physical sensations in skin, muscles, joints, and other parts of the body that may be accompanied by perceptual stimuli (visual, auditory, tactile).</td>
<td>Itchy, tense, or tight sensation with a specific anatomic location, which leads to the feeling of wanting to release the repetitive behavior.</td>
</tr>
<tr>
<td>Just-right experience</td>
<td>A force, triggered by visual, auditory, or tactile perceptions, as well as a feeling of</td>
<td>A need to feel that objects look a certain ‘just-right’ way; that objects and people sound a certain ‘just-</td>
</tr>
</tbody>
</table>
imperfection about actions and intention, that leads to the individual performing compulsive acts until the actions are felt by the individual to be complete.

right' way; or that objects and people have to be touched in a certain 'just-right' way.

<table>
<thead>
<tr>
<th>Urge</th>
<th>A drive or impulse to perform the repetitive behavior in the absence of any obsession, worry, fear, or bodily sensation.</th>
<th>A need to perform repetitive actions that is not preceded by obsessions or sensory phenomena.</th>
</tr>
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</table>

PU’s can be successfully evaluated in all age groups. Steinberg et al. 2010 conducted a study in children with below 10 years and over 10 years of age. Result showed, children in older age group has better consistency perceiving sensory abnormalities compared to younger age group[69], which is already been suggested by earlier studies [6] where Leckman et al, showed that awareness for PU’s usually spiked at age 10, on average 3 years after the onset of tics.

In recent time, PU’s received much attention from both clinicians and researchers and have been rated using a research rating tool called the Premonitory Urge for Tics Scale (PUTS)[70] PUTS is a self report of a patient’s subjectives experiences consisting of ten questions of frequency of specific pre-tic related symptoms on a scale of 1-4, from ‘not at all’ to ‘very much true’ in each category except item number ten. It is rated on a total score of maximum 40 points. The minimum score can be as low as nine. Empirically, a score of
12.5-24.5 indicates medium, 25-30.5 indicates high intensity, and scores 31 and above indicate extremely high intensity with probable severe impairment (Appendix-2).

Although administering PUTS is not a standard practice in clinic, studies have shown PUTS severity to be modestly correlated with overall tic severity as measured by the Yale Global Tic Severity Scale (YGTSS)[70] as well as obsessive compulsive symptoms rated on the Child Yale-Brown Obsessive Compulsive Symptoms Scale (CY-BOCS)[71]. PUTS does not appear to be associated with severity of anxiety and ADHD symptoms [69]. This implies a common pathophysiology might exist between TS and OCD. Implementation of PUTS to the everyday care in order to evaluate sensory phenomenon would have potential to improve care of TS and its associated disorders. To date there are not many valid methods to quantify the SP except two - PUTS and University of Sao Paulo Sensory Phenomena scale (USP-SPS)[72, 73]. PUTS quantifies the frequency while USP-SPS evaluates frequency, severity and timing of precise pre tic related symptoms [73]. However, neither of these necessarily addresses the external sensory hypersensitivity.

Since tics are almost always preceded by the PU’s and if there are fewer PU’s there will be fewer tics. Understanding the sensory component (i.e. PU’s) of the tics and its pathogenesis is crucial for better management of tics. The exact cause has not been identified yet is speculated to originate from neuronal dysfunction below tic generating threshold which might give rise to the subjective experiences of unpleasant sensations[74]. Theoretically, tics can be modeled as due to inadequate suppression or gating of irrelevant somatosensory information by the brain, probably due to
dysregulation of specific corticostriatal pathways. This dysregulation leads to increased activation of premotor cortex including supplementary motor areas (SMA) observed in 2 sec before performance of tics on event related functional MRI [75]. Awareness of PU’s and the feeling of temporary relief are crucial in Habit Reversal Training (HRT)[76]; a type of behavioral treatment. HRT consist of five components with the first one being “awareness training” where the patient learns to become familiar with the awareness of premonitory urges, followed by adapting a competing or more comfortable response when a patient feels a premonitory urge building to replace the tic[77].

Quantifying SP is vital from both clinical and research perspective in that they serve as behavioral correlate that can be used in neurophysiologic and neuroimaging studies in an attempt to ultimate improvement of treatment and prognosis of the disease.

2.2 Past research related to involvement of sensory system in TS

There is scarce research to address the sensory issues in TS. One important study was conducted in early nineties by Leckman et al [6], in order to evaluate SP mostly PU’s age ranges 8-17. It was a cross sectional survey, 135 patients completed questionnaire regarding onset, frequency, perception, location and character of PU and other SP. Concurrently, they have also answered about the physical or mental nature of these symptoms. Clinical tic severity scale (YGTSS) was also obtained in these patients. They showed that 93% to 95% have subjective experience of PU and 92% also revealed that their tics were a voluntary response of their PU[6]. The latter finding argues against the popular belief of involuntary nature of tics observed in TS. These results actually
provided an window to the researcher interested studying SP. With better understanding, recognition and dissecting the presence of subjective experiences might escalate the patient’s ability to abolish tics [78] and ultimately precede to the development of sophisticated medicine or behavioral intervention that address SP and would also act as a predictor for treatment responses [65].

A more recent study[66], more specifically investigated external sensitivity in TS. They have included 19 adults with TS and matched controls. Results showed 80% of patients self-reported of increased sensitivity across all five modalities: sound, light, smell, touch and taste (Figure 8). This heightened sensitivity or intolerance was significant in all modalities except taste. Sensitivity to touch was increased by 65%, second highest to smell. Regarding tactile stimuli, most of the patient experiences irritation from rough texture of fabrics, pressure exerted by collar or wrist bands and sensitivity were equally distributed among all regions of the body.
Tactile sensitivity was further tested in regards to sensitivity and suggested to be increased with faint stimuli compared to intense stimuli. Sensory thresholds for olfactory and tactile sensation also were evaluated and found no significant differences between two groups (Figure 9). Tactile thresholds were obtained from active tic site, neck area and leg area (non-tic prone area) sites. They have used “vonfrey monofilaments” to determine tactile thresholds and “sniffin sticks” for olfactory threshold. The crucial findings revealed from this study suggested that there are no observable differences in measurement of detection threshold for olfactory or tactile stimulation. Based on these results since patient with TS do not have an increased ability to detect stimuli therefore their perceived heightened sensitivity or sensory intolerance might be originated from an
error occurring in central nervous system rather than processing in peripheral nervous system. Which is consistent with the general consensus about involvement of basal ganglia, part of CNS in the pathogenesis of TS [49]. This supports, at least in some individuals with TS, that dysfunction of sensory gating in CSTC circuits might contribute to tic symptoms[79].

Figure 9: No significant differences of thresholds between TS and HV. Olfactory threshold were obtained using the validated instrument “Sniffin’ Sticks” and Tactile Threshold using a geometric series of (Semmes Weinstein) VonFrey monofilaments, ranging from 2 to 0.008 g. (Reproduced from Belluscio et al; 2011). HV- healthy volunteer.
Additional evidence of the role of abnormal sensory processing in TS comes from neuroimaging studies showing evidence of structural alteration in somatosensory cortex. An important study by Sowell et al.[80] used magnetic resonance imaging in twenty five children with TS and compared cortical volumes with aged matched peers. They reported significant thinning of the ventral portions of frontal area including pre and post central gyrus (primary sensory/motor cortex) along with right dorsal parietal area, which actually represents the most common areas involved in motor and vocal tics i.e. facial, orolingual and laryngeal areas (Figure 10).

**Figure 10.** Thinning of the ventral portions of frontal area including pre and post central gyrus (primary sensory/motor cortex) along with right dorsal partial area (Sowell E.R et al; Nature Neuroscience, 2008).
The involvement of the somatosensory system is further emphasized by diffusion tensor imaging [81]. In this study, 15 adults with TS (unmedicated) were compared with their aged matched peers. TS patients had an increase of Fractional Anisotropy (FA) in white matter of pre and post central gyrus (Area 3a) bilaterally, left supplementary motor area (SMA) along with right VPL of thalamus (Figure 11, 12)- the areas involved in sensory-motor processing. Increased FA was peaked below the left SMA, the area responsible for control of movements that are internally generated rather than triggered by sensory events (not stimulus driven). Increased FA might imply less fiber branching within these regions, reflecting abatement of cortico-cortical connection of somatosensory pathways, which ultimately might help reduce the transmission of information from overactive sensory system to motor system.

Figure 11. Showed regional increase of FA in the white matter below pre and post central cortex (Thomalla G, et al; 2009. Brain).
Interestingly, the sensorimotor cortical findings in both studies [80, 81] were negatively correlated with the clinical score of tic severity. Sowell et al. has shown that the negative correlation of total tic score with cortical thinning of sensory motor cortex (Figure 13). Thomalla et al. has shown similar correlation of tic score and regional FA (Figure 14).

**Figure 12.** Increase diffusion parameter (FA) in patient with TS compared to healthy controls. FA-Fractional anisotropy, HC- healthy controls, TS- Patient with TS (Thomalla G, et al; Brain 2009).
This result of documented white matter abnormalities of somatosensory pathways with clinical correlation emphasizes the possible involvement of sensory systems in the pathogenesis of TS.

**Figure 13.** Decreased cortical thickness in superior portion of sensory cortex correlates with increased tic severity (Sowell et al; 2007).
Potential for TS to be considered a Sensory Processing (SPD)/Sensory Integration Disorder (SID):

SPD and SID are terms widely used by clinicians, therapists, and parents to describe sensory problems that children with developmental disorders encounter in the classroom and at home. These terms are often used interchangeably. Although widely used in the setting of occupational therapy to capture important clinical phenomena, neither SPD nor SID is officially included in the DSM as a distinct disorder. Similar to executive function deficits in ADHD, some consider these as nonspecific indicators of neuro developmental immaturity, present in many neurobehavioral diagnoses.

Figure 14. Correlation of FA with tic severity. Increased FA in TS patients in the left mesial sub central white matter with total MRVS score (A) and total number of tics/minute (B) (Thomalla G, et al; Brain, 2009.). MRVS-Modified Rush Video scale; FA- Fractional anisotropy; HC-healthy controls; TS- Patient with TS.
Sensory integration and processing is an innate biological process in which sensory stimuli is transduced, detected, modulated, discriminated, coordinated and finally organized to produce appropriate action. The theory of sensory integration was developed by a clinical psychologist Dr. Ayre in early seventies. According to his theory, development of children depends on the neurological processes where various sensory experiences of everyday life from the environment are brought together and synthesized in order to organize the child’s behavior effectively [82]. Dr. Ayre’s theory hypothesized that impairment in any of the steps of sensory integration and processing could result in atypical behavior. According to him, SPD is presumed to result from immaturity of the developing brain at birth or later and this persists in people who experiences sensory processing dysfunction. In theory, modulation is the capacity of the brain to regulate self-activity through facilitation and inhibition at cellular level, hence dysfunction is as a result of impairment in processing distinct sensory stimuli at the central processing level. This hypothesis suggests that deficiency in inhibiting sensory information results in excessive CNS stimulation or arousal- a notion that shares with traits of TS as well (Stern, 2008-Inhibitory Deficits in Tourette syndrome). Although the relationship between pathophysiology of TS and SID/SPD is somewhat ambiguous, yet there are a considerable number of similarities in the clinical presentation of these two conditions such as showing adverse responses to sensory stimuli, hyperactivity, anger outburst etc. These are more often found in TS associated with Attention Deficit Hyperactivity Disorder (ADHD) and or Obsessive Compulsive Disorder (OCD).
Dr. Ayre also stated that Sensory processing and Integration is a multimodal process – visual, auditory, proprioception depends on functional body-centered senses to learn a behavior with special importance to tactile system, which considered key to maintain focus and attention in steady level.

SI and SPD, in general is the disturbance of ability to process sensory input or dysfunction with sensory modulation. SI and SPD can present as an alteration of responsiveness to the external stimuli such as hyper and hypo responsiveness. It can also be presented as difficulties in sensory discrimination. In this study we have obtained multiple sensory measurements which might provide more information about sensory dysfunction observed in children with TS. To date there has been no research directly questioning TS might have a sensory processing deficit, except few studies I have already discussed in 2.2 (Past research on SP in TS). Thinning of the sensorimotor cortex [80] in patients with TS described earlier might result in some form of sensory processing disorders.
Chapter 3
Sensory Physiology

3.1 Sensory System:

The sensory system is the part of the nervous system which is responsible for sensory processing. Sensation and perceptions are fundamental elements for mental processes and behavior. Generally identified sensory modalities are auditory, visual, gustatory, olfaction, vestibular, and somatic (pain, touch, temperature, proprioception) systems. Despite different types of stimuli all sensory systems provide four types of information when stimulated: modality, location, intensity and timing. Modalities refer to the general class of stimulus and the type of energy it might produce. Stimulus location is represented by sensory receptors.

Depending on the type of stimuli, receptors are categorized into four groups: chemoreceptors- responsible for detecting chemical stimuli, photoreceptors-responsible to convert light into energy and further processing, thermoreceptors- responsible to detect changes of temperature and mechanoreceptors- responsible to detect mechanical forces such as pressure and vibration. Regardless of sensory modality all of the senses shares three components – 1) A Stimulus 2) Transformation of stimulus into nerve impulses and 3) Response of the stimulus in the form of perception. Perception considers the conscious experience of a sensation. Perception starts with sensory receptors which then transduces the signal in action potentials and travel along sensory neurons to the specific regions of cortex where it is perceived and acted upon. Studying these neuronal events is a key to understand the basis for Sensory Physiology. For our
study purpose we will focus on processing of sensory information by sensory cortex.

Sensory pathways usually follow a common route of 3 neuron systems-

1) Its way from source of stimuli to spinal cord (SC),

2) from SC to brainstem,

3) from brainstem to cortex via thalamus except olfaction which has no relay on thalamus.

For this study, we will focus on somatosensory system, more specifically on tactile system.

Table 2. Overview of sensory system and modalities (Reproduced from 'sensory integration' by Gardner EP, 2006)

<table>
<thead>
<tr>
<th>Sensory System</th>
<th>Modality</th>
<th>Stimulus energy</th>
<th>Receptor class</th>
<th>Receptor cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>Vision</td>
<td>Light</td>
<td>Photoreceptor</td>
<td>Rode’s, Cones</td>
</tr>
<tr>
<td>Auditory</td>
<td>Hearing</td>
<td>Sound</td>
<td>Mechanoreceptor</td>
<td>Hair cells (Cochlea)</td>
</tr>
<tr>
<td>Vestibular</td>
<td>Balance</td>
<td>Gravity</td>
<td>Mechanoreceptor</td>
<td>Hair cells (Vestibular labyrinth)</td>
</tr>
<tr>
<td><strong>Somatosensory</strong></td>
<td>Somatic Senses</td>
<td></td>
<td></td>
<td>Dorsal root ganglia</td>
</tr>
<tr>
<td></td>
<td>Touch</td>
<td>Pressure</td>
<td>Mechanoreceptor</td>
<td>Cutaneous mechanoreceptor</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------</td>
<td>---------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Pain</td>
<td>Chemical, thermal or mechanical</td>
<td>Chemoreceptor. Thermoreceptor or mechanoreceptor</td>
<td>Polymodal, thermal and mechanical nociceptors</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>Thermal</td>
<td>Thermoreceptor</td>
<td>Cold and warm receptors</td>
<td></td>
</tr>
<tr>
<td>Proprioception</td>
<td>Displacement</td>
<td>mechanoreceptor</td>
<td>Muscle and joint receptors</td>
<td></td>
</tr>
<tr>
<td>Gustatory</td>
<td>Taste</td>
<td>Chemical</td>
<td>Chemoreceptor</td>
<td>Taste buds</td>
</tr>
<tr>
<td>Olfactory</td>
<td>Smell</td>
<td>Chemical</td>
<td>Chemoreceptor</td>
<td>Olfactory sensory neurons</td>
</tr>
</tbody>
</table>

### 3.2 Somatosensory System:

Somatosensory systems, is the branch of sensory system which is concerned with the perception of touch, pressure, pain, temperature, position, movement, and vibration.

Their receptors are located within muscles, joints, skin, and fascia. Each of the stimulus modalities are divided into sub-modalities. For example, pain is divided into dull, sharp, deep or touch into discriminative and no discriminative/crude touch. As described in the 3.1 section, like all other sensory systems, the somatosensory system consists of three neuron pathways from receptor to cortex. Depending on the type of information it...
carries, these somatosensory systems take different anatomical routes to reach to the cortex (Table 3). For somatosensory information, the ultimate destination is the primary sensory cortex, as these neurons show modality specificity. When a somatosensory neuron is stimulated naturally or artificially (e.g., by electrical stimulation of the neuron), the sensation received by the neuron is specific to that stimulus. For our study we will focus on touch or tactile part of the somatosensory system, which will be discussed in details in following section 3.3.

Table 3. Different types of Sensory Modalities and their different Sensory Pathways.

<table>
<thead>
<tr>
<th>Modality of Stimulus</th>
<th>Sub-Modality</th>
<th>Sensory pathway (Body)</th>
<th>Sensory pathway (Face)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Sharp</td>
<td>Spinothalamic Tract</td>
<td>Spinal Trigeminal Tract</td>
</tr>
<tr>
<td></td>
<td>Dull</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>Warm</td>
<td>Spinothalamic Tract</td>
<td>Spinal Trigeminal Tract</td>
</tr>
<tr>
<td></td>
<td>Cold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td>Crude Touch</td>
<td>Spinothalamic Tract</td>
<td>Spinal Trigeminal Tract</td>
</tr>
<tr>
<td></td>
<td>Discriminative touch</td>
<td>Posterior column medial lemniscus</td>
<td>Main Sensory Trigeminal</td>
</tr>
<tr>
<td>Proprioception</td>
<td>Position (Static)</td>
<td>Posterior column medial lemniscus</td>
<td>Main Sensory Trigeminal</td>
</tr>
<tr>
<td></td>
<td>Movement (Dynamic)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.3 Tactile (Touch) Processing:

The tactile system plays pivotal roles in perceiving the environment and sends alerting signals to the nervous system as part of the defense system as well as discriminates between different stimuli. Sense of touch in human constitutes two modalities - cutaneous and kinesthetic depending on their origin of sensory input. Kinesthetic sense receives information via receptors placed within muscle, ligaments, and tendons. For cutaneous senses receptors are located in the skin, known as cutaneous or tactile receptors. According to Loomis JM[83], awareness of cutaneous sensation requires physical contact of the stimulus with its respective receptors and associated somatosensory cortex. Thus, touch processing starts at cutaneous end organs or sensory receptors and follows large amount of processing and filtering at multiple level before its conscious perception. The pathways of tactile stimulation from its origin on the skin (the site of physical stimulus) to the brain (Somatosensory cortex) will be discussed in the following sections.

3.3.1 Tactile receptors and primary sensory neurons:

Touch or tactile information perceived by the cutaneous receptors embedded in the skin, then carried the information by primary sensory neuron in ascending hierarchical manners towards somatosensory cortex. In human, touch sensations are perceived by four types of mechanoreceptors in glabrous skin [84, 85], which are responsible to provide information about submodalititis of tactile senses; pressure, flutter, or vibration. Similar to other senses, tactile receptors are stimulus-specific, and distinct types of tactile sensation activate distinct types of receptors (table 4). These receptors respond
to mechanical stimuli and are innervated by Aβ fibers. Mechanical stimulation that produces physical interaction such as pressure or vibration depolarizes the receptors and results in excitatory post synaptic potential (EPSP), excites the sensory neurons connected with the receptors. Sensory neurons are distinct in properties as they are devoid of dendrites and synaptic input instead they terminates in receptors that are embedded in the skin [86](Figure 15). These receptors can be classified based on following criteria- a) morphology; b) Kind of stimulation they perceive; c) stimulus specificity or receptive field; and d) rate of adaptation.

Figure 15. Sensory neuron, directly terminating on skin receptors
(http://www.biologymad.com/nervoussystem/nervoussystemintro.htm)

After receiving stimulus receptors begins to fire which is directly proportionate to the stimulus intensity however if stimulus continuously present without a change in intensity or position, firing decreases and gradually diminishes the sensation which is known as adaptation. Receptor adaption is presumed to be an important basis for perceptual adaptation where persistent stimulation gradually fades away. Depending on their rates
of adaptation receptors are categorized as fast and slow. Some receptors adapt rapidly (RA) whereas some adapt slowly (SA). RA receptors respond only to beginning and end of the stimulation but do not fire continuously for the duration of the stimulus. RA receptors are often called ‘phasic’. On the other side SA receptors respond to vibrotactile stimulation throughout the duration of stimulus and are known as ‘tonic’.

Another property of receptor is receptive field (RF); a restricted area of body surface directly innervated by receptors where a stimulus could evoke a response. Each mechanoreceptor responds only when stimulation reaches the RF. Tactile mechanoreceptors with small RF are found in lips and finger tips have stronger tactile acuity compared to receptors with larger RF. Any stimulus that affects surrounding areas than RF of one receptor might activates the adjacent receptors and has less specificity for discrete tactile stimulation given on finger tips. Detail properties of four cutaneous mechanoreceptors are described as follows and on Fig 12 and table -3

i) Merkel’s Disk: Detect sustained pressure, form and texture of an object [87]. They have small receptive field and slow adaptive.

ii) Ruffini endings: Respond to skin stretch, are slow adaptive and have large receptive field, as large as in entire finger.

iii) Pacinian Corpuscle: Respond to high frequency vibration, RA and have large receptive field[88].

iv) Meissner’s Corpuscle: Respond to slow/flutter vibration (20-50 Hz)[87] Also known as tactile corpuscle. These are located under the glabrous skin, that are rapidly adapting receptors comprised of rapidly adapting Aβ fibers but have small receptive
fields. More than 40% of sensory innervations of hands are represented by Meissner’s Corpuscle. Details of tactile mechanoreceptors are summarized in Table 4 and Figure 16.

Table 4. Details of different off Cutaneous Mechanoreceptors (This table is reproduced based the findings on Johansson et al; 2009, McNulty et al; 2001).

<table>
<thead>
<tr>
<th>Sensory Modality</th>
<th>Receptor</th>
<th>Location on skin</th>
<th>Sensation</th>
<th>Signal</th>
<th>Receptive Field</th>
<th>Adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touch</td>
<td>Merkel’s Disk</td>
<td>Epidermis</td>
<td>Detect sustained pressure, form and texture of an object</td>
<td>Location and Magnitude</td>
<td>Small</td>
<td>Slow</td>
</tr>
<tr>
<td></td>
<td>Ruffini endings</td>
<td>Dermis</td>
<td>Detect skin stretch</td>
<td>Direction and Force</td>
<td>Large</td>
<td>Slow</td>
</tr>
<tr>
<td></td>
<td>Pacinian Corpuscle</td>
<td>Dermis</td>
<td>Detect Fast Vibration</td>
<td>100-300 Hz</td>
<td>Large</td>
<td>Rapid</td>
</tr>
<tr>
<td></td>
<td>Meissner’s Corpuscle</td>
<td>Dermis</td>
<td>Detect light touch, flutter vibration</td>
<td>20-50 Hz</td>
<td>Small</td>
<td>Rapid</td>
</tr>
</tbody>
</table>
Connections of Tactile receptors to Spinal cord (SC) and Brain:

Regardless of types of stimuli and receptors connected, sensory information travels to dorsal root of spinal cord (SC), into various nuclei. In the SC, the axons are organized according to the information type (i.e. tactile, visual, smell). Tactile stimulation regarding
touch and slow vibration are conveyed through dorsal column of spinal cord via a fiber bundle called dorsal column-medial lemniscus (DCML) or posterior column–medial lemniscus (PCML) pathway to the final destination of post central gyrus of cerebral cortex [89].

3.3.2.a Receptors to Spinal Cord (SC):

Tactile stimuli sensed by the receptors. Receptors convert physical stimuli to action potentials, which proceed as sensory information sequentially to the SC-Medulla-Thalamus-Cortex. The nerve fibers innervating these tactile receptors have their cell bodies in the dorsal root ganglia (DRG) near the SC. First-order neurons arising from dorsal root ganglia make contact with the second order neurons located in posterior column of SC. Posterior columns consist of the fasciculus gracile and cuneate (for thoracic and cervical regions). Here axons are organized based on specific regions of the body or maps of the body surface (Somatotopy) [90].

3.3.2.b Spinal Cord to Brain:

From the dorsal column, arises the second order neuron which then sends information to medulla. In medulla second order neurons decussates, take a position on contralateral side and travel up the brainstem as medial lemniscus followed by projecting to thalamus as Dorsal Column Medial Lemniscus (DCML) pathway. Second order neurons transmitting ‘flutter’ vibration project to ventral of posterior nucleus (VPL) of Thalamus. The third order neurons arise from thalamus and ultimately transmit information to postcentral gyrus of cerebral cortex (Figure 17 and 18). This flow of
information ultimately leads to processing in the primary somatosensory cortex. During the sequential step in ascending process from the peripheral nervous system these fibers relay in an orderly fashion so that information from the entire body surface is maintained on a neural map at each stage of processing.

Figure 17. Schematic presentation of Sensory Pathway from receptors to sensory cortex.
Figure 18. The ascending medial lemnisci pathway for somatosensory/Tactile information. Sensory information enters the nervous system through the dorsal root ganglion cells in the spinal cord. Information then send to medulla followed by medial lemniscus to VPN of thalamus and ultimately to sensory cortex (Principle of neural science, 4th edition- Kendell and Schwartz).
Thalamus, situated between cerebral cortex and midbrain, plays a crucial role to relay information to the cortex. It is composed of 52 nuclei, each of them involved in carrying distinct type of sensory signals to distinct areas of cortex. Functionally best defined cortical areas (motor, sensory, visual, etc.) depend for their functional properties on the messages the areas received from thalamic nuclei. Almost all the information we receive from outside world or within bodies pass through the thalamus except sense of smell. It is basically considered the ‘gateway’ to the cortex. As a gatekeeper, the thalamus modulates the transportation of sensory information depending on different behavioral states and provides links between sensory perception and desired movement or action. The somatotopy is maintained in primary sensory cortex (S1), where the area representing specific body part is proportional to the extent of its innervations. Face and fingers represents most of the areas in post central gyrus/primary sensory cortex therefore is highly discriminative to touch.

3.4 Somatosensory Cortex:

Somatosensory Cortex receives mechano-sensory information via sensory pathways ascending from SC, brainstem and thalamus [91]. Somatosensory cortex consists of primary, secondary, and association cortices. All these areas collectively contribute to the sensory processing at cortical level. Primary Somatosensory cortex (S1) located in post central gyrus is the main receptive region to the sense of touch. S1 receives information from Ventral- postero- lateral nucleus of thalamus (VPL) (for touch) It then send axons to the secondary somatosensory cortex (S2)[92] located in the partial operculum on the floor of the lateral sulcus [91], S2 send their axons to association
cortex which is located in the superior parietal lobe on posterior parietal cortex as well as other cortical areas such as, motor cortex, and insula. Association cortex, the region where highest degree of convergence of information occurs receives it’s axons from both S1 and S2. Association cortex is responsible for higher order processing of sensory stimuli. Lesion studies have provided evidence for simple and more complex recognition of tactile stimulation by S1. Lesions in S1 resulted in impairment in detection of tactile stimuli and lesion in association cortex in the posterior parietal lobe resulted in loss of recognition of more complex functions like shape and texture of an object [93, 94].

Primary sensory cortex or S1 is the area where sensory integration occurs at conscious level [95], constitutes four Brodmann areas, 3a, 3b, 2 and 1 caudal to rostral (Figure 19) [96] and each of these regions represent full body maps from toe to face, arranged medial to lateral [97]. Different tactile responses are perceived by different areas such as 3b and 1 responds to cutaneous stimulation whereas 3a responds to proprioceptive stimulus only. For this current study, we have used electrical stimulator to give stimulation to the finger tips i.e. Index finger (D2) and Middle finger (D3) which suggested to activate S1 more specifically area 3b suggested by research study [98, 99]. In contrast to small receptive field for area 3b, the area 1 and 2 responds to multiple digit stimulation. Hernandez et al.[99] used protocol and parameters similar to our current study, where stimulation sites were D2 and D3. In his study, 12-50Hz frequency was used for discrimination task in trained monkeys in order to identify the neuronal activities in S1, which is the area responsible for meaningful perception. They have
delivered mechanical stimulation via computer controlled Chubbuck monitor stimulator on distal finger tips while recorded neuronal responses as a function of periodicity and mean firing rate during stimulus period from QA neurons of S1 area 3b. This study is objective evidence that mechanical stimulus on distal finger tips activates neurons of S1. In our study, electrical stimulation were used with Cortical Metrics-5 (CM-5) to D2 and D3 to quantify several sensory measurements in children with TS and TDC.

Figure 19.: Primary sensory cortex showing area 3, 1, 2.

http://mybrainnotes.com/memory-language-brain.html
3.5 Sensory (Tactile) Discrimination:

Sensory system is a multimodal process, beginning with the sensation - a process receiving stimulus, perception - a process of organization and interpretation of higher order of processing involving cognitive and memory centers to allow us to respond functionally and efficiently to a given stimuli. One of the core concepts in Neuroscience is to understand how two sensory stimuli are differentiated. Detection and integration of these differences of physical elements in our environment is one of the best ways in which we coordinate and respond to the external world. More than 180 years ago, in 1834 a German psychophysicist Weber explained effects of physical stimulus in quantitative way for the first time. In his experiment, he gave two weights of equal magnitude on both hands while subjects were blindfolded. Then subsequently added heavier weights to one hand and subject were required to compare the weights of the heavier one. He concluded that regardless of magnitude in order to be differentiated and detected as two stimuli, two stimuli must need to differ by a constant minimum percentage. Research has shown the consistency of Weber’s law for range of stimulus intensities that can be applied to other senses including auditory as sound and visual as brightness frequencies [100-102]. This discriminative behavior of the brain is ultimately a decision process, based on multiple theories. One of these is Thurstone’s theory (the measurements of values- Thurstone’s, 1959). According to this theory, the brain uses paired comparison strategy to make the decision when two sequential stimuli need to interpreted regarding their intensity or duration. Graphical representation of discriminative process, where two stimuli are presented sequentially and the subject is asked to answer which one seems intense is shown in Figure 20. Two stimuli(S1 and
S2) produce evoked neural responses (N1 and N2). The P1 and P2 are the final processes of neural activities to make the decision. Theoretically when first P1 develops, it goes to the memory center, next when the second response of the P2 arrives, the P1 from memories been retrieved and brain uses paired comparison strategy to make the final decision.

**Figure 20.** Decision process during two point discrimination task (Reproduced from Johnson et al, 1980).

Neurophysiology of tactile discrimination is a complex process. Tactile sensation is received by two areas of somatosensory cortex primary (S1) and secondary (S2) cortex. S1 and S2 maintain the somatotopy. Somatotopy is the homunculi organization of the cortex representing each body parts. Clusters of cells are organized to the receptor fields representing each body parts, although overlapping is not uncommon.
somatosensory cortex is organized into mini columns[103], group of mini columns makes the macro column or “segregates”. These segregates are responsible for keeping similar types of information together in neurons of columns that have the same receptive fields. Neurons within a column contained both excitatory and inhibitory connectivity. Excitatory neurons receive sensory information from thalamus and located in layer 4, whereas inhibitory neurons are located more superficial on layer cortex and work as lateral inhibition between micro columns. Any tactile stimulation activates both excitatory and lateral inhibitory interneuron's of multiple columns. Simultaneously applied stimuli on any two region of the body such as two digits activate adjacent cortical regions. As the intensity of stimuli increase, it evokes more spatially extensive responses [104]. More simultaneous activities engage the GABA-ergic pericolumnar lateral inhibition [105] and increase spatial receptive fields[106], thus discriminate the two stimuli from each other. Stimulus driven synchronization [107] of neighboring cortical areas plays important role to discriminate two stimuli perceptually.

Research regarding tactile discrimination in human is sparse and use of vibrotactile stimulator for this purpose is very recent. Hernandez et al. [99] applied vibrotactile stimuli of different frequencies to the fingertips of monkeys and suggested that the monkeys have the ability to discriminate two separate stimuli. In their study, they have trained monkeys to respond by pressing one of the two buttons to discriminate. The performance of discrimination was measured by obtaining neurophysiological findings using microelectrode on area 3b and 1 (S1). Stimuli were given glabrous part of fingertip of digit 2 and 3. Their result suggested quickly adapting (QA) neurons in area 3b and 1
are responsible to tactile discrimination between 2 stimuli of different frequencies and neurometric thresholds are lower than psychometric threshold (subjective feeling of stimuli).

3.6 Sensory measurements relevant to central hypothesis:

3.6.1 Sensory Threshold:
Threshold is described as the energy level below which no sensation would be perceived. Absolute threshold is one of the earliest and fundamental concept to understand sensory function in human described in Fechner’s psychophysics. Fechner proposed the first psychophysical relationship between stimulus and sensation by integrating *weber’s theory* [108]. He stated that subjective sensation is proportional to the logarithm of the stimulus intensity (*S=klogI*), where *S* considers thresholds and *I* is the physical intensity. The lowest stimulus intensity that produces subjective feeling of detection of stimulus is called sensory threshold. Thresholds are determined as function of psychometric analysis by applying stimulus of different intensities and documenting their subjective responses of perceived stimulus or not. Proportions of correct responses to stimuli are computed in a dose-response curve (*Figure 21*). The sensory threshold of a stimulus for an individual is determined by the point of the curve where 50% of the stimuli perceived sensation. Thus, sensory thresholds are defined as the lowest stimulus intensity that produces a sensation in 50% of the trials. Subjective experience of a sensation can quantify for an individual which is inversely related to the sensitivity (high thresholds indicate low sensitivity and low thresholds indicate high sensitivity). There are two types of sensory thresholds. *Absolute threshold* is the
minimum stimulus intensity of a stimulus perceived by an individual. *Discrimination threshold* (difference) is the minimum difference of intensity between two stimuli perceived by an individual. To determine discrimination threshold, two stimuli with minimal difference in energy applied to produce a noticeable increase in sensation that can be identified separately. Sensory thresholds are important diagnostic criteria for evaluating sensory function. Alteration of thresholds is a marker of dysfunction in sensory processing pathways including sensory receptors, nerves and central nervous system.

**Figure 21**: Describes calculation of sensory threshold from stimulus detection and intensity curve in humans. A sigmoid curve with percentage of stimuli detected by a human subject as a function of stimulus intensity (A). Threshold is defined as the stimulus intensity detected on 50% of the trials. Probability of stimulus detection as a function of stimulus intensity (B). An arrow pointing to curve b is the absolute sensory threshold. Depending on the ability of sensory system to detect the stimulus, curve a represent increased threshold and curve c represent decreased threshold of subjective responses ("Coding of Sensory Information" by Gardner EP, 2000).
3.6.2 Neuroadaptation/Habituation:

The process of transformation of sensory information into cognitive concept is the basic tenet of sensory biology. Neuronal responses to incoming stimuli are circumstantial such as behavioral state or stimulus history [109-111]. A ubiquitous element of sensory system is the progressive reduction of the neuronal responses with repeated stimuli [112-114]known as neuroadaptation or sensory adaptation. Subjective experiences of these neurophysiologic adaptation process present as gradual attenuation of behavioral responses called habituation. Sensitization and habituation is a form of non-associative learning process to ignore stimuli without any meaning. Following recognition of repeated stimuli as familial, neuron downturn its firing rates (Kandel and Schwartz-Principle of neuronal science, 4th edition. 2000). Thus, habituation makes a platform for learning at neuronal level to cancel out the noises so that resources are retained for meaningful sensory input. Although sensory adaptation can happen anywhere along sensory pathways beginning from sensory receptor [115], brainstem [116], thalamus [117] and the cortex. However, cortex plays the major role in the process [117] through thalamocortical processes involving short term depression [118]. Neuroadaptation is referred as neuronal marker of inhibition. Inhibition happening at multiple stages of afferent pathways and ultimately tuned up the adaptive responsive behavior. The main purpose of adaptation is to adjust the sensitivity of the neuron by effective coding [119] to response in harmony with surrounding conditions of both inside and outside world.

The relationship between repeated stimulation and habituation has not been widely investigated in clinical settings. McIntosh et al. studied [120] basal electrodermal responses and rate of habituation in children ages 3-9 years (mean age 9) with Sensory
Processing Disorder. The results suggested that children with sensory processing disorder had slower rate of habituation compared to their age matched peers [120]. A similar previous study by Mangoet et al. did not find any significant differences of habituation in children with ADHD ages 5-13 years (mean age 8) compared to matched healthy children. The study reported enhanced reaction to sensory stimuli in ADHD without any neuroadaptation compared to healthy control (Figure 22)[121].

Electrodermal response (EDR) were used as outcome in previous two studies[120][121]. ADHD is one of the most common co-morbidities associated with TS.

Figure 22. Sensory neuroadaptation in children with ADHD. Increased reactivity (baseline response, trial 1) to sensory stimuli in children with ADHD but no differences in habituation (subsequent responses, trials 2 to 8) compared to healthy kids. Y= magnitude of EDR responses, X= trials. EDR= Electrodermal responses.
Perceptual Processing of tactile stimuli:

Perception is the process responsible for recognizing and interpreting sensory stimuli. It combines incoming sensory messages with complex memory and cognition network for proper identification and response to a given stimulus. Perceptual processing of tactile stimulus starts with the exposure of a stimulus, followed by receiving the stimulus by sensory neurons. Organization next step is, where sensory information's are organized into primary sensory cortex and unimodal association cortex. From here information travels to the posterior multimodal association cortex; the posterior parietal and temporal cortices which are highly connected to the memory and cognitive areas which in turn are responsible for proper interpretation of the input and planning the motor actions.

In sensory physiology, selective attention (or selecting stimuli) is an important criteria used by the organizational process, not all the stimuli received by sensory system accepted by perceptual organization. An abnormality in the process of filtering information may results in experiencing to sensitivity or hyperawareness to external stimuli. Abnormalities in the perceptual and behavioral experiences associated with external sensory input such as visual, auditory and tactile stimuli [66] and tic-related premonitory urge sensations are frequently observed by patient with Tourette syndrome. This suggested there might be an altered somatosensory perceptual processing in this group of patients. Perceptual latency and temporal order of judgment are two relative measures to evaluate perceptual processing of tactile stimulation.
3.6.3.a Perceptual latency:

Perceptual latency, the latency between exposures of a stimulus to its conscious perception is one of the key elements to understand the basic of perceptual processing. A motor response given to a physical stimulus proceeds in two stages. First, the stimulus gives rise to conscious perception (this duration is known as “Perceptual Latency”) and then the desired motor response is executed [122]. The temporal duration between exposures of physical stimuli until its perception is called “Perceptual Latency”.

The processing of information and its nerve conduction velocity plays an important role determining Perceptual Latency. Type of sensory modalities and its physiology are known to play an important role to the speeding of the process, such as auditory stimuli which processes information faster and has shorter latency [123] than visual stimuli [124]. Perceptual Latency for tactile events induced by mechanoreceptors are usually found to range between auditory and visual values and depended on the distance between site of the stimuli to the somatosensory cortex [125].

Reaction time (RT), measurement of reaction time has been considered the one of the oldest and best methods to evaluate perceptual latency. In a simple reaction time task (sRT), a participant is given a stimulus and asked to respond as soon as he receives the sensation (time required to respond to a sensory event). There is also a motor component included in the simple reaction time, as the participant executes the response. According to Miller et al [126] sRT has two components, detection Time (D-RT) and a motor component (M). Similar to sRT, during a Choice reaction time task, a participant is asked to respond to a given stimulus as soon as possible (detection time) but also asked to respond to a choice question as well. For example, if stimuli are given
sequentially on two fingers, they determine on which finger they are receiving the stimulus. So cRT has three components, sensory, motor and a cognitive component (Figure 23).

![Choice Reaction Time (cRT)](image)

\[ cRT = \text{Detection time} + \text{Cognition} + \text{Motor} \]

\[ DT + C + M \]

**Figure 23.** Choice Reaction time and its components. cRT-Choice reaction time, DT-detection time, C-cognition, M-Motor component.

### 3.6.3.b Temporal order of Judgment (TOJ):

Perception of Temporal order of judgment (TOJ) or time perception is an alternative to investigate perceptual processing of time[127]. In TOJ sensory discrimination and judgment are used to identify the order of two stimuli that are separated by time[127]. In TOJ two stimuli are presented with stimulus onset asynchrony (SOA). The two stimuli presented on each trial are assumed to be detected at some point time (Detection time...
or DT-TOJ) and the subjects are asked to report which stimulus comes earlier (Figure 24-A). SOA varies between trials and gradually behavioral responses are used to yield a psychometric function related to onset of first stimuli, the median of these known as point of subjective simultaneity (PSS) (Figure 24-B). PSS considers the 50% of the response value, where possibilities of two responses are equally likely. For tactile stimuli normal values for TOJ is 50-60 msec.

![A](image.jpg)

**Figure 24A.** Stimuli presentation from a temporal-order experiment. On each trial stimuli A and B are presented at times tA and tB. Subject judges which stimulus appeared to occur first. Rectangles indicate stimulus processing by channels; their left edges represent stimulus-presentation times (Reproduced from 'The Perception of Temporal Order: Fundamental Issues and a General Model' By Saul Sternberg and Ronald L. Knoll, 1973).
Figure 24B. (‘Temporal Order of Judgment’ by Yamamoto S. 2015).

Showed psychometric function of temporal order judgment. Sternberg and Knoll (1973) hypothesized that there is a decision mechanism that receives signals A and B through independent channels and yields an “A-first-then-B” judgment according to the difference in the arrival times (TB-TA)(Figure 24A). The probability function G was hypothesized to be a non-decreasing (monotonous) function of the time difference. SOA: stimulus onset asynchrony, JND: just noticeable difference, PSS: point of subjective simultaneity.
It is suggested that reaction time (RT) and TOJ tasks usually share common pathways on the perceptual detection and decision processes (Gibbon & Rutschmann, 1969) [126, 128]. Based on Miller’s model [126] perceptual latency or detection time (DT) for both tasks is similar; DT-RT=DT-TOJ.

Unlike cRT and sRT, TOJ is free from motor processes instead having only sensory and a cognitive component (Figure 25). Sensory components suggested being involved in spatiotemporal perception of TOJ are sensory coding and adaptation [129]. TOJ is unique in a way that it is able to detect PSS and just noticeable differences (JND) which considers a measure to detect sensitivity.

<table>
<thead>
<tr>
<th>Temporal Order of Judgement (TOJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 1</td>
</tr>
<tr>
<td>ISi</td>
</tr>
<tr>
<td>Response</td>
</tr>
<tr>
<td>Site 2</td>
</tr>
</tbody>
</table>

TOJ= Which Stimuli comes first?

TOJ= DT + Cognition

Figure 25. Component of Temporal Order of Judgment (TOJ). DT, detection time
Chapter 4
Generation of Hypothesis and Aims

4.1 Rationale:
Sensory symptoms such as exteroceptive sensory sensitivity or intolerance and premonitory urges are frequently present in patient with Tourette syndrome. There has been limited work addressing sensory phenomena in standard clinical practice or in research studies. This is surprising given that SP are so frequently observed in patients with TS and, according to many patients, SP can be equally troublesome as tics. Current medication largely aimed at controlling motor symptoms results in poor control of tic even with multiple medications. Interestingly, medications treating tics do not diminish the sensory symptoms. These sensory abnormalities suggest potential dysfunction in the system which might play a key role in the development of tics in TS. The well-established motor theories involving Cortico-striato-thalamo-cortical (CSTC) pathways may need augmentation with better understanding of the influence of sensory input and processing. We expect that the present study focusing evaluation of sensory measurements would help the future researcher and clinicians to better understand the pathophysiology of TS and develop appropriate intervention.

3.7.2 Objectives:
In response to the scarce research to address the sensory issues in patient with Tourette syndrome, the current study aimed to quantify the sensory measures in children with TS and their age matched peers. Furthermore this study would also
examine the relationship of clinical tic severity score with sensory measurements. From PU’s to sensory Hyperawareness- imply there are cortical areas might play a role in the pathogenesis of tic and this cortical participation of perception is largely overlooked. The central question asked in this study was whether patients with TS process sensory information somewhat differently than TDC. This question was explored the evaluating three important components of the sensory system. We would evaluate sensory thresholds- both detection and discrimination threshold, sensory adaptation (habituation), and perceptual latency and perception of time. We have chosen the tactile system as a model to evaluate the sensory system in part because many of the premonitory urges and self-reported hypersensitivities involve touch.

3.7.3 Central Hypothesis:
Tourette syndrome is associated with sensory dysfunction including abnormalities in sensory threshold, neuroadaptation and perceptual processing to tactile stimuli.

Specific Aim 1
To compare tactile sensory thresholds between children with Tourette Syndrome (TS) and Typically Developing Children (TDC).
Hypothesis: Sensory thresholds (absolute and discriminatory) are decreased in TS compared to TDC.
Prediction 1: The absolute sensory threshold is reduced in TS compared to TDC
Prediction 2: The sensory discrimination threshold is reduced in TS compared to TDC.
**Specific Aim 2:**
To compare sensory neuroadaptation between TS and TDC.

Hypothesis: Neuroadaptation is decreased in TS and associated with clinical severity of TS.

Prediction 1: Neuroadaptation is decreased in TS compared to TDC.
Prediction 2: Neuroadaptation in TS is negatively associated with clinical tic severity score of TS.

**Specific Aim 3:**
To compare perceptual processing using Choice Reaction Time (cRT) and Temporal Order of Judgment (TOJ) tasks between TS and TDC.

Hypothesis: Perceptual processing is faster in TS compared to TDC.

Prediction 1: Perceptual latency obtained via cRT task in children with TS is shorter compared to TDC.
Prediction 2: Time perception obtained via TOJ in children with TS is shorter compared to TDC.
Chapter 5

Methods

5.1 Participants:

21 children with Tourette Syndrome (TS) aged between 9 and 17 years were recruited from TS clinics at Cincinnati Children’s Hospital Medical Center (CCHMC). TS patients with or without comorbid disorders including ADHD and OCD were included in the study. 21 typically developing children (TDC) matched for age and gender were recruited from Greater Cincinnati area though community advertisement. All subjects were right handed except two left handed subjects in each group. All the subjects were recruited between July 2014 and January 2015. The study was conducted in a single visit between 8 am to 5 pm. Both parental consent and assent from the children above 14 years of age were obtained from all subjects before participation in the study protocol. The study was approved by Cincinnati Children’s Institutional Review Board, Cincinnati, Ohio, USA.

5.2 Inclusion and Exclusion criteria:

5.2.1 Inclusion Criteria:

Diagnosis of TS was based on DSM-5 criteria. TS patients with common comorbid developmental and psychiatric conditions of ADHD, OCD, and Anxiety were included in the study. Presence of a significant psychiatric illness was diagnosed by a Psychiatrist. Subjects were recruited irrespective of gender, race, ethnicity or socio-economic status. Typically developing children (TDC) were without any known neurological, psychiatric or developmental disorder.
5.2.2 Exclusion Criteria:

Children were considered not eligible for the study if they were unable to read or understand verbal instructions to complete the tasks, or had any malformation of their hands or finger that would prevent proper placement of the hand on the sensory device. Children with neurological disorders or any systemic diseases which might have potential long term effect on nervous system including Diabetes Mellitus and/or other sensory problems including neuropathy also were excluded from the study.

5.3 Study Details:

The study has three components.

I. Collection of demographic and routine clinical data

II. Administration of sensory testing using a noninvasive stimulator, known as cortical metrics (CM-5). The CM-5 uses vibrotactile stimuli to quantitatively measure sensory function of the central nervous system.

III. Data storage, offline analysis and comparison with data between Tourette syndrome and healthy control.

5.3.1 Collection of Demographic and routine clinical data:

Age at the time of the experiment, sex, race, ethnicity, height, weight, education and time of the experiment were collected.

Diagnoses of TS and associated conditions were made using history, physical examination, and standard DSM-5 diagnostic criteria in Tourette Clinics in the United
States. A preliminary screening was conducted upon first contact regarding age and diagnosis of TS and debilitating neurological disorders. The diagnostic process at the CCHMC includes a structured questionnaire for medical history, past medical/social history, family history, school/academic performance, total tic score (YGTSS tic scores), and associated co-morbidity evaluations including ADHD and OCD. In TS, other documented variables were, height in cm, weight in pounds, heart rate, blood pressure, awareness of PU’s, functional or social impairments due to tics and time of the experiment. Time of experiment was documented as am (before or at noon) and pm (after 12 pm) in order to rule out potential medication effects on the tasks. Premonitory urges for Tourette Syndrome (PUTS) is a scale to measure subjective responses of patient to describe sensory experiences observed with tics [70]. Since this is not a standard clinical practice, we have inquired about PU’s by asking the patient whether they have the symptom or not.

TS tic symptom severity was assessed using Yale Global Tic Severity Scale (YGTSS) [27]. In standard clinical practice YGTSS is a commonly administered measure by the clinicians to evaluate the severity of motor and vocal tics. Clinicians first ask about the number of tics at present and their duration. The interviewer then uses the YGTSS to rate tics over the past week. The YGTSS (Appendix-3) includes descriptions of scores from 0 to 5 for the 5 categories of number, frequency, intensity, complexity, and interference of motor and vocal tics separately. The total tics score thus ranges from 0 to 50 (0 to 25 for motor; 0 to 25 for vocal).
5.3.2 Administration of sensory testing:

5.3.2.1 Sensory Measurements:

Irrespective of the modality, all of the senses share three main common steps:

i) A physical stimulus

ii) A series of events that generate energy and transform stimuli to afferent nerve impulses

iii) Conscious experience of this sensory stimulus, known as perception.

In order to study sensory physiology in children with TS, tactile stimuli were administered using electrical stimulator called Cortical Metrics-5 (CM-5).

Following three sensory measurements were obtained.

1) **Sensory thresholds**: Tactile Sensory thresholds were obtained using two different techniques – "absolute detection "threshold and "difference/ discrimination threshold. Details of experimental protocol will be discussed in section 4.3.3.1 under experimental design.

2) **Sensory neuroadaptation**: Sensory neuroadaptation was measured using amplitude discrimination task. Amplitude discrimination was measured at baseline and after single site adaptation. The differences between two values considered the state of adaptation. Details of obtaining sensory adaptation will be discussed in section 4.3.3.2 under experimental design.

3) **Perceptual latency using cRT task and Time perception using TOJ task**: These measures were obtained for exploratory purposes. Two different techniques were used
to obtain perceptual latency and time perception. Details of the technique will be discussed in section 4.3.3.3 under experimental design.

- Choice reaction time task was used to obtained Perceptual latency
- Minimum time interval for accurate temporal order of judgment was used to obtain time perception

5.3.2.2 The Electrical Stimulator: Cortical Metrics-5 (CM-5):

The CM-5 is a portable, non-invasive, easy to operate device. It works as a four digit vibrotactile stimulator. Electrical stimulus was given at the finger tips in order to quantitatively measure sensory system.

5.3.2.2.a Description of the device:

CM-5 (Figure 26) consists of four independently controlled vibrating tips (Fig-9) It functions as a two site/ two point stimulator. Before running the stimulator CM-5 related software (Google chrome and brain gauze apps) was employed to the PC. Subjects would sit comfortably in a chair with height adjusted so that nondominant hand can rest on the stimulator like shown in (Figure 27, 28). Different sensory tasks are shown on a laptop screen. The subject uses his/her dominant hand to manipulate the mouse to follow and respond to the instructions. Each of the probes protruding from the device is positioned by rotating the four independently positioned drums to maximize contact between finger pads and stimulator. Electrical stimuli would be given to the finger tip of two second digit/index finger(D2) and third digit/Middle finger (D3).
During the experiment internet access is required in order to run the software, Brain Gauze app. Additional information about the device can be found at the company’s website: https://www.corticalmetrics.com/

![CM-5 Device and its different parts](image)

Figure 26. Overview of CM-5 Device and its different parts
Figure 27. Non-dominant hand (here left hand) and the fingers where tactile stimuli would be given. Picture was taken as a snap shot directly during a task (not during experiments)
Figure 28. CM-5 device, Nondominant hand is placed on the machine, finger tips are touching the white probe protruding from the device. D2 and D3 will receive the stimulation. On laptop screen Brain Gauze App is running.
5.3.2.2.b Delivery of Stimuli:
CM-5 was used for delivering vibrotactile stimulus. Finger pads of the index finger/D2 and middle finger/D3 of the non-dominant hand were chosen to give the stimuli via a 5 mm cylindrical probe protruded from the machine. Most of the stimuli were in flutter range (25-50 Hz) except frequency discrimination task, where different frequencies were used to measure the outcome (frequency discrimination thresholds). (https://www.corticalmetrics.com/system/pub/instructionmanual.pdf).

5.3.2.2.c Tactile Assessments:
Responses to each task are “left” or “right” or two alternate forced-choices (2AFC) depending on which finger they have perceived the stimulus. D2 denotes to the answer “RIGHT’ and D3 “LEFT.” For the choice reaction time task, subjects were asked to click left button of the mouse while responding to a perceived stimulus on D3/middle finger and to click right button of the mouse for stimulus perceived on D2/index finger. For rest of the task, subjects were asked to follow command displayed on the monitor. Subjects were asked to select RIGHT for perceived stimulus on D2/index finger and select LEFT for stimulus onD3/middle finger. For each task described below, there were three practice trials before the actual experimental tasks of 20 trials to determine the results.
5.3.3 Experimental Design:

This is a single visit, cross-sectional, matched case control study. Data were collected without any interventions other than training for each task.

5.3.3.1 Experiments related to Aim 1:

Hypothesis: Sensory thresholds are lower in TS than TDC

Two separate experiments were conducted to measure sensory thresholds.

a) Absolute Detection Threshold.

b) Discrimination Threshold.

5.3.3.1.a Absolute Threshold:

To measure the absolute threshold, “Dynamic Threshold Task” was performed.

Purpose of this task/metric:

The purpose of this task was to determine the minimum detection level of stimulus intensity/amplitude in µm.

Stimuli/Parameters(Figure 29):

Vibrotactile stimuli started as null value and progressively increased till perceived. A constant 25 Hz of stimulus started from zero intensity (µm) was applied. Rate of amplitude was increased by 2 µm/sec. There were seven trials with inter-trial interval (ITI) of 10 seconds. The final value of Dynamic Threshold was calculated from the mean stimulus amplitude across all correct trials.
Directions:
If they detect a vibration on their D2/index finger then the subject would click the RIGHT button on the screen, and if they think it is on their D3/middle finger then the subject would respond by clicking the button LEFT on the laptop screen.

Outcome measurement:
Absolute threshold in $\mu$m.

**Figure 29.** Dynamic Threshold task, stimulus started as null value and progressively increased till perceived.
5.3.3.1.b Discrimination Threshold:

To measure the discrimination threshold, “Frequency Discrimination Threshold (FreD) task” was conducted.

Purpose of this task/metric:
The purpose of this task was to determine the ability to discriminate two stimuli of different frequencies.

Stimuli/Parameter (Figure 30):
Two vibrotactile stimuli of different frequencies were given sequentially. The standard one was at 25 Hz and comparison stimulus was at 35 Hz with an initial difference between two stimuli was 10 Hz. On sequential trials the differences were decreased one unit after a correct answer (to make the task more difficult) and increased one unit after an incorrect answer (to make the task easier). Through this staircase process the final differences approached to the “discrimination threshold” for each individual participant. There were total 20 trials with ITI of 5 seconds.

Directions:
The subjects were asked to choose the “faster” vibration by clicking on the LEFT or RIGHT button on the screen depending on the finger they had perceived the stimulus. Details of the direction for responding to the tasks were described in Tactile Assessments (5.3.2.2.c).
Outcome measurement:

Discrimination threshold of frequency in Hz

The two stimuli were with different frequencies: The standard one at 25 Hz and comparison stimulus at 35 Hz with an initial difference between two stimuli being 10 Hz. On sequential trials the difference was decreased one unit after a correct answer and increased one unit after an incorrect answer. The final result was calculated from the average of last 4 trials.

Figure 30: Stimuli/parameters for Frequency Discrimination Thresholds
5.3.3.2 Experiments related to Aim-2:

Hypothesis: Neuroadaptation is decreased in Children with TS and associated with clinical severity of TS.

Sensory adaptation was evaluated as follows, a) Amplitude discrimination threshold at baseline/without adaptation and b) Amplitude discrimination threshold after single site adaptation.

5.3.3.2.a Amplitude Discrimination Threshold at baseline/without adaptation (nAD):

Purpose of this task/metric:

The purpose of this task was to determine the ability to discriminate between the two stimuli of different amplitudes without an adapting stimulus.

Stimuli/Parameter (Figure 31):

Two vibrotactile stimuli of 25 Hz but different amplitudes were given simultaneously. Standard one was at 200 µm and comparison stimulus was at 400 µm with an initial difference of amplitude between two stimuli was 200 µm. On sequential trials the difference was decreased 20 units after a correct answer and increased 20 units after an incorrect answer. Other parameters of the stimulus such as frequency, duration of stimulus and inter stimulus interval (ISI) were similar.
Directions:
The subjects were asked to choose the most “intense” vibration by clicking on the LEFT or RIGHT button on the screen depending on the finger they had perceived the stimulus. Details of the direction for responding to the tasks were described in Tactile Assessments (5.3.2.2.c).

Outcome measurement:
Amplitude Discrimination threshold (nAD) in μm. There were twenty trials and the result was obtained by averaging the last four trials.
5.3.3.2.b Amplitude Discrimination Threshold after single site adaptation

Purpose of this task/metric:

The purpose of this task was to determine the ability to discriminate between two stimuli of different amplitudes after administering a single site (single digit) adapting stimulus.
Stimuli/Parameter (Figure 32, 33):

A conditioning stimulus (100 µm, 25 Hz, 1 sec) was given to one of the digits followed by two sequential stimuli of different amplitudes as was done for the baseline AD. The initial stimuli were at 200 µm 400 µm amplitudes, with an initial difference of amplitude between two stimuli of 200 µm. On sequential trials the difference was decreased 20 units after a correct answer and increased 20 units after an incorrect answer. Other parameters of the stimulus such as frequency, duration of stimulus and inter stimulus interval (ISI) were similar.

Directions:

The subjects were asked to “ignore the first vibration” (the conditioning stimulus), then choose the most “intense” vibration by clicking on the LEFT or RIGHT button on the screen depending on the finger they had perceived the stimulus. Details of the direction for responding to the tasks were described in Tactile Assessments (5.3.2.2.c).

Outcome measurement

Amplitude Discrimination thresholds in µm. There were twenty trials and the results were obtained by averaging the last four trials. Conditioning stimulus was expected to produce a measurable change or adaptation in discrimination capability. The state of ‘Sensory adaptation’ was obtained by measuring the differences between baseline and single site adaptation (ssAD and baseline (ssAD- nAD). Details of the results will be discussed in section 7.4.5 under results.
**Figure 32.** Stimuli/parameters of Amplitude Discrimination Threshold after single site adaptation stimuli (ssAD).

<table>
<thead>
<tr>
<th>A Stim1</th>
<th>A Stim2</th>
<th>Stim1</th>
<th>Stim2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude</td>
<td>0</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Frequency</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Duration</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

**Stimuli/Parameters**
- Frequency: 25 Hz
- Amplitude: 200 μM (Standard) 400 μM (Comparison)
- Conditioning stimulus (100 μM, 25 Hz, 1 sec)
- Rate of Amplitude increase/decrease: 20 units
- Total trials: 20
- ITI: 5 sec
Figure 33. Amplitude Discrimination Threshold after single site adaptation stimuli (ssAD). Showing conditioning stimulus on single site followed by two stimuli of different intensities. Higher intensity was chosen as correct response by the subject.
5.3.3.3 Experiments related to Aim 3:

Hypothesis: Perceptual processing is faster in TS compared to TDC.

This is an exploratory hypothesis. We have explored perceptual latency and time perception via Choice Reaction time (cRT) and Temporal Order Of Judgment (TOJ) tasks respectively.

5.3.3.3.a Choice Reaction Time (cRT):

Purpose of this task:

The purpose of this task was to determine perceptual latency, the time interval between exposures of tactile stimuli and conscious perception.

Stimuli/Parameter (Figure 34, 35):

One vibrotactile stimulus was given to either D2 or D3 with 300 µm, 25 Hz duration of 40 sec. There were total of 20 trials.

Directions:

The subject needed to determine which finger have they received the stimulus. Subjects were asked to click left button of the mouse while responding to a perceived stimulus on D3/middle finger and to click right button of the mouse for stimulus perceived on D2/index finger. Details of the direction for responding to the tasks were described in Tactile Assessments (5.3.2.2.c).
Outcome measurement:

Reaction time in msec is a continuous variable. Mean of the median 6 trials out of 20 trials was used.

Stimuli/Parameters for Choice Reaction Time

- Amplitude: 300 μM
- Frequency: 25 Hz
- Total trials: 20
- ITI: 3 sec

Figure 34. cRT task stimulus parameter. One vibrotactile stimulus was given to either index (D2) or middle (D3) finger
**Perceptual Latency** between stimulus and response via Choice Reaction time

![Diagram](image)

**Figure 35.** Choice Reaction Time task. Single stimulus was delivered (either to D2 or D3) and subject was asked to detect the site of the stimulus.

### 5.3.3.3.b Temporal Order Judgment:

**Purpose of this task:**

The purpose of this task was to determine the time perception by judging temporal order of the two given tactile stimuli.

**Stimuli/Parameter(Figure 36, 37):**

Two vibrotactile stimuli of 25 HZ and 200 µm but varying inter-stimulus interval (ISI) were given to D2 or D3. The duration of the pulses also varied, one being 40 msec and
the other lasted 200 msec. ISI was 150 msec at the beginning. On sequential trials, the difference was decreased after a correct answer and increased after an incorrect answer. There were a total of 20 trials. The final result was calculated from the average of the ISI of last 6 trials.

Directions:
The subjects were asked to choose the stimulus "perceived earlier" by clicking on the LEFT or RIGHT button on the screen depending on the finger they had perceived the stimulus. Details of the direction for responding to the tasks were described in Tactile Assessments (5.3.2.2.c).

Outcome measurement:
Minimum time required to identify the temporal order of the two given tactile stimuli (Time perception) in msec.

Figure 36. Stimuli parameters for TOJ. Two vibrotactile stimuli would be given at identical intensities and different intervals to different sites, index and middle fingers.
Figure 37. TOJ, showing two stimuli are given on two sites (D2 and D3) at two time points.
Chapter 6
Data acquisition, storage and analysis

6.1 Study Design:

All patients with TS underwent routine collection of demographics and clinical data including personal and family history, medication use and presence of PU's, functional and social impairment due to tics. A clinical severity scale using YGTSS was also obtained from each TS patients. All control subjects underwent clinical assessment of height, weight and a brief history regarding any conditions related to inclusion and exclusion criteria. To ensure study compliance, patients and families were given detail demonstration of the experimental equipment and the study protocol before signing the consent and assent (Children above 14 years).

All subjects were studied at the morning or afternoon hours. After 15 min quite rest period, the study protocol was started for the measurement of sensory thresholds, adaptation and perceptual processing. Each test was preceded with a trial experiment to familiarize patients with the experimental procedure. Data were saved in the computer for off line analyses. Data of10 subjects from each group were excluded from further analyses due to random pressing of the decision button or taking unusual longer time to finish the protocol. The study design is summarized in Figure-38.
Data storage and analysis:

All the data were collected using CM-5 (Cortical Metrics Inc., Chapel hill, NC) and stored in an encrypted data base (as JSON data) in chrome web store. JSON to TSV was used to retrieve data from the storage site for further analysis. For accuracy, subject data recorded in the CM-5 program were matched with the demographic data. Prior to analysis, data from individual participants were reviewed and excluded if the participant was clearly unable to understand the task or execute the function properly as

Figure 38. Study design.
evidenced by 1) taking unexpectedly longer time to finish the task or 2) evidently pressing the buttons randomly.

6.3 Data Management:

Data management includes creating a secure database, in which most collected subject data were entered. All databases and folders have access restricted to study physicians, research coordinators, study biostatisticians, Graduate students and the information technology specialists. To further restrict access, the databases and folders had read and write password protection. Private health information (PHI) including patient name, birth date, and medical record were stored in the database. PHI was not included in any data analysis, nor made public in any way. Data was checked to ensure completeness, validity and accuracy. Missing data was identified and excluded from the analyses.

6.4 Statistical analyses:

6.4.1 Descriptive Analysis:

Descriptive analyses were performed with calculation of means, standard deviations, standard errors, and ranges for continuous variables and proportions for categorical variables. Chi-square test, Student’s t-test or ANOVA were used to compare TS and TDC for categorical or continuous variable, accordingly. Potential confounders identified from the literature were age, gender, use of medication, comorbidities, and functional impairment. Statistical program JMP version 10 (SAS Institute, Cary, NC) was used for statistical analyses.
6.4.2 Statistical analysis related to specific aims:

i. Specific Aim 1:
Unpaired Student’s t–test was used to compare sensory thresholds, both absolute and discrimination thresholds, between TS and TDC. ANCOVA was used to adjust for covariates i.e., age and sex.

ii. Specific Aim 2:
To determine ‘Neuroadaptation’, changes of amplitude discrimination threshold were evaluated at baseline (nAD) and after single site conditioning stimuli (ssAD). The differences of amplitude discrimination thresholds between the two states (ssAD-nAD) were considered as the level of ‘Neuroadaptation’. Level of ‘Neuroadaptation’ was also calculated as a percent change from baseline after single site stimulation (ssAD-nAD/NAD*100) and quantified as percent change of baseline. Skewed neuroadaptation data were normalized using log transformation [Log(ssAD-nAD/NAD*100)]. Unpaired Student’s t-test was used to compare amplitude discrimination threshold at baseline and also after single site stimulation between TS and TDC.

The levels of neuroadaptation (ssAD-nAD), (ssAD-nAD/NAD*100), [Log(ssAD-nAD/NAD*100)] were analyzed using unpaired t test to compare between TS and TDC. Paired Student’s t-test was conducted to compare amplitude discrimination threshold at baseline and after single site stimulation within TS and TDC.
Simple liner regression was used to demonstrate relationships of neuroadaptation quantified as difference of ssAD-nAD, percent change (ssAD-nAD/NAD*100), and log of percent change with clinical severity scale (total tic score) obtained via YGTSS.

A multivariable linear regression model was used to assess relationships between neuroadaptation (ssAD-nAD) with covariates including age, sex, and diagnosis, medication status, associated comorbid disorders, presence of sensory symptoms, functional impairments, and total tic score. A multivariable linear regression model was also used to assess relationships between neuroadaptation described as percent change (ssAD-nAD/NAD*100) with covariates including age, sex, diagnosis, medication status, associated comorbid disorders, presence of sensory symptoms, functional impairments, and total tic score.

iii. **Specific Aim 3:**

To compare perceptual processing described in Aim 3, perceptual latency obtained via choice reaction time (cRT) task and temporal order of judgment (TOJ) were analyzed using unpaired Student’s t-test between TS and TDC.

6.5 **Sample Size Calculation:**

Sample Size Calculation was based on published and pilot data for Aim 2, as this was the primary thesis for the study. Sample size calculations require a prediction of the difference in means of the groups being tested and an estimate of the variation. At the beginning of the study, there were data available for healthy children, but no data for
children with TS. Moreover, the data for healthy children was obtained using an early version of the cortical metrics machine, the CM4, which had different default settings for stimulus intensity and duration for the adapting stimulus. Based on the CM4 data in healthy children, the difference in detection thresholds after an adapting stimulus was 16 uM (SD 33 uM). We predicted that on average TS children would not adapt. So the difference in mean adaptation would have been 16 (16-0). Assuming the same variances in that study, in order to have 80% power at an alpha of 5%, to detect a difference of 16 with a SD of 33 we would have needed 53 children per group.

However, the CM5 was re-designed to have a larger amplitude, shorter duration adapting stimulus with the idea that this might enhance adaptation. With no published data with this new device, we did not know if our values would be directly comparable to those of prior research in healthy children or adults using the CM4. We also did not know if “no adaptation in TS” was realistic. The new device could induce either more or less adaptation in healthy children and in TS children. For this reason, we decided to recalculate our sample size calculations on a post-hoc analysis of the first 10 participants that we recruited. In this group, there was a baseline difference, prior to the adapting stimulus, of 30 uM (TS group was 64 um; SD 40 and TDC group was 34 uM; SD 20). After the habituating stimulus, the TS group’s discrimination performance was at 123 uM (SD 90), an increase of 59; whereas the TDC group’s discrimination was 137 (SD 109), an increase of 103. So adaptation appeared to be greater in the healthy children, as we predicted. Using this difference in adaptation of 44 (103 – 59) and a pooled SD of 60 (midpoint of the baseline and post adaptation SDs), in order to have
80% power at an alpha of 5% to detect a difference we would need n=25 per group. We used this number as an approximate sample size and added 20% to account for dropouts. 31 per group were recruited initially. The final analysis involved 21 per group due to factors such as device malfunction or children not understanding instructions, see below.
Chapter 7

Results

7.1 Demographics:

7.1.1 Demographic data of TS and TDC:

21 children, from the age between 9-18 were recruited for each group. Mean age were 13 years for both groups. Tourette children were recruited from three TS clinics of Cincinnati Children’s Hospital. 21 typically developing children, were recruited though community advertisement. All of the participants were right handed except four, 2 in each group were left handed. Among 21 of TS, five were female and 16 were male (3.2 to 1 ratio) which is expected as TS is three to four times prevalent in boys compared to girls. Among TD group sex ratio was almost similar, nine female and 12 male were recruited. Detail demographic data between groups are presented on Table 5.

<table>
<thead>
<tr>
<th></th>
<th>TS (N=21)</th>
<th>TDC (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Years (Mean)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>SEX (F:M)</td>
<td>5:16</td>
<td>9:12</td>
</tr>
<tr>
<td>Race (A:AA:C:H)</td>
<td>0:2:17:2</td>
<td>6:0:15:0</td>
</tr>
<tr>
<td>Handiness (L:R)</td>
<td>2:19</td>
<td>2:19</td>
</tr>
</tbody>
</table>
7.1.b Demographic and clinical data in subjects with TS:

Among 21 subjects within cohort of TS, only four (19%) have an unique diagnosis of primary TS, or “tics-only TS”. This is consistent with the literature that ~80% of children coming to medical attention for TS have one or more comorbidities. Almost all of them have associated ADHD and OCD except one who was also diagnosed with bipolar mood disorder. 17 out 21 subjects were on multiple medications, alpha adrenergic antagonist was the frequently prescribed medication from the list. Questioning about PU’S and functional impairments due to tics reveals positive in 11 out of 21 subjects in both variables. Since majority of our subjects are medicated we have added another variable, time of experiment to evaluate weather medication has any effects on the current experiment. On a Detail demographic data within TS group is presented on Table 6. All the subjects with TS were further categorized into two groups based on the presence of ADHD which is presented on Table 6.

All of the subjects have current tics either motor or vocal, except one 14 year old female who stated that her tics are in control (with two medications). Details of tic data from rest of the 20 subjects are depicted on Table 7 where I have categorized the number of subjects according to their tic score measured by Yale Global Tic Severity Scale (YGTSS) (Appendix 3).
Table 6. Clinical data within group of TS subjects

<table>
<thead>
<tr>
<th>Associated disorders</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Comorbidity (i.e. ADHD, OCD etc.)</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>TS with ADHD (and other diseases i.e. OCD, anxiety)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>TS without ADHD</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Use of Medication</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>PU's</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Functional impairment due to tics</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

11 out of 21 subjects had experiment conducted in the morning and rest of the 10 is in afternoon.

Table 7. Number of subjects in each group depending on their total tic score measured by YGTSS.

<table>
<thead>
<tr>
<th>Total Tic scores</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Minimal</td>
<td>5</td>
</tr>
<tr>
<td>Mild</td>
<td>8</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
</tr>
<tr>
<td>Marked</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
</tr>
</tbody>
</table>
7.2: **Results of All Sensory Measurements:**

Sensory measurements of all the sensory tasks are described in two ways, first between children with TS and TDC (Table 8.1) followed by among three groups, in TS with ADHD, in TS without ADHD and TDC (Table 8.2).

**Table 8.1** Sensory measurements of all the sensory tasks (Results are shown in Means ± SEM).

<table>
<thead>
<tr>
<th>Sensory Measurements</th>
<th>TS</th>
<th>TDC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Threshold (μm)</td>
<td>8.95±0.44</td>
<td>8.44±0.45</td>
<td>0.43</td>
</tr>
<tr>
<td>Difference Threshold (By Frequency Discrimination) (Hz)</td>
<td>4.70±0.58</td>
<td>5.75±1.23</td>
<td>0.44</td>
</tr>
<tr>
<td>Amplitude discrimination threshold at baseline (μm) (nAD)</td>
<td>61±8.3</td>
<td>48±6.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Amplitude discrimination threshold after single site adaptation (μm) (ssAD)</td>
<td>101±24</td>
<td>126±16.5</td>
<td>0.40</td>
</tr>
<tr>
<td>Choice Reaction Time (msec)</td>
<td>877±62</td>
<td>715±52</td>
<td>0.05</td>
</tr>
<tr>
<td>Temporal Order of Judgment (msec)</td>
<td>38±5.05</td>
<td>54±6.9S</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Table 8.2 Post hoc analysis of all sensory measurements among three groups, in TS with ADHD, in TS without ADHD and TDC (Results are shown in Means ± SEM).

<table>
<thead>
<tr>
<th>Sensory Measurements</th>
<th>TS with ADHD (n=12)</th>
<th>TS without ADHD (n=9)</th>
<th>TDC (n=21)</th>
<th>ANOVA p value</th>
<th>TS+ADHD vs Control p value</th>
<th>TS - without ADHD p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Threshold (µm)</td>
<td>9.04±0.61</td>
<td>8.83±0.66</td>
<td>8.44±0.45</td>
<td>0.7</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Difference Threshold (By Frequency Discrimination) (Hz)</td>
<td>4±0.75</td>
<td>5.7±0.85</td>
<td>5.7±1.2</td>
<td>0.5</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Amplitude discrimination threshold at baseline (µm)</td>
<td>68±13.5</td>
<td>50.78±6.7</td>
<td>48±6.7</td>
<td>0.3</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>nAD</td>
<td>Amplitude discrimination threshold after single site adaptation (µm) (ssAD)</td>
<td>89±27.23</td>
<td>117.1±45.05</td>
<td>126.33±16.45</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>----------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>ss AD-nAD (Level of Adaptation)</td>
<td>21.8±34.5</td>
<td>66.33±45.4</td>
<td>78.33±18</td>
<td>0.3</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Choice Reaction Time (msec)</td>
<td>906.7±86.45</td>
<td>838.2±91.5</td>
<td>716±52</td>
<td>0.1</td>
<td>0.05</td>
<td>0.2</td>
</tr>
<tr>
<td>Temporal Order of Judgment (msec)</td>
<td>37±2.6</td>
<td>40±11.6</td>
<td>54±7</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

7.3. Results of Aim 1:

Hypothesis: Sensory thresholds were lower in TS compared to TDC.

Two experimental protocols were used to evaluate absolute threshold and discrimination threshold.
7.3.1 **Absolute threshold.** The absolute thresholds were not significantly different in TS compared to TDC (8.95±0.44 µm vs 8.44±0.45 µm; p=0.43; **Figure 39**).

![Figure 39](image.png)

**Figure 39.** Absolute threshold in TS and TDC. Data are means ± SEM.

7.3.2 **Discrimination threshold:** The frequency discrimination thresholds were also not significantly different in TS compared to TDC (4.7± 0.98 Hz vs 5.75± 0.95 Hz; p=0.44; **Figure 40**).
**Results of Aim 2:**

Hypothesis: Neuroadaptation is reduced in TS and associated with clinical severity of tic score in Children with TS compared to TDC.
To assess the sensory neuroadaptation, amplitude discrimination thresholds were measured at baseline and after single site stimulation. Changes in adaptation from baseline after single site stimulation were considered as sensory neuroadaptation.

### 7.4.1 Amplitude discrimination thresholds at baseline (nAD).

The amplitude discrimination thresholds at baseline were not significantly different in TS compared to TDC (61±8.3 µm vs 48±6.7µm; p=0.24; Figure 41A).

### 7.4.2 Amplitude discrimination thresholds after single site stimulation (ssAD).

The amplitude discrimination threshold after single site stimulation were not significantly different in TS compared to TDC (101± 24.3 µm vs 126±16.5 µm; p=0.4; Figure 42B).

---

**Figure 41.** Amplitude discrimination thresholds at base line (nAD) (A) and after single site stimulation (ssAD) (B) in TS and TDC.
7.4.3 Baseline amplitude discrimination thresholds in normalized data.

The amplitude discrimination thresholds at baseline after normalization were not significantly different in TS compared to TDC (3.95±0.12 vs. 3.65±0.16; p=0.15; Figure 42A)

7.4.4 Amplitude discrimination thresholds after single site stimulation in normalized data.

The amplitude discrimination thresholds at baseline after normalization were significantly different in TS compared to TDC (3.85±0.31 vs. 4.65±0.14; p=0.03; Figure 42B)
7.4.5 Quantification of sensory neuroadaptation.

Level of sensory neuroadaptation were quantified as (i) the differences between baseline thresholds and thresholds after single site stimulation (ssAD-nAD); (ii) percent change from baseline after single site stimulation (ssAD-nAD/NAD*100); and (iii) normalized percent change after single site stimulation [Log(ssAD-nAD/NAD*100)] (Table 9).

The differences between baseline thresholds and thresholds after single site stimulation (ssAD-nAD) were not significantly different in TS compared to TDC (41±28 vs. 78±18 µm; p=0.24; Table 9).

Percent change from baseline after single site stimulation (ssAD-nAD/NAD*100) were not significantly different in TS compared to TDC (256±73 vs. 449±123 % of baseline; p=0.21; Table 9).

Normalized percent change after single site stimulation [Log(ssAD-nAD/NAD*100)] were significantly different in TS compared to TDC (4.51±0.37 vs. 5.61±0.21; p=0.001; Table 9).

Table 9: Level of neuroadaptation in TS and TDC. The neuroadaptation are described as differences between baseline thresholds and thresholds after single site stimulation, percent change and log percent change. Results are shown in Means ± SEM.
7.4.6 Neuroadaptation in TS and TDC:

Our results showed presence of sensory neuroadaptation in both TS and TDC groups. The sensory neuroadaptation was double in healthy children compared to children with TS. To determine level of adaption in each group separately, amplitude discrimination thresholds at baseline and after single site stimulation were compared. In TS patients, amplitude discrimination were not significantly different between baseline and after single site stimulation (61±8 vs. 101±24; t ratio = 1.49; p=0.15; Table 10 and Figure 43).

<table>
<thead>
<tr>
<th>Level of Adaptation</th>
<th>TS</th>
<th>TDC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ssAD–n AD</td>
<td>41±28</td>
<td>78±18</td>
<td>0.26</td>
</tr>
<tr>
<td>Percent change (%)</td>
<td>256±101</td>
<td>499±101</td>
<td>0.21</td>
</tr>
<tr>
<td>Log(ssAD-nAD/NAD*100)</td>
<td>4.51±0.37</td>
<td>5.61±0.21</td>
<td>0.01*</td>
</tr>
</tbody>
</table>
In TDC subjects, amplitude discrimination were significantly different between baseline and after single site stimulation (48±7 vs. 126±17; t ratio = 4.53; p=0.0003) (Table 10; Figure 44).

Figure 43. State of adaptation within TS (Means ± SEM). nAD = amplitude discrimination with no adaptation. ssAD = amplitude discrimination with single site adaptation.
**Figure 44.** State of adaptation within TDC (Means ± SEM). nAD = amplitude discrimination with no adaptation. ssAD = amplitude discrimination with single site adaptation.

**Table 10:** Amplitude Discrimination thresholds before and after single site stimulation among groups of TS and TDC (using paired t-test). nAD = amplitude discrimination with no adaptation. ssAD=amplitude discrimination after single site stimulus within children with TS and TDC.

<table>
<thead>
<tr>
<th>Matched pair of n AD</th>
<th>Matched pair of ssAD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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7.4.7 Relationship between sensory neuroadaptation and clinical severity of tic score in TS:

The relationships between clinical severity in TS (total tic score) and level of neuroadaptation were quantified as (i) the differences between baseline thresholds and thresholds after single site stimulation (ssAD-nAD); (ii) percent change from baseline after single site stimulation (ssAD-nAD/NAD*100); and (iii) normalized percent change after single site stimulation [Log (ssAD-nAD/NAD*100)].

In TS patients, clinical severity of total tic score were strongly associated for the ssAD-nAD (r=0.55, p=0.01, Figure 45); ssAD-nAD/NAD*100 (r=0.53, p=0.01); and Log(ssAD-nAD/NAD*100) (r=0.5, p=0.04).
Neuroadaptation in TS patients after adjustment of covariates.

Effects of covariates such as age, sex, diagnosis, medication status and associated comorbid disorders, presence of sensory symptoms, functional impairments, and total tic score on neuroadaptation quantified as ssAD-nAD, ssAD-nAD/NAD*100 and Log(ssAD-nAD/NAD*100) were determined. Total tic score is the only variable that have significant effect on sensory neuroadaptation quantified as ssAD-nAD (p=0.01) and Log (ssAD-nAD/NAD*100) (p=0.04).

7.5 Results of Specific Aim 3:

Hypothesis: Perceptual processing is faster in TS than TDC.
This aim is an exploratory hypothesis. In order to assess perceptual processing of tactile stimulation perceptual latency via Choice Reaction time (cRT) task and time perception via Temporal Order Of Judgment (TOJ) were obtained.

7.5.1 Choice Reaction time (cRT):

The perceptual latency (reaction time) was significantly slower in TS compared to TDC (877±62 vs. 715±52 msec; p=0.05; Figure 46).

7.5.2 Temporal Order Of Judgment (TOJ).

Time perception obtained by TOJ was not significant in TS compared to TDC (38±6.08 vs. 53±6.08 msec; p=0.07; but was only significant at a trend level (Figure 47).

![Figure 46: Perceptual latency (Reaction time) in msec during cRT task (Means ± SEM)](image)

Figure 46: Perceptual latency (Reaction time) in msec during cRT task (Means ± SEM)
Figure 47. Time perception obtained by Temporal Order Judgment in msec (Means ± SEM)
7.6 Relationship of all sensory measurements with total tic score and each other within children with TS.

Results are shown on Table 11

Table 11: Co-relation matrix of all sensory measurements in TS

<table>
<thead>
<tr>
<th></th>
<th>YGTS</th>
<th>dL</th>
<th>Fre-D</th>
<th>nAD</th>
<th>ssAD</th>
<th>ssAD- nAD</th>
<th>cRT</th>
<th>TOJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>YGTSS</td>
<td>1</td>
<td>0.02</td>
<td>0.03</td>
<td>0.16</td>
<td>0.22*</td>
<td>0.3**</td>
<td>0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Absolute Threshold (dL)</td>
<td>0.02</td>
<td>1</td>
<td>0.02</td>
<td>0.06</td>
<td>0.12</td>
<td>0.15</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>Fre-D</td>
<td>0.03</td>
<td>0.03</td>
<td>1</td>
<td>0</td>
<td>0.17</td>
<td>0.13</td>
<td>0.17</td>
<td>0.05</td>
</tr>
<tr>
<td>nAD</td>
<td>0.16</td>
<td>0.06</td>
<td>0</td>
<td>1</td>
<td>0.05</td>
<td>0.25**</td>
<td>0.18*</td>
<td>0</td>
</tr>
<tr>
<td>ss-AD</td>
<td>0.23*</td>
<td>0.12</td>
<td>0.16</td>
<td>0.05</td>
<td>1</td>
<td>0.91**</td>
<td>0.07</td>
<td>0.33**</td>
</tr>
<tr>
<td>ssAD-nAD</td>
<td>0.3**</td>
<td>0.15</td>
<td>0.13</td>
<td>0.25**</td>
<td>0.91**</td>
<td>1</td>
<td>0.01</td>
<td>0.27**</td>
</tr>
<tr>
<td>cRT</td>
<td>0.1</td>
<td>0.01</td>
<td>0.17</td>
<td>0.17*</td>
<td>0.08</td>
<td>0.01</td>
<td>1</td>
<td>0.15</td>
</tr>
<tr>
<td>TOJ</td>
<td>0.03</td>
<td>0</td>
<td>0.05</td>
<td>0</td>
<td>0.33**</td>
<td>0.27**</td>
<td>0.16</td>
<td>1</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01
7.7 Relationship of all sensory measurements with total tic score and each other within TDC.

Results are shown on Table 12

Table 12: Co-relation matrix of all sensory measurements in TDC

<table>
<thead>
<tr>
<th></th>
<th>DL</th>
<th>Fre-D</th>
<th>nAD</th>
<th>ssAD</th>
<th>ssAD-nAD</th>
<th>cRT</th>
<th>TOJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threshold (dL)</td>
<td>1</td>
<td>0.02</td>
<td>0.02</td>
<td>0</td>
<td>0</td>
<td>0.16</td>
<td>0.07</td>
</tr>
<tr>
<td>FreqD</td>
<td></td>
<td>0.02</td>
<td>1</td>
<td>0</td>
<td>0.01</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>nAD</td>
<td>0.02</td>
<td>0.02</td>
<td>1</td>
<td>0</td>
<td>0.17</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>ssAD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.86**</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>ssAD-nAD</td>
<td>0</td>
<td>0.01</td>
<td>0.17</td>
<td>0.86**</td>
<td>1</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>cRT</td>
<td>0.16</td>
<td>0</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>TOJ</td>
<td>0.07</td>
<td>0.01</td>
<td>0.01</td>
<td>0.04</td>
<td>0.02</td>
<td>0.06</td>
<td>1</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01
Chapter 8
General Discussion

8.1 Discussion of the results:

8.1.1 Main Findings:

Two groups of children, aged 9-17 years including children with Tourette Syndrome (TS) and their healthy aged matched peers – typically developing children (TDC) – were evaluated. The objective of this study was to evaluate and compare crucial aspects of sensory perception - thresholds, adaptation and perceptual latency and time perception. Result of this study showed no differences in sensory thresholds, perceptual latency and time perception but significant changes in sensory neuroadaptation in children with TS compared to TDC.

8.1.2 Tactile sensory thresholds in TS:

Our study showed no differences in sensory thresholds, neither absolute nor discrimination thresholds between TS and TDC. This result is consistent with one of the earlier studies [66]. Similar to our study Belluscio et al have also evaluated the tactile threshold in addition to olfactory thresholds. There finding showed no differences of threshold with any of these modalities. There are two major differences between their study and ours. One is the age of the subjects and the second one is ‘discrimination threshold’. Belluscio et al. evaluated 19 adults, mean age of 32 years while our subjects were children with mean age of 13 years which is similar to the peak prevalence rate of the disease [4]. Spontaneous recovery of the disease by adulthood [8] is a common
phenomenology that may have contributed to their results of not identifying a difference in thresholds. We argue that our findings might be robust based on our age selection. Belluscio’s evaluated only the detection threshold whereas in our study we have also evaluated discrimination threshold. Discrimination threshold is usually referred as the minimum difference (in regard to intensity/frequency or time perception) required identifying two separate stimuli individually. It looks at the capabilities above the detection threshold and might work as important sensory measurements for the detection of differences in noise patient with TS.

8.1.3 Sensory Neuroadaptation in TS:
We found significant changes in sensory adaptation in children with TS compared to age matched healthy children. On average, less adaptation was observed after a priming stimulus in TS children (p=0.15) compared to healthy children (0.003). Furthermore this reduced ‘level of neuroadaptation’ is correlated with clinical severity of tic scores (r=.55, p=0.01). This implies the more severe the clinical tic symptoms, the less the adaptation. Neuroadaptation is a normal neuro-physiological response. It is a form of non-associative learning process where neuron learned to adapt with repeated stimuli by progressively reducing its firing rate [112]. This process gradually allows us to learn to cancel out noises that have no meaning. Similar to sensory adaptation, neuroplasticity confined to the motor areas in patient with TS were also investigated in [130][131]. Neuroplasticity is the ability of the neuronal cells to alter their properties via long-term potentiation (LTP) and long-term depression (LTD) to adapt with ongoing stimulation, which is the key for learning and memory [132, 133]. Wu et al. suggested
reduced cortical plasticity after administering repeated stimulation using Transcranial magnetic Stimulation (TMS) over primary motor area in 10 adult with TS. Two years later Brant et al. also measured cortical plasticity using TMS with a slightly different approach than Wu et al. Wu et al. had used intermittent Theta burst stimulation (iTBS) as their mode of stimuli and Brant et al had used Paired Associative Stimulation (PAS). In PAS, as name implies two stimuli are paired repeatedly with one given to the periphery i.e. Wrist and another given at central, over primary motor cortex (M1). Motor evoked potential (MEP) induced by TMS is obtained from M1 before and after the PAS stimuli considers the neuroadaptation [134]. Brant et al. also evaluated LTP like effects and it’s correlation with clinical symptom severity of both motor tic and PU’S. They had failed to observe LTP in TS compared to HC and this finding was negatively correlated with clinical symptoms of tic’s and PU’s. In this study, our findings of sensory adaptation obtained from sensory cortex and its correlation to clinical severity of tic score measured by YGTSS [135] made an additional impact by identifying sensory system as potential pathogenesis in the development of TS.

8.1.4 Perceptual processing in TS:

Perceptual latency and Time perception were also evaluated to assess perceptual processing for tactile stimulation in this study. ‘Perceptual latency’ or duration of the perceptual process is a key aspect in neuroscience. cRT task was administered to evaluate perceptual latency. A physical stimulus proceeds in two stages. First, the stimulus gives rise to conscious perception (this duration is known as “Perceptual Latency” and then the desired motor response is executed [122]. Reaction time
measured via cRT tasks evaluates the duration between exposures of the stimulus to its conscious perception. Time perception is another key concept in perception. In this study time perception was evaluated using (TOJ) task. It evaluated the minimal processing time to identify temporal order of two given stimuli.

In our study, we predicted that both cRT and TOJ would be shorter in TS, as indicators of faster perceptual processing of tactile stimuli. Our study showed reaction time for cRT was longer (p = .05) and time perception obtained via TOJ was, at the trend level (p = .07), shorter in TS (Table 8 and Figure 46, 47).

One possible reason for the longer cRT could be associated ADHD in our sample. In an earlier study by Shucard et al [136] found slower reaction times on Continuous Performance Test (CPT) in children with TS plus ADHD compared to Healthy controls. Attention is one of the most investigated factors to modulate reaction time in patients with ADHD [137]. Slower reaction time due to ADHD were observed in multiple studies; in patients with ADHD only [138, 139], in patient with ADHD with TS [136].

A well characterized study by Sukhodolsky et al [140] with a large sample size investigated several neurophysiological measurements in four groups of children with TS only, TS with ADHD, ADHD only and healthy controls (HC). Continuous attention, response inhibition, fine motor control and visual-motor integration employing neurophysiologic tasks were evaluated. Compared to HC and Children with TS only, children with ADHD and children with ADHD plus TS have demonstrated slower
reaction time. The results showed an indication of deficiency in sustained attention associated with ADHD. These results suggested that presence of ADHD in TS patients with their underlying attention deficit may contribute to the slower reaction time in our study.

However, in this study time perception obtained by TOJ in children with TS was at the trend level shorter compared to TDC. A difficulty with this interpretation is that poor attention should also have resulted in worse TOJ in this study, which was not what we found. During a Choice reaction time task, a participant is asked to respond to a given stimulus as soon as possible (detection time) but also asked to respond to a choice question as well. So cRT has three components, sensory, motor and a cognitive components. In TOJ, the two stimuli presented and the subjects are asked to report which stimulus comes earlier. The two stimuli presented on each trial are assumed to be detected at two time point (Detection time or DT-TOJ) and the subjects were asked to report which stimulus comes earlier. According to Miller et al. [126] both TOJ and RT share a common internal pathway and detection time (DT) for both tasks is similar (DT-RT=DT-TOJ).

Accepting this argument, any variables, considering attention is the predominant co-factors in our study group we expected to observe similar effects on both tasks, which again we did not. Our study showed huge differences in reaction time, significantly slower reaction time in TS and normal to faster TOJ. This pattern of results cannot be explained by attention deficit only. ADHD itself produces slower reaction time which
correlated with impairments in motor developments [141]. Impairments in motor
development and motor controls in children with ADHD were also observed by other
studies [142, 143]. In his study Gilbert et al [143], had shown that children with ADHD
had slower reaction time in choice reaction time task. Furthermore this slower reaction
time was related with worse motor functioning obtained using Physical and Neurological
Examination for Subtle Signs (PANESS). Based on their study, we propose that
perceptual latency obtained from cRT is substantially more affected than TOJ in this
study because of additional motor component of cRT task. Motor component of cRT
may have contributed to the slower perceptual latency obtained via cRT task. Now
accepting this we speculate that performing another task like TOJ, which is free from
motor component (TOJ= DT-TOJ+ Cognition) might improve the detection time in this
patients. This may explain the relatively slower CRT but faster TOJ in our sample of
children with TS.

Our hypothesis was that the perceptual processing based on detection time
measurement by cRT and TOJ would be faster in TS. However, our results showed
slower cRT and a tendency of faster TOJ (P=.07). A recent study also showed
enhanced time processing in children with TS only without any comorbid diseases [142].
The study used ‘time reproduction task’ to assess temporal intervals between two
stimuli, a different approach compares to our TOJ measurements. Therefore the time
perception in our study could have been cofounded by the presence of comorbid
diseases, especially ADHD. Studies with larger sample size and TS only patients
without any comorbid diseases might provide accurate measurement of perceptual processing.

In summary, my data supports the idea of significant central sensory dysfunction, particularly sensory neuroadaptation, in children with TS.

8.2 Limitations of the present study:

There are several limitations of this study. First, characterization of the patients based on subjective sensory complaints, such as external sensory sensitivity, intolerance, and Premonitory Urges (PU’s), might have been informative. Unlike the YGTSS tic severity assessment that we employed, there are no scales for sensory symptoms that are clinically validated or in wide use in Tourette Syndrome. The PU scale has emerged relatively recently and is just starting to be incorporated into controlled clinical trials. Sensory profile would allow us to quantify sensory experiences. Considering sensory function is the major focus of our study, it could be informative in future studies to characterize the patients based on sensory profile. At present, no sensory profile scale nor PU scales is part of routine clinical care in TS clinics, so neither was available for this study. It would be of interest in future studies to determine whether, in healthy or TS children, sensory profile data is associated with sensory adaptation or other measures. The second limitation has to do with TS heterogeneity and the trade-off between validity and generalizability. About 80% patients with TS have at least one co-existing cognitive or emotional disorder. In addition, most patients with moderate or severe tics or co-morbid symptoms take medication to improve their quality of life. This means that a
representative, generalizable sample will have two potential confounders: 1) co-morbid diagnoses, and 2) medications. With regard to the comorbid diagnoses, to determine the most valid estimate of the relationship between sensory dysfunction and tic symptoms per se, a group of TS patients without comorbidities would be appropriate. However it is challenging to recruit such a sample given its low prevalence. Concurrently – it is difficult in convenience sample like this with a large variety of co-morbid diagnoses to apply statistical adjustment for comorbid diagnosis or to estimate independent relationships between those diagnoses, the severity of their symptoms, and the sensory physiology we measured. We expect however that the net effect of a heterogeneous sample would tend to bias results toward the null, i.e. increasing risk for type 2 errors. With regard to medications, the patient population in the current study includes TS patients who were mostly (17 out of 21) prescribed medication. Use of medication may confound our results of sensory function. Additionally, TS patients were treated with varieties of medication for the primary TS and associated comorbid conditions. Statistical adjustments for confounder for the medications require larger numbers of subjects. Unmedicated TS patients, larger sample size, will provide accurate measurements of sensory dysfunction in TS. However, unmedicated TS patients will be without severe symptoms of TS and the sensory dysfunction might not be significant, considering our results of significant relationships between sensory dysfunction and severity tic in patients with TS.

Finally, our current study has all the limitations of a cross-sectional study design. We are unable to establish a causal relationship of sensory dysfunction in TS. A future longitudinal study with larger sample size might allow us to establish causal
relationships. Ideally such a study would enroll children at the onset of their illness.
Unfortunately, in most cases the onset occurs before the age of 10 years, and at that age it is unclear whether a good proportion of children could cooperate with and perform the sensory studies accurately.

8.3 Directions to future research:
In pursuance of extending this present study, some of the limitations of the present study needed to be addressed. Present study should be extended to-

i) Include sensory profile in the clinical data to assess the sensory complaints in details. Also correlation of sensory complaints (i.e. PU’s) or other sensory scale with sensory measurement, specially neuroadapation.

ii) Include other comparison groups in different categories such as Pure TS, TS+ADHD, TS+OCD and to identify the true predictors for clinical symptoms of TS and have better plan for their management.

iii) Include comparison groups in different categories based on the use of current and or prior medication, duration of medication and weather controlled with medication to minimize the potential medication effects and to determine whether these responses can predict medication responses.

iv) Plan to perform a longitudinal study in future to compare those who do and do not improve in adulthood. This might allow us to predict the potential group of children might goes for spontaneous resolution.
This study provides evidence of reduced sensory adaptation and its negative correlation with clinical tic severity scale. This clinical correlation is unique and to my knowledge is the first ever conducted in children with Tourette syndrome. We plan to use this neuroadaptation as a potential biomarker to determine effects of successful pharmacological and behavioral interventions.

Also use the baseline amplitude discrimination threshold (measurement before administering adapting stimulus) to predict response to behavioral or pharmacological interventions.

An additional direction is to apply intervention in order to increase the adaptation in patient with documented reduced neuroadaptation. Then compare the finding with pre and post intervention correlating with clinical scores. For clinical intervention, we would use repetitive stimulation to the sensory cortex using Transcranial Magnetic Stimulation (TMS) in the form of intermittent theta burst (iTBS) to induce adaptation to the sensory cortex. Pre and post intervention follow up can be measured using CM-5.

Finally, we would like to apply this unique technique of assessment of neuroadaptation in other diseases specifically to autism. Similar to TS, patient with autism often complains about heightened sensitivity to external stimuli. Understanding the mechanisms of altered sensory processing might act as a potential novel biomarker to and in long run might help ease the sufferings in these patients.
8.4 Conclusions

The primary objective of our present study was to determine sensory function in children with TS who have clinically significant tics. Multiple fundamental aspects of sensory processing including both absolute and discrimination thresholds, neuroadaptation, perceptual latency and time perception were quantified in children with TS and healthy children using a newly developed device. Our results demonstrated for the first time that reduced sensory neuroadaptation in children with TS is correlated with clinical tic severity score. Reduced adaptation may indicate an abnormal processing of somatosensory information. Thus, TS patients are unable to ignore non-salient stimuli compared to healthy controls, resulting in sensory hyperawareness. Furthermore, significant negative correlation between sensory adaptation and clinical tic score in TS suggest a potential causal association between sensory dysfunction and clinical symptoms in TS. Future research will determine whether reduced neuroadaptation at cortical level may impair the proper transport of information to the downwards neuronal circuits in the basal ganglia. Knowledge about sensory adaptation at cortical level and it's subsequent influences on Cortico-striato-thalamic-pathway of the basal ganglia in patients with TS would help researcher and clinicians to better understand the pathophysiology of TS and develop interventions accordingly.
Chapter 9

Reference


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135. Shahana, N., Reduced Sensory Adaptation Correlates with Tic Severity in Children with Tourette Syndrome, in 1st World Congress on Tourette Syndrome and Tic Disorders, 2015: London, UK.


Appendices

Appendix-1: Diagnostic criteria of Tourette Syndrome according to DSM-5 (2013)

Diagnostic criteria for TS according to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (2013) include:

For a person to be diagnosed with TS, he or she must:

1. Have two or more motor tics (for example, blinking or shrugging the shoulders) and at least one vocal tic (for example, humming, clearing the throat, or yelling out a word or phrase), although they might not always happen at the same time.
2. Have had tics for at least a year. The tics can occur many times a day (usually in bouts) nearly every day, or off and on.
3. Have tics that begin before he or she is 18 years of age.
4. Have symptoms that are not due to taking medicine or other drugs or due to having another medical condition (for example, seizures, Huntington disease, or postviral encephalitis).
Premonitory Urge for Tics Scale

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

- Right before I do a tic, I feel a sensation inside my body.  
  Yes  ☐  No  ☐

- 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.  
  ☐  ☐
Premonitory Urge Scale

Please answer the following questions. Try to be very honest when you answer them. Check the number that best describes how you feel.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not at all true</th>
<th>A little true</th>
<th>Pretty much true</th>
<th>Very much true</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right before I do a tic, I feel like my insides are itchy.</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>2</td>
<td>Right before I do a tic, I feel pressure inside my brain or body.</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>3</td>
<td>Right before I do a tic, I feel “wound up” or tense inside.</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>4</td>
<td>Right before I do a tic, I feel like something is not “just right.”</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>5</td>
<td>Right before I do a tic, I feel like something isn’t complete.</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>6</td>
<td>Right before I do a tic, I feel like there is energy in my body that needs to get out.</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>7</td>
<td>I have these feelings almost all the time before I do a tic.</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>8</td>
<td>These feelings happen for every tic I have.</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>9</td>
<td>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.</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>10</td>
<td>I am able to stop my tics, even if only for a short period of time.</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
</tbody>
</table>

Appendix-4: Yale Global Tic Severity Scale (YGTSS)